

Research Priorities for Complementary Medicine in Australia

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New research studies and data on complementary medicine appear on a monthly basis. This ever-developing evidence profile may influence and shift priority areas for investigation in complementary medicine. The work documented in this report was completed at various stages over the last three years so, in some cases, the key data may already be 18 months old. Hence, the recommended research priorities in this report should be taken as a starting point for further discussion and exploration, rather than as a defined, fixed program of recommended research. NICM will continue to update recommended research priority areas and undertake reviews in additional clinical discipline areas.

Currency

All figures quoted in this report are given in Australian dollars, unless otherwise indicated.

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Research Priorities for Complementary Medicine in Australia

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Highlighting
Complementary
Medicine Research



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INITIATIVE HOSTED BY THE
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Director's message

Australians are among the world's highest users of complementary medicines. Two in three Australians use complementary medicines or therapies each year, many of them on a regular basis, representing an expenditure of over \$3.5 billion each year.

About half of this use is in relation to the management of major chronic diseases. Increasingly we are finding that complementary medicine has the potential to contribute positively to the management of chronic diseases and improve health outcomes, through increased effectiveness, improved safety or cost-effectiveness of patient care, often when integrated with conventional medical care.

Despite this, Australia has one of the lowest rates of investment in research into complementary medicine. This limits the ability of Australian consumers and health practitioners to make informed, evidence-based decisions about the therapies they use. It also opens the door for some medical scientists and practitioners to question the validity of many complementary medicine interventions due to a lack of evidence.

As a longstanding advocate of evidence-based complementary medicine, it therefore gives me great pleasure to introduce this report, which articulates a rigorous strategy to guide research in complementary medicine. The report focuses on target areas that have a higher burden of disease, that accord with the Australian Government's National Health Priority Areas, and that have a greater probability of success.

It is a critical step to building our national research effort in complementary medicine for the better health of the Australian community.

Professor Alan Bensoussan

Director

National Institute of Complementary Medicine

University of Western Sydney

National Institute of Complementary Medicine

The National Institute of Complementary Medicine (NICM) was established in 2007 with initial seed funding from the Australian Department of Health and Ageing and the NSW Office for Science and Medical Research (now part of the NSW Department of Trade and Investment, Regional Infrastructure and Services). The University of Western Sydney hosts NICM at its Campbelltown campus.

The role of NICM is to provide leadership and support for strategically directed research into complementary medicine (CM) and translation of evidence into clinical practice and relevant policy to benefit the health of all Australians.

The establishment of NICM followed the 2003 recommendation by the Expert Committee on Complementary Medicines in the Australian Health System that the government has a social responsibility to fund complementary medicine research given the high community use of complementary medicines and therapies.

The NICM's projects have included:

- An investigation into the cost-effectiveness of CM – NICM commissioned Access Economics to evaluate the cost-effectiveness of five complementary medicine interventions. Access Economics found that some CMs would have a positive impact on the national healthcare system if their integration into daily medical practice were improved.
- The establishment of collaborative centres – NICM seeded three national collaborative centres in Traditional Chinese Medicine; Natural Medicine and Neurocognition; and Nutraceuticals and Herbal Medicine. In doing so, it has built research capacity in the area and supported professional development.
- Integrative care grants – NICM awarded six integrative care grants (two in partnership with the National Breast Cancer Foundation) to provide evidence and insight into optimal integrative care for target diseases.
- Standard operating procedures for clinical trials - While these procedures were initially designed for use in traditional Chinese medicine, they may be adopted and modified for all complementary medicine sectors and are available on the NICM website.

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Glossary

ABS	Australian Bureau of Statistics
AIHW	Australian Institute of Health and Welfare
ARC	Australian Research Council
ASMI	Australian Self Medication Industry Association
CAM	Complementary and alternative medicine
CHC	Complementary Healthcare Council
CHD	Coronary heart disease
CM	Complementary medicine
CRC	Cooperative Research Centre
CVD	Cardiovascular disease
DALY	Disability adjusted life year
DHA	Docosahexaenoic acid
DIISR	Department of Innovation, Industry, Science and Research
DOHA	Department of Health and Ageing
DHA	Docosahexaenoic acid
MCI	Mild cognitive impairment
MI	Myocardial infarction
mmol/L	Millimoles per litre
MSKC	Musculoskeletal conditions
n=	The number of participants in a study
NCI	National Cancer Institute
NHMRC	National Health and Medical Research Council
NICM	National Institute of Complementary Medicine
NIH	National Institute of Health (United States)
NSAIDS	Non-steroidal anti-inflammatory drugs
N-3 FA	Omega-3 fatty acid
OSMR	NSW Office for Science and Research
PUFA	Polyunsaturated fatty acids
QALY	Quality adjusted life year
RA	Rheumatoid arthritis
RACGP	Royal Australian College of General Practitioners
RCT	Randomised controlled trial
ROS	Reactive oxygen species
SAC	Scientific Advisory Committee
TCM	Traditional Chinese medicine
TENS	Transcutaneous electrical nerve stimulation
TGA	Therapeutic Goods Administration
UK	United Kingdom
US	United States
WHO	World Health Organisation

Summary

Why this report is important

This report identifies research priorities in complementary medicine (CM) that will lead to more targeted research and, as a result, better health outcomes for all Australians. Of critical importance, it reflects the professional opinions of experts from both the conventional and complementary medical streams, who have reached consensus on research priorities.

Background

Australians are among the world's highest users per capita of CM. Two in three Australians use CM each year – over 40% for the prevention or management of major chronic diseases.

Yet Australia has one of the lowest rates of investment in CM research.

To provide a starting point for improvements in CM healthcare – and to respond to uncertainties associated with the use of complementary medicine – high quality evidence of its safety, efficacy and cost-effectiveness is essential. This requires research.

To help identify priorities for research in Australia, the National Institute of Complementary Medicine (NICM) commissioned a review of the available evidence for the therapeutic use of CM in addressing some of the diseases in the Australian Government's National Health Priority Areas. The review addressed the following areas: cardiovascular health, cancer control, dementias, diabetes mellitus and arthritis and musculoskeletal conditions. A chapter on wellness also addresses this area.

However, the review did not address the following National Health Priority Areas: asthma, mental health, obesity, and injury prevention and control. It is envisaged that NICM will address these areas in coming years.

This report documents the key findings of the review, and articulates a strategy to guide investment in CM research. Because the field of CM is so broad, it was not possible to investigate the claims of every intervention. Instead, the review targeted areas that have a higher burden of disease, that accord with the Australian Government's National Health Priority Areas, and that have a greater probability of success.

Key research areas

The key areas investigated in this report are:

- **Cardiovascular health** – Patients commonly adopt CM to promote cardiovascular health. There is a public health need to determine if these therapies work and if they are safe, particularly when taken in conjunction with conventional medicine. Research is also required to develop novel treatments.
- **Cancer** – Cancer patients frequently use CMs concurrently with conventional cancer treatments, often without evidence of the efficacy of those CMs or of the potential interactions between CMs and conventional treatments.
- **Arthritis and musculoskeletal conditions** – Patients with arthritis and musculoskeletal conditions are using CM approaches extensively, but more research is needed to establish their efficacy, safety and cost effectiveness.

- **Dementia** – Dementia is the leading single cause of disability in older Australians and constitutes the seventh largest burden of disease in Australia. There are a number of candidate CMs that could be efficacious in the treatment and prevention of dementia.
- **Diabetes** – There are numerous interventions that claim to treat blood sugars and reduce the risk of diabetes, but the quality of the data in relation to these claims varies greatly. There have been very few properly controlled clinical tests and no herbal preparation has achieved sufficient acceptance as a safe, effective, reliable agent for the management of diabetes of any type or for the complications of diabetes. Therefore, this working group was not able to reach any conclusions regarding priority areas for research into CM interventions for diabetes.
- **Wellness and disease prevention** – There are a number of wellness and disease prevention initiatives that hold substantial potential to benefit Australians and reduce the burden on the health system.

Research priorities

Cardiovascular health

A number of nutrition and dietary supplements, herbal preparations, and mind-body and body-based practices have potential to promote cardiovascular health. This report recommends that the priority should be to investigate the efficacy of:

- Soluble fibre (oats, psyllium, pectin and guar gum) in reducing total cholesterol.
- Nuts in reducing the magnitude of the coronary heart disease risk.
- Tea drinking in protecting against coronary heart disease.
- Hawthorn extract in reducing heart failure-related signs and symptoms.
- Ginkgo leaf and its extracts in treating heart disease.
- Padma 28 in treating heart disease.
- Red rice yeast in lowering LDL.
- Spirulina in lipid lowering and blood pressure control.

- Ginger and, specifically, certain ginger extracts, in modifying risk factors for developing coronary heart disease.
- Acupuncture in treating myocardial ischaemia, hypertension and arrhythmias.
- Yoga, Qi Gong and meditation in reducing heart disease risk factors.

Cancer

There are numerous therapies with potential for the treatment of cancer. This report recommends that the priority should be to:

- Conduct preclinical and clinical studies investigating the interactions and impact of biological treatments (including herbal medicines, Chinese herbal medicines and nutritional supplements) taken concurrently with conventional cancer treatments in reducing the side effects of conventional cancer treatment, alleviating cancer symptoms, reducing tumour load, and prolonging disease-free survival.
- Investigate the best means to provide accurate, readily accessible and regularly updated information about CM for patients and healthcare practitioners.
- Study the effect of herbal medicines and nutritional supplements on quality of life and survival, following conventional cancer treatment.
- Study the role of exercise/physical activity in ameliorating cancer side effects and in secondary cancer prevention.
- Study the role of acupuncture for symptom relief (due to cancer or its treatment), reducing opioid dependence/treatment-induced leucopenia, etc.

Arthritis and musculoskeletal conditions

This report recommends that further research is required to establish the efficacy, safety and cost-effectiveness of the following CM approaches:

- **Acupuncture** – This intervention is already widespread.
- **Rosehip** – There is reasonable evidence for the effectiveness of this therapy, and the product can be grown locally.
- **Avocado-soybean unsaponifiables** – This natural

extract, made from avocado and soybean oils, can be locally produced and the evidence to support its efficacy is reasonable.

- **Phytodolor®** – This herbal medicine was chosen because of its accessibility and because there is a reasonable evidence base for its effectiveness as an anti-inflammatory and in relieving pain.

Dementia

This report recommends that further research is required to establish the efficacy of the following candidate CMs in treating and preventing dementia:

- **Docosahexaenoic Acid (DHA)** – Given the strong epidemiological evidence linking high fish consumption to lower incidences of dementia, large-scale clinical trials investigating the efficacy of Docosahexaenoic Acid (DHA) are warranted.
- **Precursor loading with N-acetylcysteine** – Boosting endogenous supplies of Glutathione through precursor loading with N-Acetylcysteine holds promise for both the treatment and prevention of dementia, and requires large-scale clinical trials to establish the cognitive benefit of this strategy.
- **The polyphenol antioxidants** – Curcumin, resveratrol, epigallocatechin gallate (EGCG) and Pycnogenol® should be examined via large-scale clinical trials due to their well established mechanisms of action and considerable epidemiological evidence of efficacy.
- **Herbal treatments** – Huperzine A, Bacopa monnieri and Salvia officinalis are worthy of further research due to their well established mechanism of action and long history of usage.
- **Mitochondrial cofactors** – Alpha-lipoic acid and ALCAR should be candidates for clinical trials.
- **Wellness metrics** – The multiple dimensions of wellness are unclear and there is no single metric for measuring integrated functioning. Research is needed to quantify wellness and integrate physiological, psychological, socio-economic, demographic and ecological measures and thus enhance the rigor of future research.
- **Public health programs** – While preventable lifestyle related chronic disease mainly associated with alcohol and tobacco use and obesity account for over 70% of the current disease burden, only 2% of the health budget is allocated to prevention. There is therefore an urgent need to explore programs aimed at reducing risk factors, especially in the areas of smoking, alcohol, nutrition, physical activity and stress management.
- **Information technology** – Information technology has an untapped potential to enhance the collection of wellness-related data and assist in the implementation of wellness initiatives. Research is needed to determine the best use of technology to assist with the monitoring and mapping of wellness metrics and the design, implementation and evaluation of wellness and prevention interventions.
- **The integration of lifestyle management into the healthcare system** – Research is required to determine the educational needs and skill sets required for health practitioners to effectively engage in preventative and wellness initiatives and to design appropriate education to meet these needs.

Next steps

This report presents an important set of priorities in CM research, but is a starting point only. There will be many other areas of potential which are worthy of further investigation. NICM commits to undertaking additional research priority reviews with potentially a more defined framework to increase uniformity and comparability of findings. The next step is also for Australian funding agencies (such as NHMRC, ARC, and disease foundations) to adopt these priorities, with the aim of finding better, and more cost-effective ways, to manage chronic diseases that fall within the National Health Priority Areas.

Wellness and disease prevention

A number of therapies hold substantial potential to benefit Australians and reduce the health burden on the health system. This report recommends that the key research priorities should be in the following areas:

1 | About this report

Each year, the number of complementary medicine (CM) options is expanding. A quick trip to Wikipedia finds a list of ‘branches of alternative medicine’ that starts with acupuncture and ends with 11 forms of yoga. The list includes well-known options such as massage, homeopathy and traditional Chinese medicine, as well as more arcane therapies such as ear eyeology, journaling and orgonomy (http://en.wikipedia.org/wiki/List_of_branches_of_alternative_medicine).

In Australia, some CMs are widely used, and there is scope for greater use of well-evidenced CMs in the treatment of a range of diseases. Research to date indicates that some CMs offer potentially cheaper, more cost-effective and safer treatment when used in an integrative healthcare environment – factors that are going to become even more important as the Australian population ages and the cost of health care increases. Novel CMs may also provide benefits for patients where conventional medicine has failed, particularly in some chronic diseases.

To provide a starting point for improvements in CM health care – and to respond to uncertainties associated with the use of CM – it will be essential to gather high quality evidence of its safety, efficacy, cost-effectiveness and interaction with other treatments. This requires research.

To help identify priorities for research in Australia, the National Institute of Complementary Medicine (NICM) commissioned a review of the available evidence for the therapeutic use of CM in Australia’s National Health Priority Areas. This report documents the key findings of the review, and the process that was undertaken to arrive at the findings.

1.1 How this report is different

There has been a plethora of research into CM but, to date, much of the research effort has been disaggregated and scattered. This report seeks to ‘narrow the field’ and identify those treatments that offer the greatest potential to meet Australia’s healthcare needs. The approach involved harnessing the expertise of some of Australia’s leading experts, in a cooperative and collaborative process, to shortlist the best candidates for future research investment.

The end result is a considered perspective of where future research investment should be directed. Medical research consumes large amounts of both time and money. Whilst priority research areas are proposed in this report, they still require extended and consistent investment over an adequate period of time to achieve worthwhile outcomes. Through the seeding of collaborative research activities in recent years, NICM has invested in building relevant research teams and capacity in CM by funding 23 higher-degree research students and/or post-doctoral fellowships. Building capacity and identifying research priorities are the initial steps in an ongoing research effort that will help ensure funding bodies receive the best return on their investments.

1.2 Aims of this report

The aims of this report are to:

- Identify key targeted areas for future research in CM that is driven by National Health Priority Areas.
- Provide evidence-based guidance to funding bodies (government and non-government), with a view to increasing funding in priority areas.
- Highlight the need for greater investment in CM research in response to high levels of use by the community and perceived benefits in the management of chronic illnesses.

1.3 Who should read this report?

This report is of interest to:

- State and Commonwealth government ministers.
- Department of Industry, Innovation, Climate Change, Science, Research and Tertiary Education.
- State-based departments of industry, trade, science and research..
- National Health and Medical Research Council (NHMRC).
- Australian Research Council (ARC).
- Disease-based organisations (e.g. Cancer Council Australia, Heart Foundation, Diabetes Australia).
- Complementary Healthcare Council (CHC).
- Australian Self Medication Industry Association (ASMI).
- Health insurers and other stakeholders

2 | What is 'complementary medicine'?

To determine the scope for the review, it was necessary to identify those healthcare modalities and practices that are included under the designation of 'complementary medicine' (CM).

2.1 International definitions of CM

There is no internationally agreed definition for CM; it encompasses a heterogeneous group of therapies that aim to prevent or treat illness. Some therapies offer complete systems of diagnosis and treatment, while others complement conventional medical practices with supportive therapy. The designation of a therapy as a CM does not differentiate between those therapies that are provided alongside conventional medicine (complementary) or those used as a substitute for it (alternative).

Some authorities use the term 'complementary and alternative medicine' (CAM). For example:

- In the United Kingdom, the House of Lords Select Committee on Science and Technology uses CAM to refer to a diverse group of health-related therapies and disciplines that are not considered to be part of mainstream medical care.
- In the United States, the National Center for Complementary and Alternative Medicine suggests that CAM practices are best described as those not currently considered an integral part of conventional medicine.

- The international Cochrane Collaboration describes CAM as "a broad domain of healing resources that encompasses all health systems, modalities, and practices and their accompanying theories and beliefs, other than those intrinsic to the politically dominant health system of a particular society or culture in a given historical period."

(Source for above: http://en.wikipedia.org/wiki/Portal:Complementary_and_Alternative_Medicine)

The therapies and products included in CM vary from country to country and may change with time, depending on whether the practice is adopted as part of mainstream healthcare practice. To avoid the temporal, cultural and often subjective judgement as to whether a specific therapy or product is 'complementary' or 'alternative' to conventional practice or whether it is part of a country's mainstream healthcare practice, in this report the term CM is defined as those therapies and associated products that are commonly considered to fall outside conventional medical practice.

In this report, the term 'complementary medicine' is defined as those therapies and associated products that are commonly considered to fall outside conventional medical practice.

Modality	Example of CM therapy
Biologically based practices	Herbal medicines; vitamins and minerals; other nutrient and non-nutrient substances derived from animal, plant and marine sources such as shark cartilage, soy phytoestrogens, Coenzyme Q10, tea polyphenols, methylsulfonyl methane (MSM)
Mind-body therapies	Meditation, hypnosis, relaxation therapy, support groups and counselling, music therapy, spiritual healing, including prayer
Manipulative and body-based practices	Chiropractic, therapeutic massage, osteopathy, reflexology, tai chi, yoga, shiatsu, exercise
Energy therapies	Acupuncture, Reiki, Qigong, electromagnetic field therapy
Whole medical systems	Complete systems of theory and practice, such as traditional Chinese medicine (TCM), Ayurvedic medicine, Kampo medicine, and homoeopathy

Table 2.1 | Classification and examples of complementary medicine

2.2 Classifications of CM

The suggested classifications of CM and their associated therapies are included in Table 2.1. The list of therapies is broadly based on that of the US National Center for Complementary and Alternative Medicine. The list is not intended to be all-inclusive, but is an attempt to provide an indication and framework for the five main modalities of CM therapy to be considered. The classification includes:

- Long-established and traditional systems of healthcare, such as traditional Chinese medicine and Ayurvedic medicine.
- The principal CM disciplines, such as osteopathy, chiropractic, acupuncture, herbal medicine and homeopathy.

- Therapies that are most often used to complement conventional medicine, such as manipulative and body-based practices (e.g. massage), counselling, stress therapy, hypnotherapy, reflexology, aromatherapy, hypnotherapy and meditation.

Many other therapies without a prominent evidence base – such as flower remedies, crystal therapy, iridology and radionics – are not included in this review.

Researchers have previously identified key criteria for consideration in prioritizing and funding CM research. The criteria reported by different authors for CM research prioritisation are listed in Table 2.2.

Criterion / author	Lewith et al, 2000, UK36	Nahin et al, 2005, US38	Ernst, 2001, UK39
Identified need for CAM research among stakeholders	Yes		
Level of CM use in the population/ availability	Yes	Yes	Yes
Available research capacity	Yes		
Public health significance/ burden of disease addressed		Yes	Yes
Scientific opportunities available		Yes	
Cost and feasibility		Yes	Yes
Weight of existing evidence			Yes

Table 2.2 | Comparing criteria used for CM prioritisation in different studies

2.3 How does CM differ from conventional medicine?

Complementary medicine can differ from conventional medicine not only in methodology but also in the underlying philosophy of some modalities. For example, the way that some CM disciplines define health, illness and the healing process can depart significantly from the beliefs that underlie conventional medicine. This point of difference between CM and conventional medicine can have implications for approaches to research design and their integration into the health system.

2.4 Why invest in CM research?

There are three broad reasons to invest in CM research:

- To provide quality, timely and evidence-based health care that impacts positively on the health and wellbeing of all Australians.
- To identify CM treatments that offer a safe, efficacious and cost-effective alternative to mainstream treatments. This is particularly important given our escalating health costs, and the growing evidence that CM can make a significant, cost-effective contribution, particularly to chronic disease. However, there is a need to strengthen this evidence and identify and utilise validated interventions.
- To build on our significant strengths in CM research, build critical mass and better co-ordinate the national research effort.

Many countries, including the US and China, are investing heavily in CM research. It is vital that Australia is part of this global research effort.

Reference

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- Nahin RL (2005). 'Identifying and pursuing research priorities at the National Center for Complementary and Alternative Medicine'. *Faseb Journal*; 19: 1209-1215.
- Ernst E (2001). 'Research priorities in CAM'. *Complementary therapies in medicine*; 9: 186-187.

3 | How priorities were selected

For this report, research priorities were established through a process that involved:

- Setting overarching research priorities.
- Identifying research priority areas that accord with the Commonwealth Government's National Health Priority Areas.
- Establishing expert working groups to devise a shortlist of research priorities.

This process is described below.

3.1 Overarching research priorities

One of the roles of NICM is to articulate national priorities in basic and translational research.

Determining priorities for CM research is critical given the scope of CM practices, the need to make best use of limited resources for research, and the need to achieve early returns in research and health outcomes.

Key considerations in setting priorities are the need for a timely and manageable process, and the challenges (time and cost) presented by the breadth of the field and volume of research material. Undertaking substantive reviews (e.g. meta-analyses) in one field alone, such as cancer, could conceivably consume more than the entire NICM budget.

Therefore, in 2007–08, NICM developed overarching research priorities, informed by nationwide consultations. These overarching priorities were to focus on research that:

- Has the potential to impact positively on the health and wellbeing of all Australians. Emphasis is on areas where the burden of disease is high, and where preliminary evidence is strong and demonstrates a likelihood of positive impact.

- Elucidates the safety, efficacy and cost-effectiveness of CM and translates this into policy and practice.
- Investigates methodological issues taking into account the often complex nature of CM, including development of methodological tools that may impact on the understanding of the practice, concepts and mechanisms underpinning CM.

This research prioritisation process goes beyond the preparation of a list of potential areas of interest. It also involves mapping evidence for CM interventions against the burden of disease and the Australian Government's National Health Priority Areas, and risks; identifying CM interventions already the subject of clinical practice guidelines; and recommending areas of further work.

3.2 Research priority areas

The NICM's over-arching research priorities needed to be translated into a plan to concentrate research efforts both within NICM and across the CM field nationally.

In 2008, following advice from its Scientific Advisory Committee (SAC), NICM developed a process to help identify research priorities.

The initial research focus was to be in some of the Australian Government's eight National Health Priority Areas. The National Health Priority Areas that were selected for the study were cardiovascular health, cancer, arthritis and musculoskeletal conditions, and diabetes mellitus.

In addition, dementia was added to the list, together with wellness and disease prevention. (This latter area was included in light of the Commonwealth Government's

primary healthcare strategy, which puts greater focus on preventive care (Towards a National Primary Health Care Strategy: A Discussion Paper from the Australian Government, Commonwealth of Australia 2008)). The National Health Priority Areas that were not considered in the process were asthma, injury prevention and control, mental health (affective disorders) and obesity. (In the longer term, NICM will address these other National Health Priority Areas.)

Table 3.1 shows how this report responds to the National Health Priority Areas

National Health priority areas	Covered in this report?
Arthritis and musculoskeletal conditions	Yes
Cancer control	Yes
Cardiovascular disease	Yes
Diabetes mellitus	Yes
Mental health	Dementia only
Asthma	No
Injury prevention and control	No
Obesity	No

Table 3.1 | How this report responds to the National Health Priority Areas

Under the auspices of the Memorandum of Understanding between NICM and the China Academy of Chinese Medical Sciences (CACMS), a meeting between Chinese and Australian scientists and clinicians was also held in Beijing in November 2008 to further debate (and refine) research priorities in Chinese medicine (acupuncture and herbal medicine).

3.3 Expert groups

The NICM established five expert working groups (comprising industry, academic and clinical experts) to identify priorities for future CM research in each research priority area (i.e. cardiovascular disease, cancer, musculoskeletal, diabetes and wellness promotion).

Each group was required to review the evidence for CM interventions and make recommendations for future research in the context of both mainstream and CM research strengths in Australia and overseas, including access to research infrastructure, human capacity and the methodological requirements of the work.

In some areas, where there was an absence of empirical scientific evidence, or where only poor quality evidence was available, the expert groups made judgements outside the usual evidence hierarchy, particularly where there was a long history of traditional use unsupported by scientific studies.

- Each expert group made recommendations based on:
- The overall evidence.
 - The relative importance of a CM intervention to health compared to conventional medicine.
 - The feasibility of conducting the research in Australia.

The recommendations of each expert group are presented as individual chapters in this report.

3.4 Priority-setting matrix

To help the expert groups identify key research priorities, NICM requested the expert groups to:

- Identify at least three interventions (medicine or therapy) in each priority area.
- Rank each medicine or therapy in terms of safety, efficacy and cost-effectiveness.
- Describe the systematic reviews that have been undertaken.
- Describe the relevant clinical trials that have been undertaken (including multi-centre trials).
- List the type of research required or recommended, including research questions and issues that should be pursued to advance evidence in this area (e.g. a systematic review, the scale-up of a clinical trial, etc).
- Comment on and rank whether Australia has the people (skills and expertise) to do the work proposed.
- List current research being undertaken (research centre, location and research focus), both local and overseas.

- If the identified area is strongly covered overseas, explain why research should be pursued in Australia.
- Identify what, if any, methodological challenges or issues would need to be addressed to undertake the research.
- Identify other areas of disease or risk that should be considered for priority attention that do not fall within the major priorities (e.g. a disease area with poor or life-threatening outcomes and no current satisfactory management regime; or areas in which Australia may not have current strength but a niche area could be developed).
- Rank the priority areas (either high, medium or low).

3.5 The importance of evidence

Criteria used for ranking evidence

As discussed above, the process for determining research priorities involved mapping current evidence for CM interventions against key disease areas and National Health Priority Areas.

However, CM has long suffered from a lack of research activity and scientific rigour when compared to conventional medicine. Randomised controlled trials, which provide the highest level of evidence, are often

not available for many CM interventions, especially with placebo as a comparison intervention. In the absence of such data, other forms of evidence needed to be assessed for this review, such as the results of observational studies. (It is worth noting that a high quality observational study may provide stronger support than a methodologically poor, randomised controlled trial. However, methods for rating the quality of evidence from observational studies are less well established.)

To assist with the process of gathering evidence, the National Health and Medical Research Council (NHMRC) provides general guidance for the level of persuasiveness provided by evidence obtained from different types of studies (e.g. randomised clinical trials, non-randomised experimental studies, cohort studies, case-control studies, etc). In addition, conclusions from lower quality studies – or where an expert group has made recommendations based on opinion outside the usual evidence hierarchy – may need to be re-considered in the light of subsequent, higher quality studies.

The overall ranking and assessment of CM evidence in helping to determine the need and opportunities for research in Australia are determined by the strength, size and clinical relevance of the evidence available for review. These criteria for ranking evidence are explained in Table 3.2.

Criteria	Explanation
Strength of evidence	Level of evidence: the type of study is ranked according to its place in the hierarchy of studies. NHRMC level of evidence gradings are listed at http://www.asid.net.au/hicsigwiki/index.php?title=NHMRC_Evidence_level . In addition, Oxford Centre for Evidence-based Medicine Levels of Evidence are listed at http://www.entkent.com/html/Oxford_CEBM_Levels_5[1].htm .
	Quality of evidence: the study is critically appraised in terms of its methodological quality. In particular, the study is assessed according to the likelihood that bias, confounding and/or chance have influenced the results.
	Statistical precision: the primary outcome of the study is critically appraised to determine whether the effect is 'real' as opposed to being due to chance.
Size of effect	The size of effect is important in assessing the clinical importance, as opposed to statistical significance, of the primary outcome of the study.
Relevance of evidence	Although interventional studies are generally the most reliable to determine cause-effect relationships, generalising from study populations can present problems. It is important to ascertain whether the outcomes are applicable to groups other than the study population (e.g. to groups of different age, gender or ethnicity).

Table 3.2 | Criteria used for ranking evidence

The role of evidence in traditional medicine

For many traditional (indigenous) medicines and therapies there is limited scientific evidence to support their traditional role.

However, traditional medicines have an extensive history of use, sometimes measured over hundreds of years in large and diverse population sets. This history provides an accumulated repository of observation that underpins the use of these medicines. Medicines that have been prescribed over a long period of time usually result in preparations where the dosage and formulation have empirically evolved to maximise their therapeutic effectiveness and minimise risk.

Traditional medicines include traditional Chinese medicine (TCM), Ayurvedic medicine, Kampo medicine and some western herbal medicines.

Many traditional forms of medicine use medicinal products in a holistic context involving lifestyle changes, such as diet and behaviour. In those cases, holistic principles are usually part of the therapy and need to be considered when assessing evidence and addressing research questions.

3.6 Conclusion

The methodology devised by NICM – and used for most of the health areas – achieved consensus of opinion among a very diverse group of stakeholders. Through a structured interaction, the groups agreed on a list of research priorities that was acceptable to all stakeholders.

Significantly, the process of developing priorities is serving to identify and engage mainstream research and clinical networks in specific disease areas that will help lay the foundation for future partnerships. The process being undertaken by the NICM is unique and of national and international relevance and interest.

4 | Cardiovascular health

This chapter reviews the current evidence for complementary medicine (CM) interventions in the area of cardiovascular health, and makes recommendations for future research that can translate into improved health outcomes. It was prepared by Associate Professor David Colquhoun and Antonio Ferreira-Jardim following input from the expert group on cardiovascular health. The expert group comprised:

- Associate Professor David Colquhoun (Chair) – Wesley and Greenslopes Private Hospitals, University of Queensland.
- Dr Lesley Braun – Alfred Hospital, Melbourne.
- Kelvin Hill – National Stroke Foundation, Melbourne.
- Professor Anthony Keech – NHMRC, and Department of Medicine, University of Sydney.
- Dr Karam Kostner – School of Medicine, Mater Hospital.
- Professor Frank Rosenfeldt – Alfred Hospital and Baker Heart Institute, Melbourne.
- Professor Basil Roufagalis – Herbal Medicines Research and Education Centre, Faculty of Pharmacy, University of Sydney.
- Dr Ross Walker – Cardiologist, IM Medical.
- Professor Gerald Watts – School of Medicine, University of Western Australia.

Some content from this chapter was presented at the International Atherosclerosis Society meeting in Sydney, Australia, in March 2012.

Prevalence of cardiovascular disease in Australia

Cardiovascular health relates to the health of the heart, brain and lower limbs, specifically related to arterial blood supply. The major cardiovascular diseases are coronary heart disease, stroke, heart failure and peripheral vascular disease.

The main underlying causal pathology of cardiovascular disease is atherosclerosis. This is a process marked by the abnormal build-up of fat and other substances in the inner lining of the arteries. It is most serious when it affects the blood supply to the heart (causing angina or heart attack) or to the brain (causing a stroke).

According to the Australian Institute of Health and Welfare, cardiovascular disease – in particular, coronary heart disease and stroke – is the largest cause of premature death in Australia (AIHW, 2005). Although death rates have declined considerably in recent decades, it continues to be one of the biggest health problems requiring attention in Australia, and its health and economic burden continues to exceed that of any other disease (www.aihw.gov.au/cardiovascular-health-priority-area/). For this reason, the Australian government has made the maintenance of cardiovascular health and prevention of cardiovascular disease a national health priority.

Cardiovascular disease is the largest cause of premature death in Australia. Its health and economic burden continues to exceed that of any other disease.

Australian Institute of Health and Welfare

In 2007, cardiovascular disease accounted for just over a third of all deaths. Over 78% of these deaths were of people aged 75 years and over. In addition, in that year, it is estimated that 3.5 million Australians aged 16–85 years had a long-term chronic cardiovascular condition. As with the NHS, estimates are based on self-reported responses. Of those reporting with a CV condition, 23.1% (800,000 people) reported also having a disability that led to a mild to profound restriction to core activities such as self-care, mobility and communication.

The major, preventable risk factors for cardiovascular disease are tobacco smoking, high blood pressure, high blood cholesterol, insufficient physical activity, overweight and obesity, poor nutrition, and diabetes. The psychosocial factors of depression and social isolation are of similar importance to the biological factors.

In 2010 (latest data), cardiovascular disease was likely to have accounted for 16% of the overall disease burden in Australia. Most of the cardiovascular disease burden comes from premature death; it is estimated that cardiovascular disease was responsible for 26% of total years of life lost due to premature mortality in 2010, second only to cancer (34%).

In addition, cardiovascular disease is the most expensive disease group in Australia in terms of direct healthcare expenditure.

4.1 Some limitations of conventional treatment

Despite dramatic progress over the last 30 years in the prevention of first and recurrent coronary events, recent studies show significant cardiovascular events.

For example, the recent Platelet Inhibition and Platelet Outcomes (PLATO) trial involved 18,624 patients who had an acute coronary syndrome and were randomized to Ticagrelor (n=9323) or Clopidogrel (n=9291). Despite excellent adherence to proven conventional drug therapy at 12 months, 9.8% of those randomized to Ticagrelor either died from cardiovascular causes, had a myocardial infarction or stroke versus 11.7% of those randomized to

Clopidogrel (James et al, 2009; and Wallentin et al, 2009). These numbers are similar to the results of multiple trials undertaken over the last five years.

Due to the close follow-up, patients in clinical trials generally have a better outcome than contemporary patients in the community, who often have a poor adherence to medications; this has been noted in Sydney by Leon Simons, who found that less than 50% of patients on cholesterol and blood pressure medications were adhering to their medication at six months (Simons, Colquhoun et al, 2002).

There are many causes of poor adherence to medications. These include depression, patient beliefs, side effects and cost (although cost is not a major issue in Australia due to the Federal Government subsidy).

For every 1 mmol/L reduction of LDL-cholesterol irrespective of therapy there is a 25% reduction of heart attack and a 20% reduction of stroke over a five-year period. When the LDL-cholesterol is around 1.5 mmol/L, two-thirds of patients show demonstrable regression of disease during a two-year period (Baigent, Keech, et al, 2005; and Cholesterol Treatment Trialists' (CTT) Collaboration, 2010).

In the OASIS 17 Trial, the major predictors of recurrent cardiovascular events from three months to six months was whether patients smoked, followed a healthy diet or exercised (Chow et al, 2010).

In clinical trials, less than 5% of patients have significant side effects – mainly aches and pains from statins – but in practice it is up to 20% of patients. Statins are the mainstay of lowering LDL and improving survival, but side effects make it difficult for many patients to reach goals to optimize outcomes.

Even with optimal therapy and optimal adherence there is a residual risk in patients and this has been termed the 'treatment gap'.

The role of complementary medicine

Complementary medicines are widely used in Australia to promote cardiovascular health and/or prevent the onset of risk factors that lead to cardiovascular disease.

For example, in a group of 161 pre-surgical inpatients admitted to the wards in a tertiary hospital in Victoria by cardiothoracic surgeons between September and December 2004, it was found that:

- 51% of inpatients took CM in the two weeks pre-admission.
- 42% of patients intended to continue their use in hospital.
- Pharmacists and medical practitioners were the most utilised sources of information about CM.
- Multivitamins, fish oil supplements, glucosamine and vitamin C were the most used complementary and alternative medicines.
- 94% of patients using CM did not tell their anaesthetist and 84% did not tell their surgeon that they were using these products (Bensoussan and Lewith, 2004).

The prevalent use of CM underlines the importance of these therapies in promoting cardiovascular health and the need to review evidence supporting various therapies to guide practitioners and consumers.

4.2 Methodology

Information for this chapter was obtained from:

- Known published reviews and textbooks (Mashour et al, 1998; Mantle and Tiran, 2009; Bratman and Girman, 2002).
- A systematic review of major databases including the Cochrane Library and National Institute of Health (complementary and alternative medicine sections).
- PubMed.
- Google.
- Manual searches in review articles.
- Experts in the field, who were personally contacted.
- A search of registries of clinical trials.

4.3 Evidence of efficacy

What determines efficacy?

The therapeutic efficacy of any treatment depends on the intrinsic efficacy – be it a drug, herb, manipulation or surgical intervention – and the therapeutic environment in which it is given.

The therapeutic environment can enhance the efficacy of the treatment, and this has been termed the placebo effect; it may also inhibit the intrinsic efficacy, and this has been termed the nocebo effect. The therapeutic environment includes the health practitioner and the surrounding rituals. In addition, when a patient goes to a pharmacy or a health food store the practitioner dispensing may further enhance the therapeutic effect with positive reinforcement or inhibit the benefit with negative reinforcement regarding side effects. There can also be a misunderstanding in communication, which inhibits a therapeutic benefit.

Measuring efficacy

It is difficult to gauge how much of the benefit a patient receives relates to the intrinsic effect of the medication or therapy and to the therapeutic environment placebo/nocebo. Clinical trials to assess the efficacy of a treatment beyond the therapeutic environment or placebo effect have only been conducted over the last 60 years or so. (Penicillin was not evaluated in clinical controlled trials prior to its introduction in the 1940s and the Second World War.)

Not all therapies need to have randomised controlled trials to assess efficacy, but most treatments in medicine need to be evaluated in clinical trials to assess whether there is benefit beyond placebo.

Some clinical conditions such as depression are particularly sensitive to the therapeutic environment. In the SAD-HART trial of patients following a heart attack who had significant depression, 50% of patients responded to placebo but 70% responded to the standard SSRI anti-depressant Sertraline. Placebo is effective in angina and has even been noted to lower fever in patients who have infection (Glassman, et al, 2002). Surprisingly, in some trials adherence to placebo (taking 80% or more of the inert substance) is associated with less heart attacks and improved survival.

Over the last few decades, medical statisticians have established clear guidelines to assess whether or not a treatment is beneficial beyond the placebo effect. Levels of confidence in the robustness of the results are well established.

In addition, over the last decade, statistical methods for aggregating results from multiple trials have been developed to help establish the efficacy of treatments when small trials have given unclear results. Meta-analysis of clinical trials is looked upon as the best way of knowing whether a therapy is effective, and the extent of effectiveness (Baigent et al, 2005).

Levels and strength of evidence

In this review, the scientific basis and strength of evidence of various complementary medicines is assessed in the area of cardiovascular medicine. The assessment includes possible evidence of improving cardiovascular endpoints, be they stroke, heart attack, unstable angina and heart failure, and whether or not various therapies favourably influence an established risk factor for these vascular events and in some cases benefit in emerging risk factors.

Strength of evidence of efficacy	Description of strength of evidence of efficacy
1	Very strong evidence
2	Moderately strong evidence
3	Strong trend
4	Little evidence

Table 4.1 | Grading of strength of evidence
Source: Grundy et al, 2002.

Level of Evidence	Study Design
A	Major randomised controlled clinical trials
B	Smaller randomised controlled clinical trials and meta-analyses of other clinical trials
C	Observational and metabolic studies
D	Clinical experience

Table 4.2 | Grading of level of evidence
Source: Grundy et al, 2002.

The evidence is graded on its strength according to the Adult Treatment Panel III (ATP III) 2001, with a category 1 grading being very strong evidence. An additional category – category 4: little evidence – has been included for the purposes of this review (Grundy et al, 2002; and 2004). (Note: ATP III is a report written by the US National Cholesterol Education Program that provides guidelines for healthcare professionals on how to prevent, detect, evaluate and treat high cholesterol in adults.) The grading of strength of evidence is shown in Table 4.1.

Table 4.2 presents the grading of level of evidence according to four levels – A, B, C and D.

Table 4.3 presents the efficacy of a range of complementary therapies in treating different cardiovascular diseases. The table also shows the type of evidence and the strength of this evidence.

The findings summarised in Table 4.3 are discussed in the following sections in terms of:

- Nutrition and dietary supplements.
- Bioactive food components.
- Herbal preparations.
- Other therapies.

4.4 Nutrition and dietary supplements

The United States Dietary Supplement Health and Education Act (DSHEA) of 1994 defines a dietary supplement as a product (other than tobacco) intended to supplement the diet for such ingredients as vitamins, minerals, herbs or other botanicals, amino acids, and substances such as enzymes, organ tissues, glandulars and metabolites.

Marine omega-3 fatty acids

The consumption of fish, fish oils and n-3 polyunsaturated fatty acids (PUFA) is associated with a reduced risk of cardiovascular disease. (n-3 PUFA refers to the class of n-3 or omega 3 class of polyunsaturated fatty acids, such as eicosapentaenoic acid (EPA)).

Since the National Heart Foundation of Australia report Review of the relationship between dietary fat and cardiovascular disease (1999), new findings have been

CM therapy or product	CVD conditions treated	Type of evidence	Strength of evidence
Acupuncture	Angina	B	3
	Blood pressure reduction	B	3
Beta-carotene	CHD events	A	4
Bioenergetics	CHD events	C	4
Chelation therapy	Claudication	C	4
	Regression of atherosclerosis	C	4
Co-enzyme Q10 (CoQ10)	Blood pressure reduction	B	2
	Heart failure	B	3
	LDL-C reduction	B	3
	Statin side effects	B	3
Folic acid, vitamin B ₆ and B ₁₂	CHD events	B	4
Garlic	LDL-C reduction	B	4
	Blood pressure reduction	C	2
	CHD events	C	4
Ginger	LDL-C reduction	C	3
	Regression of atherosclerosis	C	3
	Anti-platelet	C	3
Ginkgo biloba	Claudication	B	2
Guggulipid	LDL-C reduction	C	4
	Triglyceride reduction	C	4
Hawthorn	Heart failure	B	2
	CHD events	B	3
Healing touch	CHD events	C	4
Homeopathy	CHD events	B	3
Homocysteine	CHD events	B	4
	Stroke	B	3
L-carnitine	Mortality decrease post AMI	B	2
	Angina reduction	B	2
Marine omega-3 fatty acids	SCD, triglyceride reduction	A	1
	CHD events	A	1
	Blood pressure reduction	B	2–3
Meditation	Blood pressure reduction	C	3
	CHD events	C	3
	Regression of atherosclerosis	C	3
Nuts	LDL-C reduction	B	1
	Triglyceride reduction	B	1
Olive leaf extract	LDL-C reduction	C	3
	Blood pressure reduction	C	3
	Anti-platelet	C	3
Padma 28	Claudication	B	2
Policosanol	LDL-C reduction	C	4
Qi Gong	Blood pressure reduction	C	3
	Stroke	C	3
Red rice yeast	LDL-C reduction	B	2
Reiki	CHD events	C	4
Soluble fibre	LDL-C reduction	A	1
Soy	LDL-C reduction	B	2
	Triglyceride reduction	B	2
Spirulina	LDL-C reduction	C	4
Sterol/stanol esters	LDL-C reduction	B	1
Tea	CHD events	C	3
Vitamins (antioxidant)	CHD events	A	4
Vitamin C	CHD events	B	4
Vitamin E (natural)	CHD events	B	4
	Regression of atherosclerosis	B	2
Yoga	Regression of atherosclerosis	C	3
	LDL-C reduction	C	3

Table 4.3 | Level and category of evidence for CM therapies and products

published in Australia and internationally regarding n-3 PUFA consumption. In summary, these findings are that:

- Individuals with a higher intake of fish have a lower risk of coronary heart disease mortality, total coronary heart disease and total stroke.
- Consuming fish at least once a week is associated with a lower risk of total stroke and coronary heart disease mortality in the general population and in post-myocardial infarction patients.
- In secondary prevention, at least 850 mg per day marine n-3 PUFA supplementation reduces the risk of coronary heart disease mortality, and at least 1,800 mg per day reduces major coronary events.
- In secondary prevention, there is conflicting evidence about the effects of marine n-3 PUFA supplementation on the risk of sudden death in patients due to three underpowered trials in patients at low risk of sudden cardiac death. Recent meta-analyses have even included trials in patients that couldn't be located (Singh et al, 2002).
- Marine n-3 PUFA supplementation of 1,000–4,000 mg per day decreases serum triglyceride by 50% or more and increases high-density lipoprotein (HDL) cholesterol levels by up to 5%. A dose relationship exists between intake of marine n-3 PUFA and decreased serum TG levels.
- The GISSI-HF study that involved 6,975 patients with Class II-IV heart failure demonstrated that 850–882 mg per day EPA and DHA supplementation decreased total mortality over a 3.9-year period (the absolute risk reduction (ARR) was 2% $P=0.04$). The effect was greater in diabetics (ARR 4.4%).
- 1000 mg or more of EPA/DHA improved heart function in patients with heart failure.

Plant stanols and sterol esters

Plant sterols or phytosterols have been known to have a cholesterol-lowering effect since the 1950s. Phytosterols, stanols and their esters are found in leaves, nuts, vegetable oil, seeds and other plants. Plant sterol esters can significantly reduce serum total and low-density lipoprotein (LDL) cholesterol levels without affecting HDL-cholesterol or triglycerides. A dose of two to four grams

decreases LDL cholesterol levels by 10% (Hendriks et al, 1999; Gylling and Miettinen, 1999; Weststrate and Meijer, 1998). Patients who are high absorbers of cholesterol have a greater response.

The therapeutic dose is most conveniently found in two to four teaspoons of margarine enriched with plant sterol. Similar benefit is seen when this margarine is added to statin therapy (Blair et al, 2000; Miettinen and Gylling, 2004; Simons and Colquhoun, et al, 2002).

Garlic

Garlic has been used for thousands of years as a food and spice. Garlic potentially affects plasma lipids, fibrinolytic activity, platelet aggregation, blood pressure, and blood glucose (Rahman, 2001). A meta-analysis (Stevinson et al, 2000) included 13 randomised, placebo-controlled trials concluded that the use of garlic for hypercholesterolemia was of questionable value (Stevinson et al, 2000).

Soy

The cholesterol-lowering effects of soy protein compared to animal protein have been known for over 100 years (Ignatowsky, 1908).

Soy supplementation lowers cholesterol, specifically LDL-cholesterol. Soy-based foods also reduce lipid oxidation, promote increased vascular reactivity, improve arterial compliance and exhibit statin-like activity (Marsh et al, 2011; Lu, et al, 2001). A meta-analysis of 38 trials of soy protein demonstrated reductions in total cholesterol of 9.3%, LDL cholesterol of 12.9% and triglycerides levels of 10.5% accompanied by an increase of 2.5% in HDL cholesterol (Anderson et al, 1995).

However, more recent studies in post-menopausal women fail to show improvements in plasma lipids (Kreijkamp-kaspers et al, 2004; Clarkson, 2002).

The most recent meta-analyses of soy protein intervention trials included 20 parallel designs and 23 crossover studies. A median of 30 grams of soy protein per day was associated with a net reduction of serum LDL cholesterol of 0.23 mmol/L – a reduction of 5.5% – in the parallel studies and a reduction of 4.2% in the crossover studies. HDL-cholesterol increased by 3.2% and serum triglyceride levels were lowered by 10.7% (Anderson and Bush, 2011).

Soluble fibre

Soluble or viscous fibres, such as oat bran, psyllium, guar gum and pectin are thought to reduce heart disease by lowering total and LDL cholesterol levels without affecting serum triglycerides. Insoluble wheat fibre and cellulose have no cholesterol lowering effects unless used in the diet to replace foods supplying saturated fats (Kris-Etherton et al, 1988).

The hypocholesterolemic effects of psyllium (Olson et al, 1997), guar gum (Todd et al, 1990), and oat bran (Ripsin et al, 1992) are documented in meta-analyses (Brown et al, 1999). For example, a meta-analysis of 67 controlled trials studying the cholesterol-lowering effect of oats, psyllium, pectin and guar gum reported small but significant reductions in total cholesterol (1.7 mg/dl per g of soluble fibre) and LDL (cholesterol 1.9 mg/dl per g of soluble fibre) (Kris-Etherton et al, 1988). Higher cholesterol levels experienced the most significant reductions. Triglycerides and HDL-cholesterol were not significantly influenced by soluble fibre.

Nuts

The few studies that have looked at consumption of whole nuts in relation to coronary heart disease have reported a consistent and substantial protective effect regarding lower rate of coronary heart disease. Increasing nut consumption is associated with lower plasma triglycerides, lower LDL-C and increase in HDL-C. These favourable effects have been noted in greater than 30 randomised trials with tree nuts and peanuts.

Epidemiologic studies have found that the consumption of nuts a few times per week is associated with 40–50% lower rates of coronary heart disease compared to those who do not eat nuts. This does not seem able to be explained by serum lipid reductions alone. In one prospective study of 86,016 women aged 34–59 without previously diagnosed coronary heart disease, eating five ounces of nuts per week was associated with a relative risk of 0.66 (P for trend = 0.005) (this is known as the Nut Study) (Hu et al, 1998). The cardioprotective effect of regular nut consumption is only partly explained by plasma lipid changes. Unfortunately, there have not been any randomised controlled trials that assessed the effectiveness of increasing nut consumption in preventing coronary heart disease events.

Tea

Tea drinking appears to be protective against coronary heart disease in a number of epidemiologic studies (Hertog et al, 1993; Hertog et al, 1995; Keli et al, 1996; Sesso et al, 1999).

Results are inconclusive for clinical and case-control studies. A recent prospective cohort study of 1,900 patients hospitalised with an acute myocardial infarction followed for 3.8 years found a significantly reduced hazard ratio for subsequent total and cardiovascular mortality of 0.56 (95% CI 0.37 to 0.84) (Sesso et al, 1999). The dose associated with lower recurrent coronary heart disease events was one to two cups per day. It is important to note that this was not a randomised controlled trial. It is hypothesis generating. No studies have prospectively documented a reduction in cardiovascular risk with tea drinking.

4.5 Bioactive food components

The term ‘bioactive food component’ refers to ‘nonessential’ biomolecules that are present in foods and exhibit the capacity to modulate one or more metabolic processes, which results in the promotion of better health (www.answers.com/topic/bioactive-food-components).

Antioxidant vitamins

Antioxidant vitamins may prevent both atherosclerosis and its complications by decreasing LDL cholesterol oxidation and inhibiting the proliferation of smooth muscle cells platelet activation. However, there are no randomised trials that have proven the hypothesis.

In addition, various epidemiological studies such as The Physician’s Health Study showed no benefit from multi-vitamin intake, and the Nurses’ Health Study showed possible harm (Diaz et al, 1997).

Vitamin E

Two large introduction epidemiologic trials found lower event rates in subjects who took at least 100 units of vitamin E per day (Rimm et al, 1993; Stampfer et al, 1993). However, these benefits were not found in other studies:

- In an Alpha-Tocopherol, Beta-Carotene Cancer Prevention trial of male smokers (by U.S. National Cancer Institute), a dose of 50 mg vitamin E did not

decrease non-fatal myocardial infarction and increased haemorrhagic stroke (Virtamo et al, 1998; Leppala et al, 2000).

- A meta-analysis of seven randomised trials of vitamin E (with dosage of 50 to 800 International Units) in 81,788 patients confirmed that vitamin E did not reduce mortality, decrease cardiovascular death, or cerebrovascular accident (the activity of 1 mg of dl- α -tocopherol acetate is defined as equivalent to one International Unit of vitamin E) (Vivekananthan et al, 2003).

A more recent and larger meta-analysis of 19 clinical trials (135,967 participants) considered the dose-dependent effects of vitamin E. It is unclear whether the investigators isolated the effects of vitamin E from those of other supplements. Most of the evidence of elevated mortality risk came from two trials that administered vitamin E together with beta-carotene. It is uncertain whether high-dose of vitamin E cause an increased risk of death (Miller et al, 2005).

Importantly, there are physiological differences between synthetic and natural vitamin E. The most effective studies in terms of cardiovascular prevention and regression of coronary disease used more than 500 International Units of natural vitamin E.

Vitamin C

When examined individually, most observational and prospective cohort studies do not demonstrate a relationship between vitamin C and cardiovascular disease (Rimm and Stampfer, 2000; Manson et al, 1992). There have been no randomised controlled trials specifically examining the effects of vitamin C supplementation on cardiovascular endpoints (Ascherio et al, 2000; Losonczy et al, 1996).

The current consensus does not find a value for supplemental vitamin C in preventing heart disease (Kris-Etherton et al, 2004).

Beta-carotene

Randomised clinical trials of beta-carotene supplementation versus placebo have demonstrated no cardiovascular benefit, and perhaps an increase in all-cause mortality. For example:

- An increased incidence of lung cancer and cardiovascular disease mortality were observed in the Alpha-Tocopherol, Beta-Carotene Cancer Prevention trial (see Vitamin E, above) (Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group, 1994).
- A meta-analysis of eight trials evaluating beta-carotene in 138,113 patients revealed a small but significant increase in all-cause mortality and cardiovascular death (Osganian et al, 2003).

Therefore, the use of beta-carotene as a supplement is discouraged (Krauss et al, 2000).

Combination vitamin trials

Several trials have studied the efficacy of combination treatments of supplements added to standard drug therapy. Efficacy was assessed by clinical events or imaging of coronary arteries by angiograph, or carotid artery wall thickness by ultrasound. No benefit was demonstrated. For example:

- The Heart Protection Study. This was a large randomised controlled trial of 20,536 subjects in the United Kingdom that studied the use of statin medication (simvastatin 40 mg) and vitamin supplementation (vitamin E, vitamin C and beta-carotene) in patients at risk of cardiovascular disease. After 5.5 years of study, no benefit from combination vitamin therapy was evident (Heart Protection Study Collaborative Group, 2002).
- The HDL cholesterol Atherosclerosis Treatment Study. This was a small, randomised controlled trial that assessed progression of coronary atherosclerosis by repeat coronary angiography. It found that vitamin C (1 g), vitamin E (800 units), beta-carotene (50 mg) and selenium (100 mcg) reduced the benefit of simvastatin plus niacin therapy on coronary artery disease progression and cardiovascular events, suggesting a potential supplement interaction affected the efficacy (Cheung et al, 2001).

- The Antioxidant Supplementation in Atherosclerosis Prevention Study. This was a negative trial of 440 hypercholesterolemic patients, randomised to vitamins E and C. It reported that combination therapy decreased the rate of atherosclerosis progression over a six-year period as measured by carotid artery intima-media thickness (That is, the study was negative for vitamins E and C by themselves, but positive for the combination of both.).

Homocysteine

Homocysteine is a waste product of protein metabolism. Elevated homocysteine levels are associated with increased risk of coronary artery and vascular disease.

A recent meta-analysis combining 30 prospective and retrospective studies concluded that elevated homocysteine is less strongly related to ischaemic heart disease and stroke risk in healthy populations than had previously been suggested (Homocysteine Studies Collaboration, 2002).

A recent review of seven randomised trials has shown that lowering homocysteine by about 20% with B vitamin therapy does not decrease cardiovascular disease, stroke or all-cause mortality (Bazzano, 2009).

Elevated homocysteine is now classified as a strong marker of increased risk of CVD but no longer is a target of therapy.

Folic acid, vitamin B6 and vitamin B12

In secondary prevention studies, two non-randomised trials in patients with vascular disease found an inverse relationship between the intake of folic acid and vitamin B6 and vascular events (de Jong et al, 1999).

Co-enzyme Q10 (CoQ10)

Co-enzyme Q10 (CoQ10) is a vitamin-like substance found throughout the body, but especially in the heart, liver, kidney, and pancreas. It is found in higher quantities in meat and fish, vegetable oils, parsley, and avocado (http://en.wikipedia.org/wiki/Coenzyme_Q10). Co-enzyme Q10 is involved in oxidative phosphorylation and the generation of adenosine triphosphate in the mitochondria of all cells.

There have been over 40 trials of the clinical effect of CoQ10 on risk factors such as blood pressure, heart function and as predictors of cardiovascular events.

The most recent placebo-controlled trials found that the addition of 100–200 mg per day of oral CoQ10 to conventional medical therapy did not result in significant improvement in left ventricular ejection fraction, peak oxygen consumption, exercise performance or quality of life (Watson et al, 1999; Khatta et al, 2000).

Serum CoQ10 levels following a heart attack do not predict recurrence of cardiovascular events. This was demonstrated in the Australian and New Zealand LIPID trial. This trial involved 9,014 survivors of myocardial infarction or unstable angina and were randomized to the statin pravastatin or placebo and followed for six years. The serum CoQ10 level at baseline not only did not predict cardiovascular events, it did not predict statin response nor statin related side effects.

Recently, the GISSI-HF trial demonstrated improved cardiovascular outcomes and survival with 1 g of ethyl ester EPA/DHA but not rosuvastatin 40 mg/day. Baseline CoQ10 levels did not predict cardiovascular outcomes and on treatment where the CoQ10 level dropped by 50% or so with rosuvastatin this also did not prevent predicted cardiovascular events. Importantly, the marked decrease in serum CoQ10 in those randomized to rosuvastatin was not associated with any organ dysfunction, including the heart, or myalgia.

Co-enzyme Q10 has not been investigated in contrast to angiotensin-converting enzyme inhibitors, beta-blockers, and aldosterone antagonists. Studies of CoQ10 for decreasing myalgias and myositis are not definitive.

In conclusion, the benefit of CoQ10 supplementation in patients with cardiovascular disease or in conjunction with statin therapy has not been clearly established (Keogh et al, 2003).

4.6 Herbal preparations

Hawthorn

Preparations made from flowers with leaves are sold as a prescription medication in parts of Europe and Asia. In Germany, hawthorn can be prescribed for ‘mild cardiac insufficiency’.

Hawthorn has positive inotropic effects and is a peripheral vasodilator. It increases myocardial perfusion and stroke volume and reduces afterload. Anti-arrhythmic effects have been reported in ischemia-reperfusion models. Several double-blind clinical studies of patients diagnosed with heart failure have shown objective improvement in cardiac performance using bicycle ergometry (Schmidt et al, 1994; Weihmayr and Ernst, 1996) or spiroergometry. In one study, hawthorn was found to be as effective as captopril in improving exercise tolerance (Weigl et al, 1996).

The efficacy and safety of hawthorn extract WS 1442 (900 and 1800 mg) were evaluated in a 16-week randomised controlled trial in 209 patients with New York Heart Association functional class III heart failure. The investigators found a dose-dependent effect of hawthorn extract WS 1442 on enhancing exercise capacity and reducing heart failure-related signs and symptoms. The preparation was shown to be well tolerated and safe (Tauchert, 2002).

In addition, a large randomized trial in Germany of over 1,000 individuals showed the addition of hawthorn improves survival, in particular in sudden death in patients with moderate impairment of systolic function (SPICE Trial). However, in another trial the same preparation was used in patients with heart failure and showed no benefit at all. There is no explanation for these contradictory results.

Ginkgo biloba

Ginkgo leaf, obtained from the Ginkgo biloba tree, and its extracts, contain several bioactive constituents including flavonoids, terpenoids, and organic acids.

Two meta-analyses of the efficacy of ginkgo leaf extract for the treatment of intermittent claudication concluded that modest benefits resulted from its use (Pittler and Ernst, 2000; Moher et al, 2000). The meta-analysis by Pittler and Ernst (2000) of eight randomised, placebo-controlled, double-blind studies involved 415 participants (Pittler and Ernst, 2000). The trials, which lasted 24 weeks, found that ginkgo significantly increased the pain-free walking distance of participants by 34 metres.

More recent trials have shown minimal effect on lipids. In the only trial done outside of India, there was no reduction in cholesterol and a small reduction of triglycerides.

Padma 28

In the 1960s, descendants of the Siberian physician, Sul Tim Padma, brought a collection of formulas to Switzerland. These included a fixed combination formula Padma 28, a mixture of 20 herbal drugs, a mineral and camphor. The traditional formula includes aconite and Neem, which are not approved for human use in Australia.

In 2006, a review of 19 randomised trials involving 2,084 patients and six randomised controlled trials involving 4,044 patients with peripheral vascular disease showed that walking distance improved by greater than 100 metres in 80% of patients with Padma 28 versus 2% with placebo ($P < 0.01$) (Melzer, et al, 2006).

Padma 28 may have greater efficacy than Ginkgo in preventing claudication, and both are at least as good as a prolonged supervised physical training and possibly better than standard drug therapy such as Pentoxifylline (Melzer, 2006).

Guggulipid (Guggul gum)

Guggulipid has a long history of use in Ayurvedic medicine, which is an ancient Indian system that uses an integrated approach of diet, lifestyle, herbs, exercise and meditation for the prevention and treatment of illness.

Clinical studies performed in India have demonstrated that 254 mg of guggulsterone extracts three times daily may be an effective treatment for hypercholesterolemia and hypertriglyceridemia. In a study of 125 hyperlipidemic patients, a standardised extract of guggulsterone was compared with clofibrate with mean reductions in cholesterol and triglycerides of 11% and 16%, respectively (Singh et al, 1994).

The more recent trials in guggulipid have shown minimal effect on lipids. In the only trial done outside of India there was no reduction in cholesterol and a small reduction of triglycerides.

Red rice yeast

Red rice yeast is the fermented product of rice on which the 'red yeast' (*Monascus purpureus*) has been grown. It has been used in food and health remedies for over 1,000 years in China. The most important bioactive compound

isolated is monacolin K, which is identical to the statin drug lovastatin.

In a review of 93 randomised trials involving 9,625 participants with three types of red yeast rice, the average low-density lipoprotein-cholesterol reduction was 0.73 millimoles per litre (mmol/L), which equates to about a 20% reduction of mortality over a five-to-six-year period and a 15–20% reduction of major coronary events over the same period.

In 2008, Lu et al reported the results of a trial involving about 5,000 Chinese patients who had survived a myocardial infarction. They were randomised to placebo or a red yeast rice extract and followed up for 4.5 years. Over this follow-up period, the major event rate was lower in this population than usually seen in the west, with 10.4% of patients having a major coronary event in the placebo group and 5.7% in the red rice yeast group. The absolute and relative risk reductions were 4.7% and 45% respectively. There were no serious untoward effects seen with the red rice yeast extract and, importantly, no episodes of myositis or rhabdomyolysis. The outcomes are consistent with red rice yeast derived lovastatin induced LDL-cholesterol reduction.

A red yeast rice extract is now made of predictable consistency (Cholesen capsules) and an unpublished Australian study by Myers et al has shown a good safety profile with LDL lowering by about 20%. It is suggested that there may be synergies with other natural statins leading to greater LDL lowering than one would expect from lovastatin in the rice per se. Because of the ready availability of statins its use is not recommended (Li et al, 2009; Wang et al, 1995; Heber et al, 1999). Unfortunately, this preparation is not TGA approved (due to lack of pharmacokinetic studies).

Policosanol

Policosanol is a sugarcane extract that contains a mixture of aliphatic alcohols. Lipid-lowering effects of policosanol have apparently been shown in a variety of animal species. However, little is known about its mechanism of action or its exact composition.

Over 1,000 subjects have been studied for periods of six weeks to one year in 15 randomised, placebo-controlled

trials using policosanol (5 to 20 mg per day) for lipid lowering. At doses of 10 to 20 mg per day, significant reductions were observed for total cholesterol (17–21%) and LDL cholesterol (21–29%) with increases in HDL cholesterol (8–15%) (Gouni-Berthold and Berthold, 2002). Those positive trials were done from the one centre.

The two trials conducted outside of Cuba have shown no benefit in lowering cholesterol or triglycerides. One of the authors of this chapter (Colquhoun) has 15 patients prescribed policosanol with no effect on lipids after one to six months of therapy. These patients were highly motivated and adherent. The lack of efficacy outside of Cuba is inexplicable. At this stage, policosanol cannot be recommended for any condition.

Spirulina

Spirulina refers to a large number of cyanobacteria or blue-green algae. These algae are found in warm alkaline waters of the world especially in Mexico and South America. Spirulina is a rich source of nutrients containing up to 70% protein, B complex vitamins, chlorophyll, phycocyanin and numerous minerals. Spirulina contains more beta-carotene than carrots. It is reported as being useful in many conditions including lipid lowering.

In a non-randomised trial in humans, in which 36 volunteers took 4.5 g of Spirulina per day over a six-week period, a significant lowering of total cholesterol and triglycerides, and a lowering of blood pressure, occurred.

Spirulina is a promising therapy but randomised trials need to be performed before it can be recommended (www.nlm.nih.gov/medlineplus/druginfo).

Ginger

Ginger, the rhizome of *Zingiber officinale*, is one of the most commonly used species of the ginger family. It is used widely in foods and has been used for medical purposes for over 2,500 years in China and India (Grant and Lutz, 2000). Ginger contains a number of pungent constituents and potential active ingredients relevant to medicine. Its extracts possess anti-oxidative action and can scavenge superoxide anions and hydroxyl radicals. Gingerol can inhibit lipid peroxidation (in rat liver microsomes). It also may inhibit platelet aggregation and inhibit thromboxane production.

Ginger lowers cholesterol (LDL-cholesterol) in various animal models. Feeding rats ginger significantly elevated hepatic cholesterol-7- α -hydroxylase (a rate limiting enzyme in bile acid biosynthesis) and this aids cholesterol conversion to bile acids, resulting in elimination from the body (Srinivasan and Sambaiah, 1991). Ginger has also been shown to inhibit cholesterol biosynthesis in homogenated rat liver (Nammi et al, 2009). It may be a HMG CoA reductase inhibitor like classic statin drugs.

In recent work supported by NICM, Nammi, Kim et al (2010) demonstrated that a standardised extract of ginger significantly decreased hepatic triglyceride and tended to decrease hepatic cholesterol levels when administered over six weeks to rats fed a high-fat diet. In parallel, the extract restored the depressed levels of LDL receptor mRNA and protein. Of particular interest was the finding that HMG-CoA reductase protein expression in the liver of the high-fat-fed rats was elevated and the ginger extract restored the protein levels towards normal. This provides an important mechanism for understanding the lipid modifying effects of ginger (a statin-like effect).

Further work by Roufogalis et al (2009) demonstrated that when ginger is given to rats on a high-fat diet there is prevention of weight gain.

Other animal studies over the last decade have shown variable results and it may relate to the type of extract of ginger and the dosage. In the study by Thomson et al (2002), doses of 500 mg/kg of ginger lowered serum cholesterol whereas doses of 50 mg/kg did not.

Few human trials have assessed the lipid-lowering properties of ginger extracts. Bordia et al (1997) assessed the effect of ginger and fenugreek in healthy individuals, patients with CHD and patients with non-insulin-dependent diabetes. At a dose of 10 g of powdered ginger there was inhibition of platelet aggregation but no effect on lipids and blood glucose levels. Similarly, fenugreek by itself had no effect on lipids and glucose. However, administered together, fenugreek and ginger lowered cholesterol and triglycerides with no effect on HDL.

Alizadeh-Navaei et al (2008) assessed the effect of 3 g of ginger per day in 85 hyperlipidaemic patients in a randomised trial of ginger versus placebo that ran over 45 days. The study found that, compared to placebo, active

ginger lowered total cholesterol by 0.37 mmol/L and triglycerides by 0.11 mmol/L. There was a slight increase in HDL-cholesterol.

The basic biochemistry of ginger and, specifically, certain ginger extracts, suggests significant potential in modifying risk factors for developing CHD. The few human studies undertaken are also supportive, but significantly more work is needed in this area. Therefore, no recommendation can be made at this time.

Olive leaf extract

Olive leaf extract has considerable potential. The polyphenols in the extract are highly concentrated and laboratory animal studies show interesting properties of LDL lowering, an antioxidant effect and an anti-fibrotic effect. However, no adequate human trials have shown benefit, so no recommendation can be made at this time.

4.7 Other therapies

Chelation therapy

Chelation therapy has been used to treat atherosclerotic cardiovascular disease. Despite decades of use of this controversial therapy, there is no compelling clinical trial data to support use.

Chelation therapy consists of a series of intravenous infusions containing the chelating agent, disodium ethylene diamine tetracetic acid (EDTA), in combination with other substances such as vitamins. Use of EDTA has been found to be effective in chelating and removing toxic heavy metals from the blood (Green, 1993). It is hypothesised that the removal of polyvalent cations, notably calcium ions, can lead to the regression of atherosclerotic plaques by a yet undefined mechanism.

The problem with the hypothesis is that the calcium apatite (bone in fact) is only one of many components in the atherosclerotic plaque. The calcium in plaques very slowly exchanges with calcium in plasma. The hallmark of the plaque is cholesterol accumulation and is reasonably predictably removed by plasma LDL-C reduction.

Use of EDTA chelation therapy is FDA-approved in treating lead poisoning and toxicity from other heavy

metals. However, a review of chelation therapy for peripheral arterial occlusive disease has shown that chelation therapy is not superior to placebo and is associated with considerable risks (Seely et al, 2005).

In addition, a systemic review of EDTA chelation therapy for cardiovascular disease concluded that there was no evidence to support the therapeutic use of EDTA chelation therapy. At present, the benefit of chelation therapy remains controversial.

The US National Center for Complementary and Alternative Medicine (NCCAM) conducted a trial to assess chelation therapy. All patients enrolled into the study had a myocardial infarction at least six weeks prior to commencement of the chelation therapy. Unfortunately, this trial was stopped in late 2012 due to poor governance.

Acupuncture and /transcutaneous electrical nerve stimulation (TENS)

Texts on acupuncture date back to 206 BC, although the Yellow Emperor, Huang Di, the originator of traditional Chinese medicine, lived in 2697 BC (Helms 1999).

In acupuncture, fine needles are inserted into various points related to a specific organ – they may be near or distal points.

Acupuncture has been used for a wide variety of conditions, but it is most accepted for treatment of pain (Pomeranz, 1996; Andersson et al, 1973; Group of Acupuncture Anesthesia PMC, 1987; Mayer, 2000). The mechanism by which acupuncture is believed to benefit the subject is through its ability to modulate neural activity in several regions of the brain and thus reduce sympathetic outflow to the heart and vascular system (Longhurst, 2002; Yao et al, 1982).

Studies by several groups, have examined the role of acupuncture in patients with stable angina. For example, Ballegaard compared true acupuncture to sham acupuncture. He did not document a decrease in angina or change in exercise time to angina (Ballegaard et al, 1990; Ballegaard et al 1991). Two other later studies by the same group showed an acupuncture-related improvement in exercise capacity and rate-pressure product, particularly when acupuncture reduces sympathetic neural outflow (Ballegaard et al 1991; Ballegaard et al 1986).

Transcutaneous electrical nerve stimulation (TENS) may be considered a modern version of acupuncture. It involves placing small pads on the skin and applying electrical stimulation at various frequencies and intensity.

TENS has been used in a number of trials by Mannheimer to decrease angina and improve exercise time to angina (Mannheimer et al, 1985). One of the authors (Colquhoun, 1993) published a case report of three patients with severe refractory angina who responded very well to this therapy.

In addition, several small trials suggest that acupuncture may improve hypertension (Chiu et al, 1997; Williams et al 1991; Acupuncture Research Group of An Hui Medical University 1961; Zhang, 1956; Rutkowski et al, 1980; Tam and Yiu 1975). The magnitude of the effect of acupuncture on blood pressure in patients with hypertension is small but significant; reductions of 5–10 mmHg systolic have been noted.

Acupuncture can also inhibit ventricular ectopic beats induced by stimulating the hypothalamus (Guo et al, 1981). A recent review of the literature suggests the use of acupuncture/TENS for managing angina, but further clinical trials are needed.

Yoga

Yoga movements and positions and the associated breathing exercises can acutely lower blood pressure and heart rate, and improve heart rate variability. The mechanism is probably due to a decrease in sympathetic outflow. Whether there are long-term benefits from this practice remains to be determined. There is one report of improved lipid profile (Mahajan et al 1999). However, overall the data are too preliminary to make a recommendation at this time.

Qi Gong

Qi Gong (or qigong) is the philosophy and practice of aligning breath, movement, and awareness for health of mind, body, and spirit. It is based in traditional Chinese medicine, martial arts, and philosophy. There are several forms of Qi Gong. It is a self-discipline that trains body and mind to alter the flow of 'vital energy'.

In 76 post-myocardial infarction patients, Qi Gong was associated with an improvement in lowering heart rate (Kuang et al, 1981) and hypertension in preliminary studies (Omura and Beckman, 1995).

However, no recommendation can be made at this time, and more well-conducted trials are needed.

Healing and therapeutic touch

Healing touch and therapeutic touch use the concept of energy fields (auras), energy centres (chakras) and energy tracts (medians) to empower healing.

Healing touch was developed by Janet Mentgen RN. Healing supposedly results from the transfer of 'excess energy' from healer to patient. However, the practice is based on unscientific principles and there are no clinical trials to support efficacy beyond placebo.

Therapeutic touch, also known as Non-Contact Therapeutic Touch (NCTT), was developed in the 1970s by Dolores Krieger (Mansour et al, 1999). Practitioners claim that by placing their hands on, or near, a patient, they are able to detect and manipulate the patient's energy field to promote healing and reduce pain and anxiety. Like healing touch, this is not based on a plausible scientific hypothesis. A meta-analysis by Astin et al (2000) of 11 trials found that seven showed a positive treatment effect on at least one outcome. The results are not robust and are consistent with placebo and the play of chance.

Meditation

Transcendental meditation has been linked to a reduction in cardiovascular mortality (MacLean et al, 1997; Bagga and Gandhi, 1983; Elson et al, 1977; Schneider et al, 2001; Calderon et al, 1999; Cauthen and Prymak, 1977; Castillo-Richmond et al, 2000). It has also been shown to lower blood pressure (Lehrer et al, 1983; Malec and Sippelle, 1977; Delmonte, 1984).

Zen meditation has been associated with improved heart rate variability. These data are preliminary and techniques cannot be recommended at this time.

Homeopathy

Homeopathy is a system of medicine that originated in 1796 by Samuel Hahnemann on the doctrine "like causes like". The hypothesis is that a substance that causes symptoms and signs of a disease in a healthy people will, in extremely low concentrations, cure disease with similar symptoms and signs in sick individuals.

There are no data to demonstrate health benefits for cardiovascular disease (Stevensen, 1999). The Lancet documents a study in which 110 homeopathy trials and 110 matched conventional-medicine trials were analysed. Biases are present in placebo-controlled trials of both homeopathy and conventional medicine. When the analysis took account of these biases, there was weak evidence for a specific effect of homeopathic remedies, but strong evidence for specific effects of conventional interventions. This finding is compatible with the notion that the clinical effects of homeopathy are placebo effects (Shang A, Huwiler-Müntener, et al, 2005).

4.8 Recommended CM therapies

The survey of CM therapies found that proven CM therapies are:

- Marine n-3 fatty acids.
- Plant sterols/stanols.

It also found that possibly useful preparations are:

- Red rice yeast.
- Co-enzyme Q10.
- Gingko biloba.
- Padma 28.
- Hawthorn.
- Multivitamins, vitamin D, and (natural) vitamin E.

Table 4.4 presents an overview of recommended dosages for nutrition, bioactive food components and dietary supplements in the prevention and treatment of cardiovascular disease.

The efficacy of chelation therapy, acupuncture, and various forms of bioenergetics is variable. Their potential beneficial effects may be in part due to an undefined psychological impact that might ultimately create a physiological effect.

While there are as yet no specific proven cardiovascular benefits from any of these therapies, preliminary data indicate that they could have benefits.

In addition, it will be worthwhile to assess other polyphenol derivatives in food such as citrus products from Italy (namely, Bergamot).

Supplement	Dose
Supplements/interventions that can be recommended	
Omega-3 supplements	1 to 4 g/day of EPA/DHA if insufficient omega-3 intake from fish
Stanol/sterol ester margarines	2 to 4 g/day (2 to 4 teaspoonsful of margarine enriched)
Soluble fibre	5 to 20 g/day
Soy foods and soy protein	Equivalent to 25 g/day soy protein
Red rice yeast	Dose to give 10 to 20 mg lovastatin/day; extracts vary 10-fold in concentration
Possibly useful for indications noted	
Tea for cardiovascular risk reduction	1 to 2 cups/day
Magnesium	Adult men 420 mg/day; adult women 320 mg/day Consider supplementation for those at risk (due to poor dietary intake or conditions that increase renal magnesium losses)
Co-enzyme Q10	100 mg/day
Ginkgo biloba	40 to 60 mg dry extract twice/day
Padma 28 *	Two tablets/403 mg 2 bd
Hawthorn	WS (Schwabe) 1442; 2/day
Cannot recommend at this time (probably not harmful)	
Folic acid supplementation if homocysteine is not elevated for vascular disease	1 mg/day in pregnant women NOT recommended for CHD
Garlic for lipid lowering	200–1500 mg/day
Soy isoflavones for lipid lowering	47 gm soy protein/day
L-Arginine supplementation for nutritional support	5 gm/day
Policosanol	NOT recommended – dose used 5–20mg/day
Olive leaf extract	Unknown
Guggulipid	Unknown (possible 250 gm, 3 times/day Guggul stone)
Supplements/interventions not recommended (possibly harmful)	
Levels exceeding the upper tolerable limits (IOM, 2001) for vitamins C and E	> 2,000 mg/day vitamins C > 1,000 mg/day vitamin E (natural)
Beta-carotene supplementation	NOT recommended
Ephedra, oleander, and other herbs/botanicals with well-defined contraindications to cardiovascular drug and/or CVD conditions (ACCF Complementary Medicine Expert Consensus Document, 2005)	NOT recommended

Table 4.4 | **Recommended doses for nutrition, bioactive food components and dietary supplements**

* The American Botanical Council, M Blumenthal 2003

4.9 Conclusions and recommendations

The key findings of the expert working group are that:

- There are many CM therapies with vague claims for improving heart health based on weak epidemiological or surrogate end-points.
- Claims of a CM therapy being an anti-oxidant are meaningless regarding value in preventing coronary artery disease.
- Test-tube and short-term trials of surrogate outcomes in genetically modified mice are no substitute for clinical outcome trials in humans.

- There is an urgent public health need to determine if CM therapies for cardiovascular health work and if they are safe, particularly when taken in conjunction with conventional medicine. This should be accomplished with more scientifically rigorous clinical trials, at the standard of drug trials.

The working group strongly recommends research on the development of novel treatments. The most promising areas of research that should be prioritised for investment and study in relation to cardiovascular health are presented below.

Priority Research Areas for Cardiovascular Health

Nutrition and dietary supplements:

- ✓ The effect of eating soluble fibre (namely, oats, psyllium, pectin and guar gum) in reducing total cholesterol.
- ✓ The effect of eating nuts in reducing the magnitude of the coronary heart disease risk.
- ✓ The effect of tea drinking in protecting against coronary heart disease.

Bioactive food components:

- ✓ No further research is warranted at this time.

Herbal preparations:

- ✓ The efficacy of hawthorn extract in reducing heart failure-related signs and symptoms.
- ✓ The efficacy of ginkgo leaf and its extracts in treating heart disease.
- ✓ The efficacy of Padma 28 in treating heart disease.
- ✓ The efficacy of red yeast rice in lowering LDL.
- ✓ The efficacy of spirulina in lipid lowering and blood pressure control.
- ✓ The efficacy of ginger and, specifically, certain ginger extracts, in modifying risk factors for developing coronary heart disease.

Other therapies:

- ✓ The efficacy of acupuncture in treating myocardial ischaemia, hypertension and arrhythmias.
- ✓ The efficacy of yoga, Qi Gong and meditation in reducing heart disease risk factors.

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5 | Cancer

This chapter describes the process used by the cancer expert working group tasked with identifying complementary medicine (CM) research priorities that can translate into improved health outcomes for patients with a cancer diagnosis in Australia. It reviews the current evidence for CM interventions and makes recommendations for future research.

Dr Monica Robotin and Catherine Holliday prepared this chapter with input from the expert group on oncology. The expert group comprised:

- Dr Monica Robotin (Chair) – The Cancer Council NSW.
- Dr Kerry Bone – MediHerb Pty Ltd.
- Sue Carrick – National Breast Cancer Foundation.
- Professor Stephen Clarke – Department of Medicine at the Concord Hospital Clinical School of the University of Sydney.
- Catherine Holliday – The Kinghorn Cancer Centre.
- Professor Bogda Koczwara – Flinders Centre for Innovation in Cancer.
- Sue Murray – National Breast Cancer Foundation.
- Professor Ian Olver – Cancer Council Australia.
- Professor Avni Sali – National Institute of Integrative Medicine, Melbourne.
- Professor Allan Spiegelman – Faculty of Medicine, University of NSW.
- John Stubbs – Cancer Voices Australia.
- Professor Alan Bensoussan – Executive Director, National Institute of Complementary Medicine, University of Western Sydney.

5.1 Prevalence of Cancer

According to the Australian Institute of Health and Welfare and the Australian Association of Cancer Registries, cancer is the second most common cause of death in Australia, exceeded only by cardiovascular diseases. Cancer accounts for about 30% of deaths in Australia. (AIHW and AACR, 2012).

In addition, cancer is the major cause of illness in Australia. In 2012, it is estimated that more than 120,700 Australians were diagnosed with cancer, excluding basal and squamous cell carcinoma of the skin. The most commonly reported cancers were prostate cancer, followed by bowel cancer, breast cancer, melanoma of the skin and lung cancer.

The most common cancers in Australia (excluding non-melanoma skin cancer) are prostate, colorectal (bowel), breast, melanoma and lung cancer. These five cancers account for over 60% of all cancers diagnosed in Australia. In addition, over 434,000 people are treated for one or more non-melanoma skin cancers each year. Cancer costs more than \$3.8 billion in direct health system costs.

An estimated 124,910 new cases of cancer will be diagnosed in Australia this year, with that number set to rise to 150,000 by 2020. One in two Australian men and one in three Australian women will be diagnosed with cancer by the age of 85.

More than 60% of people diagnosed with cancer in Australia will survive more than five years after diagnosis. The survival rate for many common cancers has increased by 30 per cent in the past two decades. Although survival has improved over time, it has not been consistent across all cancers. The cancers with the largest survival gains over this time were prostate cancer, kidney cancer and non-Hodgkin lymphoma.

5.2 Some limitations of conventional treatment

Conventional treatment for cancer typically involves chemotherapy, molecular therapeutics, radiotherapy and/or surgery. The side effects of these treatments are not insignificant and may include lymphoedema following surgery or radiotherapy, which may persist for the remainder of a patient's life (AIHW, 2008). Other late side effects of radiotherapy may include neurocognitive changes following brain irradiation, dry mouth and swallowing difficulties (following head and neck radiotherapy) and impaired lung function (following lung radiotherapy). Less common but important complications of both radiotherapy and chemotherapy include permanent infertility and an increased risk of a second cancer.

5.3 The role of complementary medicine

Use of CM

Complementary medicines are widely used by cancer patients. A recent Australian study showed that 65% of cancer patients use some form of complementary medicine (Oh et al, 2008). In another Australian survey 87% of breast cancer patients reported using CM (Kremser et al, 2008).

This trend for cancer patients to increasingly seek out supportive and CM therapies to serve as adjuncts to standard medical care has been driven by a growing desire for more holistic care. The reasons for using CM therapies include: reducing of therapy-associated toxicity, assistance of conventional therapies, improvement in cancer-related symptoms, boosting the immune system, direct anti-cancer effects, prevention of recurrence and improvement in quality of life (Oh, Butow, et al, 2010).

However, this high and increasing use of CM by cancer patients has been occurring despite limited research available on the efficacy and safety of their use. This prompted a study into the use and perceived benefits of CM use by cancer patients in Australia (Oh, Butow, et al, 2010). The researchers found that:

- 90% of CM users believed that CM provided potential health benefits.

- Less than 3% reported adverse effects experienced from the use of CM.
- Most survey respondents (80%) believed CM can provide health benefits even when efficacy has not been proven.
- Most patients (90%) believed that doctors should consider learning about CM to provide appropriate advice to their cancer patients.

Despite this high and increasing use of CM by cancer patients, less than half the people surveyed in another study said they disclose this information to their doctors (Adams et al, 2005; Girgis et al, 2005; Markovic et al, 2006; Sibbritt et al, 2003).

Oncologists remain generally reluctant to endorse CM use (Hyodo et al, 2003; Novak et al, 2001). However, the high rate of CM use by cancer patients and the establishment of integrative medicine units have resulted in more dialogue between 'unconventional' and 'conventional' healthcare providers (Kremser et al, 2008). In addition, a government enquiry into cancer treatment services and complementary therapies recommended increasing CM research activity and CM funding in Australia (Community Affairs References Committee, 2005).

In Australia, the high level of patient involvement in their own treatment has been recognised in the National Framework for Consumer Involvement in Cancer Control (Cancer Australia and Cancer Voices Australia, 2011).

Why invest in CM research for cancer treatment?

Identifying research priorities that can inform the evidence base for CM treatment is critical to the national interest and, more specifically, relevant for many stakeholders, including funding bodies, researchers and cancer patients.

Investment in CM research affords the opportunity to investigate potential treatments that may be safer, less expensive and more cost-effective than conventional treatments.

Investment in CM research would also identify whether CMs are efficacious in providing symptomatic relief for patients suffering the side effects of conventional cancer treatments, and safe to use in tandem with these

conventional cancer treatments. A systematic review conducted in the UK confirmed the lack of reliable information concerning the use of herbal medicines among people with a diagnosis of cancer, and showed that much existing research was of “relatively poor quality” (Wilson, Gratus, et al, 2011). Currently, adverse risks are only well known in relation to a few CM interventions – such as the adverse interaction of St John’s wort with chemotherapeutic agents (Wilson, Gratus, et al, 2011). Another study, by the Society for Integrative Oncology, recommends a number of CM treatments as part of a multidisciplinary approach to cancer treatment (Deng and Frenkel, et al, 2009). These include mind-body modalities (eg support groups, stress management), massage therapy, physical activity, and acupuncture.

5.4 Methodology

The approach by the cancer expert group began with a Delphi process to identify and rank promising research directions in CM in cancer. This was followed by a nominal group process. These steps are outlined below. For more detail on the study process, refer to the publication ‘Defining research priorities in complementary medicine in oncology’ (Robotin, Holliday and Bensoussan, 2012).

Overview of the Delphi process

Determining which research should take priority in CM remains a significant challenge due to the diversity of opinions about CM held by different stakeholders. For example, patients and healthcare providers may be more interested in issues of safety and effectiveness; governments in cost-effectiveness, CM practitioners in the effectiveness of different therapies; and scientists in extending the general knowledge base of CM and how therapies work (Bensoussan and Lewith, 2004).

The diversity of opinions surrounding CM use in cancer and the large number of stakeholder groups prompted the selection of a consensus-building method to define priorities for research. The group chose the Delphi process to identify research priorities for CM therapies.

The Delphi process involves sending the participants a series of questions interspersed with controlled opinion feedback. Individual responses are collated and analysed in an anonymous manner and summarised by the research team, before being returned to respondents for further consideration in a subsequent round; the process is repeated until consensus is achieved (Linstone and Turoff, 1975).

Discussion of the Delphi process in this study

The Delphi process allowed a structured interaction of a very diverse stakeholder group, with different views on research, while keeping the interaction on topic and on time – the entire process took only three weeks.

The participants in the Delphi process were drawn from those who were representative of their profession, had the power to implement the findings of the process, or had an established reputation as experts in CM research. The participants included 27 Australian and international experts, and included integrative medicine practitioners, researchers and academics, clinicians, practitioners of CM, representatives of funding and government organisations, and trained consumer representatives.

The participants were provided with the National Cancer Institute (NCI) Annual Report on Complementary and Alternative Medicine: Fiscal Year 2007, which includes the major categories of CM therapies (see Table 5.1).

Category	Definition	Examples
Alternative medical systems	Systems built upon complete systems of theory and practice, often evolved earlier than the conventional medical approach used in the United States	Acupuncture, Ayurveda, homeopathy, naturopathy, traditional Chinese medicine, Tibetan medicine
Energy therapies	Involve the use of energy fields: Biofield therapies: affect energy fields purported to surround and penetrate the body Electromagnetic-based therapies: the unconventional use of electromagnetic fields	Qi Gong, reiki, therapeutic touch Magnet therapy
Manipulative and body-based methods	Based on the manipulation and/or movement of one or more parts of the body	Chiropractic, therapeutic massage, osteopathy, reflexology
Mind-body interventions	A range of techniques designed to enhance the mind's capacity to affect bodily functions and symptoms	Meditation, hypnosis, art therapy, biofeedback, imagery, relaxation therapy, support groups, music therapy, cognitive-behavioural therapy, aromatherapy
Nutritional therapeutics	A range of nutrients and non-nutrients used as chemopreventive agents and specific foods or diets used in cancer prevention or treatment	Macrobiotic diet, vegetarianism, Gerson therapy, vitamins, soy/ phytoestrogens, antioxidants, selenium, coenzyme Q
Pharmacologic and biologic therapies	Off-label use of prescription drugs, hormones, complex natural products (these include botanical preparations and other extracts from natural substances), vaccines and other biological interventions not yet accepted in mainstream medicine	Herbs and herbal extracts, mistletoe, mixtures of tea polyphenols, shark cartilage
Spiritual therapies	Focus on deep, often religious beliefs and feelings	Intercessory prayer, spiritual healing

Table 5.1 | **Major categories of CM therapies identified by the National Cancer Institute**

How the Delphi process was undertaken

The Delphi process was conducted over three rounds in September–October 2009.

The top 10 recommendations that came from the Delphi process were to:

- Conduct randomised controlled trials investigating the effects of herbal medicines and nutritional supplements used in conjunction with standard cancer therapy on treatment side effects, in alleviating cancer symptoms and in reducing tumor load.
- Investigate the best means to provide accurate, readily accessible and regularly updated information about CM for patients and health practitioners.
- Conduct preclinical and clinical studies on the interactions/impact of biological CM treatments on conventional therapies in cancer.
- Study the effect of herbal medications and nutritional supplements on quality of life and survival following conventional cancer treatment
- Study the role of Chinese herbal medicines as supportive treatments in cancer, in conjunction with conventional chemotherapy, or as standalone treatments.
- Study the role of exercise and physical activity in ameliorating cancer side effects and in secondary cancer prevention.
- Study the role of acupuncture for symptom relief (due to cancer or its treatment) in reducing opioid dependence and treatment-induced leucopenia.
- Study the role of nutritional interventions in reducing cancer recurrences.
- Study the role of probiotics in reducing nosocomial infections and mucositis during chemotherapy.
- Conduct preclinical studies focusing on the mechanism of action of CM therapies.

This list was further refined by:

- A literature search, defining their role in cancer care, available evidence (and gaps) regarding their effectiveness, safety, potential of integration.
- A survey of Australian research groups inquiring as to whether they are investigating any of these treatments currently or are planning to do so in the future.
- A nominal group, which used the information derived from these processes to refine the proposed research directions (see below).

The Nominal Group Process

The focus of the nominal group was on either the opportunities for Australian research, or those that would most effectively leverage strategic research partnerships.

For each issue, the group aimed to identify, clarify, evaluate and prioritise:

- The type of research that would best address the identified priorities and how this should be progressed.
- Whether local expertise and competitive advantage exists to carry this research through.
- The methodological challenges associated with the proposed research and how they can be circumvented.

5.5 Conclusions and recommendations

There were significant areas of overlap between some of the top-ranking propositions identified in the Delphi process. Propositions addressing the same themes were therefore consolidated. At the completion of the nominal group process, five research priorities were identified and a process agreed upon to ensure they will be adequately nurtured, developed and enjoy government support in order to reach their potential. The final list of priority areas is presented below.

The list of CM research priorities was circulated to Delphi participants for further comment and a final report prepared for public comment. This represents a first step

in a process of priority setting, envisaged to also include a survey of Australian research groups conducting CM research and a nominal group to finalise and endorse the strategic plan for future CM research.

The process of identifying research priorities was not only successful in highlighting five strong candidates for future research. It also showed the importance of the consensus-building Delphi process in reaching these recommendations.

Priority Research Areas for Cancer

- ✓ Conduct carefully designed preclinical and clinical studies investigating the interactions and impact of biological treatments (including herbal medicines, Chinese herbal medicines and nutritional supplements) taken concurrently with conventional cancer treatments on:
 - reducing side effects of conventional cancer treatments
 - alleviating cancer symptoms
 - reducing tumour load
 - prolonging disease-free survival.
- ✓ Study the effect of herbal medications and nutritional supplements on quality of life and survival, following conventional cancer treatment.
- ✓ Investigate the best means to provide accurate, readily accessible and regularly updated information about CM for patients and healthcare practitioners.
- ✓ Study the role of exercise/physical activity in ameliorating cancer side effects and in secondary cancer prevention.
- ✓ Study the role of acupuncture for symptom relief (due to cancer or its treatment), reducing opioid dependence/ treatment -induced leucopenia, etc.

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6 | Arthritis and musculoskeletal conditions

This chapter presents a review of current evidence for complementary medicine (CM) interventions in the area of arthritis and musculoskeletal conditions, and makes recommendations for future research that can translate into improved health outcomes. The report was prepared by Dr Sarah Yarmand, Associate Professor Ken Williams and Professor Richard Day with assistance and guidance by other members of the NICM Musculoskeletal Expert Group. The Expert Group comprised:

They were assisted by other members of the NICM Musculoskeletal expert group, which comprised:

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- Professor Nicholas Bellamy – Centre of National Research on Disability and Rehabilitation Medicine, Brisbane.
- Professor Stephen Myers – NatMed-Research Unit, Special Research Centre, Southern Cross University.
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- Professor Alan Bensoussan – Executive Director, National Institute of Complementary Medicine, University of Western Sydney.

6.1 Prevalence of arthritis and musculoskeletal conditions

Definition of arthritis and musculoskeletal conditions

Arthritis and musculoskeletal conditions are characterised by pain, stiffness and reduced function, which contribute to sleep disturbance and a decreased quality of life.

Arthritis is a long-term condition marked by inflammation of the joints. The prevalence of arthritis increases with age; fewer than 1% of people aged less than 25 years report having arthritis, compared with 48% of people aged 65 years or over.

There are over 100 types of arthritis. The most common types are:

- **Osteoarthritis** – This is a degenerative condition caused by wear of the cartilage, which overlies the ends of the bones in a joint. Its main symptoms are inflammation, joint pain, swelling and stiffness leading to reduced mobility.

- Rheumatoid arthritis – This is an inflammatory autoimmune disease, which can affect many organs of the body as well as the joints. It can cause joint pain and swelling, often leading to deformity and disability (AIHW website, 2011).

Musculoskeletal pain affects the muscles, ligaments and tendons, along with the bones. The causes of musculoskeletal pain are varied. Muscle tissue can be damaged with the wear and tear of daily activities. Trauma to an area (from jerking movements, auto accidents, falls, fractures, sprains, dislocations, and direct blows to the muscle) can also cause musculoskeletal pain. Other causes of pain include postural strain, repetitive movements, overuse, and prolonged immobilization. Changes in posture or poor body mechanics may bring about spinal alignment problems and muscle shortening, which causes other muscles to be misused and become painful (www.webmd.com/pain-management/guide).

Severity of the condition

Arthritis and musculoskeletal conditions are the most common source of disability in Australia.

These conditions place a significant burden on the community – personally and financially – due to the use of hospital and primary care services, disruptions to the patient's daily life, and lost productivity in the workplace. In 2007–08 there were 421,000 hospitalisations due to musculoskeletal conditions (AIHW website, 2011). In addition, the chronic nature of arthritis and osteoporosis can affect the way people perceive their health. People with arthritis are more likely to experience psychological distress compared to those people who do not have a long-term condition (ABS website).

As a consequence, in 2002 the Australian Government declared arthritis and musculoskeletal conditions a National Health Priority Area.

A snapshot of the enormity of the condition is provided by the data in the box below (AIHW website, 2011).

How prevalent are arthritis and musculoskeletal conditions?

- More than six million Australians have arthritis or a musculoskeletal condition.
- Arthritis and musculoskeletal conditions are the most common source of disability in Australia.
- Three million Australians have arthritis, of whom 1.6 million have osteoarthritis and 430,000 have rheumatoid arthritis.
- Arthritis and musculoskeletal conditions accounted for \$4 billion or 7.5% of health system expenditure in 2004–05. This was the fourth highest rate of expenditure, behind cardiovascular disease (\$5.9 billion), oral health (\$5.3 billion) and mental disorders (\$4.1 billion).
- Back pain or disc-related disorders are the most common of musculoskeletal conditions, reported by more than 3 million Australians.
- About 4,000 Australian children have arthritis.
- An estimated 690,000 Australians have osteoporosis, which is a large contributor to fractures in older persons.
- Musculoskeletal conditions were the third most common reason for a person visiting a GP in 2007–08.
- More than 50,000 total knee and hip joint replacements are performed each year, the majority due to osteoarthritis.
- Arthritis and musculoskeletal disease was identified as either an underlying or associated cause of death for 6,400 (4.6%) deaths registered in 2009. Of all deaths due to arthritis or musculoskeletal disease in 2009, 71% were females.
- Early diagnosis and treatment can reduce symptoms and help to prevent damage to the joints due to arthritis.
- A healthy diet, regular exercise and not smoking can help to prevent osteoporosis and reduce its insidious effects.

Source: Australian Institute of Health and Welfare and ABS websites, <http://www.aihw.gov.au/arthritis-and-musculoskeletal-conditions/>, <http://www.abs.gov.au/ausstats/>

6.2 Treatments

Medications and supplements are commonly used to manage arthritis (in its various forms) and osteoporosis. The ABS reports that, in 2007–08, 59.3% of people with arthritis took some form of medication for their condition, while 44.2% took medication for their osteoporosis (ABS, 2011).

The most common medications for arthritis were:

- Vitamin, mineral and herbal treatments – these were the most common type of medication used for arthritis (45%).
- Fish oils – these were the most common supplement used for arthritis (29.4%), followed by glucosamine (26%).
- Pharmaceutical medications – 30.2% of people took pharmaceutical medications to treat their arthritis, with half of these people taking non-steroidal anti-inflammatory drugs.

The most common medications for osteoporosis were:

- Vitamin, mineral and herbal treatments – these were the most common type of medication used for osteoporosis (33.8%).
- Calcium supplements – were the most common supplement taken by people with osteoporosis (28%), followed by fish oils (16.7%).
- Pharmaceutical medications – 21.4% of people took pharmaceutical medications to treat their osteoporosis.
- Medication – biophosphonates (which slow the breakdown of bone) were the most common type of medication taken, used by 4.5% of people with osteoporosis.

After medications and supplements, the most common action taken for arthritis or osteoporosis was exercise on most days (19% of people). Massage was the third most common action taken by women (9.2%), whereas for men it was weights, strength or resistance training (8.3%). Approaches to the management of non-arthritic musculoskeletal pain also include both oral and manual therapies.

6.3 Some limitations of conventional treatment

Conventional treatments include:

- Injections with anaesthetic or anti-inflammatory medications in or around the painful sites.
- Non-steroidal anti-inflammatory drugs (NSAID), and creams or gels.
- Paracetamol
- Opiate analgesics
- Physical or occupational therapy (www.webmd.com/pain-management/t/guide).

These conventional therapies for rheumatoid arthritis and osteoporosis are effective in controlling or reducing the progression of these disorders and also, to some degree, in reversing the pathologies (biological plus methotrexate for RA; and Vitamin D and calcium for osteoporosis). In these cases, CM is generally considered only as a possible adjunct to conventional treatments (albeit noting that Vitamin D and calcium are also regulated as CMs).

However, sustained use of NSAID therapy for chronic illnesses such as rheumatoid arthritis is associated with gastrointestinal side effects such as dyspepsia and gastrointestinal bleeding, as well as both renal and cardiac toxicity, resulting in hospitalisations and, occasionally, death (Day and Roughead, 1999, referenced in Access Economics, 2010). NSAID can also lead to myocardial infarction-related mortality (people with rheumatoid arthritis have an elevated risk of myocardial infarction-related mortality; NSAID further increases this risk).

6.4 The role of complementary medicine

Partly in response to some of the concerns about the side effects of conventional medicine (particularly NSAID), Australians are using CM approaches extensively to help manage arthritis and a broad range of musculoskeletal conditions (MacLennan, 2002; ABS, 2011).

The effectiveness of CM therapies seems to be more promising for conditions such as osteoarthritis, non-specific back pain and fibromyalgia for which there are no highly

effective conventional treatments to control symptoms or prevent progression and joint damage. For these chronic diseases, CM may have potential to provide a safe and cost-effective alternative.

However, research is needed to establish a rigorous, informative and evidence-based platform for the efficacy, safety and cost effectiveness of these therapies.

6.5 Methodology

Overview

In preparing its review, the expert group:

- Nominated five conditions to target.
- Conducted a literature search to identify promising CMs.
- Conducted interviews with CM research leaders.
- Classified potential therapies according to risk:benefit ratios and cost-effectiveness where known.
- Undertook additional database searches of the specific CM treatments identified through interviews.
- Considered the strategic value of pursuing research into each CM therapy from an Australian perspective.

Challenges

During the process of identifying priority research areas, the expert group needed to allow for the following challenges and deficiencies in the data:

- The lack of an exact definition of CM and musculoskeletal conditions.
- The lack of an established grading of the evidence for the domains of effectiveness, safety and cost-effectiveness.
- The variable and often large gaps in the evidence base for many CM treatments.
- Common research biases in CM trials – For the manipulative and body-base therapies, the central role of the practitioner, their unique skill set and the importance of the practitioner–patient relationship contribute to the wide range of variability in responsiveness. These considerations make it difficult to design a conventional clinical trial (e.g. a randomised controlled trial) for these treatments. Therefore, researchers in these fields primarily use ‘ecological’ (i.e. ‘real world’) observational clinical trials to assess the effectiveness of the therapy. The conventional

Level	Explanation
1	There is, overall, no evidence to suggest that the therapy works or only a little evidence, which is outweighed by stronger evidence that it does not work.
2	There is only a little evidence to suggest the therapy might work. The evidence from studies in this category often come from only a single study which has reported positive results and there are, therefore, important doubts about whether or not it works.
3	There is some promising evidence to suggest that the therapy works. The evidence will be from more than one study. However, there may also be some studies showing that it does not work. Therefore, it is still uncertain whether therapies in this category work or not.
4	There is some consistency to the evidence, which will come from more than one study, to suggest that the therapy works. Although there are still doubts from the evidence that it works, on balance it is more likely to be effective than not.
5	There is consistent evidence across several studies to suggest that this therapy is effective.

Table 6.1 | Ranking of evidence (Arthritis Research UK)

pharmaceutical development approach of seeking the efficacy of an individual active ingredient may also be inappropriate when assessing herbal therapies, the effectiveness of which has been traditionally explained by the synergistic activities of various compounds.

- Size of the clinical effect –the size of the effect needed for a clinically meaningful outcome has often not been adequately considered. However, this is a very important consideration when translating research results into the spectrum of clinical practice.

Where key deficiencies significantly affected the data these CM interventions were not considered suitable for prioritised research at this stage.

Levels of evidence

For the ranking of the level of evidence supporting each CM intervention, the expert group used Table 6.1 in the report prepared by the UK Arthritis Research Campaign (since 2010, known as Arthritis Research UK): Complementary and Alternative Medicines for the Treatment of Rheumatoid Arthritis, Osteoarthritis and Fibromyalgia. This grades evidence from Level 1 (no/little evidence that the therapy works) to Level 5 (consistent evidence across several studies that the therapy is effective).

There are other approaches to ranking levels of evidence, but given the wide range of interventions encompassed by CM, it was considered that this categorisation was sufficiently flexible for the purpose of this report (see Table 6.1).

Identifying and ranking CM treatments

At the start of the process, the expert group nominated five common arthritis and musculoskeletal conditions to be targeted:

- Osteoarthritis.
- Rheumatoid arthritis.
- Osteoporosis.
- Pain of spinal origin (low back pain, neck pain).
- Fibromyalgia (a label not universally accepted; widespread musculoskeletal pain, characterized by allodynia).

To begin the process of identifying the most promising CM interventions, a provisional list of potential treatment categories was produced during the first meeting of the expert group and amended after inspecting the results obtained from literature searches and interviews with selected experts, as discussed below.

Interviews with experts

To obtain information about the most popular forms of CM for managing arthritis and musculoskeletal conditions in Australia, the expert group compiled a list of expert CM practitioners and researchers. The NICM Scientific Advisory Committee also made suggestions. Semi-structured interviews were undertaken with each of these representatives (n=15).

An interview guide based on eight open-ended questions was used to elicit, inter alia, the CM interventions for arthritis and musculoskeletal commonly used in Australia, their efficacy, and level of evidence for their effectiveness. The interview questions were:

- Do you have preferences for the best medicines/interventions from your CM specialty that have value for musculoskeletal problems?
- Is there any good quality evidence for these CM interventions for arthritis, osteoporosis, and general musculoskeletal pain?
- From your point of view, what kinds of patients with musculoskeletal problems use these specific CM?
- What kinds of patients are referred by GPs for these CM?
- What are the most common CM treatments used in Australia for musculoskeletal problems?
- What are the barriers for individuals using CM interventions?
- What are the methodological problems in CM trials in the musculoskeletal disorders?
- What are the outcome measures used for CM trials in musculoskeletal medicine trials?

Literature search

The most common CMs used for managing arthritis and musculoskeletal disorders were also identified by a systematic literature search of the following databases: Cochrane library, Pubmed, EMBASE, and the Natural Medicine Comprehensive Database. The search terms used were ‘complementary medicine’, ‘alternative medicine’, ‘allied health’, ‘arthritis’, ‘osteoarthritis’, ‘musculoskeletal problems’, ‘joint disease’, ‘pain’, and their combinations. No time limit was applied to the literature search.

The types of reports targeted were limited to meta-analyses and systematic reviews of randomised controlled clinical trials published in English. The expert group informally considered an assessment of the methodological qualities of the trials included in these meta-analyses and systematic reviews by the original authors.

Shortlist of 20 promising treatments

Using the data from the interviews and the literature search, the expert group identified 20 of the most promising treatments for detailed review. The expert group then undertook a search of the same databases to:

- Link specific CM treatments with specific musculoskeletal disorders.
- Find articles that addressed the mechanism of action for these 20 treatments.
- The CM treatments that were identified were divided into the two broad categories noted previously – manipulative and body-based therapies, and biologically-based practices. The biologically-based practices were divided into two further sub-sections – single herbs or substances, and multiple herbs. This led to the creation of three categories:
- Manipulative and body-based therapies – This included acupuncture, chiropractic, massage, osteopathy and tai chi.
- Biologically-based practices using single herbs or substances – This included capsaicin, celery seed, chondroitin, devil’s claw, ginger, glucosamine, methylsulfonylmethane, fish oil omega-3 fatty acids, plant-derived omega-3 fatty acids, and S-adenosylmethionine, rose hip and willow bark.

- Biologically-based practices using multiple herbs – This included avocado-soybean unsaponifiables, Phytodolor® (a combination of extracts from aspen, golden rod and common ash), and traditional Chinese medicines.

The potential therapies were classified according to risk:benefit ratios and cost-effectiveness. An overview of findings for each treatment is presented in Table 6.2 and 6.3.

Rating of CM therapies

The expert group then considered the strategic value of pursuing research into each CM therapy from an Australian perspective. To assign a priority rating for Australian research, the expert group discussed each of the conditions and potential CM therapies and considered seven points that were recommended by the cost-effectiveness reference group of the NICM Scientific Advisory Committee:

- The size and the societal burden of the condition.
- The importance of finding a new or more effective intervention for the condition.
- The current comparative evidence for any CM for the condition.
- The gaps in knowledge.
- The potential risk/benefit assessment of the CM for that condition.
- The specificity of the treatment for the condition.
- The potential cost-effectiveness of the intervention.

Each CM treatment was ranked according to the level of importance of each treatment in the context of the Australian healthcare, research and economic systems. The ranking was also based on a consideration of, and integration of, the answers to three questions:

- Are there good quality clinical trials currently being conducted in Australia?
- Are there important gaps in knowledge that need to be dealt with?
- Where products are considered, are they readily accessible in Australia?

In view of these considerations, the CM treatments were ranked as low, moderate or high priority as regards future research investment (see Table 6.2 and 6.3).

	Acupuncture	Chiropractic	Massage	Osteopathy	Tai chi
Indications	Chronic musculoskeletal pain (fibromyalgia) Rheumatoid arthritis	Osteoarthritis Lower back and neck pain	Lower back and neck pain	Spinal cord pain Pain in limbs and joints	Arthritis and joint pain Rheumatoid arthritis
Specificity of therapy	Education standards and practice guidelines exist but there remains variability between practitioners	–	–	–	–
Research biases	Selection bias, performance bias, attrition bias, detection bias				
Gaps in knowledge	Cost-effectiveness studies	–	–	–	–
Priority for Australian research	Moderate	Moderate	Moderate	Moderate	Moderate
Level of evidence					
Rheumatoid arthritis	2	NTI	2	2	2
Osteoarthritis	4	2	3	2	3
Osteoporosis	NTI	NTI	2	2	3
Pain	4	3	3	3	3
Fibromyalgia	4	3	3	3	3

Table 6.2 | CM treatments selected for consideration – manipulative and body-based therapies/interventions

Notes on the above table:

MSK – musculoskeletal, RA – Rheumatoid arthritis, OA – Osteoarthritis, OP – Osteoporosis
 SP – Pain (low back pain, neck pain) of spinal origin, Fi – Fibromyalgia, NTI – No therapeutic indication

6.6 Conclusions and recommendations

Final priorities were selected by the working group on the basis of the ranking and processes outlined above and summarised in Table 6.3. Conclusions were subject to the biases of the individuals that constituted the NICM Expert Groups itself and those of the CM experts and advisors. Nevertheless, every effort was made to come to a reasonable consensus opinion. It remains the case that more research is needed to establish the efficacy, safety and cost-effectiveness of these CM approaches to musculoskeletal disease.

Four priorities have been selected for Australian research into CM in arthritis and musculoskeletal conditions. These are:

- **Acupuncture.** This intervention was recommended because of the widespread practice of this form of therapy including use by medical general practitioners. Strong local geographic and migration-related ties to South East Asia have added to the local interest.

	Celery seed / apium graveolens (powder, tablets)	Capsicum anuum (topical cream)	Chondroitin	Devil's claw (tablets)	Ginger (powder, tablets)	Glucosamine (tablet, caps, solutions, topical)
Indications	Anti-inflammatory	RA MSK pain (registered product for topical application)	OA pain	Back pain OA	MSK pain	OA Joint pain and stiffness
Possible active ingredients	Cumarine, phtalides, polycetylenes, terpenoids	Extracted fruit of capsicum/ chilli pepper	Chondroitin sulphate	Harpagoide, beta-sitosterol, flavanoid, procumbides, stigmaterol, triterpenes	Gingerol, shagol, paradols	Glucosamine sulfate
Gaps in knowledge	Small amount of efficacy	–	Studies about the synergistic effect with glucosamine and pain relief without glucosamine	Cost-effectiveness	Cost-effectiveness	Disease modifying. One sponsor sponsored the successful studies. Relative effects of components of salt.
Priority for Australian research	High	Low	Low	Moderate	High	Low

- Rose hip. There is reasonable evidence for the effectiveness of this therapy. We can access and grow the product locally.
- Avocado-soybean unsaponifiables (a natural vegetable extract made from avocado and soybean oils). The product can be locally produced and the evidence to support its efficacy reasonable. Further work remains to be done to establish its place in the CM as an effective alternate to conventional medicine.
- Phytodolor® (a herbal anti-inflammatory and pain relieving medicine). This was similarly chosen because of its accessibility and because there is a reasonable evidence base for its effectiveness.

Priority Research areas for arthritis and musculoskeletal conditions

- ✓ Acupuncture.
- ✓ Rosehip.
- ✓ Avocado-soybean unsaponifiables (ASU).
- ✓ Phytodolor®.

Methyl-sulfonyl-methane (MSM) (powder, tablets)	Fish oil omega-3 marine origin (capsules, solutions)	Omega-3 plant origin	Rosehip (Rosa canina)	SAMe / S-adenosylmethionin (tablets, multi-brands)	Willow bark Salix species	ASU avocado-soybean unsaponifiable (tablets) France	Phytodolor (oral liquid, trade name in Europe)
OA	RA MSK pain OP	RA MSK pain OP	OA RA	MSK pain and stiffness (OA of hip and knee)	Back pain OA RA	OA of knee and hip	MSK pain
A metabolite of Dimethylsulfoxide (DMSO)	Eicosano-pentanoic acid (EPA) Docosa-hexaenoic acid (DHA)	Alpha-linoleic acid (ALA)	Powder of Rosa Canina pseudofruit and seeds	An endogenous co-enzyme	The bark of the Salix tree	Soy/avocado oil 3:1	Populus tremole, franxinus exceloir, salidago virgaura
Australian evidence for efficacy. Old studies	Cost-effectiveness for efficacy of GMP+ products	Efficacy of fatty acids where GMP were not yet established	Cost-effectiveness. One sponsor sponsored the successful studies	Efficacy studies	–	Cost-effectiveness Lack of Australian-based evidence	Cost-effectiveness Lack of Australian-based evidence. All studies sponsored by single manufacturer
High	Moderate	High	High	High	Low	Moderate	Moderate

Table 6.3 | **CM treatments selected for consideration – biologically-based practices/medicine**

Notes on the above table:

For single herb, biologically-based practices, the amount of active ingredient in a given preparation could vary according to environmental and genetic factors. Variability of product could therefore affect the consistency of the outcomes of clinical trials.

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7 | Dementias

This chapter presents a review of current evidence for complementary medicine (CM) interventions in the area of dementia, and makes recommendations for future research that can translate into improved health outcomes. Professor Andrew Scholey and Professor Con Stough prepared this chapter and also led the expert group on dementias. The expert group comprised:

- Professor Con Stough (chair) – Faculty of Life and Social Sciences, Swinburne University.
- Associate Professor Dennis Chang – Centre for Complementary Medicine Research; and School of Sciences and Health, University of Western Sydney.
- Professor Gerald Edmunds – The Brain Foundation.
- Professor Andrew Scholey – Centre for Human Psychopharmacology and Department of Behavioural and Brain Sciences, Swinburne University.
- Professor Nikolaus Sucher – School of Medicine and Centre for Complementary Medicine Research, University of Western Sydney.
- Dr David Camfield – Centre for Human Psychopharmacology, Swinburne University.

7.1 Prevalence of dementias

Definition of dementias

Dementia describes a syndrome associated with a range of diseases that are characterised by the impairment of brain functions, including language, memory, perception, personality and cognitive skills. Dementia is not a single specific disease. It affects people differently, and the impact on their carers and families also varies.

Alzheimer's disease is the most common form of dementia, accounting for 50–70% of all dementia cases. The second most common form is vascular dementia, accounting for 15–25% of cases (Qiu, Kivipelto and von Strauss, 2009).

Dementia is not a natural part of ageing, although most people with dementia are older. After the age of 65 the likelihood of living with dementia doubles every five years and it affects 24% of those aged 85 and over (Henderson and Jorm, quoted in AIHW website, 2011).

Global trends

An epidemiological study of dementia in 2005 estimated that 24.3 million people were living with the disease worldwide, and it was predicted that the number of people living with dementia will almost double every 20 years, to 42.3 million in 2020 and 81.1 million in 2040 (Ferri et al, 2005).

Around 10% of the population over 65 in the United States is affected by Alzheimer's disease (Mishra and Palanivelu, 2008), with the age-specific prevalence almost doubling every five years after age 65, and it is estimated that more than one-third of people aged 85 or older may have dementia-related symptoms and signs (von Strauss et al, 1999). The disability weight for dementia, estimated by an international multidisciplinary panel, has been estimated to be higher than for almost all other diseases, with the exception of spinal cord injury and terminal cancer (WHO, 2003). Unless effective preventative measures and treatment options for dementia are developed, the world is facing an ever-increasing health burden as the population ages.

Severity of the condition in Australia

Dementia is the leading single cause of disability in older Australians and constitutes the seventh largest burden of disease in Australia.

The Australian Institute of Health and Welfare (AIHW, 2007) has published data on the prevalence of the condition in Australia. The AIHW website (<http://www.aihw.gov.au/publication-detail/?id=6442467941>) states that:

Dementia is the most significant neurological disorder experienced by those over 80. It is the greatest single contributor to burden of disease due to disability at older ages as well as the second greatest single contributor to the cost of care in residential aged care after incontinence. The service needs experienced by someone with dementia may vary greatly with the severity of the cognitive impairments. People with dementia eventually become dependent on

their care providers in most or all areas of daily living, placing considerable strain on those who care for them.

Because Australia's population is ageing, there has been growing recognition that dementia represents a significant challenge to health, aged care and social policy. In the 20 years to 2024, the proportion of the population aged over 65 is projected to increase from 13% to 20%. The number and proportion of people in the 'older old' age groups (85 years and over) are expected to rise even more rapidly, from 298,300 (1.5%) to 725,300 (2.9%).

The number of people with dementia will grow correspondingly from over 175,000 in 2003 to almost 465,000 in 2031, assuming the continuation of current dementia prevalence rates.

In recognition of the challenges this presents to governments, families and health and care providers, the Australian Government introduced Helping Australians with dementia, and their carers—making dementia a National Health Priority in the 2005 Federal Budget.

7.2 Some limitations of conventional treatment

Current pharmaceutical treatments for dementia approved by the US Federal Drug Administration (FDA) are the cholinesterase inhibitors (ChEI) tacrine, donepezil, rivastigmine and galantamine, as well as the NMDA receptor antagonist memantine (May et al, 2009; Wang et al, 2009). (The NMDA receptor is the predominant molecular device for controlling synaptic plasticity and memory function.)

The ChEIs are not always well tolerated, with all four having adverse effects related to cholinergic hyperactivity including nausea, vomiting, diarrhoea, fatigue, muscle cramps and dizziness. There is also little data to support the notion of ChEIs providing any more than symptomatic relief, increasing the dwindling supplies of acetylcholine as the disease progresses (Jones, 2003). Further, few studies have been conducted that assess their efficacy for longer than one year or answer the question of whether ChEIs can significantly delay the progression from mild cognitive impairment to Alzheimer's disease in the elderly (Raina et al, 2008).

7.3 The role of complementary medicine

Current understanding of dementia and cognitive decline points to multiple etiological factors at a neurophysiological level, including depletion of endogenous antioxidants, elevation in nitric oxide and homocysteine levels, chronic inflammation, glutamatergic excitotoxicity, accumulation of redox metals, mitochondrial dysregulation and abnormal amyloid- β formation.

Given the diverse etiology of dementia, together with the limitations of current pharmaceutical treatments, it is now advantageous to consider CM treatments that simultaneously target multiple disease mechanisms (Van der Schyf et al, 2006). The evidence so far points to greater tolerability for these substances in comparison to the currently used ChEIs. Complementary medicines have a role in both the treatment/amelioration of mild cognitive impairment and dementia and in their prevention, when adopted during early to middle adulthood as a dietary supplement. Due to the great promise that CMs hold in the treatment of dementia, there has been intense research focus on these substances in recent years.

7.4 Methodology

To identify research priorities, the expert group:

- Compared CM treatments that are most prominent in the current literature on dementia prevention and treatment, with a focus on Alzheimer's disease as the most common form of dementia. The review excluded discussion of the role of vitamins other than vitamin B12.
- Presented evidence for the mechanisms of action of various CM products as derived from experimental studies and animal research.
- Assessed the evidence for the efficacy of these CM products through a review of epidemiological studies and randomised controlled trials.

Through this process, the expert group identified the CM treatments with the greatest potential for the future prevention and treatment of dementia.

The treatments reviewed by the expert group are presented in the following sections.

7.5 Comparison of CM treatments

This section compared CM treatments that are most prominent in the current literature on dementia prevention and treatment, together with the findings of studies.

Docosahexaenoic acid (DHA)

What it is

Docosahexaenoic acid (DHA) is a polyunsaturated omega-3 fatty acid commonly found in fish oils. It constitutes more than 30% of the total phospholipid composition of plasma membranes in the brain (Gomez-Pinilla, 2008).

DHA plays an important role in supporting neural plasticity and cognition, stimulating hippocampal levels of brain-derived neurotrophic factor (BDNF), which facilitates synaptic transmission and long-term potentiation required for memory and learning (Gomez-Pinilla, 2008). BDNF is found to be depleted in the hippocampus of patients with Alzheimer's disease and has been implicated in the positive effects of exercise on cognition (Neeper et al, 1995). DHA has also been found to stimulate mitochondrial function and glucose utilisation and transport, resulting in reduced oxidative stress in the brain (Pifferi et al, 2007; Wu A et al, 2004). Further, a lipoxygenase metabolite of DHA, neuroprotectin D1 (NPD1), plays an important neuroprotective role by up-regulating anti-apoptotic and down-regulating pro-apoptotic mediators of cell death (Bazan, 2005).

The human body is inefficient in synthesising DHA itself, and for this reason we are largely reliant on dietary sources (Plourde and Cunnane, 2007). Epidemiological studies have linked dietary deficiency of DHA to an increased risk of several disorders including ADHD, dyslexia, mood disorders and dementia (Freeman et al, 2006).

Studies

In 2005, the US Department of Health and Human Services requested a meta-analysis of research into omega-3 fatty acid and dementia. On the basis of this

review it was concluded that there was sufficient evidence to warrant clinical trials for the treatment and prevention of Alzheimer's disease using omega-3 fatty acids (Maclean, et al, 2005). Notwithstanding the potential positive effects of DHA as a dietary supplement for cognition, few randomised controlled trials with DHA have been conducted; of those that have been conducted, no clear benefit of DHA supplementation on cognitive function is yet to emerge. Cunnane and colleagues (2009) recently conducted an extensive review assessing the current status of DHA in the treatment and prevention of dementia, comparing evidence from epidemiological studies, randomised controlled trials and animal research. They concluded that future randomised controlled trials need greater focus in addressing specific mechanisms of action by which DHA may exert a neuroprotective effect and that, at this stage, there is greater evidence for DHA playing a preventative role in Alzheimer's disease, rather than being an effective treatment.

Cole and colleagues (2009) argue strongly for the use of antioxidants in combination with DHA supplementation, particularly in cases of late stage Alzheimer's disease. They base this argument on the fact that amyloid beta (A β) increases oxidative damage to the brain, and considering that DHA is readily oxidized, antioxidants such as vitamin E and C are necessary in order to stop toxic oxidized forms of DHA from forming. Their argument is in line with the findings from previous independent clinical trials by Freund-Levi (2006), Kotani (2006) and Chiu (2008) in which DHA was found to stabilise Mini-Mental State Examination (MMSE) scores in cases of mild cognitive impairment (MCI) but not once Alzheimer's disease was established.

Another factor that appears to play an important role in the efficacy of DHA for cognitive improvement is polymorphisms in Apolipoprotein E (ApoE). It has been estimated that 23% of the Caucasian population carries the ϵ 4 allele of ApoE, which is the genetic risk factor most associated with late-onset Alzheimer's disease (Jofre-Monseny et al, 2008). A recent study provides evidence to indicate that higher fish intake is not associated with the same benefit in dementia risk for carriers of the ApoE4 allele in comparison to non-carriers (Huang et al, 2005). Cunnane and colleagues (2009) provide preliminary findings to indicate that the ApoE4 genotype

influences the metabolism of DHA, with DHA not being incorporated into plasma lipids to the same extent for carriers of the $\epsilon 4$ allele in comparison to non-carriers.

Summary of findings

In summary:

- There is some evidence that DHA can lead to cognitive improvement.
- There is some evidence for DHA playing a preventative role in Alzheimer's disease.
- There is a case for the use of antioxidants in combination with DHA supplementation, particularly in cases of late-stage Alzheimer's disease.

N-Acetylcysteine (NAC)

What it is

The endogenous tri-peptide Glutathione (GSH) is the most abundant low-molecular-weight thiol in human cells and plays a central role in antioxidant defence from reactive oxygen species (ROS) (Aitio, 2006) as well as protection against toxic compounds (Townsend et al, 2003). Glutathione is synthesised in tissue from the amino acids L-cysteine, L-glutamic acid and glycine, where the availability of cysteine is generally the rate-limiting factor in its production (Wu G et al, 2004). N-Acetylcysteine (NAC) is the N-Acetyl derivative of cysteine, and is less reactive, less toxic and less susceptible to oxidation than cysteine, as well as being more soluble in water. For these reasons, it is a better source of cysteine than the parenteral administration of cysteine itself (Bonanomi and Gazzaniga, 1980). When taken orally, NAC is readily taken up in the stomach and gut and sent to the liver where it is converted almost entirely to cysteine and used for GSH synthesis (Atkuri et al, 2007). Across a number of studies, supplementation using NAC has been found to be an effective way of increasing intracellular GSH levels, both in clinical cases of deficiency (Bridgeman et al, 1991; De Rosa et al, 2000; Skrzydlewska and Farbiszewski, 1999) as well as amongst healthy volunteers (Roes et al, 2002).

Studies

Due to its effectiveness in raising GSH levels and protecting the human body from oxidative stress and

toxins, NAC supplementation has been investigated as a treatment for a wide number of conditions including paracetamol intoxication, HIV, cancer, radiocontrast-induced nephropathy and chronic obstructive pulmonary disease (Aitio, 2006). Oral doses of NAC up to 8,000 mg per day have not been known to cause clinically significant adverse reactions (De Rosa et al, 2000), and in a review of over 46 placebo controlled trials, with NAC administered orally to a total of 4,000 people, no significant adverse effects from NAC treatment were observed (Atkuri et al, 2007). One potential cause for concern over NAC supplementation was raised in a study by Palmer and colleagues (2007) in which rats receiving high-dose NAC in vivo for three weeks developed pulmonary arterial hypertension (PAH). The authors linked the finding of PAH to the conversion of NAC to S-nitroso-N-acetylcysteine (SNOAC) and a resultant hypoxia-mimetic effect. However, it is important to note that the rats were continuously exposed to a dose per weight roughly 40 times higher than the dose typically used in human studies.

The efficacy of NAC supplementation in the treatment of age-related cognitive decline and neurodegeneration has also been investigated in a number of experimental studies. In vitro research by Chen and colleagues (2003) revealed that pre-treatment of cortical neurons with NAC protected mitochondrial function and membrane integrity under conditions of oxidative stress. Similarly, Olivieri and colleagues (2001) found a neuroprotective effect for NAC in neuroblastoma cells exposed to oxidative stress. Pre-treatment with NAC resulted in a reduction in oxidative stress resulting from exposure to Amyloid β proteins, as well as a reduction in phospho-tau levels. Research by Martinez and colleagues (2000) revealed that aged mice fed NAC for 23 weeks performed better on a passive avoidance memory test than age-matched controls. Further, lipid peroxide and protein carbonyl contents of the synaptic mitochondria were found to be significantly decreased in the NAC-supplemented animals compared to the controls.

There is evidence to suggest that in Alzheimer's disease, GSH levels are decreased in both cortical areas as well as the hippocampus (Adams et al, 1991). For this reason it is foreseeable that NAC may play a neuroprotective role by restoring GSH levels to a normal state.

Mice deficient in apolipoprotein E undergo increased oxidative damage to brain tissue and cognitive decline when maintained on a folate-free diet. Tchantchou and colleagues (2005) found that dietary supplementation with NAC (1 g per kg diet (g/kg)) alleviated oxidative damage and cognitive decline, and restored GSH synthase and GSH levels to those of normal mice.

There is also evidence to suggest that NAC supplementation may bring about a reduction in Amyloid β formation. In an animal model of Alzheimer's disease using 12-month-old SAMP8 mice with an over-expression of the amyloid precursor protein (APP), Farr and colleagues (2003) found chronic administration of NAC to bring about significantly improved memory performance on the T-maze avoidance paradigm and lever press appetitive task. In an animal model of Alzheimer's disease using TgCRND8 mice, Tucker and colleagues (2005) found chronic treatment of NAC for three months to result in a significant reduction of Amyloid β in cortex. Similarly, research by Fu and colleagues (2006) revealed that mice with Amyloid β peptide intracerebroventricularly injected performed significantly better in behavioural tests of memory and learning when pretreated with NAC in comparison to those without pretreatment. NAC pretreatment was also found to significantly reverse reductions in GSH and ACh.

While considerable experimental evidence exists for the neuroprotective role of NAC, there is currently a scarcity of clinical studies examining its efficacy in the treatment and prevention of dementia. One such study, a double-blind clinical trial of NAC in patients with probable Alzheimer's disease was conducted by Adair and colleagues (Adair et al, 2001). In the trial, 43 patients were randomised to either placebo or 50 mg/kg per day NAC for six months and tested at baseline as well as at three and six months on MMSE as well as a cognitive battery. The NAC supplementation was not found to be associated with significant differences in MMSE scores compared to placebo at either three or six months, but patients receiving NAC showed significantly better performance on the letter fluency task compared to placebo, as well as a trend towards improvement in performance on the Wechsler Memory Scale immediate figure recall test. Further, ANOVA using a composite measure of cognitive tests favoured NAC treatment at both three and six months.

In a 12-month open-label study of the efficacy of a CM and vitamin formulation in the treatment of early-stage Alzheimer's disease, Chan and colleagues (2009) administered 600 mg of NAC daily as part of a larger formulation of substances including ALCAR, alpha-tocopherol, vitamin B6, folate and S-adenosyl methionine to 14 community-dwelling individuals. Participants were found to be significantly improved on the Dementia Rating Scale (DRS) at both six and 12 months, with an overall improvement of 31%. However, a limitation of this study was that no placebo group was used for comparison, although the authors claim that the efficacy of their CM formulation exceeded that of historical placebos in previous studies of mild-to-moderate Alzheimer's disease.

In a follow-up study by the same group (Remington et al, 2009) the efficacy of the same CM formulation containing NAC was tested in a group of 12 nursing home residents with moderate to late-stage Alzheimer's disease over a nine-month period. This time, participants were randomised to either treatment or placebo. The CM formulation was found to delay cognitive decline as measured by the DRS for about six months, whereas in the placebo group a similar rate of decline was observed at only three months. While it is difficult to differentiate the efficacy of NAC from the other substances included in the formulation, these studies provide preliminary evidence for the efficacy of NAC in improving symptom severity in early-stage Alzheimer's disease, and delaying the onset of decline in moderate to late-stage Alzheimer's disease.

Summary of findings

In summary:

- There is considerable experimental evidence for the neuroprotective role of NAC, but a scarcity of clinical studies examining its efficacy in the treatment and prevention of dementia.
- There is preliminary evidence for the efficacy of NAC in improving symptom severity in early-stage Alzheimer's disease, and delaying the onset of decline in moderate to late-stage Alzheimer's disease.

Ginkgo biloba

What it is

Ginkgo is taken from a single type of tree, Ginkgo biloba (G. biloba), known to be one of the world's oldest living species, a living fossil that has existed for over 150 million years (McKenna et al, 2001). Recorded uses of G. biloba in traditional Chinese medicine date back over 5,000 years, with the seeds and leaves used to treat a range of ailments including pulmonary disorders, alcohol abuse, bladder inflammation, heart and lung dysfunctions and skin infections (Mahady, 2002; Smith and Luo, 2004). However, despite intense research focus on the cognitive effects of G. biloba, there is still no conclusive evidence as to its efficacy in the treatment or prevention of dementia (Birks and Grimley Evans, 2009).

A standardised extract of G. biloba, EGb 761, has been available in Europe since the early 1990s (Frank and Gupta, 2005). There are two active groups of compounds in this extract: flavonoid glycosides (24%) and terpene lactones (6%) (Smith and Luo, 2004). The flavonoids consist of quercetin, kaempferol and isorhamnetin, which are antioxidants that can trap ROS, modify the expression of endogenous antioxidants and chelate transition metal ions. The terpene lactones consist of the ginkgolides A, B, C, J and M, as well as bilobalide. The ginkgolides improve blood circulation through their action as platelet-activating factor antagonists (Ramassamy et al, 2007). In relation to neuroprotective mechanisms of action associated with ginkgo, a number of mechanisms have been proposed, including: antioxidant, anti-inflammatory, preservation of mitochondria function/increased ATP production, inhibition of the formation of A β from the APP, reduction in neuron apoptosis, and enhancement of cholinergic transmission (Mahadevan and Park, 2008; Ramassamy et al, 2007).

Studies

A recent meta-analysis of G. biloba for the treatment of dementia and mild cognitive impairment (MCI) by Cochrane reviews (Birks and Grimley Evans, 2009) concluded that there is currently inconsistent and unreliable evidence to suggest a clinically significant benefit from the use of G. biloba in the treatment of dementia or cognitive impairment. The Cochrane's meta-analysis analysed 36

randomised, double-blind studies up until September 2007. Out the four most recent trials (McCarney et al, 2008; Napryeyenko and Borzenko, 2007; Schneider, 2008; Van Dongen et al, 2003), three of these reported no significant difference in cognitive function between G. biloba and placebo. All four of these studies contained large samples in excess of 150 dementia patients (McCarney et al. n = 176, van Dongen et al. n = 214, Napryeyenko et al. n = 395, Schneider et al. n = 513). The Napryeyenko (2007) study from the Ukraine reported a large treatment effect, but this was restricted to patients with neuropsychiatric features of dementia. A study by Mazza and colleagues (2006) also reported a positive treatment effect of G. biloba over placebo, but used a smaller sample size (n=76).

Since the completion of the Cochrane review, the results of a large-scale community-based longitudinal study by DeKosky and colleagues (2008) have been published. The Ginkgo Evaluation of Memory Study (DeKosky et al, 2006; DeKosky et al, 2008; Fitzpatrick et al, 2006) was the first study of its kind to investigate the effect of G. biloba on dementia incidence over an eight-year period. The study was conducted at five academic centres between 2000 and 2008 as part of the National Institutes of Health's complementary medicine initiative. The study compared a 240 mg daily dose of EGb 761 to placebo in 3,069 elderly participants (2,587 with normal cognition and 482 with amnesic MCI) with incident dementia and Alzheimer's disease as the primary outcome measure. Participants were assessed every six months over the course of the study, with a median follow-up of 6.1 years. The study found that 523 individuals developed dementia, with a numerically larger number from the ginkgo group developing dementia (246 receiving placebo and 277 receiving G. biloba), although this difference was not statistically significant. Further, G. biloba was also found to have no effect on the rate of progression to dementia in participants with MCI. From the findings of this study, the authors concluded that there was no evidence to suggest that G. biloba was effective in reducing the overall incidence rate of dementia in elderly individuals with either normal cognition or those with MCI.

These findings were corroborated by a smaller scale feasibility study investigating the efficacy of G. biloba in the primary prevention of dementia by Dodge and

colleagues (2008). In this study, 118 elderly adults of mean age 87 years were administered a 240 mg daily dose of G. biloba extract or placebo and assessed every six months for an average follow-up of 3.15 years. Three primary outcome measures were examined: progression to MCI defined as an increase from 0 to 0.5 on the Clinical Dementia Rating Scale (CDR), decline in memory function using a Word List Delayed Recall Test, and adverse events. In the primary analysis, no reduced risk of progression to MCI and no less of a decline in memory function were observed amongst the G. biloba group. However, in a secondary analysis controlling for medication adherence levels, the ginkgo group was found to have a lower risk of progression to MCI and a smaller decline in memory scores. In regards to adverse events, more ischemic strokes and TIA were observed in the G. biloba group.

Summary of findings

In summary:

- Despite intense research focus on the cognitive effects of G. biloba, current evidence for the efficacy of G. biloba in the treatment and prevention of MCI and dementia is not strong.

Huperzine A

What it is

Huperzine A is an alkaloid originally derived from the Chinese herb Qian Ceng Ta, which acts as a potent selective Acetylcholinesterase (AChE) inhibitor (Frank and Gupta, 2005). Pharmacokinetic research suggests that huperzine A has better penetration of the blood-brain barrier, higher oral bio-availability, and longer duration of AChE inhibitory activity compared with tacrine, donepezil and rivastigmine (Bai et al, 2000). The several benefits that have been associated with huperzine A include a reduction in ROS formation and caspase-3 activity, as well as favourable changes in apoptosis-related proteins and a protection of neuronal and glial cells against the cytotoxicity of beta-amyloid and free radical-induced cell toxicity, and a reduction in glutamate-induced cell death through NMDA receptor antagonism (Frank and Gupta, 2005).

Studies

There have been a number of randomised controlled clinical trials conducted using huperzine A. However, to date, no results have been published outside of China, where huperzine A has been approved for the treatment of Alzheimer's disease since 1994 (Wang et al, 2009).

Recently, Li and colleagues (2008) conducted a Cochrane's review of huperzine A in the treatment of Alzheimer's disease amongst elderly participants. Six Chinese randomised controlled trials with a total of 454 patients were included in the review (Dong et al, 2002; Liu et al, 1995; Xu et al, 1997; Yang et al, 2003; Zhang, et al, 2002; Zhou et al, 2004). Eleven trials were excluded for a variety of reasons, including not diagnosing Alzheimer's disease according to ICD, DCM of NINCDS/ADRDA criteria, non-Alzheimer's disease dementia and inappropriate comparisons between groups. It was found that huperzine A administered at a dosage of between 0.2 – 0.4 mg per day significantly improves global cognitive function as measured by MMSE and ADAS-Cog, global clinical assessment measured by CDR and CIBIC-plus, behavioural disturbance measured by ADA-non-Cog and functional performance measured by ADL.

However, the results should be interpreted with caution due to the sample sizes being no greater than 200 participants in any of the trials, and the longest course of therapy included as 36 weeks. Adverse effects were also found to be mild, but it is hard to draw conclusions from small sample sizes and short-term follow-up periods. Li and colleagues (Li J et al, 2008) also draw attention to the low methodological quality of the trials with regards to method of randomisation, allocation concealment and blinding. It is also of concern that no published findings in regards to huperzine A have been published outside of China, with Vickers and colleagues (1998) drawing attention to the fact that an unusually high proportion of positive results appear to be published in China in relation to other countries.

Since the Cochrane review, Wang and colleagues (2009) conducted an updated meta-analysis of huperzine A in the treatment of Alzheimer's disease. Four Chinese randomised controlled trials with a total of 474 patients were included in the study (Xu et al, 1995; Yang et al, 2003; Zhang ML et al, 2006; Zhang et al, 2002). However, two of these trials (Yang et al, 2003; Zhang et al, 2002) were already included

in the Cochrane's review, so it is difficult to see how this meta-analysis added much to current understanding of huperzine A efficacy. Nevertheless, the authors reported that administration of huperzine A (300–500 micrograms per day) over an 8–24 week period led to significant improvements in MMSE as well as ADL. The analysis also suggested that huperzine A was well tolerated and that no serious adverse events occurred.

While the results from Chinese trials of huperzine A are promising, it is important that these findings are confirmed in larger randomised controlled trials conducted in other countries. An open-label trial of huperzine A for the treatment of Alzheimer's disease was conducted in the US by Mazurek (2000). It was reported that the addition of 100 micrograms of huperzine A to existing treatment regimens such as donepezil and tacrine could improve scores on the MMSE by 1.5 points at one month, 1.75 points at two months and 2.2 points at three months.

A phase II multi-centre double-blind placebo controlled trial was completed in the US in November 2007. In the trial, 210 patients with mild to moderate Alzheimer's disease were administered 200–400 micrograms of huperzine A BID for 16 weeks, with about half the participants also receiving memantine (Aisen, 2009). Significant cognitive enhancement, as measured by the ADAS-cog, was observed after 16 weeks of treatment with the 400 microgram BID dose of huperzine A, but not with the 200 microgram BID dose (Sabbagh, 2009). Huperzine A was found to be better tolerated than conventional ChEIs.

Summary of findings

In summary:

- While the results from Chinese trials of huperzine A are promising, it is important that these findings are confirmed in larger randomised controlled trials conducted in other countries.

Alpha-lipoic acid (LA)

What it is

Alpha-lipoic acid (thioctic acid) is a coenzyme involved in mitochondrial metabolism. Once it has crossed the blood brain barrier it is reduced to dihydrolipoic acid which is a powerful mitochondrial antioxidant reacting with oxidants such as superoxide radicals, hydroxyl radicals, hypochlorous acid, peroxy radicals and singlet oxygen (Liu J et al, 2008).

Studies

There is evidence to suggest multiple mechanisms of action with this compound including increased ACh production by activation of choline acetyltransferase, increased glucose uptake, chelation of redox-active transition metals, scavenging of ROS reducing inflammatory cytokine levels, scavenging of lipid peroxidation products and induction of enzymes required for glutathione synthesis (Mazurek et al, 2008). Animal research using Alpha-lipoic acid has been promising, with studies of aged rats claiming a partial reversal of memory loss (McGahon et al, 1999) as well as an improvement in long-term memory in aged mice (Stoll et al, 1993) attributed to an improvement in NMDA receptor density due to protection from oxidative damage. There is also evidence from animal research to suggest that Alpha-lipoic acid restores endogenous antioxidants in mitochondria (Arivazhagan et al, 2001) and restores the activity of Acetylcholinesterase (Arivazhagan et al, 2006).

The use of Alpha-lipoic acid as a treatment for dementia was discovered serendipitously in 1997 due to a case study featuring an elderly patient with mild Alzheimer's disease concurrently receiving Alpha-lipoic acid for treatment of diabetic polyneuropathy. (Alpha-lipoic acid has been used as a treatment for diabetic polyneuropathy in Germany for over 30 years.) The patient received 600 mg Alpha-lipoic acid on a daily basis in conjunction with a standard course of ChEI for Alzheimer's disease. Over the following years, neuropsychological tests revealed an unusually slow progress of cognitive impairment, and the diagnosis of mild Alzheimer's disease was reassessed several times (Mazurek et al, 2008). On the basis of this case study, the first open pilot study of Alpha-lipoic acid in the treatment of dementia was conducted in 2001. Hager and colleagues (2001) administered 600 mg Alpha-lipoic acid daily to nine elderly patients with probable Alzheimer's disease

in conjunction with their standard ChEI treatment over a period of 337+/- 80 days. Treatment with Alpha-lipoic acid was found to stabilize previously declining scores in cognitive function, as measured by MMSE and ADAS-Cog for approaching 12 months.

A follow-up study was conducted by Hager and colleagues (2007), in which the analysis was extended to 43 patients receiving the same 600 mg daily dose of Alpha-lipoic acid over a 48-month period. In patients with mild dementia, the disease was found to progress extremely slowly, while for patients with moderate dementia it progressed at around twice the rate. The authors reported that the rate of cognitive decline was dramatically lower than that reported for untreated patients or patients on standard ChEI treatments in the second year of long-term studies. While these preliminary findings are promising it is important to note that this trial was not randomised or double-blinded and patients were only diagnosed with probable Alzheimer's disease, and for these reasons a larger scale phase II randomised controlled trial is needed to gain stronger evidence of efficacy of Alpha-lipoic acid in the treatment of Alzheimer's disease.

These sentiments were echoed by the Cochrane review (Klugman et al, 2004), in which no current randomised double-blind trials were discovered. Two recently completed clinical trials that have combined Alpha-lipoic acid with other interventions are yet to be published. Shinto (2004) has presented an abstract from a randomised controlled trial using omega-3 fatty acid in conjunction with lipoic acid for 39 participants with probable Alzheimer's disease, with findings suggesting advantages over placebo in MMSE and activities of daily living. Galasko (2005) conducted an randomised controlled trial using vitamins C and E in conjunction with Alpha-lipoic acid in a sample of 75 participants with probable Alzheimer's disease, but the findings are yet to be released. At present no other ongoing trials for Alpha-lipoic acid have been found.

Summary of findings

In summary:

- There have been some promising results, but a larger scale phase II randomised controlled trial is needed to gain stronger evidence of efficacy of Alpha-lipoic acid in the treatment of Alzheimer's disease.

Acetyl-L-carnitine (ALCAR)

What it is

Acetyl-L-carnitine (ALCAR) is an endogenous mitochondrial membrane compound involved in the maintenance of mitochondrial function and the production of acetylcholine in cholinergic neurons. ALCAR facilitates the transport of long-chain fatty acids from the cytoplasm to the mitochondria, where they can be used as substrates for the oxidative phosphorylation process that produces ATP (Pettegrew et al, 2000). ALCAR also helps protect mitochondria from oxidative damage and boosts the production of ATP (Beal et al, 2003; Mazzio et al, 2003). It has been found that ALCAR has a beneficial effect in Alzheimer's disease by reducing Amyloid β formation, via the stimulation of α -secretase activity and cleaving APP to block Amyloid β from forming (Epis et al, 2008). It has also been found that ALCAR up-regulates levels of the endogenous antioxidant glutathione as well as heat shock proteins that have a neuroprotective effect against A β toxicity (Abdul et al, 2006).

Studies

In an early study by Pettegrew and colleagues (1995), ALCAR was administered to seven probable Alzheimer's disease patients, while a placebo was administered to five probable Alzheimer's disease patients and 21 healthy age-matched controls over a 12-month period. Magnetic resonance spectroscopy (MRS) scans were taken at baseline and at follow-up, together with MMSE and ADAS cognitive behaviour tests. The MRS showed that brain measures of membrane phospholipid and high-energy phosphate metabolism were normalised at follow-up compared to baseline in the ALCAR group in comparison to the placebo group. This corresponded with significantly less deterioration in MMSE and ADAS scores in the ALCAR group in comparison to the placebo group.

In a meta-analysis of the efficacy of ALCAR in the treatment of MCI and mild Alzheimer's disease using randomised controlled trials of 3–12 months in duration and 1.5–3.0 g per day ALCAR dose, Montgomery and colleagues (2003) concluded that ALCAR had a clear benefit over placebo in slowing the rate of cognitive decline from three months onwards. However, a more recent Cochrane's review (Hudson and Tabet, 2003) of 16 studies

ranging from three to 12 months using 30–431 participants given 1–3 g ALCAR for the treatment of Alzheimer’s disease concluded that there was no evidence to recommend its routine use in clinical practice. Interestingly, a statistically significant treatment effect for MMSE was observed at 24 weeks, but was not present at 24 or 52 weeks. Similarly, clinical global impression of change was found to be significantly higher for the ALCAR treatment in comparison to placebo at 12 and 24 weeks when treated as a dichotomous variable.

While the authors attribute these findings to statistical chance, it appears that ALCAR may require further investigation. Hudson and Tabet (2003) also draw attention to the fact that there is limited pharmacokinetic data available regarding ALCAR metabolism in humans. For this reason, there may exist large inter-individual variability in ALCAR plasma levels across patients in these studies. It is foreseeable that more consistent results may appear if the dose selection were determined using pharmacokinetic analysis. Since the time of the Cochrane’s review, no further randomised controlled trials have appeared in the literature, but a clinical trial has been completed amongst MCI patients as part of the Memory XL study, where ALCAR is administered together with a range of other vitamins. The authors have reported that “benefits of study did not appear to outweigh subject inconvenience, so study was stopped prematurely.”

Summary of findings

In summary:

- There have been some promising findings, but large-scale trials are necessary. The latest such trial recruited only 10 participants (eight active, two placebo) and found no benefit for the active arm.

Co-enzyme Q10 (ubiquinone)

What it is

Co-enzyme Q10 (CoQ10) is a lipid soluble antioxidant. CoQ10 has been found to:

- Up-regulate mitochondrial function and facilitate the synthesis of ATP. CoQ10 plays a crucial role in oxidative phosphorylation, passing electrons from

complexes I and II to complex III, while also providing antioxidant protection for the inner membrane of the mitochondria (Alberts, et al, 2002). A deficiency in CoQ10 is associated with an increase in the production of reactive oxygen species (ROS) as well as a reduction in ATP synthesis (Quinzii et al, 2008).

- Be implicated in the production of α -tocopherol (vitamin E), with α -tocopherol acting as a direct scavenger of radicals to form tocopheroxyl radical, and the reduced form of ubiquinone, ubiquinol, reacting with tocopheroxyl radical to convert it back into α -tocopherol (McDonald et al, 2005). CoQ10 exerts neuroprotective effects by activating mitochondrial uncoupling proteins, which reduces mitochondrial free radical generation (Chaturvedi and Beal, 2008).
- Have a wide-reaching effect on the pattern of gene expression, affecting the expression of hundreds of human genes involved in cell signalling, metabolism and nutrient transport (Groneberg et al, 2005). With particular relevance to neurodegenerative diseases, CoQ10 has been found to exert anti-inflammatory properties via modulation of gene expression controlling tumor necrosis factor alpha (TNF- α) secretion (Schmelzer et al, 2008).

Studies

Despite the popularity of CoQ10 as a dietary supplement, relatively few studies have been conducted to assess its efficacy in enhancing mitochondrial function in non-clinical populations. In regards to age-related changes in CoQ10 levels in humans, a common trend is yet to emerge from the literature (Sohal and Forster, 2007). There is a widespread assumption that CoQ10 levels decline over the course of the lifespan (Ernster and Dallner, 1995), but there is little evidence to support this view. Analysis of differences in blood plasma levels of both ubiquinone and ubiquinol in young compared to older adults has revealed that these levels are largely unchanged (Miles et al, 2003; Miles et al, 2004). However, there is evidence to suggest that the redox status of CoQ10 (%CoQ10), essentially the ratio of oxidised CoQ10 (ubiquinone) to reduced CoQ10 (ubiquinol), is greater in older people. This is presumably due to the increased oxidation of ubiquinol back to ubiquinone associated with enhanced oxidative stress in the

elderly. For this reason it has been proposed as a potential biomarker of aging (Wada et al, 2007).

The evidence for differences in tissue homogenates is also non-conclusive. An oft-cited earlier study by Kalen and colleagues (1989) reported that CoQ10 in human tissue homogenates from various organs was lower in older compared to younger people. However, a study by Beyer and colleagues (1985) reported no age-related changes in CoQ10 levels in homogenates of rat brain and lungs and decreases for heart, kidney and skeletal muscles. Sohal and colleagues (2006) reported no age-related losses in CoQ10 content in tissue homogenates of mouse liver, heart, kidney, skeletal muscle or brain. A review by Sohal and Forster (2007) concluded that age-associated changes in CoQ10 content were most evident in mitochondria rather than tissue homogenates (Kamzalov and Sohal, 2004; Lass et al, 1999), which is in line with current understanding that there is a preferential cellular uptake of CoQ10 into the mitochondria (Saito et al, 2009). However, there is insufficient evidence to suggest that this pattern occurs throughout the body, as so far age-related declines in mitochondrial CoQ10 levels have only been observed in certain tissues.

Sohal and colleagues (2007) reviewed the results of a series of studies investigating CoQ10 supplementation in healthy mammals. They demonstrated that CoQ10 administration via food to young adult mice or rats resulted in augmentation of CoQ10 levels in plasma as well as in homogenates and mitochondria of liver, heart and skeletal muscle. An increase was also observed in mitochondria of the brain, but of a lesser magnitude. Greater increases in CoQ10 were observed in mitochondria in comparison to homogenate across all tissues. It was also found that the longer the period of CoQ10 administration, the greater the augmentation of CoQ10 levels in the body. However, despite the resulting increase in CoQ10 levels due to dietary supplementation, no evidence has been found to suggest that supplementation affects levels of oxidative stress and mitochondrial respiratory function in healthy mammals. Sohal and colleagues (2006) found that long-term CoQ10 intake lasting 2.5 to 25 months in mice had no effect on mitochondrial respiratory capacity, levels of oxidative stress or long-term survival. It was concluded that while CoQ10 acts as an antioxidant *in vitro*, it has no

discernable *in vivo* effects on levels of oxidative stress or mitochondrial respiratory functions.

A lesser known function of CoQ10 is its role as a lipid-soluble carrier of electrons across the cellular membrane. External quinine oxidases, known as ENOX proteins, can generate superoxide at the cell surface. The superoxide can then form H₂O₂ and other reactive oxygen species (ROS) that spread to adjacent cells and tissues, resulting in oxidative damage. Before the age of 30 years arNOX proteins are barely detectable, and then steadily increase with age until 60–70 years. CoQ10 has been found to inhibit the formation of arNOX by binding to a site that is unique to arNOX (Morre and Morre, 2003; Morre and Morre, 2006). A study by Morre and colleagues (2008) investigated the effect of CoQ10 supplementation on the activity of the NADH oxidase (arNOX) protein in 25 healthy female participants between the ages of 45–65 years. Participants took 60 mg of CoQ10 three times per day. It was found that arNOX activity was reduced by between 25–30% overall, and approaching 40% for ages 51–65 years compared to all participants.

Despite the lack of evidence to suggest that CoQ10 is an effective supplement for healthy adults, there is a growing body of evidence in support of its efficacy as a neuroprotective treatment in certain pathological conditions. There is evidence to suggest that CoQ10 has a neuroprotective effect on cholinergic neurons, with enhanced performance with CoQ10 supplementation observed in rats completing the Morris water maze that sustained oxidative damage to the hippocampus and cerebral cortex (Ishrat et al, 2006). There is also evidence to suggest that CoQ10 provides protection against loss of dopamine in Parkinson's disease. The MPTP neurotoxin has been used as a model of Parkinson's disease because it produces neuropathologic changes in human and non-human primates analogous to those observed in Parkinson's disease (Beal, 2001). Cleren and colleagues (2008) found that both CoQ10 and its reduced form, ubiquinol, were effective in providing neuroprotection against MPTP induced loss of DA in mice. When MPTP was administered chronically for one month, CoQ10 was also found to be neuroprotective against DA depletion. Similar findings have been reported in regards to the neuroprotective effect of CoQ10 against striatal lesions in

rats produced by aminoxyacetic acid and the mitochondrial toxin malonate and 3-NP (Chaturvedi and Beal, 2008).

Evidence for the potential of CoQ10 in the treatment of Alzheimer's disease has been provided by transgenic mice models of Alzheimer's disease. Li and colleagues (2008) administered CoQ10 to double transgenic amyloid precursor protein (APP)/presenilin 1 (PS1) mice, as well as single transgenic APP and PS1 mice for 60 days. MRI scans revealed that significantly less atrophy in hemisphere and hippocampi occurred in those treated with CoQ10 in comparison to placebo. The neuroprotective effect was greater in the APP/PS1 mice compared to the APP and PS1 mice. Recent research has also found decreased A β 42 levels, decreased β -amyloid plaque area and number, as well as improvements to cognitive performance following CoQ10 treatment in the Tg19959 transgenic mouse model of Alzheimer's disease (Chaturvedi and Beal, 2008). Research by Ono and colleagues (2003) has provided findings suggesting that CoQ10 exerts its anti-amyloidogenic effect by destabilizing preformed β -amyloid fibrils in vitro.

Despite the intensive research focus that CoQ10 has received using animals, there have been relatively few randomised controlled trials conducted in clinical patients. Of the trials that have been conducted, the majority have been in relation to Parkinson's disease. In a Phase II clinical trial in 20 early Parkinson's disease patients, Shults and colleagues (2002) administered 300, 600 and 1200 mg per day of CoQ10 together with vitamin E at 2,000 International units (IU) per day over a 16-month period. A significant dose-dependent UPDRS score reduction was observed in patients administered CoQ10 in comparison to placebo. A subsequent dose escalation study up to 3,600 mg per day revealed that plasma CoQ10 levels reach a plateau at 2,400 mg per day (Shults et al, 2004). No randomised controlled trials of CoQ10 in Alzheimer's disease have been conducted, although a few randomised controlled trials have been conducted in Alzheimer's disease patients using the synthetic, shorter chained CoQ derivative Idebenone. A double-blind, placebo-controlled multi-centre study of 300 Alzheimer's disease patients receiving Idebenone revealed a significant improvement in ADAS score after six months, as part of a two-year study (Weyer et al, 1997). Two subsequent trials reported similar improvements with Idebenone treatment slowing the progression of cognitive

deficits in Alzheimer's disease patients (Gutzmann and Hadler, 1998; Gutzmann et al, 2002). To date, no clinical trials examining the cognitive effects of CoQ10 in healthy adult populations have been conducted, and as such the role of CoQ10 in the prevention of dementia is unclear.

Summary of findings

In summary:

- Despite the lack of evidence to suggest that CoQ10 is an effective supplement for healthy adults, there is a growing body of evidence in support of its efficacy as a neuroprotective treatment in certain pathological conditions. However, there have been no clinical trials examining the cognitive effects of CoQ10 in healthy adult populations, and as such the role of CoQ10 in the prevention of dementia is unclear.
- There is evidence for the potential of CoQ10 in the treatment of Alzheimer's disease provided by transgenic mice models of Alzheimer's disease.
- Despite the intensive research focus that CoQ10 has received using animals, there have been relatively few randomised controlled trials conducted involving clinical patients

Vitamin B12 (cobalamin)

What it is

The following is quoted from the University of Maryland Medical Center website (<http://www.umm.edu/altmed/articles/vitamin-b12-000332.htm>).

Vitamin B12, also called cobalamin, is one of eight B vitamins. All B vitamins help the body convert food (carbohydrates) into fuel (glucose), which is 'burned' to produce energy. These B vitamins, often referred to as B complex vitamins, also help the body metabolize fats and protein. B complex vitamins are necessary for healthy skin, hair, eyes, and liver. They also help the nervous system function properly.

All B vitamins are water-soluble, meaning that the body does not store them.

Vitamin B12 is an especially important vitamin for maintaining healthy nerve cells, and aids in the production

of DNA and RNA, the body's genetic material. Vitamin B12 also works closely with vitamin B9 (folate) to regulate the formation of red blood cells and to help iron function better in the body. Folate and B12 work together to produce S-adenosylmethionine (S-AdoMet), a compound involved in immune function and mood.

Vitamins B12, B6, and B9 work together to control blood levels of the amino acid homocysteine. High levels of homocysteine are associated with heart disease. However, researchers are not sure whether homocysteine is a cause of heart disease or merely a marker that indicates someone may have heart disease.

Mild deficiencies of B12 are not uncommon in elderly people, either because of poor diet or because they have less stomach acid, which the body needs to absorb B12. Low levels of B12 can cause a range of symptoms including fatigue, shortness of breath, diarrhoea, nervousness, numbness, or tingling sensation in the fingers and toes. Severe deficiency of B12 causes neurological damage.

Vitamin B12 is used in relation to a number of diseases, including pernicious anaemia, heart disease, fatigue, breast cancer, and cognitive impairment.

Vitamin B12 is found only in animal foods, such as fish, shellfish, dairy products, organ meats (particularly liver and kidney), eggs, beef, and pork. It can also be found in multivitamins, B complex vitamins, and individual supplements. It is available in both oral (tablets and capsules) and intranasal forms, soft gels, and lozenges. Vitamin B12 is also sold under the names cobalamin and cyanocobalamin.

Studies

Epidemiological research has linked vitamin B12 deficiency to a greater risk of developing Alzheimer's disease. A study by Wang and colleagues (2001) reported that out of 370 elderly people monitored over a three-year period, B12 and folate deficiency was associated with double the risk of developing Alzheimer's disease. Research by Nilsson and colleagues (1996) reported decreased serum B12 levels in 69% of demented and non-demented psychogeriatric patients. In another study this group reported significant improvement to MMSE scores in a mild-to-moderate dementia group following two-month treatment with B12 as well as folate (Nilsson et al, 2001).

There is strong evidence to suggest that B12 deficiency brings about cognitive decline due to an excess build up of the amino acid homocysteine (HCy). Vitamin B12, together with folate, are cofactors for enzymes that recycle HCy back to Methionine, and when they are not present in adequate amounts the Methionine-Homocysteine cycle is disrupted, which has a significant impact on cognitive function (Miller, 2003). Homocysteine, an amino acid produced by metabolism of methionine, has been found to be a biomarker in its own right for elevated risk of developing Alzheimer's disease. Homocysteine is normally metabolized in one of two ways – it is either converted back to methionine by re-methylation, or converted to taurine and cysteine through trans-sulfuration. Abnormally high levels of HCy signal a breakdown in these biochemical processes. If not enough HCy is converted back to methionine this has important implications for brain function.

The methionine cycle involves the conversion of methionine to S-adenosylmethionine (S-AdoMet), which is the most important methyl donor in the human body, required for methylation of a host of substances including DNA and proteins such as myelin. After donating its methyl group, S-AdoMet becomes S-adenosylhomocysteine (SAH) and then homocysteine after losing its adenosine. If HCy is not metabolized properly there will be insufficient S-AdoMet available, and this will result in inhibition of methylation (Miller, 2003). The gene for the amyloid precursor protein (APP) is heavily methylated. Decreased methylation may lead to promotion of gene mutations involved in increased expression of APP and extracellular deposition of the A peptide (Rogaev et al, 1994; West et al, 1995). Further, HCy and SAH when they accumulate in the body have been found to cause oxidative stress, excitotoxicity in neurons, as well as DNA strand breakage and mitochondrial membrane damage (Kruman et al, 2000). There is also evidence to suggest that excess HCy makes neurons more sensitive to amyloid-beta toxicity (Ho et al, 2001).

Plasma total levels of HCy have been found to increase with age, reaching a plateau around the age of 60 years (Elias et al, 2005). In a study of homocysteine levels in histologically confirmed Alzheimer's disease patients by Clarke and Colleagues (1998), it was determined that people in the top third of HCy levels had a 4.5 times greater risk of Alzheimer's disease compared to those in the bottom third. The Framingham Study (Elias et

al, 2005), which followed 1,092 people for eight years, found high HCy levels to be associated with double the risk for Alzheimer's disease. A more recent 4.5-year longitudinal study by Haan and colleagues (2007) of 1,779 Mexican Americans over the age of 60 reported 2.39 times the risk of dementia or cognitive impairment associated with high HCy levels at baseline. High levels of HCy are concomitantly observed with low levels of the recycling cofactors B12 and folate. In a study by Joosten and colleagues (1997) comparing 52 Alzheimer's disease patients to 49 elderly people living at home and 50 hospitalised non-demented controls, the Alzheimer's disease group was found to have the highest levels of HCy and the lowest levels of B12. The evidence to date is that B12 is an important vitamin for maintaining proper metabolism of HCy, without which the brain becomes more susceptible to oxidative damage and apoptosis.

Summary of findings

In summary:

- There is strong evidence to suggest that vitamin B12 deficiency brings about cognitive decline. Epidemiological research has linked B12 deficiency to a greater risk of developing Alzheimer's disease.
- The evidence to date is that vitamin B12 is an important vitamin for maintaining proper metabolism of homocysteine (HCy), without which the brain becomes more susceptible to oxidative damage and apoptosis.

Bacopa monnieri

What it is

Bacopa monnieri (B. monnieri) is a herb that has been used for centuries in Ayurvedic medicine as a memory enhancer, sedative, analgesic, anti-inflammatory and anti-epileptic treatment (Jain, 1994; Stough et al, 2001). Saponins (bacosides, bacopasides or bacopasaponins) are the active ingredients that have been attributed for the memory-enhancing effects. Suggested mechanisms of action include cholinergic up-regulation, γ -aminobutyric acid-ergic modulation, antioxidant effects, brain protein synthesis, serotonin agonism, modulation of brain stress hormones, and reduction of β -amyloid (Calabrese et al, 2008).

Studies

A study by Stough and colleagues (2001) investigated the effects, after five weeks and 12 weeks, of 300 mg of B. monnieri on 46 healthy volunteers aged 18–60, who were given a battery of cognitive tests. It was found that B. monnieri significantly improved performance on the Rey Auditory Verbal Learning Test as well as state anxiety at 12 weeks. Other 12-week clinical trials of B. monnieri in elderly adults have reported similar improvements in a number of measures including the retention of new information in delayed recall of word pairs (Roodenrys et al, 2002), improvements in subsets of the Wechsler Memory Scale (Raghav et al, 2006), and improvements on the Stroop test assessing the ability to ignore irrelevant information (Calabrese et al, 2008).

A recent study by Hota and colleagues (2009) investigated the effects of B. monnieri on ameliorating the effects of hypobaric atoxia (reduced delivery of oxygen to brain tissue at altitude) on spatial memory function. It was found that B. monnieri:

- Enhanced learning ability, increased memory retrieval and prevented dentritic atrophy following hypoxic exposure in Sprague Dawley rats. It was also found to decrease oxidative stress, plasma corticosterone levels and neuronal degeneration due to the exposure.
- Increased cytochrome c oxidase activity as well as ATP levels.

Further evidence was also provided for the role of glutamatergic transmission in the memory-enhancing effects of B. monnieri, suggesting that it has an ability to modulate positive synaptic plasticity through augmentation of glutamatergic transmission, and to ameliorate cell death associated with glutamate-mediated excitotoxicity.

Summary of findings

In summary:

- There is evidence that B. monnieri improves cognitive ability. In trials, B. monnieri significantly improved performance on the Rey Auditory Verbal Learning Test as well as state anxiety; and improved the retention of new information.

Salvia officinalis

What it is

Salvia officinalis (*S. officinalis*) is part of the *Salvia* genus in the Labiatae family, containing over 700 species of plants. It has been used over several millennia across a number of different cultures – including in Ayurvedic medicine, and by early Greek and Chinese civilizations – as a treatment for the amelioration of age-related memory loss. The proposed mechanisms of action for *S. officinalis* include acetylcholinesterase inhibition (ChEI), butyrylcholinesterase inhibition (BuChe), antioxidant, anti-inflammatory and oestrogenic effects (Kennedy and Scholey, 2006; Perry et al, 1999).

Studies

To date, two randomised controlled trials have been conducted to assess the acute memory-enhancing effects of *S. officinalis*. Kennedy and colleagues (2006) examined the acute effects of *S. officinalis* on cognition in 30 healthy participants, who completed a test battery at baseline as well as one hour and four hours post-dose on three separate testing occasions. On each occasion they received a different treatment – either placebo, or 300 or 600 mg of dried sage leaf. It was found that the 600 mg dose was associated with improved performance on:

- The Stroop test (a psychological test of our mental (attentional) vitality and flexibility).
- An aggregate score obtained from a battery of tests including tasks of mathematical processing and memory search tasks at both post-dose time points.
- More recently, Scholey and colleagues (2008) examined the acute effects of *S. officinalis* on memory using 20 elderly volunteers (over 65). They were administered 167, 333, 666 and 1,332 mg of dried sage and tested post-dose at one, 2.5, four and six hours. Significant improvements in secondary memory performance (aggregate percentage accuracy in word recognition, picture recognition, immediate word recall and delayed word call from the Cognitive Drug Research battery) were noted for the 333 mg dose in comparison to placebo at all post-dose time points. The extracts used in the study were subjected to *in vitro* analysis, confirming

cholinesterase-inhibiting properties in comparison to an ethanol control sample.

These findings have been corroborated by investigations into the acute effects of *Salvia Lavandulaefolia* essential oil, another ChEI of the sage family containing similar components to *S. officinalis*:

- A study by Tildesley and colleagues (2003) reported a significant improvement in immediate and delayed word recall post-dose using a 50 microlitre (µl) dose of the oil in 20 young healthy volunteers.
- A second study by Tildesley and colleagues (2005) using the CDR battery reported an improvement in secondary memory performance at one hour post-dose and Speed of Memory at 2.5 hours post-dose using 25 µl of *S. Lavandulaefolia*. Improvements in Speed of Memory at four and six hours post-dose were also reported with the higher dose of 50 µl.

In regards to studies of the chronic effects of *S. officinalis* amongst the clinical population, a study by Akhondzadeh and colleagues (2003) examined the effects of *S. officinalis* on memory in 39 Alzheimer's disease patients. Significantly improved scores on the ADAS-cog were reported for those in the *S. officinalis* group in comparison to placebo at 16 weeks. However, this study was not without criticism, with reviewers drawing attention to the unexpectedly large effect size, an ill-defined herb extract and no description of the placebo (Kennedy and Scholey, 2006). However, an open-label trial using the *S. lavandulaefolia* essential oil from the sage family by Perry and colleagues (2003) also reported a significant improvement in the accuracy of performing a vigilance task at the six-week end point amongst 11 Alzheimer's disease patients.

To date, the findings from the relatively few studies that have been conducted using *S. officinalis* and *S. lavandulaefolia* are promising. To properly establish the efficacy of these complementary medicines in the treatment of dementia, further randomised controlled trials, as well as longitudinal studies, are warranted. These should use larger samples from both the non-clinical aged population as well as patients with mild cognitive impairment and Alzheimer's disease.

Summary of findings

In summary:

- To date, the findings from the relatively few studies that have been conducted using *S. officinalis* and *S. lavandulaefolia* are promising
- Further randomised controlled trials, as well as longitudinal studies are warranted using larger samples from the non-clinical aged population, and patients with mild cognitive impairment and Alzheimer's disease.

Curcumin

What it is

Curcumin is found in rhizomes of tropical ginger and turmeric and is the spice that gives yellow curry its vibrant colour (Frank and Gupta, 2005). For several hundred years Curcumin has been used in Ayurvedic medicine to treat inflammation and pain (Mishra and Palanivelu, 2008). More recently there has been renewed interest in its use as a treatment for cognitive decline and dementia.

Studies

Epidemiological studies have shown increased consumption of curry by Asians is associated with better performance on the Mini-Mental State Examination later in life. Further, the prevalence of Alzheimer's disease among adults aged 70–79 in India is 4.4 times less than that of adults aged 70–79 years in the United States (Ganguli et al, 2000; Ng et al, 2006).

There are a number of proposed mechanisms by which curcumin can be used to ameliorate the effects of dementia:

- Curcumin has been found to help the macrophages clear amyloid plaques from the brain, with a direct effect on beta-amyloid (Zhang ML et al, 2006).
- Curcumin has been found to have an anti-proliferative action on microglia, which decreases the activity of cytokines and other reactive substances that exacerbate amyloid plaque formation (Ambegaokar et al, 2003).
- Curcumin has been found to exert a powerful anti-inflammatory effect through inhibition of pro-inflammatory cytokine production (Mishra and Palanivelu, 2008).

As an antioxidant, curcumin has been found to be effective in the reduction of lipid peroxidation, increasing the activity of superoxide dismutase, sodium-potassium ATPase, and protecting brain mitochondria from peroxynitrite (Bala et al, 2006; Mythri et al, 2007). There is also evidence to suggest that curcumin has a direct effect on beta-amyloid plaques. Being lipophilic it crosses the blood brain barrier and binds to plaques and disrupts their self-assembly (Mishra and Palanivelu, 2008). One study found that beta-amyloid levels were decreased by around 40% in Alzheimer's disease mice given curcumin (Yang et al, 2005).

Finally, there is also evidence to suggest that curcumin has a powerful effect as a metal chelator. Certain metals, such as iron, copper and zinc, have been found to accumulate in the brains of Alzheimer's disease sufferers, increasing the process of beta-amyloid aggregation and reactive oxygen species formation. By acting as a chelator and binding with these metals, curcumin can reduce inflammation and oxidative damage (Mishra and Palanivelu, 2008).

Despite the strong experimental and epidemiological evidence suggesting that curcumin may be an effective treatment for dementia, no randomised controlled trials in humans were discovered in the western literature at the time of this review.

Summary of findings

In summary:

- There is strong experimental and epidemiological evidence suggesting that curcumin may be an effective treatment for dementia. However, no randomised controlled trials in humans were discovered in the western literature.

Resveratrol

What it is

Resveratrol is a phytoalexin polyphenolic compound found in about 300 plants including grape skin, peanuts and berries, with higher concentration in red wine. It is a powerful antioxidant contributing to the cardio-protective, anti-inflammatory, and neuroprotective properties of red wine intake (Pervaiz, 2003). The resveratrol content of wine has been used as an explanation for the 'French paradox',

whereby a lower incidence of coronary mortality is observed in France even though the nation's population consumes foods that are high in saturated fats (de Leiris and Boucher, 2008).

Studies

There is also evidence to suggest that wine intake is associated with a lower risk of developing neurodegenerative disease. A number of epidemiological studies have associated red wine intake, but not other alcoholic drinks, with a lower risk of developing Alzheimer's disease (Vingtdeux et al, 2008). A study in the Canadian population determined that wine consumption was the most protective variable against Alzheimer's disease, reducing the risk by 50%, and more protective than the use of nonsteroidal anti-inflammatory drugs (Lindsay et al, 2002).

Resveratrol has received much public attention in recent years, with research linking it to powerful anti-aging effects that could revolutionise medical science and see resveratrol-like substances used to treat a diverse range of conditions such as cancer, stroke, heart disease and diabetes, as well as neurodegenerative diseases such as Alzheimer's disease and Huntington disease (Baur et al, 2006; Sinclair, 2005).

Resveratrol's primary mechanism of action is through the activation of the Sirtuin gene SIRT1, which is believed to mediate the effects of caloric restriction in mammals and regulate a range of processes including glucose and insulin production, fat metabolism, and cell survival (Guarente, 2005). Through examination of the aging process in yeast cells, Sinclair and Guarente (1997) discovered that genomic instability of DNA repeats is a primary cause of aging. It was also identified that the over-expression of the sirtuin (SIR2) gene leads to suppression of genomic instability and a resultant increase in lifespan (Tissenbaum and Guarente, 2001).

Sirtuins mediate the physiological effects of caloric restriction by encoding NAD⁺-dependent deacetylases, which directs the behaviour of target proteins by removing acetyl groups from specific lysines (Sinclair, 2005). Through the screening of over 20,000 molecules, Howitz and colleagues (2003) identified around 25 sirtuin-activating compounds (STACs) that enhanced SIRT1 activity in vitro, increasing the affinity of the SIRT1 enzyme for certain protein targets. Of these 25 molecules, resveratrol was found to be the most potent.

Resveratrol, together with other less potent polyphenolic STACs, is produced by plants in response to stress. The xenohormesis hypothesis (combining the prefix xeno for stranger and hormesis for a protective response induced by mild stress), suggests that plants produce STACs during times of stress in order to activate their SIR2-mediated defences and that other animals have evolved to pick up on these chemical cues in plant-based foods in order to anticipate a deteriorating environment (Baur and Sinclair, 2008). Howitz and Sinclair (2003) demonstrated that through activation of the SIRT1 gene, resveratrol could extend the lifespan of yeast *cerevisiae* by 70%. Similar effects on lifespan extension have also been observed in a variety of other species including the *Caenorhabditis elegans* worm (Tissenbaum and Guarente, 2001), the *Drosophila melanogaster* fruit fly (Rogina and Helfand, 2004) and more recently the *Nothobranchius furzeri* fish, with a median lifespan increase of 59% (Valenzano and Cellerino, 2006; Valenzano et al, 2006).

Baur and colleagues (2006) also demonstrated that resveratrol, when fed to middle-aged mice on a high-calorie diet, effectively counteracted the physiological effects of the high-calorie diet, shifting their physiology towards that of mice on a standard diet and significantly increasing their chance of survival. After 114 weeks, 58% of the high-calorie control animals had died, as compared to 42% of the high-calorie animals receiving resveratrol and 42% of the animals on a standard diet.

On the basis of this research, Sinclair established Sirtris Pharmaceuticals to commercialise the resveratrol-like compounds that activate the SIRT1 gene. In 2008, GlaxoSmithKline acquired Sirtris Pharmaceuticals for US\$720 million, and is currently trialling a range of these compounds, the most recent being SRT2104, which is 1,000 times more potent than resveratrol. A phase IIa trial began in 2009. However subsequent reports suggest that there are no further pipeline studies in the field of cognition.

There is some debate as to whether the resveratrol content that can be consumed through dietary sources such as red wine is sufficient to activate the SIRT1 gene. The bioavailability of resveratrol is low, due to its rapid metabolism within 15 minutes of entering the bloodstream into sulfated and glucuronidated forms (Walle et al, 2004;

Wenzel and Somoza, 2005). In pharmacokinetic studies in humans, less than 5% of the oral dose is observed as free resveratrol in blood plasma (Boocock et al, 2007). In a study that examined bioavailability of resveratrol following red wine consumption with a meal by 10 volunteers, red wine consumption with resveratrol content of 0.8 micrograms per ml was found to result in trace amounts in blood serum of 1.1 – 6.2 nanograms per litre in only four of the 10 participants after 30 minutes. After a longer time interval (one to two hours) the glucuronide metabolites were found to predominate, with large inter-individual differences reported (Vitaglione et al, 2005).

While the finding of only trace amounts of free resveratrol in blood raises doubts about attributing the beneficial effects red wine to this compound, Walle (2004) suggests that it may be the metabolites that are responsible for beneficial effects, while Parker and colleagues (2005) provide evidence to suggest that concentration of as little as 500 nM may be sufficient to have a neuro-protective effect. Further research regarding bioavailability and metabolism of resveratrol from dietary sources is needed in order to clarify this issue.

Additional mechanisms of action of resveratrol other than SIRT1 activation have also been investigated in relation to neurodegenerative processes. There is evidence to suggest that resveratrol promotes the proteolytic clearance of beta-amyloid as well as having anti-fibril effects in vitro (Vingtdeux et al, 2008), and that it attenuates beta-amyloid induced cytotoxicity, apoptotic features, and intracellular ROS accumulation (Jang and Surh, 2003). A study by Karruppagounder (2009) reported that resveratrol fed to mice for 45 days caused plaque formation to diminish in various regions including the medial cortex, striatum and hypothalamus. Resveratrol was found to be associated with a reduction in brain glutathione and increased brain cysteine, which may be protective against plaque formation. The authors also speculate that resveratrol or cysteine may reduce plaque formation through chelation of copper or zinc.

While the epidemiological and animal research suggests there is great potential for resveratrol as a treatment for dementia, examining the effects of resveratrol supplementation in neurodegenerative disease.

However, two randomised controlled trials are currently being conducted in the US:

- A pilot study of the effects of a resveratrol supplement in mild to moderate Alzheimer's disease by the Medical College of Wisconsin. Researchers are examining the effects of a 215 mg daily dose of resveratrol in 50 patients for 52 weeks.
- A phase III trial of a supplement containing resveratrol with glucose and malate for 12 months in 60 patients with probable Alzheimer's disease, run by the US Department of Veterans Affairs.

The results of these trials will provide crucial data on the efficacy of resveratrol supplementation in the treatment and prevention of dementia.

Summary of findings

In summary:

- Epidemiological and animal research suggests there is great potential for resveratrol as a treatment for dementia. However, there are no published results from randomised controlled trials examining the effects of resveratrol supplementation in neurodegenerative disease.

Green tea catechins

What it is

Green tea has the highest content of polyphenolic flavonoids, when compared to other common forms such as black or oolong tea. These flavonoids, known as catechins, account for around 30–40% of the dry weight of green tea leaves, which is four times that found in black tea (Khokhar and Magnusdottir, 2002; Wang et al, 1994; Yang and Wang, 1993).

There are various catechins found in green tea, the major constituent being (-)-epigallocatechin-3-gallate (EGCG), which accounts for more than 10% of the dry weight. Other catechins are found in lesser amounts: (-)-epigallocatechin (EGC) > (-)-epicatechin (EC) >= (-)-epicatechin-3-gallate (ECG) (Mandel et al, 2008). All four catechins have been found to be powerful antioxidants and radical scavengers, although EGCG has been found to be the most potent (Nanjo et al, 1996; Salah et al, 1995). The catechins have

been shown to strongly inhibit lipid peroxidation and display an ability to induce endogenous antioxidant defences and chelate transitional metals such as iron and copper (et al, 2004).

Studies

In a review of in vitro research into the mechanisms of action of EGCG, Mandel and colleagues (2008) argue that activation of the protein kinase C (PKC) pathway is the main mechanism accounting for the neuroprotective and neurorescue effects of EGCG. The PKC pathway plays an important role in the regulation of cell survival, apoptosis and memory consolidation (Berra et al, 1997). Low micromolar concentrations of EGCG have been found to rapidly activate the PKC pathway, resulting in cleavage of amyloid precursor protein (APP) to the soluble sAPP α . Cleavage of APP via this nonamyloidogenic secretory pathway precludes the formation of A β , leading to a reduction in amyloid plaque formation (Levites et al, 2003). Activation of the PKC pathway has also been found to be associated with greater clearance of A β due to increased activity of endothelin-converting enzyme (ECE) (Choi et al, 2006), as well as degradation of bad proteins involved in mitochondrial cell death signalling (Kalfon et al, 2007), reduction in the expression of apoptotic genes (Weinreb et al, 2007), and promotion of neurite growth (Reznichenko et al, 2005).

A number of in vivo animal studies have demonstrated a convergence between EGCG effects at the cellular and behavioural level. These studies have demonstrated cognitive benefits in healthy animals, as well as for those with amyloid- β accumulation. Haque and colleagues (2006) provided evidence that long-term administration of green tea catechins improves spatial cognition learning ability in healthy rats. Rats fed with catechins for 26 weeks were found to have improved reference and working memory-related learning ability, together with lower plasma concentrations of lipid peroxides, greater plasma ferric-reducing antioxidant power, and lower hippocampus ROS in comparison to controls. In a follow-up study, Haque and colleagues (2008) examined the effects of green tea catechins in rats with amyloid- β (1-40) infused into the cerebral ventricle. After 20 weeks of catechin administration, a subset of rats was infused with amyloid- β . Administration of catechins for 26 weeks

was found to significantly decrease the amyloid- β induced number of reference and working memory errors made in a radial maze, and was also associated with a reduction in hippocampal lipid peroxide (LPO; 40%) and cortico-hippocampal ROS (ROS; 42% and 50%, respectively). Rezaei-Zadeh and colleagues (2008) reported similar findings when they administered green tea catechins over a six-month period to transgenic mice that were over-expressing APP. They found that plaque burdens were reduced in the cingulate cortex, hippocampus, and entorhinal cortex by 54%, 43%, and 51%, respectively. Cognitive benefits were also found to be associated with catechin administration, as revealed by better working memory in the radial maze.

Epidemiological studies together with preclinical studies have associated green tea consumption with a reduced risk of a range of disorders including cancer, cardiovascular disease and diabetes (Anderson and Polansky, 2002; Kuriyama, 2008; Kuriyama et al, 2006; Li et al, 2006). There is also epidemiological evidence to suggest that green tea consumption is associated with a reduced risk of neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. Kuriyama and colleagues (2006) conducted a cross-sectional study of 1,002 elderly Japanese participants over the age of 70 years. They administered the MMSE together with a questionnaire containing questions regarding their consumption of tea and coffee. They found that:

- Higher consumption of green tea was associated with a lower prevalence of cognitive impairment. Using <26 on the MMSE as a cut-off, those drinking two or more cups of green tea per day were found to have an odds ratio for cognitive impairment of 0.46, compared to an odds ratio of 1.00 for those drinking three or less cups per week.
- Green tea was associated with a greater reduction in risk of cognitive impairment than black tea, oolong tea and coffee.

Similarly, a large-scale 12-year prospective study by Hu and colleagues (2007) of 29,335 Finnish participants aged 25 to 74 years, found greater tea consumption to be associated with a reduced risk of developing Parkinson's disease.

To date, no randomised controlled trials have been conducted in either healthy or clinical populations. A concentrated form of EGCG taken in capsule form may potentially be an effective treatment for the prevention or treatment of dementia in humans. Considering the strong evidence for the efficacy of green tea catechins from animal and epidemiological data, these trials are urgently needed.

Summary of findings

In summary:

- There is strong evidence for the efficacy of green tea catechins from animal and epidemiological data. A concentrated form of EGCG taken in capsule form may potentially be an effective treatment for the prevention or treatment of dementia in humans.
- There have been no randomised controlled trials conducted in either healthy or clinical populations. Considering the evidence, these trials are urgently needed.

Pine bark extract – Pycnogenol® and Enzogenol®

What it is

Pycnogenol® is manufactured by Horphag Research, Geneva, Switzerland. It is the trade name given to a specific blend of procyanidins, extracted from the bark of French maritime pine (*Pinus pinaster*).

Use of the pine bark dates back over 2,000 years, with documented usage for the treatment of inflammation, skin disorders, wound healing and scurvy in Europe as well as amongst Native American Indians. Today it is used as a nutritional supplement and phytochemical remedy for a variety of diseases ranging from chronic inflammation to circulatory dysfunction (Packer et al, 1999). The procyanidins found in pycnogenol belong to the same family of flavonoid polyphenols as green tea catechins.

A similar product that is rich in flavonoid proanthocyanidins is Enzogenol®. Enzogenol® is a natural extract from the bark of New Zealand grown *Pinus radiata* trees. It is produced by ENZO Nutraceuticals.

Studies

Extensive reviews by Packer (1999) and Rohdewald (2002) have established the powerful antioxidant capacity of Pycnogenol®. Identified mechanisms of action include free-radical scavenging, metal chelation, enzyme activity inhibition and gene expression modulation.

Research by Liu and colleagues (2000) and Peng and colleagues (2002) has provided evidence that Pycnogenol® inhibits β -amyloid apoptosis of neurons and vascular cells. Further, Pycnogenol® has been found to reduce the expression of nitric oxide (NO) associated with the inflammatory response. Excess nitric oxide production due to synthesis by the inducible nitric oxide synthase (iNOS) enzyme has been implicated in the development of neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease (Calabrese et al, 2007). In particular, under pathological conditions involving the production of ROS, nitric oxide has been found to be much more harmful, combining with superoxide to form the reactive nitrogen species (RNS) peroxynitrite (Guix et al, 2005). Pycnogenol® has been found to quench the nitric oxide radical in activated macrophages and inhibit iNOS mRNA expression and iNOS activity, thus reducing nitrosative stress due to inflammation (Virgili et al, 1998).

In a double-blind trial examining the effects of Pycnogenol® on cognitive performance, Ryan and colleagues (2008) administered 150 mg per day Pycnogenol® versus placebo to 101 elderly participants (aged 60–85 years) over a three-month period. The group receiving Pycnogenol®, in comparison to controls were found to display significantly better working/spatial memory function at three months as measured by the CDR test battery. Interestingly, concentrations of F2-isoprostanes in blood plasma, which are biomarkers of lipid peroxidation, were also found to be reduced at three months in comparison to baseline for the Pycnogenol® group.

Pipingas and colleagues (2008) examined the effects of Enzogenol® in combination with vitamin C on cognitive performance in a double-blind trial using 42 males aged 42–65 years over a five-week period. They found that the speed of response for the spatial working memory and immediate recognition tasks was significantly improved for the group receiving Enzogenol® plus vitamin C after five

weeks; there was no improvement in the group receiving vitamin C alone.

These studies provide preliminary evidence for the efficacy of pine bark extracts in improving cognitive function. However, larger scale studies over a longer time period are warranted in order to establish their effectiveness in comparison to other complementary medicine substances. Testing in clinical samples is also warranted in order to examine their efficacy in the treatment of dementia.

Summary of findings

In summary:

- There is preliminary evidence for the efficacy of pine bark extracts in improving cognitive function.
- There is a need for larger scale studies over a longer time period to establish the effectiveness of pine bark extracts in comparison to other CM substances.
- There is a need to test pine bark extracts in clinical samples to examine their efficacy in treating dementia.

7.6 Conclusions and Recommendations

On the basis of in vitro experimental research and in vivo animal research there is strong evidence for mechanisms of action for the majority of CM substances discussed in this review. For substances that are regularly consumed as foodstuffs – such as docosahexaenoic acid (DHA), vitamin B12, curcumin, resveratrol and green tea catechins – there is also strong epidemiological evidence for their efficacy.

However, as shown in Table 7.1, there is a widespread lack of evidence for the efficacy of CM treatments in the form of randomised controlled trials. Even in cases where these trials have been conducted, the studies are typically of short duration (less than six months), so the efficacy of these substances as a chronic treatment is difficult to establish.

Establishing efficacy in the treatment of mild cognitive decline or existing dementia is potentially easier than establishing efficacy in the prevention of dementia, as presumably these type of studies will not need to be conducted for a far longer duration. Further, if the efficacy of these CM treatments is to be successfully compared, then measures of effect size on comparable cognitive measures need to be established.

In light of these limitations, it is still possible to use the evidence as a basis on which to identify the CMs that warrant the greatest amount of future research attention. In particular:

- Docosahexaenoic acid (DHA) – Considering the strong epidemiological evidence linking high fish consumption to lower incidences of dementia, further large-scale randomised controlled trials investigating the efficacy of DHA is warranted. It may be useful to collect pharmacogenetic samples to determine if polymorphisms in ApoE differentially affect the cognitive effects of DHA.
- Precursor loading with N-acetylcysteine – Boosting endogenous supplies of glutathione through precursor loading with N-acetylcysteine is a strategy that holds promise for both the treatment and prevention of dementia. The cognitive benefit of this precursor strategy can only be properly established through large-scale randomised controlled trials.

- The polyphenol antioxidants curcumin, resveratrol, EGCG and bark extracts such as Pycnogenol® – These antioxidants should be examined via large-scale randomised controlled trial research studies, due to their well established mechanisms of action and considerable epidemiological evidence of efficacy.
- The herbal treatments huperzine A, Bacopa monnieri and Salvia officinalis – These are worthy of further research attention due to their well established mechanism of action and long history of usage in non-western societies.
- Mitochondrial cofactors, Alpha-lipoic acid and Acetyl-L-carnitine (ALCAR) – These should be candidates for randomised controlled trials.

However, the following CMs do not warrant this level of research focus:

- Ubiquinone (CoQ10) – There may be a case for its use as a treatment in existing cases of dementia, but there is little evidence to suggest that supplementation will be of benefit in the healthy population.
- Vitamin B12 – There is strong evidence to implicate its use in correcting high levels of homocysteine in the elderly population, but its mechanism of action does not directly target causes of neurodegeneration beyond this.
- Ginkgo biloba – The case for further research concerning the neuroprotective effects of ginkgo biloba are weak, due to the fact that it has already been investigated in several well conducted randomised controlled trials and yet no clear evidence of its efficacy has emerged.

In summary, several CMs have potential to be efficacious in the treatment and prevention of dementia. In order to properly establish their efficacy, large-scale randomised controlled trials are required over periods of six months or longer in both normal and clinical populations. It would be advantageous to measure biomarkers of oxidative stress, inflammation and beta-amyloid formation in conjunction with measurements of cognitive function using well-established batteries. It may also be advantageous to collect pharmacogenetic samples in order to establish if CMs have differential effects according to genetic disposition.

It is hoped that this research will lead to effective CM interventions that may enhance cognitive health over the adult lifespan and significantly delay or halt the onset of cognitive decline and dementia.

Priority Research Areas for Dementias

- ✓ Docosahexaenoic acid (DHA).
- ✓ Precursor loading with N-acetylcysteine.
- ✓ The polyphenol antioxidants curcumin, resveratrol, epigallocatechin gallate (EGCG) and pine bark extracts such as Pycnogenol®.
- ✓ The herbal treatments huperzine A, Bacopa monnieri and Salvia officinalis.
- ✓ Mitochondrial cofactors, Alpha-lipoic acid and Acetyl-L-carnitine (ALCAR).

	Mechanisms of action	Strength of evidence		
		Experimental	Epidemiological	Randomised controlled trials
Docosahexaenoic acid (DHA)	<ul style="list-style-type: none"> Protects against Aβ Protects against oxidative stress Anti-Inflammatory Cardiovascular benefit Enhances BDNF Improves glucose transport 	Moderate	Strong	Not enough evidence
N-acetylcysteine (NAC)	<ul style="list-style-type: none"> Precursor of glutathione Indirect potent antioxidant Inhibits Aβ production Anti-inflammatory 	Strong	N/A	Not enough evidence
Curcumin	<ul style="list-style-type: none"> Clears Aβ and blocks their formation Anti-Inflammatory Antioxidant Metal chelator 	Strong	Strong	Not enough evidence
Green tea catechins (EGCG)	<ul style="list-style-type: none"> Antioxidant Free-radical scavenger Metal chelator Activates PKC pathway Reduces Aβ production 	Strong	Strong	Not enough evidence
Huperzine A	<ul style="list-style-type: none"> Acetylcholinesterase inhibitor Reduces ROS formation Provides neuroprotection from cytotoxicity NMDA receptor antagonism 	Strong	N/A	Moderate (need more research outside of China)
Alpha-lipoic acid	<ul style="list-style-type: none"> Mitochondrial antioxidant Aids acetylcholine (ACh) production Metal chelator Boosts glutathione (GSH) synthesis Anti-inflammatory Increases glucose uptake 	Strong	N/A	Not enough evidence
Acetyl-L-carnitine (ALCAR)	<ul style="list-style-type: none"> Reduces Aβ formation Up-regulates glutathione (GSH) Up-regulates heat shock proteins Reduces Aβ formation Aids acetylcholine (ACh) production 	Strong	N/A	Moderate
Ubiquinone (CoQ10)	<ul style="list-style-type: none"> Up-regulates mitochondrial function Facilitates ATP synthesis Used in α-tocopherol production Provides neuroprotection for cholinergic neurons 	Strong	N/A	Not enough evidence, particularly in regards to use by healthy populations
Bacopa monnieri	<ul style="list-style-type: none"> Antioxidant Anti-Inflammatory Protects against membrane damage 	Strong	N/A	Not enough evidence
Pine bark extract – Pycnogenol® and Enzogenol®	<ul style="list-style-type: none"> Antioxidant Anti-Inflammatory Protects against membrane damage 	Strong	N/A	Not enough evidence
Resveratrol	<ul style="list-style-type: none"> Activates SIRT1 gene Antioxidant Anti-inflammatory Clears Aβ and blocks formation Metal chelator 	Strong	Strong	Not enough evidence
Cobalamin (B12)	<ul style="list-style-type: none"> Reduces homocysteine levels Indirect antioxidant Reduces Aβ formation Enhances mitochondrial function 	Strong	Strong	Not enough evidence
Ginkgo biloba	<ul style="list-style-type: none"> Antioxidant Anti-inflammatory Preserves mitochondria function / increases ATP production Inhibits formation of Aβ from APP Reduces neuron apoptosis Enhances acetylcholine (ACh) transmission 	Moderate	Weak	Weak (despite a large number of studies)
Salvia officinalis	<ul style="list-style-type: none"> Inhibits acetylcholinesterase (ChEI) and butyrylcholinesterase (BuChe) Antioxidant Anti-inflammatory Stimulates oestrogen receptor 	Moderate	N/A	Not enough evidence

Table 7.1 | Summary of CMs and evidence in the management of dementias

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8 | Diabetes

This chapter and related appendix presents a suggested framework for investigating, and potentially developing, herbal complementary medicine (CM) interventions for diabetes and metabolic disorders. In this regard, it stands apart from the other chapters in this report, which seek to identify a short list of CM research priorities. Professor Paul Komesaroff prepared this chapter with the assistance of Dr Shanhong Ling (both from the Faculty of Medicine, Nursing and Health Sciences, Monash University).

8.1 Prevalence of diabetes in australia

Definition of diabetes

The following information is from the AIHW website (<http://www.aihw.gov.au/diabetes/>).

Diabetes is a chronic condition in which the body loses its ability to control the level of glucose in the blood. People with diabetes do not have enough insulin. (Insulin is a hormone produced in the pancreas that helps the body convert glucose from food into energy. When glucose stays in the blood instead of being turned into energy, it causes high blood sugar levels.)

Types of diabetes

Different insulin abnormalities cause different types of diabetes, as discussed below.

Type 1 diabetes

Type 1 diabetes is caused by autoimmune destruction of insulin-producing beta cells of the pancreas. The processes associated with the destruction of these cells are well understood, but the trigger mechanisms that initiate the process are still the subject of debate.

In type 1 diabetes, the body stops making insulin, in most cases because of the destruction of the insulin-producing cells in the pancreas by the body's immune system. Without insulin, the body's cells cannot turn glucose into energy

and burns its own fats as a substitute. Unless treated with daily injections of insulin, people with type 1 diabetes accumulate dangerous chemicals in their blood from the burning of fat, causing a condition known as ketoacidosis. This condition is potentially life threatening if not treated. In Australia, according to the 2007–08 National Health Survey, around 10% of all people with diabetes have this form of the disease.

Type 2 diabetes

Type 2 diabetes is caused by a combination of lifestyle and genetic factors. In many cases, this form of diabetes is inherited; several genes have been identified which are related to the risk of developing this type of diabetes. Type 2 diabetes occurs mostly in people aged 50 years and over but is becoming increasingly recognised in children.

People with type 2 diabetes produce insulin, but may not produce enough, or else the natural hormone insulin becomes less effective at lowering blood sugars (hence the term 'insulin resistant').

Type 2 diabetes may be managed with changes to diet and exercise, glucose-lowering drugs, insulin injections or a combination of these. According to the 2007–08 National Health Survey, 87% of all people with diabetes have this form of the disease.

Other types of diabetes

Another form is gestational diabetes mellitus, which may develop during pregnancy (about 5% of pregnant women are affected). It involves higher blood sugar levels appearing for the first time during pregnancy in women not previously diagnosed with other forms of diabetes. This type of diabetes is short term and, although it usually disappears after the baby is born, can recur in later pregnancies. Gestational diabetes is also a marker of increased risk of developing type 2 diabetes later in life.

Diabetes in Australia

- Every day, 280 Australians develop diabetes.
- Diabetes is Australia's fastest growing chronic disease.
- Nearly one million Australians are diagnosed with diabetes. For every person diagnosed, it is estimated there is another who is not yet diagnosed.
- There is an estimated 3.2 million Australians with diabetes and pre-diabetes.
- Diabetes is the sixth leading cause of death in Australia
- Up to 60% of cases of type 2 diabetes can be prevented.

Source: Diabetes Australia website

Other types of diabetes can occur as a result of other conditions or syndromes, such as genetic defects of beta-cell function in the pancreas and insulin action (formerly referred to as maturity-onset diabetes of the young); other diseases of the pancreas (including cystic fibrosis and cancer of the pancreas); and endocrine disorders (such as Cushing's Syndrome).

Pre-diabetes

Some people have a blood glucose level that falls between the definitive 'diabetic' and 'non-diabetic' ranges. This condition is called pre-diabetes (or impaired glucose regulation). There are two categories of impaired glucose regulation: impaired fasting glucose and impaired glucose

tolerance. People with these conditions are at greater risk of developing diabetes and some of the complications associated with diabetes itself, such as cardiovascular disease.

A number of studies suggest that early intervention may prevent progression to diabetes. However, the role of treatments in this condition is not well understood.

Severity of the condition

Diabetes mellitus is a major problem that significantly affects the health of many Australians. It is one of the major causes of hospitalisation, one of the major causes of economic loss due to illness and lost production, and one of the top 10 causes of death. The cost of diabetes is difficult to calculate but is undoubtedly in the billions of dollars each year.

Worldwide, there are an estimated 200–400 million sufferers and, as in Australia, the incidence of diabetes is increasing rapidly – in part at least because of the rapid increase in obesity.

Complications of diabetes

Diabetes may result in a range of complications that can cause disability and reduce a person's quality of life and life expectancy.

In particular, persistently elevated glucose levels lead to damage to small and large blood vessels throughout the body. This damage can lead to heart disease; kidney disease; blindness; strokes; damage to nerves at many locations, including sensory nerves in the feet and nerves controlling the actions of the heart and digestion; lack of adequate circulation to the feet, leading to infections and amputations; and erectile dysfunction in men. High glucose levels, poor blood supply and other factors also contribute to a predisposition to infection and impaired wound healing and immune function. Accordingly, susceptibility to infections is a major cause of morbidity in people with diabetes.

In Australia, diabetes is the main cause of blindness and renal failure and one of the major causes of heart disease, hypertension, stroke and lower limb disease, including lower limb amputations, and so is an important source of morbidity and mortality.

Treatment

Treatments for diabetes

In all types of diabetes the main treatment objective is to restore circulating blood glucose levels to values comparable to those found in non-diabetic people. Diet and exercise are of central importance in controlling glycaemic levels, maintaining health and avoiding complications; drug therapies are also widely employed.

People with type 1 diabetes require the administration of exogenous insulin (the condition is generally fatal unless treated with insulin). Insulin is administered by injection, often using a 'pen' system. The regime is frequently four injections a day. Another delivery system – continuous infusions using a subcutaneous pump – is now available, while the use of sprays is under investigation.

People with type 2 diabetes often initially manage their condition by increasing exercise and modifying their diet to control weight and reduce the intake of refined sugars. However, if the condition progresses, medications may be needed. There are several classes of medications available. Metformin is generally recommended as a first line treatment. Injections of insulin may either be added to oral medication or used alone.

Other classes of medications used to treat type 2 diabetes are sulfonylureas, nonsulfonylurea secretagogues, and thiazolidinediones. A newer class of agents, the peroxisome proliferator activated receptor (PPAR) antagonists, is effective and increasingly used as second-line therapy. The alpha glucosidase inhibitor acarbose is also employed, though its effectiveness is limited and it is associated with significant adverse side effects that restrict its use. Incretin mimetics such as exenatide and sitagliptin are newer forms of treatment; exenatide is administered systemically, while sitagliptin is administered orally.

In all other types of diabetes, insulin therapy is widely used where the other therapies are inadequate to control glucose levels.

Managing complications

The main treatment methods available to prevent and manage the complications of diabetes are to control glucose levels through diet, exercise and drug therapies; control blood pressure; control elevated cholesterol and other lipid

levels; manage weight; and manage problems relating to heart disease, kidney disease, large blood vessel disease and retinal disease.

While significant advances have been made in the understanding and management of diabetes over the last few years, major gaps remain. These include the need to:

- Improve understanding of the causes of diabetes and strategies to prevent its development.
- Improve understanding of the role of diet and exercise in the management of diabetes and its complications.
- Manage glucose levels through better and more acceptable drug treatments.
- Prevent and manage diabetes.
- Manage erectile dysfunction.
- Protect kidneys and eyes from damage related to hyperglycaemia.
- Prevent and manage diabetic neuropathy (nerve damage).
- Improve control of blood pressure and lipid levels.
- Enhance wound healing.
- Improve methods for assessing glucose levels, preferably though non-invasive techniques.

Mechanisms of action of treatments

Insulin

The mechanisms of action of insulin are well understood. Scientific studies have elaborated the molecular structure of insulin cellular receptors, the molecular messengers within cells that assist with the transmission of the insulin response, and the physiological outcomes at the levels of both cells and whole organisms.

Other treatments

The problem that predominates in type 2 diabetes – 'insulin resistance' – is incompletely understood and is the subject of ongoing intense research.

Insulin resistance has been identified as a major target for pharmaceutical action in the treatment of diabetes. So far, two classes of drugs – biguanides and thiazolidinediones – have been shown to contribute to improved insulin sensitivity.

The oldest class of oral medications for managing type 2 diabetes are sulfonylureas. These agents act by increasing insulin secretion from the pancreas. In this form of diabetes, it is common for insulin levels already to be high due to the presumed primary lesion of increased insulin resistance. Sulfonylureas increase insulin levels still further to a level where effective glucose control can be achieved.

Thiazolidinediones act through inhibiting the peroxisome proliferator activated receptors (PPAR inhibitors). The effect of this is to enhance insulin sensitivity, as well as some additional actions. The mechanism of action involves binding to the peroxisome proliferator-activated receptor (PPAR) gamma, a transcription factor that regulates the expression of specific genes especially in fat cells but also in other tissues. It is likely that thiazolidinediones primarily act in adipose tissue where PPAR gamma is predominantly expressed. Thiazolidinediones have been shown to interfere with expression and release of mediators of insulin resistance originating in adipose tissue (e.g. free fatty acids, adipocytokines such as tumour necrosis factor alpha, resistin, adiponectin) in a way that results in net improvement of insulin sensitivity (i.e. in muscle and liver). Nevertheless, a direct molecular effect in skeletal muscle cannot be excluded. In the last three years doubts have been raised about possible links between rosiglitazone, one of the leading members of this class, and an increased risk of cardiovascular events, as a result of which its popularity has declined sharply.

Alpha glucosidase inhibitors act by inhibiting digestion of carbohydrates in the gastrointestinal tract, thus limiting the absorption of carbohydrates that would increase circulating glucose levels.

Glucagon-like peptide-1 analogs (such as exenatide) and dipeptidyl peptidase-IV inhibitors (such as sitagliptin) are members of a novel class of diabetes treatments called incretins or incretin mimetics. These agents improve diabetes control, assist with weight loss and are said to offer the potential of preserving cell function. It is not known whether they have any effects on cardiovascular disease.

Hepatic blockade of glucocorticoid receptors suppresses glucose production and thus decreases circulating glucose

levels, but systemic glucocorticoid antagonism can produce adrenal insufficiency and other undesirable side effects were infused with various doses of a recombinant retrovirus encoding an engineered rat preproinsulin-1 gene.

Pancreatic islet cell transplantation is successful in a limited number of cases of type 1 diabetes, but with improved techniques is likely to become a more important modality.

Several additional drugs under development are said to promote the synthesis or secretion of insulin by the beta cell, to inhibit alpha-glucosidase activity in the small intestine, to enhance the action of insulin at the level of the target tissues, and to inhibit free fatty-acid oxidation.

Some limitations of conventional treatment

In many cases, treatments associated with diabetes will be life-long, leading to concerns about long-term adverse side effects.

In addition, existing treatments are often not fully effective and there are important gaps in treatment capability. For example, there are no effective treatments for the prevention and management of diabetic nephropathy (kidney disease), which is a major cause of morbidity for patients with this condition, and there is a need for treatments that reduce the incidence of diabetic eye disease.

For these reasons, there is a need for new treatments in the management of diabetes.

8.2 The role of complementary medicine

Over the last decade, significant progress has been made in elaborating the processes relating to the uptake of insulin into cells. As a result, a number of potential therapeutic targets have been identified. These include herbal treatments that are thought to be efficacious in the management and possible prevention of diabetes. However, these treatments need to be subjected to rigorous scientific testing before they are accepted for clinical use.

Evidence of actions of herbal preparations in diabetes

There are many herbal preparations for which anti-diabetic activity has been claimed. However, the quality of the data in relation to these claims varies greatly. There have been very few properly controlled clinical tests and no herbal preparation has achieved full acceptance as a safe, effective, reliable agent for the management of diabetes of any type or for the complications of diabetes. A shortlist of products and preparations for which there are some data, either in vitro or in vivo, are listed in Table 8.1 (see references for further details).

The US National Center for Complementary and Alternative Medicine website advises that: 'In general, there is not enough scientific evidence to prove that dietary supplements have substantial benefits for type 2 diabetes or

its complications' (NCCAM, 2012). It also addresses what is known about a few of the many supplements used for diabetes, with a focus on some that have been studied in clinical trials. These include:

- **Alpha-lipoic acid (ALA)**, also known as lipoic acid or thioctic acid). This is an antioxidant that is found in certain foods, such as liver, spinach, broccoli, and potatoes. Some people with type 2 diabetes take ALA supplements in the hope of lowering blood glucose levels by improving the body's ability to use insulin; others use ALA to prevent or treat diabetic neuropathy (a nerve disorder). Supplements are marketed as tablets or capsules. ALA has been researched for its effect on insulin sensitivity, glucose metabolism, and diabetic neuropathy. Some studies have found benefits, but more

Acidic polysaccharide (TAP) from <i>Tremella aurantia</i>	<i>Gymnema sylvestre</i>	<i>Silybum marianum</i>
<i>Aegle marmelos</i>	Green tea supplementation	<i>Stevia rebaudiana</i> Bertoni
American ginseng berry extract	<i>Gymnema sylvestre</i>	<i>Suaeda fruticosa</i>
<i>Biophytum sensitivum</i>	<i>Gymnema yunnanense</i> extract; Jiang-Tang-Ke-Li	<i>Swertia chirayita</i>
<i>Cinnamomum tamala</i>	Kaempferitrin (flavonol glycoside found in the <i>B. Forficata</i> leaves)	<i>T. Foenum-graecum</i>
<i>Coccinia indica</i>	Keishi-bukuryo-gan	<i>Tamarindus indica</i>
Cogent db (an Ayurvedic drug)	Keishi-ka-jutsu-bu-to (traditional herbal medicine: Gui-zhi-jia-shu-fu-tang)	Tangniaole
Cordyceps	<i>Momordica charantia officinale</i>	Tang-niao-tung extracts
Cortex Moutan polysaccharide-2b	<i>Moringa oleifera</i>	<i>Terminalia bellirica</i>
<i>Cyclocarya paliurus</i> (Batal.) Iljinskaja	<i>Mucuna prurita</i>	<i>Tinospora cordifolia</i>
<i>Dendrocalamus hamiltonii</i>	<i>Ocimum sanctum</i>	<i>Tragia involucrata</i>
Diasulin	<i>Oenanthe javanica</i> flavone	<i>Trichosanthes cucumerina</i>
<i>Eugenia jambolana</i> ;	<i>Panax ginseng</i> root and <i>Panax ginseng</i> berry	Trimetazidine
<i>Fagopyrum tataricum</i> complex	<i>Premna integrifolia</i>	Vanadate and Tiron
Fangchinoline isolated from <i>Stephania</i> (<i>Tetrandra Radix</i>)	<i>Pterocarpus marsupium</i>	<i>Vinca rosea</i>
<i>Ficus benghalensis</i>	Quei (Gui) Fu Di Huang Wan	Zingiber
<i>Ficus glomerata</i>	Rikkunshi-to	
Flaxseed meal	Saponin from <i>Tribulus terrestris</i>	
<i>Fraxinus excelsior</i>	<i>Sesbenia aegyptiaca</i>	

Table 8.1 | Products and preparations for which there are some data

research is needed. Because ALA might lower blood sugar too much, people with diabetes who take it must carefully monitor their blood sugar levels.

- **Chromium.** Some people with diabetes take chromium in an effort to improve their blood glucose control. Chromium is found in many foods, but usually only in small amounts; relatively good sources include meat, wholegrain products, and some fruits, vegetables, and spices. In supplement form (capsules and tablets), it is sold as chromium picolinate, chromium chloride, and chromium nicotinate. Chromium supplementation has been researched for its effect on glucose control in people with diabetes. Study results have been mixed. Some researchers have found benefits, but many of the studies have not been well designed. Additional, high-quality research is needed. At low doses, short-term use of chromium appears to be safe for most adults. However, people with diabetes should be aware that chromium might cause blood sugar levels to go too low. High doses can cause serious side effects, including kidney problems, which is an issue of special concern to people with diabetes.
- **Omega-3 fatty acids.** These come from foods such as fish, fish oil, vegetable oil (primarily canola and soybean), walnuts, and wheat germ. Omega-3 supplements are available as capsules or oils (such as fish oil). Omega-3 fatty acids have been researched for their effect on controlling glucose and reducing heart disease risk in people with type 2 diabetes. Studies show that omega-3 fatty acids lower triglycerides, but do not affect blood glucose control, total cholesterol, or HDL (good) cholesterol in people with diabetes. In some studies, omega-3 fatty acids also raised LDL (bad) cholesterol. Additional research is needed, particularly long-term studies that look specifically at heart disease in people with diabetes.
- **Polyphenols.** These are antioxidants found in tea and dark chocolate, among other dietary sources. They are being studied for possible effects on vascular health (including blood pressure) and on the body's ability to use insulin. Laboratory studies suggest that EGCG,

a polyphenol found in green tea, may protect against cardiovascular disease and have a beneficial effect on insulin activity and glucose control. However, a few small clinical trials studying EGCG and green tea in people with diabetes have not shown such effects.

Other supplements are also being studied for diabetes-related effects. For example:

- **Garlic.** Preliminary research has explored the use of garlic for lowering blood glucose levels, but findings have not been consistent.
- **Magnesium.** Studies of the effects of magnesium supplementation on blood glucose control have had mixed results, although researchers have found that eating a diet high in magnesium may lower the risk of diabetes.
- **Co-enzyme Q10 (CoQ10).** There is not enough evidence to evaluate the effectiveness of CoQ10 supplementation as a CM therapy for diabetes; studies of its ability to affect glucose control have had conflicting findings.
- **Ginseng and vanadium.** Researchers are studying whether ginseng (a herb) and vanadium (a trace mineral) might help control glucose levels.
- **Botanicals** such as prickly pear cactus, gurma, Coccinia indica, aloe vera, fenugreek, and bitter melon. There is limited research on the effectiveness of these botanicals for diabetes.

Obstacles for herbal diabetic treatments in Australia

There are significant obstacles that would need to be overcome for a herbal medicine to achieve success in the Australian market as a treatment for diabetes. For example:

- The diabetes treatment market is very competitive and there are already several successful products with well documented safety profiles available and in common use.
- There is major resistance to the use of unproven treatments among medical practitioners and regulatory authorities.
- There are concerns about the safety of herbal treatments.
- There is concern about the uniformity of the quality of herbal products, which is difficult to prove in the absence of reliable indicators of activity and composition.
- The management of diabetes involves the acute (that is, short-term) control of glucose levels and the long-term prevention and management of complications. While the former is relatively straightforward to test, the latter often requires large numbers of patients studied over a long period, making studies long and, sometimes, prohibitively expensive.

The key steps in developing a novel herbal treatment for diabetes are presented in Appendix 1.

8.3 Conclusions and recommendations

Our working group did not come to any conclusions regarding priority areas for research into CM interventions for diabetes. This is because there are numerous interventions that claim to treat blood sugars and reduce the risk of diabetes, but the quality of the data in relation to these claims varies greatly. There have been very few properly controlled clinical tests and no herbal preparation has achieved sufficient acceptance as a safe, effective, reliable agent for the management of diabetes of any type or for the complications of diabetes.

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9 | Wellness and disease prevention

This chapter reviews the current evidence for CM interventions in the context of wellness and disease prevention and makes recommendations for future research.

Professor Marc Cohen prepared this chapter following input from the expert group on Wellness, Disease Prevention and Complementary Medicine. The expert group comprised:

- Professor Marc Cohen (chair) – Foundation Professor of Complementary Medicine at RMIT University; and Senior Research Fellow in the Centre for Medical and Health Sciences Education at Monash University.
- Stephen Penman – President of the Yoga Teachers Association of Australia and CEO of the Australian College of Nutritional and Environmental Medicine (ACNEM).
- Professor Garry Egger – Professor of Lifestyle Medicine and Applied Health Promotion, School of Health and Human Sciences, Southern Cross University.
- Professor Bob Cummins – Personal Chair in Psychology, Deakin University.
- Professor Leonie Segal – Professor, School of Nursing and Midwifery, University of South Australia.

Wellness is a holistic concept that involves all aspects of lifestyle at all stages of life.

In 2010, SRI International released a major study that revealed that the yearly worldwide wellness industry is poised to cross the US\$2 trillion mark. The study presents wellness as an integrated industry cluster with nine core segments that include beauty and anti-aging, fitness and mind-body, healthy eating/nutrition and weight loss, and preventive/personalised health.

In Australia, reports by the Preventative Health Taskforce and the National Health and Hospitals Reform Commission have brought prevention, lifestyle and wellness to the attention of public health policy, and highlighted the need for further research in this field.

What is “wellness”?

Health and wellness

“Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity”

World Health Organization, 1940

“Wellness is the state of being well or in good health”

Oxford English Dictionary

9.1 Wellness and chronic diseases

Lifestyle-related chronic diseases are a global pandemic

A 2005 report by the WHO, *Preventing Chronic Disease: A Vital Investment*, estimates that chronic diseases – such as heart disease, stroke, cancer, chronic respiratory diseases and diabetes – were the cause of 35 million of the 58 million deaths in the world in 2005. The report suggests that 80% of premature heart disease, stroke and type 2 diabetes is preventable, 40% of cancer is preventable, and that the main modifiable risk factors for these diseases are lifestyle-related and include unhealthy diet, physical inactivity and tobacco use (WHO, 2005).

Given our ageing population, there is growing recognition that our health systems require major reform to cope with future demands. The inadequacies of our health systems was highlighted in a report by PriceWaterhouseCoopers, *Healthcast 2020*, which suggests that the health systems of nations around the world will be unsustainable if unchanged over the next 15 years. The report further suggests that “Preventive care and disease management programs have untapped potential to enhance health status and reduce costs, but require support and integration across the industry for their benefits to be realized” (PriceWaterHouseCoopers, 2005).

Australia's response

In June 2009, the National Health and Hospitals Reform Commission (NHHRC) published the report *A Healthier Future for all Australians* with recommendations to transform the Australian health system. It included a major reform goal that called for prevention and early intervention, and the establishment of an independent national health promotion and prevention agency that would “have a broad role to drive a fundamental paradigm shift in how Australians, and our health system, think and act about health and keeping well, including through better education, evidence and research...so that prevention is integrated into all aspects of our health care system” (National Health and Hospitals Reform Commission, 2009). The report estimated the net effect of the proposed reforms would save the healthcare and aged care budget \$4 billion a year by 2032–33 and “reduce the burden of disease

and deliver a better mix of more accessible and effective services at a lower cost and higher productivity.”

Similarly, the report from the National Preventative Health Taskforce, *Australia: the Healthiest Country by 2020*, recognised the need for a national prevention agency and highlighted the importance of promoting healthy lifestyles, including addressing alcohol use, nutrition, smoking and physical activity (Moodie, 2009).

9.2 Evidence of efficacy

Research into formal lifestyle interventions is a relatively recent phenomenon in the medical literature. However, there are now many systematic reviews and meta-analyses attesting to the efficacy of various lifestyle interventions, especially in relation to optimal nutrition and physical activity, relaxation and stress management interventions (Ebrahim, 2006).

In terms of nutrition, interventions commonly utilise a whole food, vegetarian diet that is low in saturated fat. The health benefits of such dietary regimes are now well established in the literature, especially in respect of heart disease, cancer, obesity, diabetes, and risk factors such as raised total and LDL cholesterol (Campbell, 2006). For example:

- Low meat intake is associated with a decrease in risk of death and an increase in life expectancy (Singh, 2003).
- Over-consumption of calories is associated with many conditions, including heart disease, cancer, and diabetes (Anisimov, 2003; Weinert, 2003).
- Greater adherence to a Mediterranean diet has been associated with a significant improvement in health status, seen by a significant reduction in overall mortality (9%), mortality from cardiovascular diseases (9%), incidence of, or mortality from cancer (6%), and incidence of Parkinson's disease and Alzheimer's disease (13%) (Sofi, 2008).

In terms of physical activity, studies consistently show exercise reduces all-cause mortality (Blair, 1995; Kampert, 1996) in all age groups, including later in life (Linsted, 1991; Maiorana, 2000). Physical inactivity ranks second only to tobacco smoking in causing disability and death

in Australia (Australian Institute of Health and Welfare, 2001), accounting for 6% of the disease burden in males (the second highest factor) and 8% in females (highest factor). This equates to about 8,000 deaths in Australia per year.

Further evidence of the efficacy of diet, exercise and stress management are presented in the following sections on cardiovascular disease, cancer, obesity and diabetes, and mental health.

Cardiovascular disease, hyperlipidaemia and hypertension

One of the first studies to rigorously examine the benefits of an integrated lifestyle intervention was the Dean Ornish Lifestyle Heart Trial (Ornish, 1990; Ornish, 1998; Anisimov, 2003). It reported reductions in coronary artery stenosis and reductions in hospitalisations, cardiac events and pain after one year of intensive lifestyle change and further reductions after five years. The Ornish program included nutrition (a whole food vegetarian diet with less than 10% fat, vitamins and supplements), exercise (moderate regular aerobic exercise), stress management techniques (stretching, breathing, meditation, relaxation), smoking cessation and love/intimacy (group psychosocial support and communication). Other studies have since replicated the Ornish results (Marshall, 2009).

It has also been found that a diet rich in vegetables, fruit, low-fat dairy foods, fish, poultry, whole grains and nuts with reduced portions of red meats, fats and sugar-sweetened foods and beverages, and alcohol limited to no more than two drinks per day, lowers systolic blood pressure by 11 mm Hg and controls systolic blood pressure to less than 140 mg in heart disease patients (Appel, 1997). The same DASH diet (Dietary Approach to Stop Hypertension) combined with a low sodium intake was found to have a greater effect than single medication.

Omega-3 fatty acids have been found to be superior to statins for hyperlipidemia, with fewer side effects and at less cost (Studer, 2005). Many other foods, such as pomegranate juice, have been found to have cardioprotective effects (Sumner, 2005). Antioxidants such as soluble polyphenols, tannins, and anthocyanins are thought to have anti-atherosclerotic properties. Blood pressure may also be

lowered by progressive muscle relaxation, cognitive/behavioural therapies and biofeedback (Dickinson, 2008).

Exercise has also been found to be beneficial. In a study of over 70,000 postmenopausal women, the number of MET-hours (a measure of energy expenditure) per week was inversely associated with heart disease risk; the faster the walking pace, the lower the risk (Owen, 1992; Manson, 2002). In another study, a 4% reduction in cardiac risk was found for each MET increase, up to a 23% risk reduction if weight training was also present (Tanasescu, 2000).

Physical inactivity has been shown to result in a 1½ to two-fold increase in the risk of cardiovascular disease (Berlin, 1990) and a three-fold increase in the risk of stroke (Shinton, 1993). Physical activity reduces blood pressure (Fagard, 1994) while preventing it from developing in those at risk (up to 25% reduction) (Kelley, 1994). Exercise has been shown to increase HDL, while diet and exercise together reduced LDL cholesterol better than diet alone (Moore, 1994).

Cancer

Cancer patients may benefit from physical exercise both during and after treatment, but the beneficial effects may vary as a function of the stage of disease, the nature of the medical treatment, and the current lifestyle of the patient (Knols, 2005).

Exercise-based interventions for cancer patients have been associated with reduced fatigue, greater quality of life, reduced emotional distress, improved immunological parameters, improved aerobic capacity and muscle strength (Galvao, 2005). All of these help patients cope with the effects of cancer treatments. Women who exercised to the equivalent of 9–15 MET-hours per week (equivalent to 3–5 hours of walking per week) had half the death rate from breast cancer over 4–18 years follow-up compared to those who did little or no exercise (Holmes, 2005), but further evaluation is required to quantify any possible long-term side effects (Markes, 2006).

A number of studies have focused on breast cancer. For example, a large-scale Norwegian study showed a 30% reduction in the risk of breast cancer in women who exercised regularly, particularly in those less than 45 years of age (Thune, 1997). In a Nurses Health Study, it was found

that seven hours or greater per week of moderate activity produced an 18% reduction in breast cancer risk (Rockhill, 1999). Another study found that brisk walking to reduced breast cancer risk by 18–22% in post-menopausal women (McTiernan, 2003). A past history of strenuous exercise at age 35 or 50 was also associated with a reduction in breast cancer risk.

Similarly, many studies have shown that physical activity reduces the risk of lung cancer independent of smoking and nutritional status (Thune, 1997) and reduces colon cancer mortality by up to 50% (Colditz, 1997; Slattery, 1997).

The Prostate Cancer Lifestyle Trial found that patients with early-stage prostate cancer choosing active surveillance might be able to avoid or delay conventional treatment for at least two years by making changes in their diet and lifestyle (Ornish, 2008).

Obesity/overweight, diabetes and metabolic (insulin resistance) syndrome

Dietary advice appears to bring about beneficial changes in diet and cardiovascular risk factors in the short term (over about 10 months) (Brunner, 2007) and to reduce the risk of diabetes by one-third over about six years (Nield, 2008). Lifestyle advice should continue to include permanent reduction of dietary saturated fat and partial replacement by unsaturated fats (Hooper, 2000).

Exercise, particularly when combined with dietary change, has been shown to be effective as a weight-loss intervention (Shaw, 2006) and also decreases the incidence of type 2 diabetes mellitus in high-risk groups (Orozco, 2008). Group-based training for self-management strategies in people with type 2 diabetes improves fasting blood glucose levels and glycated haemoglobin, and reduces systolic blood pressure, body weight and the requirement for diabetes medication (Deakin, 2005).

Weight loss strategies using diet, physical activity, or behavioural interventions produced small improvements in weight while very low or low calorie diets (Norris, 2005) and low glycaemic index diets (Thomas, 2007; Thomas, 2009) may hold promise for achieving weight loss in adults with diabetes. Wholegrain consumption may hold promise for preventing of type 2 diabetes (Priebe, 2008).

Combined behavioural lifestyle interventions have been shown to be beneficial for weight loss in overweight children and adolescents (Oude Luttikhuis, 2009), and physical activity promotion in schools has been shown to be beneficial for physical health status measures (Dobbins, 2009). In children, nearly all studies resulted in some improvement with diet or physical activity (Summerbell, 2005).

Mental health

Lifestyle factors such as chronic stress, poor nutrition, caffeine, smoking, obesity, alcohol and substance abuse may initiate or perpetuate anxiety disorders (Broocks, 1998). Therefore, there is growing interest in combining lifestyle measures with conventional pharmacotherapy and psychological therapies for anxiety or depressive disorders (Egger, 2008). These include:

- Exercise, which appears to have antidepressant and anxiolytic effects, with broad application in depression and anxiety disorders (Byrne, 1993; Mead, 2008; Wipfli, 2008). Aerobic exercise has been shown to be as effective as clomipramine in the treatment of anxiety and panic disorders (Broocks, 1998). However, it seems that higher levels of exercise may not protect against anxious or depressive symptoms initially occurring (DeMoor, 2008).
- Essential fatty acids, which have been shown to improve mood profile; increase vigour; and reduce anger, anxiety and depression states (Fontani, 2005). However, inconsistencies still remain in the evidence for fish oil supplementation in anxiety disorders and further research is warranted (Appleton, 2008).
- Relaxation techniques, which have been found to be more effective in reducing self-rated depressive symptoms than no or minimal treatment but not as effective as psychological therapies like cognitive behaviour therapy (Jorm, 2008). Relaxation was most effective for generalised anxiety disorder, panic disorder, insomnia, test anxiety and dental phobia, but less effective for post-traumatic stress disorder, obsessive compulsive disorder and specific phobias (Jorm, 2004; Ernst, 2007). Efficacy was higher for meditation and for longer treatments (Manzoni, 2008). Further research

is required using relaxation and meditation as an adjunct to first-line conventional psychological therapy (Krisanaprakornkit, 2006).

9.3 Issues around wellness

Cost-effectiveness of lifestyle interventions

Lifestyle interventions have been shown to be extremely cost-effective.

A study comparing the Mediterranean diet to a prudent Western diet for patients after a first acute myocardial infarction over 10 years estimated that the Mediterranean diet cost \$1,013 per QALY (quality adjusted life year) gained per person. The researchers concluded that, based on the published results from the Lyon Diet Heart Study (de Lorgeril, 1999) and conservative assumptions, the Mediterranean diet is highly cost-effective for persons after a first acute myocardial infarction and represents an exceptional return on investment (Dalziel, 2006).

In another study, 10 nutritional interventions were compared by QALY gained. Of these, the performance of the Mediterranean diet and 'Intensive Lifestyle Change to Prevent Diabetes' intervention was able to be estimated with most certainty; both were highly cost-effective at \$1,020 and \$1,880 per QALY gained, respectively. All the interventions appeared very cost-effective relative to conventional treatment norms. The researchers concluded that nutrition constitutes a highly efficient component of a strategy to reduce the growing disease burden linked to over-eating and poor nutrition (Dalziel, 2007).

More recently, a study examined the production gains and losses in the general economy of achieving 'feasible' reductions in the prevalence of risk factors such as obesity, alcohol, smoking, exercise, diet and domestic violence. This study concluded that while the potential benefits of reducing risk factor prevalence are substantial, "there is a paucity of effectiveness evidence for specific interventions to adequately inform judgments about feasible reductions in prevalence of many risk factors. Future research in this area is an important way forward if we are to have better evidence for prioritising specific interventions to achieve risk factor prevalence reductions and to support further modelling for health promotion" (Cadilhac, 2009).

It seems that a lack of effective economic modelling and accurate measures for estimating societal benefits from risk factor reduction programs is hindering the widespread implementation of such program throughout the general community. Similar issues face the implementation of lifestyle intervention programs in the corporate world despite a growing awareness of the cost to business from chronic disease.

Workplace wellness

In the US, the Milken Institute estimated the economic burden of chronic disease to be about US\$1.3 trillion a year, with medical expenditures accounting for US\$277 billion and health-related productivity loss accounting for nearly US\$1.1 trillion (DeVol, 2007). The current trend towards a shrinking and aging workforce, a growing prevalence of health risks and disease burden and a growing awareness of the cost of health-related productivity costs or 'presenteeism' has led to a growing recognition of the potential for workplace wellness programs to enhance staff recruitment and retention, increase efficiency at work and raise productivity.

A report by PrivewaterhouseCoopers, Working Towards Wellness, highlighted the role of workplace wellness programs. The report emphasised the role of the corporate sector in reducing the impact and cost of preventable and chronic disease and illness and recommended that corporate lifestyle and wellness programs include both individuals and their family members, integrate physical activity, healthy eating, stress/anxiety management and smoking cessation into the working day (PriceWaterHouseCoopers, 2007).

While it has been suggested that investments in employee health programs yield an average rate of return of between 2:1 and 5:1 (Moodie, 2009), these figures may be vastly underestimated and there is a need for more robust measures of both presenteeism and the returns from workplace wellness programs.

The lack of robust tools to estimate the cost of presenteeism and the return on investment of workplace wellness programs hinder the widespread adoption of such programs and indicate the need for further research.

Wellness care versus illness care

The Australian health system has traditionally focused on illness, but there are increasing calls for health funding to focus on wellness and wellbeing to prevent people from coming into the health system later in life with chronic diseases (Good, 2008). This is supported by the Productivity Commission (2006).

However, research is needed to determine the skills and expertise required from a prevention-oriented health workforce and how they can be aligned with practitioner accreditation and registration systems. Research on the development, implementation and evaluation of new wellness-oriented interventions such as the use of medical call centres and wellness and lifestyle coaching is also required.

Wellness and quality of life

The Australian Centre on Quality of Life at Deakin University regularly measures how satisfied Australians are with their lives and life in Australia and publishes the Australian Unity Wellbeing Index (Cummins, 2003), which monitors the subjective wellbeing of the Australian population based on quarterly surveys conducted on 2000 Australians since 2001.

Interest in happiness and subjective wellbeing over the past two decades has led to the development of the field of positive psychology, which examines the determinants of positive psychological states and the attributes of positive experiences such as flow, mindfulness, optimism, self-efficacy, hope, and gratitude. While it is suggested that positive emotions can offset the negative cardiovascular effects of negative emotions (Fredrickson, 2000), the relationship between subjective wellbeing and burden of disease is yet to be fully explored.

9.4 How to measure wellness

Current measures to assess wellness

Wellness assessments are distinct from diagnostic tests, which generally aim to determine the cause of a symptom or detect an established disease. Currently, different disciplines use a range of measures to assess health and wellbeing and disease risk. These include assessments of:

- Anthropometric and physiological measures, such as body mass index, waist circumference and blood pressure.
- Biochemical parameters, such as serum cholesterol, glucose and creatinine as well as genetic markers and tests available direct to consumers via the internet (Barrett, 2008).
- Organ function, such as testing of liver and renal function, and cardiovascular and respiratory performance via ECG stress testing, blood pressure testing and spirometry.
- Cognitive performance.
- Nutritional status and fitness.
- Psychosocial functioning, subjective quality of life, relationships and living conditions.
- Socioeconomic status, including demographics, access to services, wealth inequality, food and job security.
- Environmental quality, including access to clean air, water and presence of toxic pollutants.

Despite the plethora of measures, there is no integrated measure that takes into account the multiple physiological, psychological, social, demographic and ecological factors to produce a coherent wellness measure. Such a measure would serve to document a person's health status in the context of their lifestyle in order to form the basis for risk management strategies, create motivation for positive lifestyle change and document any improvement or decline (Cohen, 2010). The need for a wellness metric was highlighted as a priority by participants at the Australia 2020 Summit, where the development of a 'health and wellness footprint' was the most popular 'out of the box idea' (Good, 2008).

To effectively identify at-risk populations and monitor outcomes, further research is required to determine appropriate wellness assessment metrics. This is critical

– without standardised assessment tools it is not possible to design methodologically robust research or make meaningful comparisons of outcomes. If wellness cannot be adequately measured, it is not possible to know if and when it has been achieved.

Social measures and social capital

The following social measures are strongly linked to wellness:

- Social connection is linked with reduced morbidity and mortality.
- Social disadvantage is linked with higher rates of smoking, obesity and other lifestyle risk factors.
- Higher levels of subjective wellbeing, life satisfaction and happiness are associated with ‘social capital’ (i.e. income; employment; marital status; faith; frequency of interaction with friends, family and neighbours; community involvement; and having or receiving trust) (Helliwell, 2004).
- Frequency of religious attendance, private religious involvement, and relying on one’s religious beliefs as a source of strength and coping have a protective effect against mental and physical illness, improving how people cope with mental and physical illness, and facilitating recovery from illness (Matthews, 1998). All-cause mortality has also been found to be significantly reduced, and life expectancy increased by seven years (to 82 years), for regular churchgoers (Clark, 1999; Hummer, 1999). Presumably, some of this protective effect relates to social interaction and a feeling of ‘control’ gained from religious commitment.
- Control over working conditions is a powerful determinant for health (Marmot, 1997).
- The National Heart Foundation of Australia states that “There is strong and consistent evidence of an independent causal association between depression, social isolation and lack of quality social support and the causes and prognosis of coronary heart disease... the increased risk contributed by these psychosocial factors is deemed to be of similar order to the more conventional coronary heart disease risk factors such as smoking, dyslipidaemia and hypertension” (Bunker, 2003).

While social connectivity and intimacy are consistently seen as key determinants of wellness and recent findings show a robust relationship in which social and emotional support from others can be protective for health, the direct effects of social contacts on physiology have received less attention. Thus, further studies are needed to explain the relationship between social interventions and physical health (Reblin, 2008)

Demographic measures

There is increasing recognition of the impact of socio-economic and other demographic factors on wellness. Variables include age, ethnicity and socioeconomic group. There is also increasing recognition of the impact of urban design, locality and local amenities on the wellbeing of communities. Thus, infrastructure provision, employment, housing affordability, community interaction, access to open spaces and social cohesiveness are all important determinants for preventing chronic disease and enhancing wellness (Nardella, 2004).

The importance of the effect of demographic factors on wellness has led to attempts to quantify wellness using a raft of different measures. One such measure is the Bankwest Quality of Life Index, which attempts to track Australian living standards across municipalities using data from existing sources such as the Australian Bureau of Statistics, the Australian Tax Office and the Public Health Information Development Unit. The index includes data such as employment rate, average income, home ownership rate, type of housing, broadband access, percentage of empty homes, property-related crime, percent of adults in good health, percent of 16-year-olds attending secondary school, and percent of the population who have volunteered in the past year (Bankwest, 2008). As this index is based on demographic data from local government areas it does not provide individual assessments or take into account ecological variables.

Perhaps the most comprehensive attempt to create a metric for wellness is the Happy Planet Index, published by the New Economics Foundation. This index utilises subjective, objective and ecological data in an attempt to measure the ecological efficiency with which countries achieve long and happy lives for their citizens. The index is a composite measure that is calculated by multiplying life satisfaction

by life expectancy and dividing by ecological footprint. This measure is currently calculated for 143 countries, representing 99% of the world's population (Marks, 2006).

Ecological measures

Wellness cannot be understood outside the context of the environments in which it is experienced and thus any comprehensive view of wellness needs to take into account the effects of built, natural and social environments.

In 2008, Deakin University and Parks Victoria published a report titled *Healthy Parks, Healthy People*, which reviewed the literature on the health benefits of contact with nature (Maller, 2008). This report suggests that access to nature plays a vital role in human health, wellbeing, and development that has not been fully recognized. The report further states that “green nature’, such as parks, can reduce crime, foster psychological wellbeing, reduce stress, boost immunity, enhance productivity, and promote healing” and that “Evidence in the literature shows that among other benefits viewing nature is positive for health in terms of recovering from stress, improving concentration and productivity, and improving psychological state”.

The extent to which parks and other contact with nature can contribute to wellness requires further investigation. There is a need to develop measures of interaction with nature, to collect empirical evidence showing the health and wellbeing benefits of contact with nature, and to investigate nature-based interventions to address existing and emerging health problems (Maller, 2008).

In addition, many lifestyle interventions aimed at enhancing personal wellbeing and quality of life are similar to those targeting environmental impact and climate change. For example it has been suggested that personal carbon trading could act as a “stealth intervention” for reducing obesity by increasing personal energy use (Egger, 2009). While, exploring the link between personal wellbeing and ecological sustainability appears to be a fruitful area for research, this will require the development of standardised metrics to assess the ecological and health impact of different lifestyles.

Composite wellness measures

The multidimensional nature of wellness makes any single measure inadequate. However, there are a number

of approaches that attempt to combine measures across the different domains to create computer-based health-promotion tools such as:

- Health risk appraisals – These generally combine questionnaire-based assessments of risk factors and demographic data with algorithms to estimate specific risk of morbidity or mortality. They provide specific wellness oriented advice and recommendations, and provide motivation for positive lifestyle practices and monitoring interventions within worksite wellness programs and community-based health programs.
- Biological age assessments – These provide an integrated wellness measure that is often used as a health promotion tool. These assessments combine information from a medical history, demographic information and physiological and lifestyle parameters to provide an assessment of the difference between ‘biological’ and ‘chronological’ age (for example, see www.realage.com).

However, these measures are not based on any sound scientific framework, and leading experts on ageing have published a Position Statement on Human Aging that states: “any claim that a person’s biological or ‘real age’ can currently be measured, let alone modified, by any means must be regarded as entertainment, not science” (Olshansky, 2002).

There are also a number of risk calculators that purport to estimate an individual’s risk of a particular disease such as cancer and heart disease. These risk calculators generally use a variety of biological measures, lifestyle risk factors and medical history data including genetic testing to estimate an individual’s risk based on specific epidemiological data.

In attempting to measure ‘full spectrum wellness’ Travis adopts the concept of a ‘wellness energy system’ (Travis, 2004). Travis describes 12 aspects of wellness that include the inputs provided by breathing, eating, and sensing and outputs which are described as self responsibility and love, transcending, finding meaning, intimacy, communicating, playing and working, thinking, feeling, and moving. These 12 aspects of wellness are the basis for the wellness inventory, which evolved from health risk appraisal techniques to become the first computerised wellness assessment tool. The wellness inventory attempts to provide

a measure of personal wellbeing, but it fails to include biological, demographic or ecological data and, while it applies to individuals, it does not extend to populations.

9.5 Wellness and information technology

Over the past two decades, the development of information and communications technology (ICT) has progressed so rapidly that there is now the possibility that everyone on the globe can be linked via mobile communications technology that infiltrates almost every aspect of society.

Information and communications technology is being used for a range of purposes to promote wellness. For example, ICT is being used to:

- Support healthcare delivery by providing alerts and reminders, diagnostic support, therapy critiquing and planning, information retrieval, image recognition and interpretation (Coiera, 2003). I
- Extend the reach of the current health system through healthcare call centres that have the potential to foster the convergence of health related technologies and promote wellness and prevention. In addition to being used for triage, mental health services and disease management, call centres can also be used for clinical risk management, early intervention and prevention (Cullen 2005).
- Allow continuous measurement of various physiological, subjective and environmental parameters. Recent advances in biometric monitoring, radio-frequency identification (RFID) tags, global positioning system (GPS) devices and geographical information systems (GIS) have opened up the possibility for personal lifestyle monitoring using non-invasive technologies and hand-held devices. Personal devices can now simultaneously measure physiological variables such as heart rate, respiration, movement, galvanic skin response, metabolic rate, body temperature and brainwave activity, along with movement and personal geo-spatial mapping with recording of geographic and environmental variables such as location, speed, altitude, slope, geographic context and climate.
- Enable patients to upload personal lifestyle-related data. This enables individuals to non-invasively acquire, store and upload their personal wellness data to a personal electronic medical record from virtually any location. Placing such data into online platforms allows for personal information to be analysed and interpreted with the assistance of online experts who in turn have access to sophisticated knowledge management systems including the use of bibliographic databases and decision support systems.
- Provide the possibility for innovative interventions. Online education platforms offer unprecedented opportunities to deliver lifestyle education and wellness interventions wherever they are required. Computers also facilitate wellness and lifestyle coaching using either hybrid delivery models combining computer and web-based delivery of content with the assistance of a coach through phone calls, electronic messages and home visits (Taylor, 2008) or software-based ‘conversational agents’ that can act as virtual coaches via the internet (Grolleman, 2006).
- Provide computer-based games and interactive simulators include or enhance physical activity; these have been found to provide greater enjoyment, attendance, adherence and physical fitness compared to traditional exercise equipment (Warburton, 2007; Mark, 2009; Warburton, 2009).
- Enable social networking, which provides the potential to build social capital and facilitate positive lifestyle change. Social networking (including online multi-player games) has been touted as an enabler in health and health care (Maged, 2007).

9.6 Conclusions and recommendations

Prevention strategies and wellness-focused interventions have the potential to positively impact on all of the chronic diseases in the Australian Government’s National Health Priority Areas and are likely to be the most cost-effective interventions for reducing the overall burden of disease. There is therefore an urgent need for a ‘paradigm shift’ in health policy to a wellness and prevention approach,

particularly in view of the high quality primary evidence for the efficacy and cost-effectiveness of lifestyle and health education and interventions in most of these National Health Priority Areas.

As part of this shift, there is a need to address significant research and implementation gaps in four priority areas: wellness metrics, public health programs, information technology, and lifestyle management. This is discussed below.

Priority 1 – Develop wellness metrics

Unless wellness can be accurately measured it cannot be rigorously researched. There is therefore a need for research into valid and sensitive measures of wellness that are applicable across the lifespan and take into account both objective and subjective lifestyle data including quality of life, subjective wellbeing, physiological, psychological, social and demographic risk factors, contact with nature, ecological footprint and economics.

There are many potential paths for research into wellness metrics. These include:

- Exploring theoretical frameworks for integrating seemingly disparate data to provide an integrated wellness model that can guide future research
- Performing systematic reviews of existing tools, including the data collected and algorithms used for analysing health risk appraisals, biological age assessments and disease risk calculations, as well as linking these data to economic outcomes
- Validating wellness metric instruments by performing longitudinal analysis of both retrospective data accessed through corporate wellness programs, healthcare institutions and health insurers as well as prospective data (including data collected at different life stages).
- Developing and validating online wellness assessment tools that can be used across the corporate, primary care and community sectors and accessed by primary care practitioners and individuals to allow individuals and their carers to make their own assessments and monitor any interventions.

Wellness metrics have many potential applications:

- In industry, the development of robust measures of productivity and presenteeism (being present at work

while unproductive) would allow organisations to more accurately estimate the return on investment of corporate wellness programs. They would also further engage the business community in reducing risk factors and self-management of chronic disease.

- In the health sector, wellness metrics could be used to assess the success of different interventions and to improve on existing calculators to predict the risk of morbidity and mortality. They could also be used to predict, monitor and evaluate the impact of specific lifestyle interventions.
- In the public domain, wellness metrics could be used by schools, communities and policy-makers to target at-risk individuals and populations and help to determine the most effective interventions. They could also be used to and guide the development of new policy and the implementation and funding of new services.

Priority 2 – Implement public health programs

While preventable lifestyle related chronic disease mainly associated with alcohol and tobacco use and obesity account for over 70% of the current disease burden, only 2% of the health budget is allocated to prevention. There is therefore an urgent need to explore programs aimed at reducing risk factors, especially in the areas of smoking, alcohol, nutrition, physical activity and stress management.

Research is required to investigate the most efficacious and efficient means to implement health education, promotion and interventions at personal, family, community, corporate and national levels and inform health policy on the implementation of wellness and lifestyle programs. The ‘wellness metric’ (priority 1) would be useful in quantifying the benefits and most effective implementations of such programs. (The research required to foster the development, delivery and evaluation of wellness and prevention based programs is currently being addressed by the National Preventative Health Taskforce.)

Priority 3 – Use IT to enhance wellness

Information and communications technology provides an unprecedented opportunity for personal lifestyle and wellness monitoring that can be used to record individual wellness metrics and help monitor and implement lifestyle interventions. This technology also provides the prospect for innovative wellness interventions ranging from one-

on-one online wellness and lifestyle coaching, corporate wellness interventions, and interventions that build social capital through social networking, local cooperatives and local grassroots community-based interventions that disseminate messages and engage various sectors of the community in wellness activities.

Research is required to:

- Develop applications for mobile computing devices to record, store, analyse and feed back lifestyle and wellness-related data.
- Develop electronic medical record systems that not only record health related data but also lifestyle choices and risk factors.
- Evaluate the benefits of computer games that involve physical activity, and develop computer games and other applications that can be used to deliver healthy lifestyle messages and promote physical activity and other healthy lifestyle behaviours.
- Explore the potential for social networking platforms to promote healthy lifestyle choices and behaviours and promote a 'wellness culture' within corporations, schools and local communities.
- Review the most effective behaviour modification programs and how they may be supported, implemented and evaluated by current and future health workers.
- Explore best practice in lifestyle interventions, and to develop, implement and evaluate new wellness-oriented interventions such as the use of medical call centres and wellness and lifestyle coaching.
- Determine the educational needs and skill sets required for both conventional and CM health practitioners to effectively engage in preventative and wellness initiatives and how these can be aligned with practitioner accreditation and registration systems and funding bodies to facilitate practitioners working together in multidisciplinary teams.
- Design and implement effective health practitioner education programs aimed at addressing identified needs.
- Explore the barriers to effective integration of conventional and CM practitioners and corporate health providers and design pilot projects involving multidisciplinary teams that include CM practitioners as well as corporate wellness directors and human resource managers. This research could build on the work of the Royal Australian College of General Practitioners by exploring the implementation of the newly developed Faculty of Integrative Medicine and engaging integrative medicine practitioners in designing best practice models.
- Explore possible funding models and practice incentives, and determine any changes required at national and State policy level in order for wellness interventions to be made a priority for healthcare workers.

Priority 4 – Integrate lifestyle management into the healthcare system

Allied health practitioners are often trained and experienced in preventative health but underutilised by the current system in the delivery of lifestyle and wellness programs to the community. There is a need to engage the existing medical, allied and CM communities in the design, delivery and assessment of such programs. Research is required to:

Priority research areas for wellness

- ✓ Develop wellness metrics.
- ✓ Implement public health programs.
- ✓ Use IT to enhance wellness.
- ✓ Integrate lifestyle management into the healthcare system.

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10 | Conclusion and next steps

10.1 Conclusion

This report represents a milestone for complementary medicine in Australia, as it is the first time that research priorities have been identified in a coordinated manner.

In particular, the report finds that there are a number of CM interventions that have potential to be both efficacious and cost-effective in addressing some chronic diseases identified in the Australian Government's National Health Priority Areas. These research priorities are listed in Table 10.1.

10.2 Next steps

Evidence-based research has identified a number of CM interventions that have potential to be both efficacious and cost-effective in addressing some chronic diseases, and this study identifies the research priorities for these interventions.

The next steps in the process will be to adequately resource these research priorities. This will require a strategy that estimates:

- The resources needed to execute such a strategy. For each research priority, the strategy will need to take full account of the number of people and range of expertise, the amount of grant funding, and the type and location of infrastructure.
- The timeframe for executing each research topic. This will need to reflect funding availability and community health benefit. It may be desirable to rank those areas that could deliver the community the greatest return on investment.
- The benefits that would ensue to Australia if such a strategy were implemented.

Area	Research priority
Cardiovascular health	<p>Investigate the following therapies in treating cardiovascular conditions:</p> <p><i>Nutrition and dietary supplements</i></p> <ul style="list-style-type: none"> • The effect of the consumption of soluble fibre (oats, psyllium, pectin and guar gum) in reducing total cholesterol. • The effect of the consumption of nuts in reducing the magnitude of the coronary heart disease risk. • The effect of tea drinking in protecting against coronary heart disease. <p><i>Herbal preparations:</i></p> <ul style="list-style-type: none"> • The efficacy of hawthorn extract in reducing heart failure-related signs and symptoms. • The efficacy of ginkgo leaf and its extracts in treating heart disease. • The efficacy of Padma 28 in treating heart disease. • The efficacy of red rice yeast in lowering LDL. • The efficacy of spirulina in lipid lowering and blood pressure control. • The efficacy of ginger and, specifically, certain ginger extracts, in modifying risk factors for developing coronary heart disease. <p><i>Mind-body and body-based practices:</i></p> <ul style="list-style-type: none"> • The efficacy of acupuncture in treating myocardial ischaemia, hypertension and arrhythmias. • The efficacy of yoga, Qi Gong and meditation in reducing heart disease risk factors.
Cancer	<p>Investigate the interactions and impact of biological treatments (including herbal medicines, Chinese herbal medicines and nutritional supplements) taken concurrently with conventional cancer treatments on:</p> <ul style="list-style-type: none"> • Reducing side effects of conventional cancer treatments. • Alleviating cancer symptoms. • Reducing tumour load. • Prolonging disease-free survival. <p>Study the effect of herbal medications and nutritional supplements on quality of life and survival, following conventional cancer treatment.</p> <p>Investigate the best means to provide accurate, readily accessible and regularly updated information about CM for patients and healthcare practitioners.</p> <p>Study the role of exercise/physical activity in ameliorating cancer side effects and in secondary cancer prevention.</p> <p>Study the role of acupuncture in relieving the symptoms of cancer or its treatment.</p>
Arthritis and musculoskeletal conditions	<p>Investigate the following interventions in the treatment of arthritis and musculoskeletal conditions:</p> <ul style="list-style-type: none"> • Acupuncture. • Rosehip. • Avocado-soybean unsaponifiables (ASU). • Phytodolor ®.
Dementias	<p>Investigate the following interventions in the treatment of dementias:</p> <ul style="list-style-type: none"> • Docosahexaenoic acid (DHA). • Precursor loading with N-acetylcysteine. • The polyphenol antioxidants curcumin, resveratrol, epigallocatechin gallate (EGCG) and Pycnogenol®. • The herbal treatments huperzine A, Bacopa monnieri and Salvia officinalis. • Mitochondrial cofactors, Alpha-lipoic acid and Acetyl-L-carnitine (ALCAR).
Diabetes	No conclusions regarding priority areas for research into CM interventions for diabetes.
Wellness and disease prevention	<ul style="list-style-type: none"> • Develop wellness metrics. • Implement public health programs. • Use IT to enhance wellness. • Integrate lifestyle management into the healthcare system.

Table 10.1 | Summary of research priorities

Appendix A -

Developing a herbal diabetic treatment

This appendix provides the framework for developing a herbal diabetic treatment. Professor Paul Komesaroff prepared this appendix with the assistance of Dr Shanhong Ling (both from the Faculty of Medicine, Nursing and Health Sciences, Monash University).

A.1 Requirements for developing a herbal diabetic treatment

In any project directed at developing a novel herbal treatment for treating diabetes it will be important to clarify the goals. These could include:

- Full development of a product to the level of TGA Registration, with conduct of phase III clinical trials and the aspiration of Pharmaceutical Benefit Scheme (refer TGA website: www.tga.gov.au/industry/cm-argcm.htm).
- Development of the product to the level of TGA Listing, with incremented claims on the basis of limited clinical tests.
- Development of the product to the level of TGA Listing, with no clinical data and limited opportunity to make any useful claims about clinical use.
- Proof of concept that the product has activity in laboratory systems, including in vitro and in vivo testing with a view to establishing intellectual property that could form the basis for obtaining resources for further testing or be saleable to a pharmaceutical or biotechnology company.

- Conduct of limited human testing with a view to establishing intellectual property that could form the basis for obtaining resources for further testing or be saleable to a pharmaceutical or biotechnology company.
- Establishment of ownership of patents and intellectual property in relation to evidence of clinical applications and the specific innovations that have been introduced in the development and processing of the product.

The scientific tasks to be undertaken for the full development of such a product include:

- Botanical identification and literature review.
- Development of a standard extract preparation for laboratory testing.
- Proof of concept of biological activity in a physiological system.
- Proof of concept of clinical activity in an appropriate in vivo system.
- Proof of concept of safety in an in vivo system.
- Full toxicity testing in animals.
- Establishment of efficient bioassay procedure to permit validation of product and assessment of quality.
- Botanical studies to assess variations in activity with respect to variations in plant strains and conditions of growth and processing.
- Establishment of mechanisms of action to distinguish potential product from existing products already available.

- Analytical investigations to identify chemical constituents of product to allow further refinement, to assist in scientific studies and to help position potential product with respect to existing agents.
- Analytical studies to confirm lack of contamination with heavy metals, pesticides and other specified toxins.
- Streamlining of production processes, including agricultural and laboratory practices, and assessment of quality of product and optimal storage and transport conditions.
- Phase I studies in humans, usually directed at confirming safety.
- Phase II studies in humans to show relevant biological activity.
- Phase III studies in humans to establish clinical utility and safety in actual therapeutic settings.

A.2 Cost implications

The outcomes and scientific tasks listed above are associated with widely differing costs and potential rewards. At one extreme, full development of a product to the level of registration can be extremely expensive, in some cases costing many hundreds of millions of dollars. However, the potential rewards are very high. At the other extreme, development to the level of Listing with the Australian Therapeutic Goods Administration may be relatively inexpensive, but in the absence of clinical data and the ability to make claims in the market the potential for significant sales is small.

Investment from the pharmaceutical industry or from biotechnology companies, including the possibility of the full sale of patents and intellectual property may be an appropriate goal. In general, early phase products are of little interest to industry, and typically, relatively little investment is associated with sacrifice of large proportions of intellectual property. As scientific evidence is accumulated the value of a product increases rapidly, although the difficulty of protecting intellectual property also increases. Many developers of novel pharmaceutical agents seek to identify the optimal stage at which to seek financial assistance from private investors or industry.

It is important to emphasise that in the testing of a potential new product the outcomes of scientific testing

cannot be predicted. Accordingly, it is important that the development process proceed incrementally, with the opportunity to curtail the program at any time if the financial benefit/risk ratio falls below an acceptable level.

A.3 Testing procedures and scientific techniques

A range of in vivo and in vitro models is available for testing anti-diabetic activity of candidate herbal substances. In vitro systems include cell and tissue culture preparations. In vivo systems include rat and mouse models, and models involving rabbits, dogs, monkeys and other animals. Diabetes may be induced by administration of streptozotocin, nicotinamide or alloxan, or hyperglycaemia may be precipitated by feeding or administering adrenaline, glucocorticoids or other substances.

Each animal system is associated with both advantages and disadvantages. Advantages include the ability to test the human clinical form of diabetes that they purport to model, and prevalence of specific clinical features, such as obesity, susceptibility to cardiovascular disease, renal disease, neurological disease etc. Some of these models involve insulin deficiency and some hyperinsulinaemia and increased insulin resistance. Some are spontaneously diabetic and some develop diabetes only when subjected to particular stimuli, such as high carbohydrate feeds. Availability and cost are also significant considerations.

In vitro tissue systems include cultured cell lines from muscle, kidney, nerves, retina, endothelium, pancreatic islets and liver.

Variables or endpoints to be assessed can vary widely. Typically, these would include some of the following:

- Fasting glucose, insulin, c-peptide levels.
- Blood pressure.
- Glucose tolerance test, including intraperitoneal glucose tolerance test.
- Plasma lipids.
- Advanced glycation end products.
- Alpha-glucosidase activity in small intestine.
- Cardiovascular variables, including assessment of endothelium-dependent /- independent relaxation, vasoconstriction by free radical-induced and contractive prostanoids.

- Diacylglycerol kinase activity in smooth muscle.
- Glucose 14c-uptake in muscle.
- Glucose transporters I (GLUT I) and IV (GLUT IV).
- Hepatic and skeletal muscle glycogen content and hepatic glucokinase, hexokinase, glucose-6-phosphate and phosphofructokinase levels in diabetic mice.
- Hepatic glucose metabolic activity.
- Hyperglycaemia induced by adrenaline; insulin binding; insulin resistance.
- Lipid peroxides; liver glycogen; serum no2-/no3; viscosity.

For most purposes it will be desirable for the animal model to reflect the conditions of type 2 diabetes. This is because type 2 diabetes is the most common form of diabetes and the area of major social need, and also because the opportunities for therapeutic innovation are much greater here than in type 1 diabetes, where the main treatment is, and will remain, insulin therapy.

A.4 Process for developing herbal treatments for diabetes

In view of the above considerations, it is suggested that testing of potential novel herbal products for the treatment of diabetes adopt the provisional, primary goal of a proof of concept that the product has activity in laboratory systems, including in vitro and in vivo testing. This could establish the basis for some intellectual property rights securing resources for further testing or be saleable to a pharmaceutical or biotechnology company. This should be associated with the following steps.

Establishment of ownership of patents and intellectual property

This step would involve the establishment of ownership of patents and intellectual property in relation to evidence of clinical applications and the specific innovations that have been introduced in the development and processing of the product. From the scientific point of view the achievement of these objectives will require the accomplishment of the following tasks:

- Botanical identification and literature review – This is important because it is possible that there may already be in existence a literature on the herbal product in question. This may either render the project unnecessary – because there would be no intellectual property to develop – or it may assist with further planning and development.
- Development of a standard extract preparation for laboratory testing – This is important because it is essential to have access to a reliable and reproducible source of materials if results are to be definitive. It is possible to obtain crude herbal materials by extraction into aqueous or alcoholic media or into other solvents. Knowledge of the plant species and an understanding of the likely plant constituents might assist with this; otherwise, it may be necessary to prepare a number of extractions and test all of them.
- Proof of concept of biological activity in a physiological system – It is essential that the existence of a basic activity be established if any significant investment is to be justified. This should take the most rudimentary form possible: preferably, the proof that the substance has the effect of lowering glucose levels in animals with type 2 diabetes. If the proposed activity involved a different physiological end point – for example, an effect on blood vessels or lipid levels – this would be the focus of the primary proof of concept testing.
- Proof of concept of clinical activity in an appropriate in vivo system – Proof of clinical activity may be undertaken at the same time as proof of physiological activity, but it is important to stress that conceptually it is different. Proof of clinical activity involves testing in an animal disease model, which is thought to reflect the conditions of human disease. Testing at this level may provide preliminary information about likely therapeutic dosages, safety etc.
- Proof of concept of safety in an in vivo system – This too may be undertaken together with the initial physiological testing but represents a separate end point. Usually, safety testing in animals involves establishment of safe dosages and assessment of effects in a variety of organs.

Establishment of mechanisms of action

This step would involve the establishment of mechanisms of action to distinguish potential product from existing products already available. This stage would entail a range of more specific laboratory based studies and would aim to identify the potential place of the product in relation existing products. This would be an essential step in developing intellectual property that distinguished the product from potential competitors. If the product were to replicate the actions of existing ones its place in the market may be dependent on lack of side effects or the attractiveness of its herbal origins. If it were to act through a novel mechanism it may command a much bigger market. The mechanism of action would define the ways in which the product might be used clinically in conjunction with existing medications.

The first two bullet points would be relatively straightforward and inexpensive. The third, fourth and fifth steps would be included within a single experiment using an animal system. A successful conclusion to this experiment would provide good evidence of justification to continue or alternatively, the opportunity to curtail the project. This stage would be entail modest expense. The cost of the sixth stage would in general be modest, largely because of the relative lack of expense of the materials, but would depend on the extent of testing and the nature of the findings.

If these outcomes were satisfactorily achieved, consideration would then appropriately be given to the development of further resources for testing and development or to sale of the product to another developer. The steps that would follow would include those listed earlier.

A.5 Overarching research program

In view of the above considerations in asserting proof of concept and establishing potential mechanisms of action it is proposed that the comprehensive investigation of the herbal product in question be approached in a systematic manner in the following sequence:

- Botanical identification and literature review.
- Proof of concept physiological testing, clinical testing and toxicity assessment.

- Investigation of mechanisms of action.
- Establishment of a workable bioassay.
- Human toxicity testing and early phase clinical testing.
- Phase III clinical testing in humans.

A brief sketch of what each phase would entail follows.

Botanical identification and literature review

This would entail engagement of the services of an expert in botany who could provide advice about the species of plant involved. This would be followed by a systematic search of the scientific literature to obtain information about possible chemical constituents, their activities and toxicity, investigative systems that may have been employed in the testing of related chemical products in the past etc. Such information would greatly assist the development of the investigative program.

First stage testing: proof of concept

Proof of concept testing would entail the employment of in vivo and maybe in vitro models to ensure that there is a scientific question that is worth answering. In the first instance the most accessible, efficient and economical model should be utilised to demonstrate beyond doubt that the substance in question has relevant biological activity. In general, this will require the use of a simple animal model. Well-tested models, which are usually readily available and have been satisfactorily validated in relation to type 2 diabetes in humans, would be appropriate. Following the establishment of biological activity, more focused testing is required to demonstrate clinical activity in the animal setting and to make a preliminary assessment of safety and toxicity. Successful conclusion of testing at this level would provide a rigorous basis for an ongoing testing program that would start the process of addressing the more detailed and specific scientific questions that would define the potential clinical and economic niche of the product.

An important part of this early phase of testing is the establishment of a standard preparation for ongoing laboratory testing. If an activity can be established in the basic animal model this can be used as the benchmark laboratory variable for the preparation of a purified extract. This would usually take the form of the preparation of a crude mixture from the whole plant or an extract using

a solvent, such as water, alcohol or an organic solvent. A standardised method of preparing the product to be used for testing is important because the interpretation of subsequent results will depend on the product that is employed.

Second stage testing

Once it has been demonstrated that there is at least a circumstantial case that the herbal product is biologically active in a manner that is likely to be clinically relevant more detailed and specific testing would be undertaken to identify the nature of the product and its underlying mechanisms of action. This phase would include detailed chemical analysis using a variety of techniques, which could include high-pressure liquid chromatography, nuclear magnetic resonance testing, gas spectroscopy etc. Such studies might include both in vivo and in vitro testing.

Testing for mechanisms would generally involve specific tissue culture preparations, such as muscle or vascular cells in which insulin was known to be active. In these settings the possibility that the product acts through one of the known existing mechanisms of action (see above) would be tested.

At this stage a reliable bioassay would be established as a benchmark for the ongoing testing of quality and biological activity. This would permit the continuation of studies into storage conditions, shelf life, optimal conditions for transport and processing of the raw herb etc.

Detailed animal toxicity testing would also occur at this stage: this would include formal testing in rodent models of the effects of different dosages of the preparation on specific organ systems. Formal protocols are available for such tests, which are a pre-requisite to human testing, even if the product is available for sale in Australia.

This is the point at which the product would likely be submitted to the Therapeutic Goods Administration for Listing in Australia. This would permit it to be marketed in Australia for limited indications as permitted under the instructions of the TGA.

Third stage testing

The stage following would initiate the process of human testing. Details of such testing would be developed at the time. However, it is likely that this would take the form of a pilot study with many outcomes to collect information to design a definitive study sufficient to satisfy the needs of a registration application. Consideration would also be given at this stage to the need to conduct formal Phase I human toxicity and metabolic testing. The need for this would be assessed in relation to the available data at the time, including the results of the tests performed to this stage and other information available about the herb in questions.

Fourth stage testing

The final stage of testing would take the form of a Phase III clinical study, which is a study directed at proving that the product is both effective and safe. The end points of this study would be clinical outcomes identified in the earlier studies. Such a study would be conducted following negotiation with the regulatory authorities in the jurisdictions in which registration were being sought, typically Australia and the United States. The cost of such studies is often considerable; however it does vary widely depending on the nature of the end points being tested.

A.6 Summary of suggested plan and timelines

In summary, testing schedules for candidate herbal products for managing diabetes should have an incremental form. Defined junctures would be identified at which negative results would be likely to mean that the process was brought to an end. The commitment of resources at each stage would be justified by the likelihood of continuing success. The overall objective would be to obtain sufficient information to permit introduction and marketing of the product in Australia at a level that permits prescribers and consumers to make informed judgements about efficacy, safety and quality.

The timelines would, of course, depend on such things as the nature of the results obtained and the endpoints being tested. Decision points would need to be pre-specified.

Appendix B - traditional chinese medicine

While the other expert groups were identifying research priorities for chronic diseases, the NICM Collaborative Centre for Traditional Chinese Medicine (TCM) undertook a parallel process to identify potential research priorities in acupuncture and Chinese herbal medicine. These research priorities are documented in this chapter.

This chapter was prepared with input from various members of the NICM Collaborative Centre for Traditional Chinese Medicine.

- The anti-malarial drug artemisinin and ephedrine, which are derived from Chinese herbs.

Since 1949, TCM has been scientifically studied and integrated with western medicine. Biomedical sciences have made considerable changes to TCM. For example, standardised formulae of herbal therapies are now commonly used as tablets, capsules, and even ampoules as well as the traditional decoctions of individualised prescriptions.

B.1 What is TCM?

Traditional Chinese medicine is one of the oldest healing systems. It includes herbal medicine, acupuncture, moxibustion, massage, food therapy, and physical exercise, such as shadow boxing. It is a fully institutionalised part of Chinese health care and widely used with western medicine. In 2006, the TCM sector provided care for over 200 million outpatients and some seven million inpatients, accounting for 10–20% of health care in China.

TCM is becoming more widely used in western countries. Notable contributions include:

- Acupuncture, which was introduced in developed countries in the 1600s.
- Variolation, which was developed in the 16th century in China as a method to immunise people against smallpox. The method was introduced to Europe in the early 1700s.

B.2 Traditional chinese medicine in australia

The only national survey of TCM practitioners in Australia was undertaken in 1996 (Bensoussan and Myers, 1996). It found that TCM was being used to treat a wide range of illnesses, including neurological, musculoskeletal, rheumatologic (40%); endocrine and gynaecological (15%); respiratory (12%); gastrointestinal (8%); immunological (7%); dermatological (6%) and psychological (5%) disorders.

B.3 Current evidence for TCM

Despite decades of research and integration, the fundamentals of TCM remain largely unchanged and its theories inexplicable to science (Ling Tang, Bao-Yan Liu, Kan-Wen Ma, 2008). The absence of scientific

understanding has caused scepticism and criticism about TCM. However, randomised trials have shown efficacy for some TCM therapies. The efficacy of most assessed therapies, however, remains uncertain, often because of the low methodological quality of trials. Furthermore, most of these trials are published in Chinese, inaccessible to western doctors, and not included in systematic reviews. Selective publication of positive trials is another problem. In addition, some of the ingredients are not allowed in Australia, so, for local study, there may need to be changes in formulation, which could affect their effectiveness.

However, during the last decade, numerous Cochrane and systematic reviews have been undertaken, and systematic reviews show that Chinese herbs and acupuncture can be effective for atopic eczema and chemotherapy-induced nausea, respectively. In addition, there is promising evidence for the effectiveness of traditional Chinese herbal medicine in various pain conditions such as low back pain and dysmenorrhoea. Table A1 lists TCM therapies that show promising clinical significance.

Table A.1 | Cochrane (CR) and other systematic reviews (SR) where TCM shows promise

Title	Year	Disease / category	Conclusions
Chinese herbal medicines for induction of remission in advanced or late gastric cancer	CR: 2013	Gastric cancer Cancer	Huachansu, Aidi, and Fufangkushen were of benefit for adverse events in the digestive system caused by chemotherapy. Larger trials are needed before any definite conclusions can be drawn.
Add-On Effect of Chinese Herbal Medicine on Mortality in Myocardial Infarction: Systematic Review and Meta-Analysis of Randomized Controlled Trials	SR: 2013	Myocardial Infarction Cardiovascular	The addition of HM is very likely to be able to improve survival of MI patients who are already receiving Biomedicine.
Herbal medicines for advanced colorectal cancer	CR: 2012	Colorectal cancer Cancer	Some HM with combined chemotherapy compared with chemotherapy alone showed more beneficial effects in improving 1-year, 3-year survival and quality of life.
Ganoderma lucidum (Reishi mushroom) for cancer treatment	CR: 2012	Cancer Cancer	<i>G. lucidum</i> could be administered as an alternative adjunct to conventional treatment in consideration of its potential of enhancing tumour response and stimulating host immunity. Future studies are needed.
Chinese herbal medicines for threatened miscarriage	CR: 2012	Miscarriage Gynecology	A combination of CHM and Western medicines was more effective than Western medicines alone for treating threatened miscarriage. However, the quality of the included studies was poor.
Chinese herbal medicine for endometriosis	CR: 2012	Endometriosis Gynecology	Post-surgical administration of CHM may have comparable benefits to gestrinone. Oral CHM may have a better overall treatment effect than danazol and it may be more effective in relieving dysmenorrhoea when used in conjunction with a CHM enema. CHM appears to have fewer side effects than either gestrinone or danazol. More rigorous research is required.
Interventions for preventing infection in nephrotic syndrome	CR: 2012	Nephrotic syndrome Urology	IVIg, thymosin, oral transfer factor, BCG vaccine, Huangqi granules and TIAOJINING may have positive effects on the prevention of nosocomial or unspecified infection in children with nephrotic syndrome; but study quality is low.
Chinese Herbal Medicine in Treating Primary Sjögren's Syndrome: A Systematic Review of Randomized Trials	SR: 2012	Primary Sjögren's Syndrome (PSS) Immune System	Preliminary evidence from RCTs suggests the effect of CHM is promising for relieving symptoms, improving lacrimal and salivary function in PSS. However quality is low.
Systematic Review on the Efficacy and Safety of Herbal Medicines for Vascular Dementia	SR: 2012	Vascular Dementia Neurological	Studies suggested that HM can be a safe and effective treatment for VaD, either alone or in conjunction with OM. However, methodological design flaws limit results.
Efficacy and Side Effects of Chinese Herbal Medicine for Menopausal Symptoms: A Critical Review	SR: 2012	Menopause Gynecology	CHM may be effective for some menopausal symptoms; side effects are likely less than those of hormone therapy. More comprehensive studies are needed.

Title	Year	Disease / category	Conclusions
Chinese Herbal Medicine Danshen Formulations for Preventing Renal Disease in Henoch-Schönlein Purpura: A Systematic Review and Meta-Analysis	SR: 2012	Renal disease Urology	Danshen formulations may help prevent renal disease in children with HSP without serious side-effects. Evidence is of low quality.
Chinese herbal medicines for treatment of hand, foot and mouth disease: A systematic review of randomized clinical trials	SR: 2012	Hand, foot and mouth disease Other	This review suggests HM combined with Western medications or used separately might improve symptoms of HMFD; but quality is low.
The efficacy of Chinese herbal medicine as an adjunctive therapy for colorectal cancer: A systematic review and meta-analysis	SR: 2012	Colorectal Cancer Cancer	CHM as an adjunctive therapy with chemotherapy versus chemotherapy alone has significant efficacy in terms of prolonging survival, enhancement of tumor response, improvement of quality of life, immunoregulation, and alleviation of acute adverse effects. However, quality of the included trials is low.
Clinical efficacy and safety of Chinese herbal medicine for Wilson's disease: A systematic review of 9 randomized controlled trials	SR: 2012	Wilson's disease Other	CHM seems to be beneficial and safe for Wilson's disease; but high-quality evidences is needed.
Meta-analysis of clinical trials on traditional Chinese herbal medicine for treatment of persistent allergic rhinitis	SR: 2012	Allergic rhinitis Respiratory	CHM interventions appear to have beneficial effects in patients with PAR. However, studies are too small to draw firm conclusions.
Chinese Herbal Medicine Paratherapy for Parkinson's Disease: A Meta-Analysis of 19 Randomized Controlled Trials	SR: 2012	Parkinson's Disease Neurological	CHM adjuvant therapy may potentially alleviate symptoms of PD and generally appeared to be safe and well tolerated. However, better quality studies are needed.
Systematic review and meta-analysis of randomized controlled trials of Chinese herbal medicine in the treatment of Sjogren's syndrome	SR: 2011	Sjogren's syndrome Immune System	CHM appears to improve the symptoms of Sjogren's syndrome. However, better quality studies are needed.
Efficacy of Traditional Chinese Herbal Medicine in the management of female infertility: A systematic review	SR: 2011	Infertility Gynecology	Management of female infertility with CHM can improve pregnancy rates 2-fold within a 4 month period compared with Western Medical fertility drug therapy or IVF. Assessment of the quality of the menstrual cycle, integral to TCM diagnosis, appears to be fundamental to successful treatment of female infertility.
Chinese herbal medicines for hypercholesterolemia	CR: 2011	Hypercholesterolemia Cardiovascular	Some HM may have cholesterol-lowering effects. Our findings have to be interpreted with caution due to high or unclear risk of bias of the included trials.
Cernilton for benign prostatic hyperplasia	CR: 2011	Benign prostatic hyperplasia Urology	The available evidence suggests Cernilton is well tolerated and modestly improves overall urologic symptoms including nocturia. However with poor methodological quality additional trials are needed.
Herbal therapy for treating rheumatoid arthritis	CR: 2011	Rheumatoid arthritis Musculoskeletal	There is moderate evidence that oils containing GLA (evening primrose, borage, or blackcurrant seed oil) afford some benefit in relieving symptoms for RA. Tripterygium wilfordii products may reduce some RA symptoms; however, oral use may be associated with several side effects. Further investigation herbal therapy is warranted.
Chinese herbal medicine for chronic neck pain due to cervical degenerative disc disease	CR: 2010	Neck pain Musculoskeletal	There is low quality evidence that an oral HM, Compound Qishe Tablet, reduced pain more than placebo or Jingfukang and a topical herbal medicine; Compound Extractum Nucis Vomicae reduced pain more than Diclofenac Diethylamine Emulgel.

Title	Year	Disease / category	Conclusions
Chuanxiong preparations for preventing stroke	CR: 2010	Stroke Cardiovascular	Nao-an capsule may be a choice for the primary prevention of stroke. However, the results are potentially affected by bias from the way participants were selected, or from investigators' conflicts of interests.
Oral Chinese herbal medicine as an adjuvant treatment during chemotherapy for non-small cell lung cancer: a systematic review	SR: 2010	Lung cancer Respiratory	It was possible that oral CHM medicine used in conjunction with chemotherapy may improve quality of life in non-small cell lung cancer. This needs to be examined further with more rigorous methodology.
Chinese herbal medicine for primary dysmenorrhoea	CR: 2009	Dysmenorrhoea Gynecology	The review found promising evidence supporting the use of CHM for primary dysmenorrhoea; however, results are limited by the poor methodological quality.
Chinese herbal medicines for people with impaired glucose tolerance or impaired fasting blood glucose	CR: 2009	Diabetes Diabetes & Obesity	The positive evidence in favour of CHM for the treatment of IGT or IFG is constrained by: lack of trials that tested the same HM, poor reporting and other risks of bias.
A systematic review of the efficacy and safety of herbal medicines used in the treatment of obesity	SR: 2009	Obesity Diabetes & Obesity	HM that contained ephedra, Cissus quadrangularis, gingseng, bitter melon and zingiber were effective in the management of obesity.
Compound Chinese herbal medicines, Chinese herbal drugs and their active extracts for treatment of chronic hepatitis C: a systematic review and meta-analysis of randomized clinical trials	SR: 2009	Hepatitis C Hepatology	HM has effects in improving symptoms, liver function, and loss of HCV markers in patients with chronic hepatitis C. However, quality was low.
Herbal medicine for dementia: a systematic review	SR: 2009	Dementia Neurological	HM was potentially beneficial for the improvement of cognitive function in various age-related dementias. However quality and sample size was low and more studies are needed.
Systematic review of Chinese herbal medicine for functional constipation	SR: 2009	Constipation Gastroenterology	CHM or CHM combined treatments showed benefit for functional constipation when compared with cisapride, polyethylene glycol 4000, mosapride, phenolphthalein, itopride and bifidobacteria alone, but not when compared with massage.
A meta-analysis of Chinese herbal medicine in treatment of managed withdrawal from heroin	SR: 2009	Heroin withdrawal Other	CHM was not as effective as opioid agonists but was more effective than alpha2 adrenergic agonists in relieving managed symptom withdrawal from heroin and may have relieved anxiety with fewer side effects.
Sanchi for acute ischaemic stroke	CR: 2008	Stroke Cardiovascular	Sanchi appears to be beneficial and safe for acute ischaemic stroke; the small sample and inferior quality of studies prevented a definite conclusion.
Systematic review of the efficacy and safety of herbal medicines for Alzheimer's disease	SR: 2008	Alzheimer's disease Neurological	HM can be a safe, effective treatment for Alzheimer's disease, either alone or in conjunction with OM. However, methodological flaws in the design of the studies limited the extent to which the results could be interpreted.
Effectiveness and safety of herbal medicines in the treatment of irritable bowel syndrome: a systematic review	SR: 2008	Irritable bowel syndrome Gastroenterology	HMs have therapeutic benefit but use with caution.
Treatment of menopausal symptoms with Er-xian decoction: a systematic review	SR: 2008	Menopausal symptom Gynecology	EXD is effective in treating menopausal symptoms; but low quality of the investigated studies.
Chinese herbal medicine for mild cognitive impairment and age associated memory impairment: a review of RCTs	SR: 2008	Mild cognitive impairment Neurological	Meta-analysis of three studies found the effects of the CHMs were at least equivalent to piracetam on Mini-Mental State Examination (MMSE) scores. No severe adverse events were reported.

Title	Year	Disease / category	Conclusions
Herbal medicines for the treatment of allergic rhinitis: a systematic review	SR: 2007	Allergic rhinitis Respiratory	<i>P. hybridus</i> extract may be effective, and there are promising results for other herbal products.
Shengmai (a traditional Chinese herbal medicine) for heart failure	CR: 2007	Heart failure Cardiovascular	Shengmai may be possibly beneficial for heart failure but evidence is weak due to poor quality of studies.
Echinacea for preventing and treating the common cold	CR: 2006	Common cold Respiratory	There is some evidence that preparations based on the aerial parts of <i>E. purpurea</i> might be effective for the early treatment of colds in adults, but the results are not consistent.
The use of herbal medicine in Alzheimer's disease-a systematic review	SR: 2006	Alzheimer's disease Neurological	This review identified two herbs and herbal formulations with therapeutic effects for the treatment of Alzheimer's disease: <i>Melissa officinalis</i> , <i>Salvia officinalis</i> and Yi-Gan San and BDW (Ba Wei Di Huang Wan). <i>Ginkgo biloba</i> was identified in a meta-analysis study. All five herbs are useful for cognitive impairment of Alzheimer's disease. <i>M. officinalis</i> and Yi-Gan San are also useful in agitation as they have sedative effects. These herbs and formulations have demonstrated good therapeutic effectiveness but the results need to be compared with those of traditional drugs.
Herbal medicines for treatment of irritable bowel syndrome	CR: 2006	Irritable bowel syndrome Gastroenterology	Some HMs may improve symptoms but positive findings to be interpreted with caution due to inadequate methodology, small sample size and lack of confirming data.
Herbal medicine for low back pain	CR: 2006	Low back pain Musculoskeletal	<i>Harpagophytum procumbens</i> , <i>Salix alba</i> and <i>Capsicum frutescens</i> seem to reduce pain more than placebo; but poor quality reporting.
Chinese medical herbs for chemotherapy side effects in colorectal cancer patients	CR: 2005	Chemotherapy side effects Cancer	Huangqi compounds may stimulate immunocomponent cells and decrease side effects, but no robust demonstration of benefit. There was no evidence of harm.
Chinese herbal medicine for atopic eczema	CR: 2004	Atopic eczema Dermatology	May be effective but only four poor RCTs on the same product were reported.
Herbs for serum cholesterol reduction: a systematic review	SR: 2003	Cholesterol Cardiovascular	In addition to lowering cholesterol, several of the herbs may exert beneficial effects in cardiovascular disease by elevating high-density lipoprotein levels and inhibiting lipid oxidation. While the long-term safety of these products has not been established, the safety profiles seem encouraging.
Herbal medicines for the treatment of rheumatoid arthritis: a systematic review	SR: 2003	Rheumatoid arthritis Musculoskeletal	There was moderate support for gamma-linoleic acid having a medium to strong effect on reducing pain and tender joint count and a small effect on reducing stiffness in rheumatoid arthritis for those with active disease.
Chinese herbal medicines for type 2 diabetes mellitus	CR: 2002	Type 2 diabetes Diabetes	Some HMs show hypoglycaemic effects; but low methodological quality, small sample size, limited number of trials.
Herbal medicines for the treatment of osteoarthritis: a systematic review	SR: 2001	Osteoarthritis Musculoskeletal	Promising evidence was found for the effective use of some HM in the treatment of osteoarthritis. In addition, there was evidence to suggest that some HM reduce the consumption of NSAIDs. The reviewed HM appeared relatively safe. Some HM may offer a much-needed alternative for patients with osteoarthritis.
Chinese medicinal herbs for asymptomatic carriers of hepatitis B virus infection	CR: 2001	Asymptomatic carriers of hepatitis B virus Hepatology	Jianpi Wenshen recipe may have an antiviral activity; but quality is low.
Beta-sitosterols for benign prostatic hyperplasia	CR: 1999	Benign prostatic hyperplasia Urology	The evidence suggests non-glucosidic B-sitosterols improve urinary symptoms and flow measures. Their long term effectiveness, safety and ability to prevent benign prostatic hyperplasia complications are not known.
Pygeum africanum for benign prostatic hyperplasia	CR: 1998	Benign prostatic hyperplasia Urology	A standardized preparation of <i>Pygeum africanum</i> may be a useful treatment option for men with lower urinary symptoms consistent with benign prostatic hyperplasia. However, the reviewed studies were of low quality. Additional studies are needed.

Table A.1 | Cochrane (CR) and other systematic reviews (SR) where TCM shows promise

HM – herbal medicine; OM – oriental medicine; CHM – Chinese herbal medicine

	Adverse reaction(s)	Reasons for adverse reaction
Mercury, lead, cadmium	Various	Contamination, such as in Fu Fang Lu Hui Jiao Nang
Ginkgo biloba, garlic, Chinese angelica, Salvia miltiorrhiza	Severe bleeding	Interaction with western drugs, such as Warfarin
Radix aconiti lateralis Preparata spp, Aconite spp	Cardiotoxicity, such as severe arrhythmia	Used raw and unprocessed, inappropriately prepared form, or overdosing
Caulis aristolochiae Manshuriensis spp	Nephrotoxicity and carcinogenicity	The herb contains aristolic acid and is wrongly used as Caulis clenmatidis armandii (eg, in some weight-loss products and Long Dan Xie Gan Wan)

Table A.2 | Adverse reactions and toxic effects caused by TCM

Source: www.thelancet.com (Published online October 20, 2008
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However, TCM does have adverse effects (see Table A2). The main reasons for adverse effects are contamination and inappropriate use rather than inherent risks with the herbs themselves. Most adverse reactions can thus be avoided by quality control and guided applications. In a sceptical environment, it would be a mistake to dismiss effective therapies on the basis of adverse effects rather than benefit–harm ratios.

B.4 Methodological challenges in performing TCM research

Researchers face a number of methodological challenges in performing high quality TCM research that are particular to TCM. There is a need to:

- Recognise differing clinical patterns in TCM and to vary treatment in TCM in respect of these patterns rather than sticking to the ‘one herbal drug/acupuncture formula treats all’ concept.
- Undertake research on the whole practice of TCM – combining acupuncture, exercise, dietary changes and herbs as a single approach to treatment, rather than isolating and testing each component of treatment.

B.5 Research priorities in TCM

Research priorities in TCM remain to be fully developed and articulated. Some planning has commenced with the China Academy of Chinese Medical Sciences and it anticipates the process will be completed within 12 to 18 months. The initial suggestions from the Australian academic and practitioner groups are summarised below.

Acupuncture

- Treatment of anxiety and depression, including sleep disorders.
- Treatment of musculoskeletal disorders, including post-stroke rehabilitation, injuries and post-operative pain.
- Potential improvement of in-vitro fertilisation (IVF) outcomes.
- Support for cancer patients in relation to stress; nausea and vomiting during chemotherapy; and immunity enhancement.
- Treatment of cardiovascular diseases, including the potential to improve ischaemic heart disease and various cardiovascular parameters.
- Treatment of allergies, including asthma and hay fever, and general immune support.
- Treatment of eczema.

Chinese herbal medicine

- Treatment of neurodegenerative diseases (Alzheimer's, vascular dementia, Parkinson's disease).
- Management of the side effects of chemotherapy, and stimulation of the immune system during cancer therapy.
- Treatment of cardiovascular disease and related risk factors (such as stroke, hypertension, arteriosclerosis, elevated cholesterol, and heart failure).
- Management of type 2 diabetes, and the hypoglycaemic effects of some herbs.
- Management of obesity.
- Treatment of respiratory diseases, such as asthma, chronic obstructive pulmonary disease (COPD), hay fever, influenza, and viral diseases (the common cold, etc).
- Treatment of inflammatory disorders, including osteoarthritis.
- Treatment of functional gastrointestinal disorders, including irritable bowel syndrome.
- Treatment of eczema and other skin disorders.

Acupuncture and Chinese herbal medicine are used to treat a range of other disorders, but these have not been listed as key priorities for research as they do not align with Australian National Health Priority Areas.

In addition, there are areas where Chinese herbal medicine is utilised for particular conditions for which no commonly accepted or standard approach is available including chronic fatigue or some chronic renal disease.

Generally, there is also a need to:

- Evaluate and summarise in a consistent and meaningful fashion prior clinical studies of acupuncture and Chinese herbal medicine. Many quality-rating scales for clinical trials may be used, generating different conclusions.
- Undertake another TCM Practitioner Survey to gain current insight into the clinical experience of Australian practitioners, and update the findings of the 1996 survey.

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