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Review

Research on Traditional Chinese Medicine harmonising two approaches

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SUMMARY

While full recognition of the practical value of Traditional Chinese Medicine is being endorsed, the current stand on the research methodology of this field should be worked out. Since modern medicine has already developed a logical system of research methodology basing on the principles of deduction, any research on any system of medicine need to take reference to what is most popularly used and commonly recommended. The best way to approach research on Chinese Medicine, therefore, would be one that would take full reference to the methodology being used in modern medicine, while at the same time respecting the traditional approach. This would enable traditional medicine to be elevated to the level of general modern recognition. Nevertheless, innate problems in traditional medicine are making its research difficult. The problems lie in difficulties to achieve uniform herb supply, principles of randomization and placebo arrangements, uncertain chemical structures and toxicology etc. A practical approach centered on carefully planned evidence-based clinical trials, with parallel studies on biological activities and herb authentication is being recommended.

Key words: Chinese Medicine; Research methodology; Evidence Base Medicine

INTRODUCTION

Modern Medicine is very much a deductive science. Specific target problems are identified before solutions are found. Hypotheses are made, and using objective past data and specially designed methodology of research, they are gradually proven. Even negative results would serve subsequent attempts on related endeavors.

Modern medicine has followed the pathway of development of modern science which has been so successful that any other channel of pursue would need to stand harsh criticism and it would not be easy at all for the alternative methodology to get recognition.

Traditional Chinese Medicine has been inductive. It does not relate to very specific target, but instead, carries multiple foci of concern. It does not aim at solving a particular problem but aims at improving the general well-being of the individual by maintaining an effective balance between the various physiological functions.

Deductive Modern Medicine commands the exactness which is the basis of all brilliant scientific achievements of the past 50 years. The exactness, however, has been criticized for being over-specific and as a consequence the general

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need of the individual might be neglected. While Traditional Chinese Medicine suffers the incapability of solving specific problems basing on human biology, it follows a holistic approach with which the individual is kept balanced. The balanced, harmonious state would allow the individual to mobilise its biological reserves to take care of its own problems (Campion, 1993).

While no one would have any doubt about the remarkable achievements in modern medicine: from specific removal of problems to accurate substitution of deficiencies and the recent genomic discoveries will probably lead to a total eradication of some pathologies and diseases, one could also turn skeptical with the tread of development. The deductive approach relies on accurate targets. Specialisation and sub-specialisation thence becomes mandatory. The result of specialisation is over-specialisation, which leads the way towards highly expensive services and the tendency of losing holistic care: patients are treated as "spare parts" of a machine. The dilemma existing between modern achievements and patient disappointment because of the neglect of holistic care, is one of the important reasons behind the popular support for alternative care and "off the counter" supply of health preparations (Eisenberg *et al.*, 1993).

While acknowledging the merits of the two different streams of medical service being provided, the unbiased medical scientist would agree, that, if the two divergent systems could be harmonized, a holistic care to promote a good physiological balance to allow spontaneous adjustment and strengthened bodily defense, could supplement effectively the aggressive unifocal modern medicine, aiming at the removal of specific problems.

How could Harmonisation of the two systems be achieved?

The answer lies in research

Modern Medicine researches on a strict deductive principle and condemns any other approach. Traditional Chinese Medicine relies on individualization of management. The former works on a methodology aiming at objective data collection, biostatistics analysis and then generalization. On the other hand, Chinese Medicine insists on individualized variations of treatment which would not give strong support to generalization. If one tries to visualize the ancient situation of primitive medicine, where basic science knowledge was deficient, and means for investigation were totally absent, individualized treatment relying totally on experience and day to day observations would be the best choice of a holistic care. However, with the modern sophisticated laboratory and imaging facilities, and other diagnostic tools, should one really be insistent on strict individualized treatment and condemn generalization? Would it not be highly desirable that a generalized policy be adopted as a main line of management? After all, without generalization, clinical research on efficacy is never feasible.

Research on traditional medicine should therefore explore the way towards generalization, when either traditional means is repeated or innovative modifications are utilized.

A proposed research methodology - The efficacy driven approach

Research on Herbal Medicine in the past century has been focused on many aspects: from pharmacognosy, to quality control, biological tests in the laboratory, authentication and clinical efficacies. Of these approaches much resource have been spent on the identification of the active herbal fractions and subsequently working out the chemical equation responsible for the efficacy, with the obvious intension of developing an effective drug. There are a few successful examples in and outside China. One remarkable successful example in China was the discovery of the derivatives of Artemisinin (Qinghao) which started as the herbal treatment for malaria, then recently found to be also effective against some other parasites and certain cancers (Valecha and Tripath, 1997).

Two successful examples outside China would be vincristine and taxol, extracted from the flower periwinkle in the former case and the bark of Yew trees in the latter. The two cytotoxic drugs are produced in the National Chemistry Laboratory of France (CNRS, 1999).

One has to realize the tremendous resources and facilities required for such major successes. One also has to be aware of many other unsuccessful examples. Why are there limited numbers of successes in spite of the many attempts? It is believed that the production of chemicals of botanical origin is so complicated and extraction and identification of active fractions require innovative input as well as much laboratory investments. Procedures of chemical isolation and deduction of the exact chemical equation demand the endless efforts of a most advanced chemical laboratory and its technical team.

There is a compromise when the research establishment fails to satisfy the demand on chemical extractions and analyses. The compromise, aiming at proving the efficacy of the raw herbal materials or a combination of herbs, before considering further sophisticated analysis, would be much less expensive and less time-demanding compared with the pharmacognosic method.

This approach could be represented diagrammatically as follows (Fig. 1).

The Centre of research is the clinical trial which is targeting on an important clinical problem which fails to find perfect solution in modern medicine. Choosing a universally acceptable methodology for clinical trials would enable the results of the trial to be widely recognised by clinical experts. Efficacy is most important to the clinician. Efficacy, once proven, encourages more utilization, invites more commitments on further studies towards further improvement of the trial

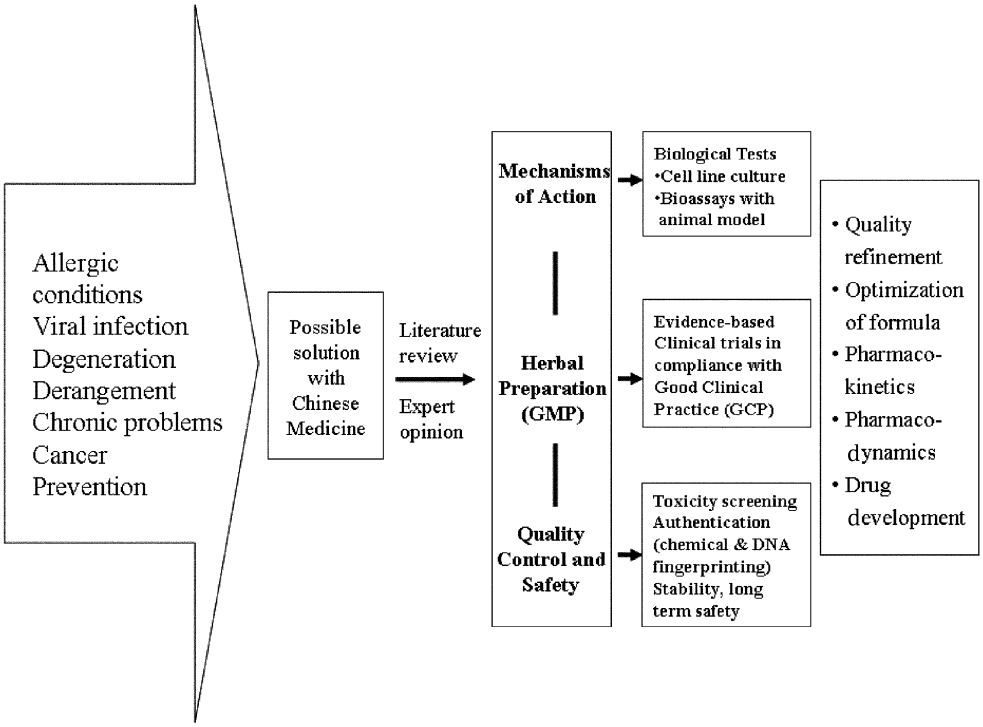

Fig. 1. The efficacy driven approach, clinical trial leading, biological tests & quality control in parallel, three prong approach.

preparation.

Once efficacy is proven and determination is made towards further research, the following principles are enforced:-

(i) Understand the details of clinical influences

Efficacy is taken as a macroscopic, crude demonstration of the effects of the modality of treatment used for a clinical problem. Once preliminary evidences are established, more details of the clinical influences could be worked out.

We had a clinical trial for the efficacy of a herbal formula on the healing of diabetic ulcers. The initial results showed that the ulcers did heal well. Further clinical studies included explorations on the objective events happening behind the healing of the ulcers. These included: details of the state of granulation, changes in the local circulation; changes in skin sensation and quality of life (Wong *et al.*, 2001).

(ii) Understand the biological mode of action of the herbal formula

This mainly involves laboratory tests. Again using the example of diabetic ulcer, one would like to know why the ulcers healed better. Was it because the herbs promoted granulation formation? Was it because they were also helping with the state of diabetes? The animal model was a streptozotocin-induced diabetic rat whose dorsal surface of the foot was de-epithelialised by removing a standard area of full thickness skin. The wound healing area of artificial ulcer was used to test the ulcer behaviour under the influence of the test herbal formula (Lau *et al.*, in press). Suitable cell cultures would further verify the details of wound healing (Lau *et al.*, 2007). The effects of the same formula on the blood glucose level of animal models could be studied thoroughly.

(iii) Understand the quality of the herbs

All herbal formulae, once applied to solve a clinical problem would need to be further authenticated. One wants to get the best provision of the herb so that clinical effects could be guaranteed. Basic records of quality control are established through chromatography studies (HPLC) while the species details related to the origin of production are established with DNA finger printing.

Since consistent quality supplies of herbs are not easily available, every item should be subjected to screening and counter-checks using standard extracts provided by the relevant academic institution in China (Zhan and Lin, 2002).

Stability tests, as required by registration authorities, need also to be completed as routines.

(iv) Prepare for the improvement and optimization of the formula

Herbal formulae aim at additive and synergistic effects by mixing many herbs together. However, if the number of herbs is large further, development by manipulating the formula becomes difficult. Four to five herbs in a formula might be the optimal number. When too many items are found in the classic formula, one could use modern concepts of pathology as guidelines of reduction. Since modern medicine works on direct targets, herbs advocated for direct actions could be eliminated because they could be substituted with modern medicine which should offer better direct actions. Those herbs that are understood to be immuno-modulating and promoting balance, on the other hands will be kept. In other words, when the major action of a herb is already covered by modern medicine, the herb could be eliminated.

In the innovative creation of a formula or in the modification of a formula, the principles which Chinese Medicine practitioners had used for centuries, could be followed. This principle identifies a main treatment herb as “the emperor”, which is being assisted by another herb of related potency, “the minister”, which might yet need further support, “the assistant”, and possibly require neutralization “the ambassador” (Principle of creating a herbal formula using classical philosophy of

君, 臣, 佐, 使, i.e. principle of enforcement, reinforcement and balance).

(v) Rule out the possible interference with other pharmaceutical drugs being used

When the general mainline clinical management is still modern medicine, and probably the Chinese Medicine preparation is playing a supplementary role, it is important that the Chinese Medicine formula being used should be tested against the modern pharmaceuticals being used, so that one could be certain that no adverse interactions are taking place. Therefore in the diabetic ulcer trial, the herbal formula should also be tested against common anti-diabetic drugs being used to rule out interference and adversity. Any other formula used for other conditions should be tested against the commonly used concomitant pharmaceuticals, before full scale popularization takes place.

An example of harmonisation

Using a Herbal Preparation to lower the Risks of Atherosclerosis:

A Clinical trial using evidence based medicine concepts and modern monitoring tools. Hypertensive subjects with left ventricular hypertrophy (LVH), diabetes mellitus or impaired renal function are particularly vulnerable to the atherosclerotic complications in spite of standard antihypertensive therapies. Accordingly adjunctive primary strategies are mandatory to improve the long-term natural history of this group of high-risk subjects, including lipid-lowering, optimal control of hypertension and diabetes mellitus, and other emerging novel programmes for improving antioxidant, inflammatory and endothelial function profiles. It is now possible to assess early vascular abnormalities more objectively and non-invasively by high resolution B-mode ultra sonography. It is highly reproducible, correlating well with severity and extent of coronary artery disease, and is predictive of stroke and coronary events in asymptomatic healthy subjects (Bots *et al.*, 1997; O'Leary *et al.*, 1999).

'Danshen' (丹參) and 'Gegen' (葛根) are commonly used in Chinese material medica as treatment agents for cardiac symptoms and atherosclerosis-related disorders (Li, 1993). 'Danshen' consists of the dried root and rhizome of the perennial herb *Salvia miltiorrhiza* Bge. 'Gegen' is the dried roots of *Pueraria lobata* (willd.) Ohwi. Our preliminary work confirmed the favourable effects of 'Danshen and Gegen' on some metabolic indices and atherogenic processes, which could be ascribed to their antithrombotic, lipid-modulating, antioxidant, anti-inflammatory and phytoestrogenic properties. On this basis, our group has successfully produced a quality preparation of this combination (in 500 mg capsule), through several meticulous processes, including the use of DNA finger printing and chemical assays for quality control and authentication, bacterial and chemical toxicology monitoring, and processing/extraction of raw herbs all according to the guidelines of Good manufacturing Practice (GMP) (Lee *et al.*, 2003). A pilot secondary prevention clinical study of 100 patients with angiographically documented coronary artery disease treated with the dried extract of this combination formula (D&G) (n = 50) (3 g/day) or identical placebo capsules (n = 50) for 24 weeks, in double-blinded and parallel fashion was completed. There was a mild decrease in total cholesterol and LDL-cholesterol ($P < 0.05$) in D&G group, associated with significant improvement in endothelial function ($P < 0.0001$), and carotid intima-media thickness (IMT) ($P < 0.05$) (11). No significant changes in these parameters were seen in the placebo group. Further improvement in carotid IMT was seen when treatment was continued (open label D&G 2 g/day) for 24 weeks. Adjunctive treatment with D&G on top of standard cardiac drugs (statins, β blockers, aspirin, ACE inhibitors or diuretics) was well tolerated, with no significant adverse event (Tam *et al.*, 2004).

Endothelial dysfunction, oxidation of circulating LDL-cholesterol and the inward migration of oxidized LDL-cholesterol-laiden monocytes in the

blood vessel wall are the critical processes in the development of atherosclerosis. Several mechanisms may explain the improvement in vascular function and structure after D&G therapy, including their lipid-lowering, antioxidant and nitric oxide production /facilitating effects as well as phytoestrogen properties. An in-vitro endothelial and monocyte cell line experiment revealed that D&G combination inhibits dose-dependently macrophage/foam cell transformation from fat-fed monocytes (Sieveking *et al*., 2005). This cell-modulating mechanism underlines the scientific basis of our favourable vascular-protective effect in coronary patients (secondary prevention).

CONCLUSION

The clinical trial using evidence-based medicine principles on the efficacy of a herbal formula against the development of atherosclerosis has demonstrated good clinical effects and modern assessment tools, e.g. high resolution B-mode ultrasonography had been used as the major monitoring instrument. In the clinical trial, no individualised treatment was considered. The simple, two herbs formula was demonstrated to have efficacy reaching biostatistical significance.

The clinical trial was accompanied with laboratories tests in parallel. With these tests, the reliability of the positive clinical observations was further strengthened. The inhibition of monocytes from twining into macrophages gave a good biological basis for the prevention of atheroma development. On the authentication side, the conventional chemical marker approach was applied and both HPLC and Thin Layer Chromatography (TLC) were used as standard requirements to provide the basic chemical profiles. The positive result from the clinical trial was well supported by laboratory explorations on the biological mechanism of action, thus encouraging further studies and consideration of drug development. The authentication tests established the objective profile of the herbs, so that in any future biological test on clinical trial using the same components, the same quality supply could be insisted on.

The efficacy driven approach therefore could well be adopted as a methodology of clinical research harmonising between the two systems of medical care.

REFERENCES

Bots ML, Hoes AW, Koudstaal PJ, Hofman Am Grobbee DE. (1997) Common carotid intima-media thickness and risk of stroke and myocardial infraction. *Circulation* 96, 1432-1437.

Campion EW. (1993) Why unconventional medicine? *N. Engl. J. Med.* 328, 282-283.

Eisenberg DM, Kessler RC, Foster C, Norlock FE, Calkins DR, Delbanco TL. (1993) Unconventional Medicine in the United States - Prevalence, costs, and patterns of use. *N. Engl. J. Med.* 328, 246-252.

Lau TW, Sahota DS, Lau CH, Chan CM, Lam FC, Ho YY, Fung KP, Lau CBS, Leung PC. An in vivo investigation on the wound healing effect of two medicinal herbs using an Animal Model of Diabetic Foot Ulcer. *Eur. Surg. Res*. (In press)

Lau TW, Chan YW, Lau CP, Chan CM, Lau CBS, Fung KP, Leung PC, Ho YY. (2007) Investigation of the effects of Chinese medicine on fibroblast viability: implications in wound healing. *Phytother. Res.* 21, 938-947.

Lee SMY, Lau KM, Koon JCM, Chan JYW, Fung KP. (2003) Biochemistry and Herbs. In: A Comprehensive Guide to Chinese Medicine, edited by Leung PC, Xue CC and Cheng YC, pp. 113-142, World Scientific Publishing Company, New Jersey, U.S.A.

Li SZ. (1993) Compendium of Materia Medica (Ben Cao Gang mu), pp. 1287-1288, 1961-1966, Shanghai: Shanghai ke xue ju shu chu ban she.

National Centre for Scientific Research France (CNRS). (1999) Report on the Successes of Development of Drugs from Botanical Plants. Special Report CNRS, France.

O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK for the Cardiovascular Health Study Collaborative Research Group. (1999)

Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N. Engl. J. Med.* 340, 14-22.

Sieveking DP, Woo KS, Lundman P, Nakhla S, Celeramjer DS. (2005) Chinese herbal medicine reduces human foam cell formation in vitro-a potentially anti-atherogenic effect. *Int. J. Cardiol.* 105, 40-45.

Tam LWY, Chook P, Poon PYK, Qiao M, Chan LLT, Cheung ASP, Chan TYK, Fung KP, Tang KSL, Lau VKM, Poon JCM, Leung PC, Celermajer DS, Woo KS. (2004) Danshen and gegen as cardiovascular tonic in coronary patients: a novel strategy for secondary atherosclerosis prevention. *J. H. K. Coll. Cardial.* 12, 32.

Valecha N, Tripath KD. (1997) Artemisinin: Current status in Malaria. *Indian J. Pharmacol.* 29, 71-75.

Wong WN, Leung PC, Wong WC. (2001) Limb Salvage in Extensive Diabetic Foot ulceration – A Preliminary Clinical Study Using Simple Debridement and Herbal Drinks. *Hong Kong Med. J.* 7, 403-407.

Zhan NP, Lin RC. (2002) The establishment of SOP for different Chinese Materia Medica in China. Res. Inform. Traditional Chinese Med. 3, 15-17. (In Chinese)