

# Applying evidence-based-medicine when prescribing herbal products

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## Abstract

### Introduction

This review is written for practitioners wishing to apply the evidence-based medicine model when prescribing herbal products for use in their clinical practise.

The paucity of well-conducted clinical trials is only one of the challenges faced by practitioners. There is also natural variability of herbs and a lack of standardisation for naming and processing herbs that has resulted in wide variations between herbal products containing the same plant, including batch to batch variations.

### Conclusion

Three steps are therefore recommended: select quality products; evaluate the evidence and apply the best available evidence in clinical practise.

High quality herbal products with product-specific evidence are recommended in preference to other unproven products. Traditional knowledge about the use of herbs should be given greater weighting compare to poor quality studies, especially if the study is investigating a novel use for an herbal product.

## Introduction

Evidence-based medicine (EBM) aims to use the best available scientific evidence to inform clinical decisions and health policy. The randomised control trial (RCT) and meta-analysis are regarded as the gold standard (Table 1). Similar to pharmaceuticals, this model is suitable for evaluating

herbal medicines and the number of clinical trials in this field are increasing exponentially<sup>1,2</sup>. A brief perusal of systematic reviews and meta-analysis evaluating herbal medicines will leave many practitioners disappointed with the conclusions. Commonly, little is concluded because of the lack of well-conducted clinical trials. As the research in the field builds, however, challenges specific to herbal medicine will become more important when evaluating the research.

Although the RCT is appropriate for assessing herbal and pharmaceutical products, there are important differences that must be addressed. Herbal products are more complicated than pharmaceuticals because they are organic and contain multiple chemicals. A 'generic' herbal product does not really exist in the same way that there are generic pharmaceutical products.

Plants contain numerous chemical ingredients—some act as agonists, others as antagonistic and for others, the action is unknown. The quantities of these chemicals may vary according to the variety of the plant; the location, year and season it was grown and harvested; and the extraction methods. Unless every stage of the process is controlled, batch to batch variations are likely. To add to this natural complexity, herbal products are available in many different forms. They may be sold as the whole raw plant or a part of the plant such as the seeds, roots, bark, leaves, flowers or fruits. The product may be consumed in its dry form, brewed into a fresh decoction, or formulated into a liquid extract, granules, capsules, tablets or creams.

Products may contain a single plant or a combination of plants. However, if a product contains other active substances (including the isolated

constituents of plants) they are not usually regarded as a herbal medicine<sup>3</sup>.

Products containing the same type of plant may have different pharmacological actions, which in turn can affect their safety, efficacy and cost effectiveness<sup>4</sup>.

The challenges arising from the natural variability of plants are compounded by quality issues with many herbal products and inadequate reporting of clinical trials and meta-analyses<sup>5,6,7,8,9</sup>. Type I or II errors (i.e. a false positive or negative result) are, therefore, more likely and will be exaggerated when the results of such studies are combined in a meta-analysis.

Another difficulty with applying the results of RCTs and meta-analyses to clinical practice is that many of the clinical trials evaluate the effects of herbs used in isolation. In clinical practice, however, herbal medicines are often combined into an individualised or standardised formula. The formula may contain a much lower dose of the herbal medicine than what was used in the clinical trials evaluating the herb in isolation. Simply applying the evidence and dose for each individual herbal medicine to a combination formula may lead to similar problems to those caused by poly-pharmacy, such as interactions and toxicity.

None of these aforementioned issues are new knowledge. Their discussion in the literature, however, has mostly focused on improving the research methods and reporting of clinical trials evaluating herbal medicine<sup>1,4,5,10</sup>. The purpose of this paper is to summarise the issues to assist practitioners seeking to translate the results of herbal medicine research into their clinical practice.

Three key steps are recommended for practitioners wishing to use the EBM model when prescribing herbal medicines:

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1. Select quality products,
2. Evaluate the evidence and
3. Apply the evidence in clinical practise.

## Discussion

### Quality issues with herbal products

The quality assurance of an herbal product is the foundation of its safe and effective use. Hundreds of thousands of herbal products are commercially available across the world that practitioners can prescribe and users self-prescribe. For many of these products it is difficult to assess their quality because there are no agreed international regulations for standardising the cultivation, authentication, profiling and naming of medicinal plants; and reporting on the processing and extraction methods used<sup>7,11,12</sup>.

The problem of the non-standardisation of herbal products is compounded for the prescribers and users of these products, who must also navigate their way through the inconsistent information provided at the point of sale. The label may or may not include information about the parts of the plant used, the quantity of dry weight equivalent, extraction details (e.g. the solvent used) or the quantity of one or two recognised active chemicals from the plant.

Practitioners need to be assured about the product's quality (including no batch to batch variations); be clear about the appropriate indications and dosages and be made aware of any potential interactions and side effects.

Whenever possible, therefore, practitioners should endeavour to prescribe herbal products where the manufacturer has addressed quality control in the production of their products and provides documentation to this end. Examples of the type of information practitioners should ask for are listed in table 2.

### Evaluating the evidence

Prescribing a high quality product does not mean, however, that there is any scientific evidence to support its use. Guidelines already exist for reporting and appraising clinical trials

and meta-analysis. Given the specific nuances of herbal products, further guidelines have been recommended to improve the transparency and comparability of results. Table 2 summarises the extra information that readers should seek when appraising clinical trials and meta-analysis' of herbal medicine<sup>1,4,5,12,13</sup>. Other tools, such as a revised Wong scale have also been proposed for rating the quality of clinical trials testing complementary medicines<sup>13</sup>.

The Consolidated Standards of Reporting Trials (CONSORT) extended checklist for herbal medicines is recommended for assessing the quality of a trial using herbal medicines<sup>4</sup>. The CONSORT herbal checklist elaborates on nine of the 22 pre-existing CONSORT checklist items to ensure where applicable, adequate information is provided about the herbal product, the placebo or control intervention and the practitioners. Unfortunately many RCTs will not meet this standard. Two reviews of clinical trials of common herbal therapies, found that on average, only 38%–45% of the information recommended by the extended checklist was reported<sup>6,8</sup>.

Similar to clinical trials, Cochrane reviews of herbal products often fail to provide adequate information<sup>5</sup>. Along with detailed information about the herbal product, the plausibility of the product and the dosage, putative adverse events and interactions are commonly underreported. There are also ongoing problems with the inclusion and exclusion criteria used in many reviews. Due to the paucity of clinical studies, exploratory studies (e.g. for calculating effect size) are often included; however, these are likely to be underpowered, which will increase the likelihood of a Type II error.

Studies have also been included when the product tested was given at the wrong dose; this also increases the risk of a Type II error, or over or under estimating the rates of adverse events and side effects. Products that contain vitamins, minerals or pharmaceuticals should be analysed in separate reviews, especially if they

**Table 1: Levels of evidence.**

Strongest	A systematic review and meta-analysis
Strong	At least one double-blind, randomised, controlled clinical trial
Medium	A well designed controlled trial or observational study that is not randomised, or blinded.
Weak	A consensus statement based on traditional knowledge, clinical experience, descriptive studies, or reports from other expert committees.
Weakest	Patient testimonials, case reports, animal and cell experiments
Note: the quality of research will also affect the overall strength of the evidence.	

do not meet the WHO criteria for a herbal medicine<sup>3</sup>. The extra challenges with searching and translating studies evaluating traditional herbal medicines not published in English must be also addressed by the investigators to ensure that all relevant studies are included<sup>12</sup>.

Much of the knowledge guiding the clinical use of herbal medicines, however, is ranked as low-level evidence because either it is traditional knowledge, the studies are in-vitro or conducted on animals, it is a case study or series, or the clinical trials are of poor quality (Table 1). In many instances, however, this evidence may be the only information available. Given that the aim of EBM is to use the best available evidence, practitioners should not ignore the weaker levels of evidence.

Traditional knowledge that is the foundation of herbal medical practise, should be given extra weight compared to other weaker levels of evidence. In vitro bioassays and in vivo studies on animals or humans that are investigating a novel, rather than a traditional use of an herbal medicine should be treated with the greatest scepticism. This is not to say that the conclusions of the studies are wrong, but rather that it is probably too premature to justify incorporating the

novel use into clinical practise. The exponential growth of reports on the pharmacological effects of herbal medicines is particularly difficult for the non-biochemist to navigate. The conclusions may look promising, but they are often misleading due to the tendency for investigators to over interpret the data<sup>14</sup>. For example, it is common for in vitro bioassays to test concentrations of a herbal extract that are too high and cannot be achieved in real life.

If clinical guidelines have been written, then the GRADE system can be used to rate the quality of evidence and strength of recommendations<sup>15</sup>. The practitioner should use a similar approach when making a decision about which herbal product is indicated. Although an RCT is rated with a higher level of evidence than a case-control study, if the quality is poor (e.g. weak study designs, inconsistent results, indirectness of evidence, imprecision with estimates or reporting bias), then the strength of the evidence is weakened considerably and the results of a well-conducted case-control study may be more substantive. As well as the quality and strength of the evidence other factors need to be considered before prescribing a therapy. The balance between desirable and undesirable effects; any uncertainty or variability in values and preferences of patients; and economic considerations should also influence the final decision.

### Applying EBM to the clinical practise of herbal medicine

The final step when selecting herbal medicines for use in clinical practise, is to match the evidence with the herbal products available on the market. Unlike pharmaceuticals, a distinction should be made between generic evidence versus product-specific evidence. Herbal products containing the same types of plants are not identical and can have different pharmacology. Similar to the recommendations from the Cochrane review of St. John's Wort for the treatment of depression, the exact herbal products that were used in the

**Table 2: Extra information pertinent to herbal medicines when reporting clinical trials and meta-analyses** <sup>1, 4, 5, 12, 13</sup>.

Characteristics of the herbal product	Latin binomial name, botanical authority, family name for each plant in the product Name of the proprietary product, extract name, manufacturer, registration details Plant parts used and preparation – e.g. raw plant, extract ratio, solvent used with extraction Authentication details for the raw plants Chemical fingerprint details and description of any special testing of the herbal product Content of all constituents in the product – native and added Dosage regimen of the product and any marker constituents Standardisation information – name of constituents and how it was done Formulae changes (note: each change should be treated as a different herbal product)
Rationale	Therapy e.g. traditional verses new indication Inclusion criteria congruent with the indication (especially if a traditional indication) Choice of control or placebo Clinical relevance of stated hypotheses
Outcomes	Appropriateness of outcome measures and duration of treatment Reporting of other important outcomes such as adverse events and interactions
Practitioner	A description of the types of practitioners, their training and practical experience (if relevant e.g. when comparing individualised verses standardised formulas)
Search strategies for a meta-analysis	Extra diligence when searching for alternative names for a herbal medicine Access to international and non-customary bibliographic databases
Exclusion criteria for a meta-analysis	Studies with products containing other non-herbal active ingredients Exploratory studies Studies with inappropriate dosages Poor quality studies (but include in discussion to highlight areas for further improvement)

clinical trials and meta-analysis should be prescribed in preference to untested products<sup>16</sup>.

In the ideal world of EBM, only high quality herbal products with strong product-specific evidence would be prescribed. This approach is possible in countries such as Germany, where there are many proprietary herbal preparations available that also have proven efficacy. In many parts of the world, however, there are only a few products, if any that meet such a high standard. If there are no products available on the market with product-specific evidence, the next best choice is to prescribe products where there is strong evidence for that type of product in general. An example would be to use a herbal extract from a

reputable manufacturer that meets the requirements for a high quality herbal product outlined in step 1, but is yet to be tested in a clinical trial.

Having selected an appropriate herbal product to prescribe, the next challenge is ensure patient compliance with taking the medication.

Unlike many pharmaceuticals, the majority of herbal products can be purchased directly by consumers. There is nothing to stop patients swapping to an alternative product. Reasons for this may include seeking a cheaper option, the shop assistant or pharmacist recommending an alternate product, or the product not being available.

Practitioners must educate their patients about the complexity of

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prescribing and using herbal medicines. It is essential they understand the problems with substituting an alternative product with the product that the practitioner has determined to be a high quality herbal product backed by the best available evidence. To help reduce the risk of product substitution, this message must also be delivered to the pharmacists, naturopaths and shop assistants selling the herbal products.

The practitioner should check on a regular basis that their patients are still using the exact product prescribed. This is particularly important at the time of the first clinical review, if the patient reports a lack of efficacy or is experiencing potential side effects, and when the product is used over a long period of time.

Not only can product substitution affect efficacy, but it can cause problems with interactions. Many potential herb-herb and herb-drug interactions are theoretical and their clinical significance is yet to be determined. However, the evidence for important interactions is slowly building<sup>17,18</sup>.

As the quality of herbal products improves, there is the opportunity to acquire product-specific information about interactions. The differences between extracts of St. John's Wort is a good example. For most high quality products, the exact quantity of Hyperforin (which is the main chemical responsible for interactions) is known. Choosing a product with negligible amounts of Hyperforin is, therefore, recommended when a patient is using pharmaceutical medications that can potentially interact<sup>19</sup>.

Patient preference is another essential factor to consider when prescribing herbal medicines. If the patient is seeking to use herbal medicines as an alternative to more evidence-based options, then it is imperative that the practitioner explains the limitations and risks along with the potential benefits to enable their patient to make an informed decision. The direct and

indirect costs to the patient should also be included in this discussion.

### Conclusion

The wide variations in the quality of herbal products creates a unique set of challenges for practitioners aiming to use the EBM model in their clinical practise. Very few products have been tested repeatedly in clinical trials. For the time being, therefore, most meta-analyses will need to combine the results of clinical trials using different herbal products containing the same plant. This generic approach to herbs is potentially misleading because of the (sometimes small and other times large) differences in the herbal products. The risks of Type I and II errors of such meta-analyses should not be overlooked. When there is a choice, practitioners should prescribe the exact herbal product that has been tested in a clinical trial.

Some may criticise this approach as being unnecessarily conservative or unrealistic. Ultimately it is up to each practitioner to decide the level of evidence they are comfortable to use to justify their clinical decisions. However, it is also worth considering that the consumers of herbal medicines, rather than academics, the health care industry and governments, are the key drivers of this market. As such, consumer behaviour can influence herbal companies to improve the quality of their products and the information they provide. Consumer demand may also help stimulate much needed funding for clinical trials from the herbal companies if the companies can benefit directly from funding research that evaluates their specific products. For this to happen, practitioners must encourage their patients to purchase products with specific evidence instead of an alternative, unproven herbal product. Academics and those writing clinical guidelines must also be aware of the difference between clinically tested and unproven herbal products using the same plant.

Although only a small proportion of herbal products have high level, product-specific evidence, this should

not stop practitioners from prescribing other less proven products. After all, the aim of EBM is to use the best available evidence and to apply this knowledge skilfully and artfully to each clinical situation.

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