Chapter 5
How to Search and Critique Scientific Evidence for Decision-Making

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ABSTRACT

A clinical decision on the use of complementary and alternative medicine (CAM) should be made based on evidence-based medicine (EBM) together with practitioner's knowledge and experiences. This chapter describes the process of EBM, including how to address a clinical question, do a systematic search for appropriate evidence with key search terms, appraise the evidence and make a clinical decision on CAM applications. An effective literature search should be performed by using a structured search strategy in searching biomedical and CAM databases, such as the National Center for Complementary and Alternative Medicine (CAM Citation Index), Research Council for Complementary Medicine (CISCOM), CAMBase, Central Council for Research in Ayurveda and Sidha (CCRAS), and Chinese medicine databases. Few standard tools are recommended to evaluate the quality of CAM studies, i.e. the CONSORT extension for herbal interventions and STRICTA for RCTs of acupuncture. Additionally, some guidelines for designing RCTs in Chinese herbal medicine (CHM) can also be adopted to critique CAM literature. A clinical decision on choosing optimal CAM for patient care should be based on the current best evidence emerged from the EBM process.

Keywords: Evidence-based medicine, Systematic search, Key search term, CAM study, CAM database, Critical appraisal, Evaluation tool, Clinical decision-making

INTRODUCTION

Decision-making on optimising the use of complementary and alternative medicine (CAM) is challenged for clinical practitioners due to a lack of robust clinical evidence. Conventionally, many alternative approaches, such as personal experiences (or anecdotes), suggestions from others, or available algorithms or decision trees, are used to rationalise clinical decisions. However, the evidence-based medicine (EBM) process which is usually employed in western or conventional medicine to facilitate clinical decision making has been considered as an appropriate approach to making a decision on CAM use. Three key components, i.e. clinical expertise, patient's values and preferences, and the best research evidence, will be

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integrated into the EBM decision-making process to ensure optimum health outcomes in terms of therapeutic, economic or humanistic impacts.

According to Sackett, Rosenberg, Gray, Haynes, & Richardson (1996), EBM refers to the conscientious, explicit and judicious use of current best evidence in making decisions about individual patient care. Another definition is "the process of systematically reviewing, critically appraising and using findings from clinical studies in order to provide optimal care for an individual patient" (Rosenberg et al., 1995). The correct concept of evidence source and quality, together with relevant skills to retrieve, appraise and apply the best current evidence is the paramount foundation for making an evidence-based clinical decision on choosing CAMs. This chapter outlines the process of systematic search, critique of scientific evidence and decision-making based on evidence for practitioners grasp the concepts and master these skills at their own pace.

The prior knowledge of "best current evidence" is cornerstone to implement EBM in clinical decision-making. Evidence is generally referred to a fact or information obtained from clinical or scientific studies using appropriate methodologies or from other sources, however the quality of evidence varies with studies. Several organisations, e.g. Oxford Centre for Evidence-Based Medicine, and Scottish Intercollegiate Guidelines Network (SIGN), have endeavoured to categorise the levels of evidence for judging the causal relationship of clinical interventions, i.e. from the highest to the lowest, based on the quality of the clinical studies. To facilitate the decision-making when choosing CAM, the category proposed by National Health and Medical Research Council (2009) is often used to facilitate the decision-making (Table 1).

Table 1. Levels of evidence (National Health and Medical Research Council, 2009)

Level	Study design
I	Systematic reviews of level II studies
II	Randomised controlled trials (RCTs)
III	Non-RCTs, observational studies, cross-sectional studies
IV	Case series, case reports, expert opinions
V	Animal studies

A systematic review of randomized controlled trials (RCTs), including meta-analysis, is the strongest evidence level, followed by RCTs, non-RCTs, observational studies (e.g. cohort or case-control studies) and cross-sectional research for judging causality. The RCT is an experimental design aimed to minimise bias and control confounding factors, and provides more rigorous evidence than observational studies or other study types as infers causality between clinical interventions and outcomes. In contrast, case reports together with expert opinions and animal studies are regarded as weak levels of evidence for causality. On the whole, if a systematic review or RCT is currently available, it should be ideally chosen as the best evidence to support clinical decision making. If no such study exists, the decision may be based on a weaker level of evidence, such as an observational study or even a case or animal study. A clinical judgement might be changed at a later date if new evidence with stronger levels emerges.

Although results derived from RCTs are deemed the 'gold standard' of evidence for evaluating the efficacy and safety of CAM as well as conventional medicine in the management of kidney disorders, it is a challenge to carry out an RCT on CAM. Currently, there have been a few systematic reviews and meta-analyses of RCTs on the efficacy and safety of CAM use for kidney diseases (Chapter 7).

Most CAM studies are small in scale and non-RCT. A large number of studies in herbal medicines are conducted in animals in order to prove the biological and toxic effects of CAM. Thus, the results of animal studies are likely to be extrapolated by clinical decision makers to support the efficacy and safety of herbal medicines used in human. In reality, CAM has been used in daily life for hundreds of years and people choose CAM based on their own experiences or knowledge.

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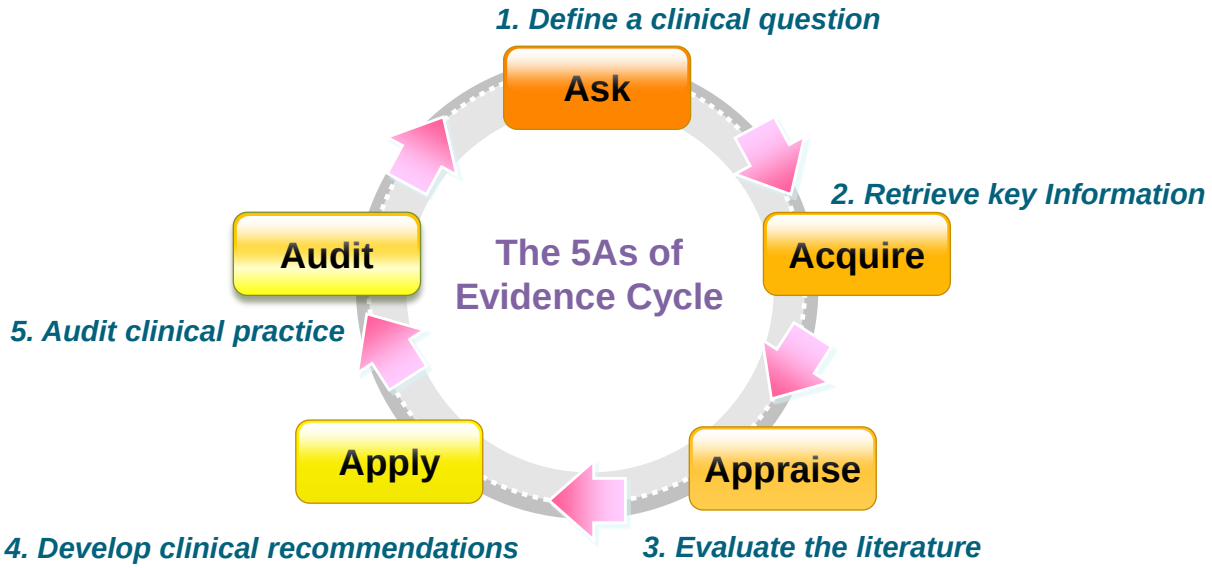
In general, the process of EBM is categorised into five steps, called "5 A's", including asking an answerable question, finding an article (or evidence), critically appraising the evidence, applying the evidence and assessing the outcome, Figure 1 (Straus et al., 2010).

Figure 1. Five steps of evidence-based medicine for complementary and alternative medicine



ADDRESSING QUESTIONS AND CREATING KEY SEARCH TERMS

First and foremost, a focused clinical question about CAM must be identified. Ideally, the question should be answerable so that practitioners could eventually make an appropriate judgement. However, it is often difficult to translate a clinical problem into a question that can be answered as the context and scope may vary. Therefore, a "PICO" framework, i.e. the population (or patient), intervention (or indicator), comparator (or control) and outcome, is recommended to guide defining a clinical question (Wilson et al., 2002). For instance, the question "Can vitamin C reduce cardiovascular events in adult patients with chronic kidney disease at stages 3 – 5?" can be constructed from the following PICO details:

Population - adult patients with stages 3 – 5 chronic kidney disease
Intervention - vitamin C given to the patients
Comparator - either a placebo or standard treatment
Outcome - cardiovascular events that may include direct and surrogate outcomes, such as all-cause mortality, length of stay, etc.

The "PICO" framework is applicable to defining different types of CAM questions. Flower et al. (2014) categorised ten types of questions related to CAM (Table 2). The most common one is about how to manage a disease or condition, which is sometimes called an "intervention" question. It should be noted that not all question types requires all "P, I, C and O" elements to define a question. For example,in a qualitative approach to explore an experience or phenomenon, the question may only require 'P' and 'O' elements to compose a CAM query.

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Table 2. Questions related to CAM adapted from Flower et al. (2014)

	Type	Question
1.	Treatment/intervention	What is the efficacy of CAM for a specific disease/condition?
2.	Treatment/intervention	What is the effectiveness of CAM in practice?
3.	Risk/safety	Are there any adverse effects from CAM?
4.	Health promotion	How effective is CAM to promote/boost health?
5.	Disease prevention or protection	How effective is CAM to prevent a disease/condition?
6.	Health rehabilitation	How effective is CAM for the rehabilitation?
7.	Experience	What is the patient's experience of using CAM?
8.	Indication/prediction	Which conditions seem to respond well to CAM?
9.	Prognosis	When (or how long) will CAM have an effect?
10.	Component	What are the active ingredients of a particular herbal medicine?

SEARCHING MEDICAL DATABASES

To answer a focused CAM question, appropriate evidence or relevant literature are needed to be retrieved, and hence a systematic literature search is recommended. The process includes identifying key search terms, selecting suitable databases (or information sources), searching for pertinent literature and keeping the literature records. Initially, either 'narrow' or 'broad' search terms can be applied to the literature search. Considering the example above, the narrow terms may be adult patients, advanced chronic kidney disease, vitamin C and cardiovascular events. If the search terms only render limited records or evidence, broader terms (e.g. antioxidant therapy and kidney diseases) may be used instead. Alternatively, we can make use of the keywords provided by several databases or previous systematic reviews, e.g. acupuncture, specific names of herbal medicines, hypnosis, massage and yoga, as search terms. Other CAM modalities in many databases can also be utilised to find pertinent studies, e.g. homeopathy, meditation and reflexology (Pilkington, 2007).

If CAM terminologies are not consistently indexed by standard subject headings among various databases, a wide range of search terms should be tried to identify all relevant evidence. An example is to find the evidence for meditation that helps relieve the complications of chronic kidney disease. The key search terms of the intervention, i.e. meditation, mind-body therapy, mind-body medicine, relaxation therapy and relaxation techniques, may be applied. Moreover, if we need to search for CAM efficacy in human studies, the clinical outcomes of CAM, such as a slow progression of chronic kidney disease, may be used as a key search term. As for the CAM outcome in animal studies, pharmacological or biological effects of CAM, such as diuretic effects and inhibition of angiotensin-converting enzyme, may be applicable.

Regarding the information sources, practitioners can choose a wide range of biomedical and CAM databases that may be general or specific to CAM related issues. The online general databases for primary literature include the Medical Literature Analysis and Retrieval System Online (MEDLINE or MEDLARS Online), Excerpta Medica Database (EMBASE) and SciVerse Scopus (Scopus); the Cochrane Collaboration offers the secondary literature, which is defined as the evidence is gathered or synthesised from original studies. Table 3 shows advantages and disadvantages of the biomedical databases (Coelho et al., 2007).

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Table 3. Biomedical databases

Database	Produced by	Advantages	Disadvantages
CINAHL	EBSCO	▪ Providing the largest nursing research database ▪ Coverage in complementary and alternative medicine, Traditional Chinese Medicine, herbs & medicinal plants and chiropractic medicine ▪ Indexing more than 5,400 journals	Subscription required
EMBASE®	Elsevier	▪ Strong coverage in pharmaceutical and pharmacological topics ▪ Including all MEDLINE records ▪ Including conference abstracts since 2009 ▪ Indexing more than 8,500 journals published worldwide ▪ Journal origins: 33.8% from North America and 49.7% from Europe ▪ Updated weekly	Subscription required
MEDLINE®	The U.S. National Library of Medicine	▪ Providing the core clinical literature of biomedicine, e.g. pharmacy, nursing and allied health ▪ Indexing 5,600 journal citations and abstracts worldwide ▪ Journal origins: 40.5% from North America and 48.5% from Europe ▪ Free assess ▪ Updated daily ▪ Easier to search than OVID®	▪ Limited coverage in basic sciences, e.g. phytochemistry, biology and chemistry ▪ Not include book chapters
OVID®	Ovid Technologies	▪ Searching MEDLINE database ▪ Including textbooks ▪ Providing more relevant research than MEDLINE®	▪ Subscription required ▪ 7-day less up-to-date than MEDLINE®
Scopus	Elsevier	▪ Searching both MEDLINE and EMBASE databases ▪ Coverage in health sciences, e.g. phytochemistry, life sciences and social sciences ▪ Indexing 12,850 available journals ▪ Including textbooks ▪ Updated 1-2 times weekly	Subscription required
The Cochrane Library	The Cochrane Collaboration	▪ Contained six databases: Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), Cochrane Methodology Register (CMR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment Database (HTA) and NHS Economic Evaluation Database (EED) ▪ Synthesising systematic reviews and meta-analyses of biomedical literature	▪ The secondary literature ▪ Update every two years

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Database	Produced by	Advantages	Disadvantages
		▪ Free access after 12-month publications of all new reviews since 2013	
PsynINFO®	APA PsycNET®	▪ Coverage in behavioural and social science research worldwide ▪ Included abstracts and all dissertation records ▪ Indexing 2,500 journals ▪ Updated weekly	Subscription required

CINAHL = the Cumulative Index of Nursing and Allied Health Literature

Examples of specific CAM databases are the National Center for Complementary and Alternative Medicine (CAM Citation Index) and Research Council for Complementary Medicine (CISCOM). A list of comprehensive databases for primary CAM literature is shown in Table 4. Additionally, a well-known safety database is the WHO Adverse Drug Reaction (www.who.int).

Table 4. Comprehensive databases regarding CAM

Database	Produced by	Information	Available
HerbalMed	Nonprofit Alternative Medicine Foundation	Effectiveness, adverse events and product preparations of the most commonly used herbal medicines in the US, e.g. black cohosh, horse chestnut, garlic, aloe vera, Hawthorn, Echinacea, Eleuthero (formerly Siberian ginseng), ginkgo, St. John's wort, olive, Asian ginseng, kava, elderberry, saw palmetto, milk thistle, stinging nettle, cranberry, bilberry, valerian and ginger	http://www.herbmed.org
Natural Medicines	Therapeutic Research Center	Effectiveness and adverse effects of herbal medicines and dietary supplements, including drug-herbs/ supplement interactions and use of the products in pregnancy and lactation	https://naturalmedicines.therapeuticresearch.com/ (subscription required)
AMED*	Health Care Information Service of the British Library	Bibliographic records of CAM, including occupational therapy, palliative care, physiotherapy, podiatry, rehabilitation, and speech and language	https://www.ebscohost.com/academic/AMED-The-Allied-and-Complementary-Medicine-Database (subscription required)
Alt HealthWatch	EBSCOhost	Full-texts of CAM studies from relevant journals, such as American Journal of Chinese Medicine, European Journal of Clinical Hypnosis, Journal of Asian Natural Products Research, Journal of the Australian Traditional-Medicine Society.	https://www.ebscohost.com/academic/alt-healthwatch (subscription required)
CAMbase	The Chair of Medical Theory and Complementary Medicine	Bibliographic records of CAM, including CAM in Germany	http://cambase.dmz.uni-wh.de/opencam/index_en.html

* The Allied and Complementary Medicine Database

With respect to Ayurveda medicine, practitioners have to access Indian databases, i.e. the Central Council for Research in Ayurveda and Sidha (CCRAS), IndMed, Annotated Bibliography of Indian Medicine

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(ABIM), and National Institute of Science Communication and Information Resources (NISCAIR). IndMed, ABIM and NISCAIR provide free access to full-texts of Indian journals of CAM (Table 5). To make their publications available for locals and save on the cost of publication, Indian researchers and practitioners are likely to publish their work in Indian journals rather than Western ones, such as Evidence-Based Complementary and Alternative Medicine and Journal of Alternative and Complementary Medicine (Aleem et al., 2009). Likewise, relevant literature on Chinese herbal medicine and acupuncture are provided by Chinese databases, i.e. Chinese BioMedical Literature Database (CBM), Chinese Medical Current Contents (CMCC), Traditional Chinese Medical Literature Analysis and Retrieval System (TCMLARS), Chinese Dissertation database, China Medical Academic Conference, Chinese National Knowledge Infrastructure databases and Index to Taiwan Periodical Literature. The subscription to these Chinese databases are required.

Table 5. Indian databases regarding CAM

Database	Produced by	Information	Available
ABIM	Jan Meulenbeld	▪ Coverage in a history of Indian Medical Literature ▪ Contain 50,000 records of articles and textbooks. ▪ Free access	http://indianmedicine.eldoc.ub.rug.nl/index.php?Search=&pSearch=Zoeken
CCRAS	Ministry of AYUSH, Government of India	▪ Focus on Ayurvedic sciences ▪ Coverage in three Indian journals, i.e. *Journal of Research in Ayurvedic Sciences*, *Journal of Drug Research in Ayurvedic Sciences*, *Journal of Indian Medical Heritage*, abstracts and textbooks ▪ Poor availability of full-texts	http://www.ccras.nic.in/mainpublication.html
IndMed	National Informatics Centre	▪ Contain 100 peer reviewed Indian medical journals ▪ Free access	http://indmed.nic.in/
NISCAIR	Government of India	▪ Archive of a journal of Natural Products Repository ▪ Free access	http://nopr.niscair.res.in/handle/123456789/7305

A structured-literature search strategy is constructed by key search terms (alone or) with general or CAM database specific search operators. For example, the Boolean “and, or, not”, Wild cards for single character (?) or strings (*), and field restrictions for tags (e.g. title, abstract and year of publication) are commonly used operators. Applying the CAM database specific operators usually retrieves more number of eligible literature than using the general operators. However, some of the CAM databases require a subscription, which is rather costly. The HerbMed database is suitable for users, particularly in the US. The Cochrane CAM Field includes the systematic reviews of RCTs on CAM and the benefits and safety of several CAM modalities in various conditions, such as stroke, dementia, diabetes, liver disease and kidney diseases. From 2011 to 2015, the Cochrane CAM Field has published the most systematic reviews for herbal medicines and acupuncture for rheumatological treatment. A few systematic reviews of CAM for kidney diseases are included, such as Astragalus for treating chronic kidney disease (CKD) (Zhang, Lin, Xu, et al., 2014), *Rheum officinale* for preventing CKD progression (Wang et al., 2012), *Cordyceps sinensis* for CKD management (Zhang, Lin, Tung, et al., 2014), and fish oil for kidney transplant recipients (Lim et al., 2007). Details of these findings are described in Chapter 7.

Overall, an effective searching method for CAM is to search different sources, i.e. generic and specific databases. After retrieving all relevant articles, the abstracts or full-texts of articles will then be screened for its relevance and applicability. It is also recommended to keep articles which are eligible for being

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reviewed in a personal database or reference management software, e.g. Reference Manager™, EndNote™ or Zotero™ (free software from Firefox), then they will be ready for the next step of critical appraisal.

PRINCIPLES OF APPRAISING EVIDENCE

The process of critiquing evidence or literature in CAM is the same as for conventional medicine. Critical appraisal in EBM refers to the process of systematically examining research evidence in terms of its validity, impacts and applicability before using the evidence for decision-making in practice (Sackett et al., 1996). To achieve the objectives, various checklists, scales or question sets have been investigated. However, the easiest way is to ask seven questions to efficiently appraise the literature. These include:

(1) What are the research questions or objectives? (research question)
(2) What are the study variables, i.e. independent or dependent variables (or outcomes)? (constructs/variables)
(3) Is the study designed to minimise biases and control confounders? (study design)
(4) How about the study design in terms of study type, population and samples, study instrument and procedure? (research methods)
(5) Is the statistical analysis appropriate? (statistics)
(6) Do the results answer the research questions or objectives? (validity)
(7) Are the findings beneficial to your work? (impacts and applicability)

The critical appraisal of an original article starts from assessing whether a research question or problem is aligned with the predetermined question addressed with PICO at the outset. The evaluation of research methods in a study usually comprises the study design, population and samples plus sampling procedure, study instrument, data collection and data analysis. Study designs embrace descriptive, analytical (or associational) and intervention studies. Strengths and weaknesses of different study design are summarised in Table 6. Practitioners should select an appropriate design that matches up with the primary research questions.

Table 6. Strengths and weaknesses of study designs

Study design	Strength	Weakness
Systematic review	▪ More reliable than discrete studies ▪ Minimising bias ▪ Inexpensive	▪ May difficult to synthesise evidence due to various studies with heterogeneities
Randomised controlled trial	▪ Provides efficacy of interventions ▪ Internal validity ▪ Minimising bias	▪ Not pragmatic (external validity) ▪ Expensive and time-consuming
Prospective cohort studies	▪ Establishes causality between exposure and outcome ▪ Investigates real circumstances ▪ Provides incidence of outcomes ▪ Can measure several outcomes for one exposure	▪ Requires large sample sizes ▪ Risk for confounding ▪ Inappropriate for rare diseases or outcomes ▪ Expensive ▪ Requires long periods of follow-up
Case-control studies	▪ Useful for rare diseases/outcomes ▪ Short period of studies ▪ Inexpensive ▪ Can measure several risk factors for a single outcome	▪ High confounders and biases, such as recall bias ▪ Cannot fully establish causality between exposure and outcome
Cross-sectional studies	▪ Provides prevalence of outcomes ▪ Short period of studies ▪ Inexpensive	▪ High confounders and biases ▪ Cannot fully establish causality between exposure and outcome ▪ Inappropriate for rare diseases
Case series and case	▪ Provides rare diseases or adverse	▪ Cannot establish prevalence or

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Study design	Strength	Weakness
reports	events of exposure ▪ Simplicity and inexpensive	incidence
Animal studies	▪ Provides biological and toxic effects of intervention	▪ Poor extrapolating from laboratory animals to humans ▪ Expensive and time-consuming

Relevant study designs should be used to address specific research questions (Table 7), as it was suggested by Flower et al., 2014. Take the previous question "Can vitamin C reduce cardiovascular events in adult patients with chronic kidney disease at stages 3 – 5?" as an example, to assess the efficacy of vitamin C, the most appropriate study design to address the research question is the RCT design. Another example is, if practitioners would like to check whether senna (a mild laxative) can be safely used in patients with CKD when there are no RCTs or any observation studies available, a case report may be a better information source. Some research questions are too complex to be answered by only one type of study design, or one level of evidence. As a result, a wide range of evidence, such as clinical trials together with qualitative studies, may be exploited to provide an optimal solution.

Table 7. Research questions and respective study designs adapted from Flower et al. (2014)

Research question	Study design
What is the efficacy of CAM for a specific disease/condition?	Randomised controlled trial
What is the effectiveness of CAM in practice?	Pragmatic randomised trials
Are there adverse effects from CAM?	Observational studies and case reports
How effective is CAM to promote/boost health?	Pragmatic randomised trials and observational studies
How effective is CAM to prevent a disease/condition?	Pragmatic randomised trials and observational studies
How effective is CAM for the rehabilitation?	Pragmatic randomised trials and observational studies
What is the patient's experience of using CAM?	Qualitative research
Which conditions seem to respond well to CAM?	Cross-sectional surveys of CAM practitioners
What are the active ingredients of a particular herbal medicine?	Laboratory experiments

Some CAM interventions, such as the combination of acupuncture and herbal medicine, may not be appropriate for an RCT. Instead, pragmatic clinical trials (PCTs) are used to investigate the effectiveness of the complex CAM modalities in a real world practice. PCTs normally have three salient features, including recruitment of participants with characteristics similar to actual practice (e.g. older patients with renal insufficiency), performing more than one intervention as is in practice, and providing patient-centred outcomes, such as quality of life and patient satisfaction (Elm et al., 2007). Details of PCTs are described in Chapter 10.

Observational studies and case reports are more useful in providing evidence about the adverse events of a CAM intervention rather than efficacy. The cross-sectional surveys of CAM practitioners elicit the expert opinions regarding what CAM modalities are appropriate for a particular condition with what expected outcomes.

Regarding herbal medicines, the evidence from animal studies has been used when human studies are not available, such as the nephrotoxicity, liver toxicity and teratogenicity of herbal medicines found in animal studies, this evidence informs us which herbal products are likely to cause adverse events in humans. Laboratory experiments usually reveal various active ingredients that could probably have a biological effect on a certain condition. This evidence may support the benefits of herbal medicines that have long been used for self-care especially among Asian people based on their indigenous wisdom passing on from generation to generation. In the case when a high level of evidence is not available, traditional knowledge and expert opinions may be employed to support the use of CAM.

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APPRAISING EVIDENCE DERIVED FROM DIFFERENT STUDY DESIGNS

As mentioned above, the critical appraisal of CAM evidence includes the evaluation of research questions, methods and findings with discussion as with the conventional medicine. Some standard tools for assessing studies with diverse designs adapted from the EQUATOR network (http://www.equator-network.org) are detailed in Table 8. Only the key processes of appraisal are briefly explained below.

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Table 8. Standard tools for the critical appraisal of study designs

Study design	Assessment tool	Key assessment item
Randomised controlled trials	CONSORT 2010 Explanation and Elaboration	▪ Specific objectives ▪ Methods: study design, participants, interventions, outcomes, sample size, randomisation, blinding, and statistical methods ▪ Results: participant flow, baseline data, numbers analysed, outcomes and estimation, harms ▪ Discussion: limitations, generalisability, and interpretation
	Dalhousie Assessment Instrument for natural products	▪ Intervention - Genus and species, the part of the raw material, and the process of prepared product - Products derived from a plant, microorganism or animal: active ingredients - Commercial products: the brand name, manufacturer, lot or batch numbers, and active ingredients - Qualitative and quantitative analysis of active ingredients - Dosage form and daily dose - Placebo and comparison treatments should be matched in terms of taste, smell and/or appearance, and dosage regimen
	Revised STRICTA 2010 for acupuncture	▪ Similar to the CONSORT as stated above, except the intervention - Style of acupuncture: traditional Chinese medicine (TCM), Japanese, Korean, Western medical, etc. - Details of needling - Treatment regimen - Other components of treatment, e.g. moxibustion, cupping, herbs, exercise, lifestyle advice - Practitioner background - Comparator interventions
Pragmatic clinical trials	Extension of the CONSORT statement 2008	▪ The main items of assessment are similar to the CONSORT ▪ The extension includes: - Describing eligible participants who match typical patients in practice - Describing details of an intervention in order to implement the intervention - Explaining the rationale behind the measurement of outcomes - Calculating sample size based on the minimally important difference of the outcomes - Explaining generalisation in terms of various settings, health service organisations, and practitioners

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Table 8. Standard tools for the critical appraisal of study designs (continued)

Study design	Assessment tool	Key assessment item
Cohort studies Case-control studies Cross-sectional studies	STROBE	▪ Specific objectives ▪ Methods: study design, participants, definitions of variables, measurement/data sources, bias, study size, and statistical methods ▪ Results: participant flow, characteristics of participants, information on exposures and potential confounders, and outcomes ▪ Discussion: limitations, generalisability, and interpretation
Case reports	Guidelines for submitting adverse event reports for Publication endorsed by ISPE and ISoP	▪ Patient: demographics, current health status, medical history, physical examination, patient's outcome ▪ Herbal medicine: - Latin binomial of herbal ingredients, plant part(s), and type of preparation, proprietary name and name of producer for manufactured products - Dosage regimen - Therapy duration before the adverse event - Concomitant therapies ▪ Adverse events
Animal studies	ARRIVE Guidelines for Reporting Animal Research 2010	▪ Objectives or specific hypotheses being tested ▪ Methods: study design, experimental procedures, details of the animals used, housing and husbandry, sample size, allocating animals to experimental groups, experimental outcomes, and statistical methods ▪ Results: baseline data, numbers analysed, outcomes and estimation, adverse events ▪ Discussion: interpretation/ scientific implications, generalisability/translation

Note: ISPE = International Society for Pharmacoepidemiology
ISoP = International Society of Pharmacovigilance

Randomised and Pragmatic Controlled Trials

The Consolidated Standards of Reporting Trials (CONSORT) statement has been proposed improving the quality of reporting of RCTs since 1996 and the last update was in 2010 (Moher et al., 2010). The CONSORT is a generic tool for assessing the reporting of RCTs and several tools have been further developed based on CONSORT to evaluate pragmatic trials (Elm, et al., 2007) and RCTs in CAM. Three specific tools have been developed for evaluating clinical trials of herbal medicine and acupuncture, including the CONSORT extension for herbal interventions in 2006, the Dalhousie Assessment Instrument for Critical Appraisal of RCTs of Natural Products, and the revised STRICTA for assessing clinical trials of acupuncture.

The CONSORT extension for herbal interventions was developed by expert consensus to extend the CONSORT with details of herbal interventions and proposed to evaluate RCTs of herbal medicine in 2006 (Gagnier et al., 2006). It includes herbal product name, the characteristics of the product, such as the parts of plant used, and type of product used, dosage regimen, qualitative testing, i.e. standardisation of the

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product, and practitioner background. Jurgens et al. (2009) further developed and validated the CONSORT extension for herbal interventions to describe natural products into a Dalhousie Assessment Instrument for Critical Appraisal of RCTs of Natural Products. The key principles in the Dalhousie Assessment Instrument are similar to the CONSORT for herbal interventions, but Jurgens's tool precisely described a wide range of the types of natural products (Table 8) (Jurgens et al., 2009). Therefore, the Dalhousie Assessment Instrument can be used together with the CONSORT 2010.

The STRICTA was developed from the CONSORT with added details of providing acupuncture, such as style of acupuncture, details of needling, and practitioner background (MacPherson et al., 2010). These items describe specific interventions which allows practitioners to use an intervention if the findings show positive effects of acupuncture. Therefore, the STRICTA has been recommended evaluating the evidence for acupuncture.

Other CAMs have a lack of specific guidelines to assess their RCTs. The extension of the CONSORT for pragmatic trials is able to assess PCTs of these CAMs although the details of interventions and outcomes of the CAMs should be defined in the light of CAM knowledge.

For instance, to answer the question 'Can acupressure improve depression or anxiety in patients received haemodialysis?' a literature search found one relevant RCT which was conducted in Malaysia (Hmwe et al., 2015). This trial aimed to assess the efficacy of acupressure on depression, anxiety, stress and general psychological distress in patients received haemodialysis. The researchers recruited 108 patients received haemodialysis who had either depression or anxiety, or did not have either. This study seems to match the clinical question. The study design of this research was open-label RCT, which may affect the outcomes. This study was not blind as it is a challenge of conducting CAM. The sample size had been calculated and was sufficient. The intervention during dialysis therapy was well defined by the protocol, including how to press on acupoints, the defined acupoints, defined the precision of acupressure, and the duration of acupressure session. The control group received usual care with routine haemodialysis treatment.

The target outcomes in Hmwe's study were measured by a validated questionnaire, which was the Depression, Anxiety Stress Scales (DASS-21). Although this questionnaire is acceptable to measure symptoms of depression and anxiety, it is a self-report instrument for measuring subjective outcomes, which is more likely to be biased than objective outcome measures. There was no difference in baseline characteristics between the intervention and control groups, which indicated minimal selection bias. The findings of this RCT found no difference in scores of depression and anxiety between the intervention and control groups. Meanwhile, a small number of the participants suffered from hypotension due to dialysis therapy and acupressure. The negative findings may be because the population in this study was recruited both having depression or anxiety and not having, and this may dilute the effects of acupressure. In summary, it still doubt whether or not acupressure is able to relieve depression and anxiety in patients received haemodialysis. This evidence shows the adverse effect outweighs the benefits, so this CAM is not currently recommend for relieving depression and anxiety.

Observational Studies

The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement is developed to improve the reporting of observational studies of conventional medicines (Patsopoulos, 2011). This statement could guide critiquing the quality of observational studies, including cohort studies, case-control studies, and cross-sectional studies. These studies aim to observe the associations between an exposure and outcomes in real circumstances; however, research findings may be influenced by confounding factors. There are three key items in the STROBE that differ from the CONSORT, i.e. 'Are there clearly defined exposures, potential confounding factors, and outcomes?', 'Did authors describe potential sources of bias?' and 'Did they describe an effect size between unadjusted and confounder-adjusted estimates?' The STROBE could be applied to assess the quality of observation studies in CAM. It is important to be mindful that exposure, confounders, and outcomes in CAM studies may be difficult to

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define and measure due to a variation of exposure and ambiguous outcomes, this is the same challenge found in designing and evaluating RCTs in CAM.

For example, to answer the question 'Do Chinese herbal medicine (CHM) harm kidney function in patients with advanced chronic kidney disease?', a literature search of the biomedical databases found one retrospective cohort study in Taiwan (Lin et al., 2015). The hypothesis of this study is that the use of CHM increases end-stage renal disease (ESRD) risk in patients with CKD, so this study would match the question. The study included recruited patients with stage 3-5 CKD identified by the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM), which is related to the population of the question. The exclusion criteria are well defined; older patients, having cancer, and/or were using Chinese medicine before recruitment. Therefore, this may influence the application of the research results. Exposure (prescribed CHMs within one year before dialysis initiation) and outcome (patients receiving dialysis) of this study were clearly defined. The baseline characteristics of both exposed and unexposed groups were not statistically different, thus indicating minimal confounding factors, such as age, sex, and medical history between two groups. The effects of other potential confounding factors on the outcomes were adjusted by statistical analysis, and cause-specific hazard ratios and adjusted- cause-specific hazard ratios were presented. The findings of this study revealed that two formulas of CHM, i.e. dampness-dispelling and purgative formulas, were associated with an increase in the risk of ESRD. Overall, the evidence from this study seems to be reliable, so it may be used for answering the research question.

Case Reports

For both conventional medicines and CAM, case reports of adverse events provide the signal of potential harms. The guidelines for submitting adverse event reports for publication has been proposed and endorsed by the International Society for Pharmacoepidemiology (ISPE) and the International Society of Pharmacovigilance (ISoP) (Kelly et al., 2007). These guidelines suggest standard reporting adverse drug events and adverse events of herbal medicine, and these could also be adopted for the evaluation of case reports in CAM. The key items of assessing the case reports are patient's status, exposure, therapy duration before the adverse event and concomitant therapies. Theoretically, to establish the causual relationship of a CAM related adverse event, patients should be exposed before the adverse event occurs, and there should be no other factors (such as medical history and concomitant conventional medicines) associated with the adverse event.

For example, Greene et al. (2014) reported that an energy drink had induced an acute kidney injury (Greene et al., 2014). A 40-year-old man with well controlled diabetes and hypertension, drank 100-120 oz of energy drink daily for the previous 2-3 weeks before being admitted to hospital. His serum creatinine increased 6 times compared with his baseline measurement, and this indicated acute kidney injury (AKI). After he stopped using the energy drink, his serum creatinine returned to his baseline within two weeks. He rarely used medications related to AKI (i.e. ibuprofen). One of his concomitant medications, lisinopril, is an angiotensin-converting enzyme inhibitor (ACEI) that may cause AKI; however, the patient had taken this medication over one year and had no incident of AKI. In addition, his co-morbidities, e.g. being well controlled diabetes, are less likely to cause AKI.

The authors clearly described patient's conditions and the exposure, and reported the causality of the energy drink induced AKI using the Naranjo algorithm which showed there was a probable relationship between the exposure and AKI. This can also be confirmed by the previous literature. However, there is an unknown mechanism underlying energy drink induced AKI. In short, the causality in this case report is reliable. Therefore, a middle aged man with diabetes and hypertension should be recommended not drink a high amount of energy drink.

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Animal Studies

Animal studies are likely to provide information about the efficacy and safety of herbal medicines. The Animals in Research: Reporing *In Vivo* Experiments (ARRIVE) has been developed from the CONSORT statement in order to provide guidelines for reporting animal research (Kilkenny et al., 2010). The ARRIVE could be used for assessing the quality of reporting animal studies as well. The main items recommended for reporting an animal study are similar to the CONSORT (Table 8), but they are more specified for animal research. For example, the experimental unit should be described as a single animal, group, or cage of animals. Details of the animals used, including species, strain, sex, developmental stage (e.g. mean or median age plus age range), and weight should be clearly described. In addition, the housing (e.g. the type of facility, type of cage, bedding material, and number of cage companions), and husbandry conditions (e.g. breeding programme, light/dark cycle, temperature, type of food, and environmental enrichment) should all be reported. If the methods of the reported study show the minimum bias and appropriate outcome measures, the research findings should be acceptable. It is important to keep in mind that the results from animal studies could provide evidence for benefits and adverse effects of CAM and support CAM use based on traditional knowledge; however, human studies are still required to confirm the efficacy and safety of CAM.

Information from the Internet

There are four key steps to evaluate information sources from the internet, which are: (1) identifying who wrote the website; (2) balance of information between the benefits and adverse effects of CAM; (3) up-to-date evidence; and (4) reliable references. Web sites or social media, which represent companies of health products, are likely to promote their products and provide the benefits of their products which outweigh the adverse effects. These websites, sometimes, employ conventional practitioners to guarantee the benefits of the products using their own opinion, rather than using EBM approaches to appraise the information. Therefore, customers should avoid using information from such websites, social media, or commercial websites (.com). There are trusted websites owned by governments, health organizations, such as WHO and Food and Drug Administration, and education sectors. These websites are likely to provide accurate information.

The information about CAM on websites should provide balanced information between the beneficial and detrimental effects of CAM. Customers should also consider when the websites were updated. Ideally, it should be updated every year as CAM research emerges regularly. If the information on the websites is not up-to-date, it would be unreliable and the information may not be accurate. Finally, information should be based on scientific evidence, particularly human studies, that is published in acceptable journals, such as the BMC Complementary and Alternative Medicine, the Journal of Alternative and Complementary Medicine, Evidence-Based Complementary and Alternative Medicine, or Complementary Therapies in Medicine. Evidence from animal studies should be used with great caution.

On the whole, few valid and reliable tools are available for appraising the CAM evidence. Researchers who are interested in CAM should work on developing an appropriate tool to evaluate the observational CAM studies, particularly acupuncture, herbal medicine and Chinese herbal medicine. Observational studies are comparatively easy to carry out, compared with RCTs, so there is a greater need for appraising observational studies. In addition to the tools for critical appraisal, it is vital to construct and validate a pragmatic instrument for clinical decision-making in CAM.

MAKING A DECISION ABOUT CAM USE

Making clinical decisions based on the current best evidence, is the final EBM step to provide proper care for patients. Ideally, the decision-making should also take account of practitioner's knowledge and experience, and patient's needs. Whether to use CAM in patients with kidney diseases is quite a challenging

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decision to make due to the limited quality of evidence, especially for the efficacy and safety of CAM. Some CAM modalities may satisfy patient's needs, such as improving their quality of life, but their adverse effects may be unknown and the CAM may be costly. Therefore, clinicians often face a dilemma whether to suggest CAM to supplement the mainstream medicine or to recommend CAM alone. To translate EBM knowledge to clinical practice, the decision about choosing CAM for individual patients needs to be made based on the patient's factors (e.g. conditions and constraints), practitioner's factors (e.g. best current evidence, knowledge and experience) and health care system (e.g. CAM availability and costs) (Mills et al., 2002), as listed in Table 9.

Table 9. Factors affecting clinical decision-making in CAM

Factors	Example
Patient	▪ Demographic characteristics, e.g. age, sex ▪ Prognosis of disease ▪ Co-morbidities, e.g. renal impairment ▪ Constrains, e.g. financial problems ▪ Non-adherence to medicines ▪ Patient's needs
Practitioner	▪ Evidence ▪ Guidelines ▪ Knowledge ▪ Experience ▪ Clinical skills, particularly acupuncture, massage
Health care system	▪ Availability of alternative medicines ▪ Costs

The decision-making on CAM use is a complex process. Practitioners may make use of a conventional approach with three steps to reach a clinical decision, including: (1) searching for evidence and using it together with their own knowledge and experience; (2) weighing up the benefits and risks of CAM based on patient's factors; and (3) providing the best option for their patients. The National Health and Medical Research Council in Australia suggests how to grade evidence in order to decision-making on CAM use based on levels and consistency of evidence, clinical impact and generalisability (Table 10). It is sometimes quite challenging, as one CAM option may have great benefits but with more side effects; while another therapy may provide few benefits but with less adverse effects. Therefore, practitioners may contemplate more than one modality and discuss the choices with their patients in order to help patients select the best option. This approach will encourage the patient-centred use of CAM. Chapter 6 will offer more practical recommendations for clinical decision making based on risk versus efficacy.

The traditional method may not suit inexperienced practitioners, and an alternative decision making tool is needed. Aleem et al (2009) proposed a clinical decision analysis of conventional medicine that incorporates the evidence into the patient's needs. A decision tree that is the main component of this analysis seems to be applicable to the decision-making in CAM. Each branch of the tree gives the probability of each possible choice of treatment linked to the desired outcomes of patients. The probability of each treatment is calculated using the findings of current best evidence. There are still some limitations of this tool for CAM. If the CAM modalities have no evidence, it would not be feasible to use this tool in practice. Moreover, the tool is more complex and time-consuming than the conventional approach as mentioned earlier.

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Table 10. Decision-making based on evidence (National Health and Medical Research Council, 2009)

Decision-making	Strongly recommendation	Recommendation	Probably recommendation	Not recommendation
Evidence				
Systematic review of RCTs or	≥ 1 systematic review with a low risk of bias		Systematic review with a moderate risk of bias	Systematic review with a high risk of bias
RCTs or	Several RCTs with a low risk of bias	One or two RCTs with a low risk of bias	RCTs with a moderate risk of bias	RCTs with a high risk of bias
Non-RCTs, observational studies, cross-sectional studies or		Several studies with a low risk of bias	One or two studies with a low risk of bias	One or two studies with a high risk of bias
Case series, case reports, expert opinions				Several studies
Consistency of the evidence	All studies consistent	Most studies consistent and inconsistency may be explained	Some inconsistency reflecting genuine uncertainty around clinical question	Evidence is inconsistent
Clinical impact	Very large	Substantial	Moderate	Slight or restricted
Generalisability	The target population is similar to the study population		The study population differs from the target population, but it is clinically sensible to apply this evidence to target population	The study population differs from the target population and hard to judge whether it is sensible to generalise to target population

CONCLUSION

The evidence-based approach plays an important role in CAM as well as conventional medicine. The five steps of EBM should be utilised in clinical practice, i.e. addressing a clinical question, searching and retrieving the appropriate evidence, appraising the evidence, making a clinical decision, and assessing the outcome. Decision-making in CAM use should take account of three factors, i.e. patients, practitioners and health care system, into consideration. These embrace patient's preference, best current evidence, practitioner's knowledge and experience, and CAM availability. In addition, evidence with a lower level of causality are sometimes accepted and used in decision making when there are no existing evidence from RCTs or PCTs available. Overall, the EBM approach should inform clinical decisions about CAM use in patients with chronic kidney disease. The next chapter will elaborate the types of CAM modalities recommended by standard guidelines for chronic illnesses.

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KEY TERMS AND DEFINITIONS

Clinical Decision-Making: A process of providing optimal care for an individual patient using scientific knowledge and practitioners' expertise.

Critical Appraisal: A process of evaluating objectives, methods and findings of scientific studies in order to accept or discard them.

Database: A systemic set of data from medical research is gathered on the internet or hardcopy.

Evidence-Based Medicine: A process of systematic searching, critical appraisal, and making a clinical decision.

Key Search Term: A key word is used for searching information.

Pragmatic Clinical Trial: A human study represents participants, interventions and outcomes in practice.

Systematic Searching: A process of searching through all eligible databases.

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