

Hygeia:: journal for drugs and medicines

April 2013 - September 2013

OPEN ACCESSA half yearly scientific, international, open access journal for drugs and medicines
Research article section: Traditional Medicines /editorial review

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Clinical effectiveness of Traditional Medicines

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There is a general conception that, herbs are natural therefore, they are completely safe. In fact, herbs or herbal preparations also can cause toxic adverse effects, serious allergic reactions and adverse drug /diet interactions¹⁹.

The efficacy of a drug substance is its capacity to produce a desired therapeutic effect, or the relative ability of a drug receptor complex to produce maximum functional response. Nowadays, in health care systems the term 'clinical effectiveness' or 'clinical governance' is preferred instead of efficacy, though both are having similar meanings. The term clinical effectiveness includes the sum total of the pharmacological and the non medical effects of bioactive compounds that may act synergistically, otherwise termed as placebo effect, or sometimes antagonistically or the nocebo effect.

The meaning response⁵

The non therapeutic function of medicines plays a major role in executing the 'meaning response'. The 'meaning response' mainly arise from the physiological or psychological perception of mind in the treatment of illness⁸. This includes mainly the brain mechanisms like- expectation, anxiety, and reward, in addition to other learning phenomena.

In regards to traditional herbal medicines, the socio cultural aspects are likely to elicit a physiological response in addition to the intrinsic pharmacological activity of the herb, since they often exist within religious and mythical traditions creating a collaborative 'meaning response'. Meaning response plays a very important role in the clinical effectiveness of traditional herbal medicines, for e.g. traditional healer may make magical claims, gestures, chanting or prayers while giving a crude herbal extract to the needed person ,finally result in the so called meaning response .



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Hygeia.J.D.Med. Vol.5 (1), April 2013© 2012,

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Even the packaging, shape, size, color, odor, of a herbal dosage form may affect the clinical effectiveness of the drug, a theme which can entertain many levels of pharmacy practice research.

Evidence²³

In an era of evidence based health care⁷, systematic reviews of randomized control trials (RCT) are becoming increasingly important as a source of evidence for decision making. The evidence of clinical effectiveness mainly comes from the use of high quality herbal ingredients¹⁵ in the formulations, systematic reviews and Meta analysis of randomized controlled clinical trials.

To establish the true effectiveness of herbs as medicines, they must be tested in prospective, double blind, randomized, placebo-controlled clinical trials (RCTs)¹².

The main reliable reviews²³ about the effectiveness of herbal drugs may be obtained from the well known Cochrane reviews and Medline reviews considered as the benchmark of high quality informations on health care systems. Cochrane reviews are systematic reviews of primary research in human health care and health policy and are internationally recognized as the highest standard in evidence based health care.

The major setback for the clinical effectiveness of herbal medicines is the lack of quality controlled trials¹⁵ or more precisely the lack of phase 3 and phase 4 trials. The official documents and quality reviews related to the randomized trials and post marketing surveillance studies may contribute improved clinical effectiveness indications about traditional herbal remedies.

Cochrane reviews indicated the effectiveness of devil's claw (*Harpagophyllum procumbens* DC), white yellow bark (*Salix alba*), and *Capsicum frutescence* for reducing pain⁴, compared to placebo, in short term trials. The review on St.John's wort (*Hypericum perforatum*) indicated³ its effectiveness in treating patients with depression which is found equivalent to selective serotonin uptake inhibitors. Feverfew (*Tanacetum parthenium*) indicated in migraine, found better than placebo. Reviews on Saw Palmetto (*Serenoa repens*) indicated its effectiveness in Prostatic hyperplasia.

The evidence of effectiveness was strong in the reviews for *Harpagophytum procumbens*, (grapple plant, wood spider or devil's claw) in the treatment of painful osteoarthritis and chronic low back pain. Harpagophytum preparations containing > 50 mg harpagoside in the daily dosage proved effective in reducing pain associated with osteoarthritis.

Evidences again include references from approved Pharmacopoeias, approved monographs, and independent written histories of use in the classical or traditional medical literature.

Mainly three different categories of clinical trials are performed to identify the effectiveness of therapeutic claims .They are Interventional studies, Observational studies, and Research synthesis studies.

Interventional studies

These studies are considered as the gold standard of therapeutic efficacy which involves the randomized controlled clinical trial (RCT). In a randomized controlled trial, subjects similar to each other are randomly assigned either to receive the intervention or not to receive the participation.

Observational studies

In observational studies of prospective nature, the investigators recruit subjects and observe them prior to the occurrence of the effect or outcome. In retrospective observational studies, investigators review the records of subjects and interview subjects after the effect has occurred. Various types of observational studies are available which include *Cohort studies, Case control studies, Cross sectional studies, Time series studies, ecological studies, Descriptive epidemiology, Case reports* etc.

Research synthesis studies

Research synthesis studies including meta analysis may be useful as supporting evidence for a health claim. A meta-analysis may be conducted on several clinical trials of a medical treatment, in an effort to obtain a better understanding of how well the treatment works.

Major setbacks of traditional medicines

The absence of , or very few clinical evidences²¹ for herbal medicines is not considered as a serious problem by practioners or consumers in the complementary and alternative medicine segment , since it is believed that traditional use over many generations without known side effects or health threats , reflects that they are safe .The side effects of some plant medicines are not immediate, for example the production of nephrites by aristolochic acid , a phytochemical present in many plant species of Aristolochia genus.

Another segment lacking informations in the case of herbal medicines is the unavailability of the pharmacokinetic and pharmacodynamic data¹⁶.

Only for a few phytoconstituents or herbal products, the mechanism of action is well documented. But for the rest of herbal products the mechanism of action or the pharmacodynamics is not established clearly due to the complexity of multiple compounds present in the extracts.

In both Ayurvedic and Chinese medicines the complexity is multifarious by the fact that each preparation usually contains multiple herbal /other natural ingredients with each ingredient containing a number of active constituents. This increased level of complexity¹¹ creates difficulties in establishing valid standards¹⁷, and also due to the unknown toxicity¹⁸ of constituents, safety²³ may be compromised, which directly reflects on the unavailability of registered Ayurvedic and Chinese herbal medicines in western market.

Treatment in Ayurvedic system is holistic, involving natural medicines, massage, diet and the regulation of life style. It sees each individual as having a unique mind body constitution and set of life conditions.

Other hindering factors for the non acceptance of these treatments by main stream western health care providers include the unstable nature of therapeutic efficacy of different preparations of Ayurvedic medicines and TCM and the lack of standardized clinical trials^{13, 14}.

The chemical constituents of plants vary depending on the species, variety and part of the plant, with conditions of growth (soil, water and temperature), and with the age of the plant. These complexities and variations of chemical content make standardization essential.

Newer scientific trends about herbal medicines

Application of novel trial designs such as Point Of Care clinical trial (POC –CT) ,a new clinical trial approach developed by Dr.Philip Lavori of Stanford University, compares treatments that are in use already by doctors, and collects data on, which treatment works best within the context of real-world, and in everyday practice. Enrollment and randomization of study volunteers occurs during regular care - within the framework of a patient's visit to their usual health care provider.

It is assumed⁹ that herbal medicines interact with bacteria present in the gut flora, leading to a kind of bioprocessing inside, may result in the conversion of inactive to active medicine compounds, or sometimes improve the population of beneficial bacteria which in turn improve the immune system performance. Phytopharmaceuticals proved useful in several cases as these compounds act synergistically² with the synthetic drugs and may reduce the adverse reactions to some extent.

Reports^{9,10} again indicated that the phytoconstituent, piperine present in *Piper longum* and *Piper nigrum*, increases the bioavailability, C_{max} and AUC of several synthetic drugs amoxicillin, phenytoin, propranol and theophylline. Licorice has been shown to increase the plasma concentration of prednisolone.

Recent research⁶ on several Ayurvedic medicines indicated that, the total synergistic effect^{2, 20} of the constituents lead to the inhibition of Stress activated Protein Kinase there by blocking the NFκB (Nuclear Factor kappa B) signal transduction pathway, finally results in apoptosis, and anti inflammatory responses.

The emergence of modern standardization tools^{2,6} like proteomics, bioinformatics and various chemical docking studies may improve the identification of the evidence based herbal constituents and products in the future.

Table-1: The list of herbal medicines for which the Cochrane reviews are positive compared to the placebo

No.	Name of the plant	Botanical name	Clinical condition	CR for RCT
1	St.John's wort	<i>Hypericum perforatum</i>	Depression	++
2	Fever few	<i>Tanacetum parthenium</i>	Migraine	++
3	Saw palmetto	<i>Serenoa repens</i>	Prostatic hyperplasia	++
4	White yellow bark	<i>Salix alba</i>	For pain and inflammation	++
5	Capsicum	<i>Capsicum frutescens</i>	For pain and inflammation	++
6	Grapple plant or devils claw	<i>Harpagophytum procumbens</i>	For pain full osteo arthritis	+
7	Echinacea	<i>Echinacea purpurea</i>	Immune stimulant	+
8	Evening primrose	<i>Oenothera biennis</i>	Atopic dermatitis	++
9	Ginkgo	<i>Ginkgo biloba</i>	Obesity	=
	"	"	Dementia progression	++
10	Korean ginseng	<i>Panax ginseng</i>	Immuno stimulant	++
11	Brahmi (Ayurvedic)	<i>Centella asiatica</i>	Schizophrenia -adjunct therapy	+
12	Garlic (TCM)	<i>Allium cepa</i>	Common cold preventive	+
13	Mulberry leaf (TCM) bitter ,sweet, cold	<i>Morus alba</i>	Expel wind and clear heat from the lungs	=
	"	"	Clear the liver and eyes	=
	"	"	Remove heat from blood to arrest bleeding	=
14	Cranberry fruits	<i>Vaccinium macrocarpon</i>	Urinary tract infections	-
15	Nei Yi Pills (CHM)	<i>Curcuma longa</i>	Endometriosis	= danazol , with fewer side effects
		<i>Angelica sinensis</i>		
		<i>Panax ginseng</i>		
		<i>Achyranthes bidentate</i>		
		<i>Cyperus rotundus</i>		
		<i>Cinnamomum zeylanicum</i>		
		<i>Rheum emodi</i>		
	<i>Olibanum</i>			
16	Thunder God vine	<i>Trypterigium wilfordi</i> (Active compound triptolides)	Rheumatoid arthritis	++ toxicity reported: male infertility, embryo toxicity, immune suppression, renal insufficiency
17	Gama linoleic acid GLA	<i>Evening primrose seed oil, black current seed oil, Borage seed oil</i>	Rheumatoid arthritis pain reduction	+, 1400mg/day treatment
18	Boswellic acid	<i>Boswellia serrata</i>	Rheumatoid arthritis	-
19	Cats claw	<i>Uncaria tomentosa</i>	Rheumatoid arthritis	+
20	Korean herbal mixture SK 1306 X		Rheumatoid arthritis	=:comparable to celecoxib
21	Ayurvedic herbal mixture: RA-1		Rheumatoid arthritis	Changes scores in all clinical variables of RA than in the placebo group after 16 weeks of intervention. But not statistically significant
22	Xianzhen Pian CHM	<i>Myrcia uniflora, Astragalus ,holy basil, Potentilla chinensis, Berberine, Inolter</i>	Diabetes	Xianzhen Pian along with glicazide found better in anti diabetic therapy compared to glicazide alone

++: effective /proved compared to placebo, +: effective compared to placebo
 =: equivalent to placebo, -: less than placebo

References

1. Wagner H. Phytomedicine Research in Germany. *Environ Health Perspect* **1999**; 107: 779-781.
2. Ulrich-Merzenich G, Panek D, Zeitler H et al .New perspectives for synergy research with the 'omic' technologies .*Phytomedicine* 2009; 16:495-508.
3. Linde K, Berner MM, Kriston L, St.John's wort for major depression. *Cochrane database of Systematic reviews* 2008; (4):CD000448.
4. Gagnier JJ, Van Tulder M, Berman et al. Herbal medicines for low back pain. *Cochrane data base for systematic reviews* **2006**; (2):CD004504.
5. Moerman DE, Jonas WB, Deconstructing the placebo effect and finding the meaning response. *Annals of Internal medicine* 2002; 136:471-6.
6. Kang YJ. Herbogenomics: from traditional Chinese medicine to novel therapeutics .*Experimental biology and Medicine* **2008**; 233:1059-65.
7. WHO /EDM/TRM/2000.1, General Guidelines for methodologies on research and evaluation of traditional medicine, annexe V: 39-46.
8. Straus S. Herbal medicines - What's in the bottle? *New Engl J Med* **1997**; 347.
9. Tapsell LC, Hemphill I, Cobiac L, Patch CS, Sullivan DR, Fenech M, Roodenrys S, Keogh JB, Clifton PM, Williams PG, Fazio VA, Inge KE. Health benefits of herbs and spices: the past, the present, the future. *Med J Aust* **2006**; 185 (4 Suppl): S4-24.
10. Thatte UM, Rege NN, Phatak S, Dahanukar SA. The flip side of Ayurveda. *J Post grad Med* **2006**; 39: 179-182.
11. Robert BS, Stefanos K, Janet P, Michael JB, David ME, Roger BD, Russell SP 2004. Heavy Metal Content of Ayurvedic Herbal Medicine Products. *JAMA* **2004**; 292:2868-73.
12. Pittler MH, Abbot NC, Harkness EF, Ernst E 2000. Location bias in controlled clinical trials of complementary/alternative therapies. *Int J Epidemiol* **2000**; 53: 485-489.
13. Marcus D, Grollman A 2002. Botanical medicines - The need for new regulations. *New Engl J Med* **2002**; 347: 2073-2076.
14. Linde K, Jonas WB, Melchart D, Willich S. The methodological quality of randomized controlled trials of homeopathy, herbal medicines and acupuncture. *Int J Epidemiol* **2001**; 30: 526-531.
15. Calixto JB . Efficacy, safety, quality control, marketing and regulatory guidelines for herbal medicines (Phytotherapeutic agents). *Braz J Med Biol Res* **2000**; 33: 179-189.
16. Bhattaram VA, Graefe U, Kohlert C, Veit M, Derendorf H. Pharmacokinetics and bioavailability of herbal medicinal products. *Phytomedicine* **2002**; 3:1-33.
17. Bauer R, Tittel G 1996. Quality assessment of herbal preparations as a precondition of pharmacological and clinical studies. *Phytomedicine* **1996**; 2: 193-198.
18. Chan K. Some aspects of toxic contaminants in herbal medicines. *Chemosphere* **2003**; 52: 1361-1371
19. Fugh-Berman A. Herb-drug interactions. *Lancet* **2000**; 355:134-138.
20. Wagner H. Phytomedicine Research in Germany. *Environ Health Perspect* **1999**; 107: 779-781.
21. Shukla NK, Narang R, Nair NGK, Radhakrishna S, Satyavati G. Multicentric randomized controlled clinical trial of Kshaarasootra (Ayurvedic medicated thread) in the management of fistula-in-ano. *Indian J Med Res* **1991**; 94: 177-185.
22. Robbers JE, Tyler VE. Tyler's Herbs of Choice: The Therapeutic Use of Phytomedicinals. The Haworth Herbal Press, Inc., New York. **1999**; pp 124-158.
23. Boullata JI, Nace AM. Safety issues with herbal medicine. *Pharmacotherapy* **2000**; 20(3):257-69.



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