

HEALTHY AGEING - IS THERE A ROLE FOR TRADITIONAL CHINESE MEDICINE (TCM) ?

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Abstract

Currently there are many Traditional Chinese Medicine preparations that lay claims to promoting healthy ageing. The components of healthy ageing may be considered as prolongation of life span together with maintenance of physical and mental function. Laboratory and animal studies show that therapies of Traditional Chinese Medicine have the potential to act on various processes in the components of healthy ageing. However, the evidence is largely from basic laboratory research, few randomized controlled trials having been conducted so far. Obstacles to carrying out such trials include quality assurance of herbal products and the largeness of the trial required to demonstrate the relatively small effect. Surveillance mechanisms of adverse effects is also lacking. Such trials are needed to change the basis for the use of Traditional Chinese Medicine currently recommended for healthy ageing to be elevated from that of 'wisdom' based or folklore to that of higher levels of evidence.

Key words: Ageing, Chinese Medicine, life span, disease, evidence-based practice

Introduction

With the greying of populations worldwide, increasing emphasis is being placed on the promotion of healthy ageing, to counteract the increasing burden of chronic age-related diseases on health care providers. In metropolitan cities in China (Beijing, Shanghai and Hong Kong), the top three causes of mortality are cancer, coronary heart disease and stroke, while the annual incidence rate per 100,000 population aged 70 years and over in Hong Kong for these three diseases has been estimated to be 1300, 888 and 950 respectively.¹ In 2000, the Hong Kong government has initiated a three year campaign to promote healthy ageing, while the response to the ageing population in mainland China is predominantly preventive in nature¹. The two components of healthy ageing may

be considered as prolongation of lifespan together with reversal of functional decline or maintenance of both physical and mental function. Currently, there are many over-the-counter products in the category of Western or traditional Chinese Medicine that claim to achieve both objectives. This article reviews the current evidence for the role of TCM on the various components of the ageing process, highlighting the differences in approach between Western and Traditional Chinese Medicine.

Definition of health ageing and the Western medicine approach

Health ageing may be defined as the absence of chronic disease, disability or impairment, and achievement of psychological well-being. Its components cover social aspects (adequate finances, good social support network), prevention of diseases (cardiovascular, musculoskeletal, dementia, depression), and prevention of functional decline. The Western Medicine approach to substances that may affect these components is essentially evidence-based, where evidence is obtained from research at cellular, animal, and human levels. The studies address a specific question each time, and application in humans needs to be supported by evidence of clinical efficacy and documentation of side effects and drug interactions. Levels of evidence achieved may range from the highest (ie, meta-analysis of randomized controlled trials) to the lowest (ie, expert committee reports, opinions etc)². The potential sites of action of compounds that may promote healthy ageing may be at the following levels: cellular, hormonal, organ/system, specific disease prevention, and maintenance of function.

Prolongation of lifespan

Factors determining cellular ageing include endogenous oxidative stress (generation of free radicals), activity of the DNA repair enzyme polyadenyl ribose polymerase, maintenance of

telomere length (increase telomerase activity), and modulation of the inflammatory process (cox gene expression and prostaglandin production; cytokine gene expression)^{3,4}. These processes are inter-related. For example, generation of reactive oxygen and nitrogen species from mitochondria, COX, NADPH dehydrogenase and oxidase, and xanthine oxidase results in increase in transcription factor Nck(, in turn increasing the production of pro-inflammatory genes, predisposing to diseases/ageing⁴. These are the potential sites whereby compounds may theoretically act to prolong lifespan. Currently caloric restriction without a decrease in essential nutrients is the only method shown to be effective in rodents and non-human primates⁵. Reduction in caloric intake by 30-60% reduces oxidative damage to molecules at the mitochondrial level, slows aging in many physiological systems, and increase average and maximal lifespan⁶. Observations in humans have been made that may parallel these experimental conditions. The population in Okinawa consists of large numbers of centenarians, and has lower overall mortality and mortality from cancer and cardiovascular diseases⁷. Children and adults

preliminary search was carried out by obtaining material on this topic from a graduate of the Beijing Medical University of Traditional Chinese Medicine. A review of three books and 20 articles on this topic showed that relevant information may be grouped into four aspects: TCM theories on aging and longevity and general methods of prolonging life, TCM methods on treatment of common diseases in the elderly, studies of the mechanism of individual TCM methods such as a herb, combination of herbs, or acupuncture on prolonging life, and methodological issues on studying methods of prolonging life. Almost all research in the latter three areas was laboratory-based studies. A further search was carried out into three commonly mentioned herb: Lingzhi, Ginseng, and Ginkgo Biloba, by the Institute of Chinese Medicine of The Chinese University of Hong Kong, using their database and existing Chinese pharmacopoeia. Eighty-eight articles on Ginseng, 22 on Lingzhi and 3 on Ginkgo were identified, the majority being descriptive in nature or were studies in rodents. A Medline search on these three herbs as key words was then carried out. In addition, a literature search of CBM Disc (the largest Chinese biomedical database) using a widely used search strategy was carried out²¹. Finally, this topic was presented by one of the authors (JW) as an invited speaker at a meeting in December 2001 with prominent researchers in the ageing field from USA and Europe, and representatives from various Traditional Chinese Medicine Institutions chosen by the Chinese Academy of Sciences, in Shanghai. Any further information or modification was made as a result of comments from participants. The activity of these herbs may be grouped into the following categories: enhancement of cellular capability of withstanding oxidative stress (e.g. activity of superoxide dismutase, catalase, glutathione reductase), enhancement of the immune system, improvement of lipid profile and glucose tolerance²²⁻²⁷. There is thus potential for these compounds to act on any of the processes described in the previous sections.

Currently, the majority of clinical evidence relating to use of TCM in promoting healthy ageing is laboratory-based rather than from randomized clinical trials. For example, ginseng has been shown to have a stimulant effect on the central nervous system by inhibiting the uptake of neurotransmitters, to attenuate glutamate induced neuronal damage in cultured rat cortical cells, to increase production of corticotrophin and cortisols, to have anabolic actions in stimulating DNA, RNA

and protein synthesis in tissues), to have immuno-enhancing effects and anti-proliferative effects on cancer cells, to have anti-oxidant properties, to stimulate nitric oxide production in immune system endothelial cells and erectile tissues, to inhibit platelet aggregation, and to improve glucose tolerance^{23, 28}. Clinically it is being used as a tonic to increase vitality, health and longevity, particularly in older persons. Few clinical trials have been carried out. The best documented studies showed improved physical performance in physical exercise²⁹. It had also been noted that 85% of commercial products may not contain ginseng²⁹. Lingzhi (*Ganoderma Lucidum*) has been shown to inhibit ADP-induced platelet aggregation *in vitro*³⁰. A meta-analysis of double-blind, placebo controlled trials of use of Ginkgo Biloba (120-240mg/d for >3 months) showed a significant improvement of 3% in ADAS-COG score, with beneficial effect for poor memory, concentration, confusion and fatigue³¹. Possible mechanisms of action include increased blood flow through small vessels, vasoregulatory effects, inhibition of platelet aggregation, increased tolerance to hypoxia and neuroprotection, inhibition of phospholipase A resulting in membrane stabilization and decrease capillary fragility, anti-oxidant and free radical scavenging action, and enhancement of neuronal glucose and oxygen utilization. Another compound, Huperzine A, has cholinesterase inhibitor activity and is used for dementia, although no clinical trials have been reported³². Bak Fung Pills, used by women to maintain youth, has been shown to have estrogenic action in animals³³. These are largely animal and *in vitro* studies or studies in human subjects that used short term intermediate variables rather than long term important health events, such as death and survival, as outcome. The literature search of MEDLINE and CBM Disc failed to identify any clinical trial that uses major health events, such as death, as outcome.

It can be seen that the level of evidence for the effectiveness of these compounds in promoting healthy ageing can currently be described as 4 at best, being a practice that has been passed through centuries in the Chinese Pharmacopoeia. Nevertheless, some traditions have subsequently been shown to have a scientific basis. The use of qinghaozhu for the treatment of malaria is one example³⁴. Another is the custom of eating many eggs in the post-partum period, which results in high concentration of long chain polyunsaturated fatty acids (LCPUFA) in breast milk³⁵, and LCPUFAs are currently thought to promote brain development

in the infant³⁶ and are added to formula for bottle-fed infants.

Other issues that need to be considered in the clinical use of TCM are quality assurance of herbal products, and surveillance mechanism of adverse effects to include contamination, direct toxicity and indirect toxicity from interaction with other drugs. For example, adverse effects have been documented with Ma Huang or ephedra containing alkaloids, giving rise to cardiovascular complications, permanent disability and death³⁷. Herb-drug interactions have been observed with Danshen and warfarin (increase INR), Dong quai and warfarin (increase INR), Gingko Biloba an aspirin, paracetamol and ergotamine/caffeine (spontaneous hyphema, subdural haematoma), ginseng and warfarin/phenelzine (decreased INR, headache, tremor)³⁸. TCM may have many theoretical benefits in contributing to healthy ageing at the cellular, hormonal and organ levels, and in the prevention of functional decline. To date, most experiments have been carried out in cell culture or animal studies. What is needed are clinical studies carried out as randomized controlled trials, using good clinical practice (GCP) guidelines and meeting clinical research ethics criteria. Before these can be carried out, for each preparation, reproducible dosages should be available, and for mixtures of compounds, the constituent quantities must be the same. The preparation must be free of contamination, and safe to take for prolonged periods. These clinical studies will be necessary if the basis for use of TCMs currently recommended for healthy ageing are to be elevated from that of 'wisdom' based or folklore to that of higher levels of evidence. Future studies of the role of TCM in healthy ageing could follow two approaches: a systematic search for compounds from TCM that will act on the various levels of ageing (using laboratory and animal studies), or clinical trials of compounds with putative actions on various ageing processes to substantiate the claims of efficacy. The latter approach may be more efficient in addressing the question of whether TCM has any role in healthy ageing, in that TCM with action in vitro or in animal studies may not translate into clinical effectiveness. However, such trials may require a large number of subjects in order to demonstrate an effect that is likely to be small in this circumstance. Such a search for compounds that would promote healthy ageing would fulfill the aims of the 'superior physician', who treats diseases 'before they appear', as described in the Pharmacopoeia of the Yellow Emperor³⁹.

References

1. Woo J, Kwok T, Sze FKH, Yuan HJ. Ageing in China: health and social consequences and responses. *Int J Epidemiol* 2002; **31**(4): 772-775.
2. Harbour R, Miller J. A new system for grading recommendations in evidence based guidelines. *Br Med J* 2001; **323**: 334-6.
3. Kirkwood T. Scientific understanding of the Ageing process. Symposium on Health and Ageing, Shanghai, China, 6-8 December 2001. Plenary lecture.
4. Chung HY, Kim HJ, Jung KJ, et al. The inflammatory process in aging. *Rev Clin Gerontol* 2000; **10**: 207-222.
5. Lane MA, Black A, Handy A, Tilmont EM, Ingram DK, Roth GS. Caloric restriction in primates. *Ann NY Acad Sci.* 2001; **928**: 287-95.
6. Roth GS, Ingram DK, Black A, Lane MA. Effects of reduced energy intake on the biology of aging: the primate model. *Eur J Clin Nutr* 2000; **54 Suppl 3**: S15-20.
7. Kagawa Y. Impact of Westernization on the nutrition of Japanese: changes in physique, cancer, longevity and centenarians. *Prev Med* 1978; **7**: 205-17.
8. Walford RL, Harris SB, Gunion MW. The calorically restricted low fat nutrient-dense diet in Biosphere 2 significantly lowers blood glucose, total leukocyte count, cholesterol, and blood pressure in humans. *Proc N Acad Sci* 1992; **89**: 1533-7.
9. Gale CR, Braidwood EA, Winter PD, Martyn CN. Mortality from Parkinson's disease and other causes in men who were prisoners of War in the Far East. *Lancet* 1999; **354**: 2116-8.
10. Roth GS, Ingram DK, Lane MA. Anti-ageing effects of caloric restriction and caloric restriction mimetics: implications for mankind. Abstract presented at a Danone Research Centre Workshop on Nutrition and successful ageing, Biarritz, France 25th -27th November, 1999.
11. Collins R, Peto R, Gray R, Parish S. Large-scale randomized evidence: trials and overviews. In: Weatherall DJ, Ledingham JGG, Warrell DA, editors. *Oxford Textbook of Medicine*. 3rd ed. Oxford: Oxford University Press; 1996. p. 21-32.
12. Tang JL, Zhan SY, Ernst E. Review of randomized controlled trials of traditional Chinese medicine. *Br Med J* 1999; **319**: 160-613.
13. Woo J. Relationships among diet, physical activity and other lifestyle factors and debilitating diseases in the elderly. *Eur J Clin Nutr* 2000; **54**: S143-S147.
14. Selhub J, Bagley LC, Miller J, Rosenberg ZH. B vitamins, homocysteine, and neurocognitive function in the elderly. *Am J Clin Nutr* 2000; **71**: 614S-620S.
15. Bhasin S, Tenover JS. Age-associated sarcopenia-issues in the use of testosterone as an anabolic agent in older men. *J Clin Endocrinol Metab* 1997; **82**: 1659-60.
16. Barret-Connor E, Goodman-Gruen D. Cognitive function and endogenous sex hormones in older women. *J Am Geriatr Soc* 1999; **47**: 1289-1293.
17. Martin FC, Sturges I. Growth hormone, aging and frailty. *Rev Clin Gerontol* 1999; **9**: 207-214.
18. Yen SSC, Morales AJ, Khorram O. Replacement of DHEA in Aging men and women. *Am NY Acad Sci* 1995; **774**: 128-42.
19. Morley JE. Growth hormone: fountain of youth or death hormone? *J Am Geriatr Soc* 1999; **47**: 1475-6.
20. Setchell KDR, Cassidy A. Dietary isoflavones: biological effects and relevance to human health. *J Nutr* 1999; **129**: 758S-767S.

21. Dickersin K, Scherer R, Lefebvre C. Identifying relevant studies for systematic reviews. *Br Med J* 1994; **309**: 1286-91.
22. Yan L, Liu B, Guo W, et al. A clinical investigation on zhi ling tang for treatment of senile dementia. *J Traditional Chinese Med* 2000; **20**: 83-6.
23. Ong YC, Yong EL. Panax (ginseng)-panacea or placebo? Molecular and cellular basis of its pharmacological activity. *Am Acad Med Singapore* 2000; **29**: 42-6.
24. Li Y, Higashiura K, Ura N, et al. Effects of the Chinese Medicine, TSJN on insulin resistance and hypertension in fructose-fed rats. *Hypertension Research* 2000; **23**: 101-7.
25. Lin CC, Huang PC, Liu JM. Antioxidant and hepatoprotective effects of *Anoectochilus formosanus* and *Gynostemma pentaphyllum*. *Am J Chinese Med* 2000; **28**: 87-96.
26. Liu CC, Yen FI, Hsu FF, Lin JM. Anti-hypercholesterolaemia, antioxidant activity and free radical scavenger effects of traditional Chinese Medicine prescriptions for stroke. *J Pharmacy Pharmacology* 2000; **52**: 1387-93.
27. Xiao PG, Xing St, Wang LW. Immunological aspects of Chinese medicinal plants as anti ageing drugs. *J Ethno pharmacology* 1993; **38**: 167-75.
28. Bucci LR. Selected herbals and human exercise performance. *Am J Clin Nutr* 2000; **72** (2 Suppl): 624S-36S.
29. O'Hara M, Kiefer D, Farrell K, Kemper K. A review of 12 commonly used medicinal herbs. *Arch Fam Med* 1998; **7**: 523-536.
30. Tao J, Feng KY. Experimental and clinical studies on inhibitory effect of *ganoderma lucidum* on platelet aggregation. *J Tongji Med Univ* 1990; **10**: 240-3.
31. Fugh-Berman A, Cott J. Dietary supplements and natural products as psychotherapeutic agents. *Psychosomatic Med* 1999; **61**: 712-728.
32. Zhang HY, Liang YQ, Tang XC, He XC, Bai DL. Stereoselectivities of enantiomers of huperzine A in protection against beta-amyloid (25-35)-induced injury in PC12 and NG108-15 cells and cholinesterase inhibition in mice. *Neurosci lett* 2002; **317**: 143-6.
33. Apple Daily 2001, 16th October.
34. Hien TT, White NJ. Qinghaosu. *Lancet* 1993; **341**: 603-8.
35. Chen ZY, Kwan KY, Tong KK, Ratnayake WM, Li HQ, Leung SS. Breast milk fatty acid composition: a comparative study between Hong Kong and Chongqing. *Lipids* 1997; **32**: 1061-7.
36. Willatts P, Forsyth JS, Di Modugno MK, Varma S, Colvin M. Effect of long-chain polyunsaturated fatty acids in infant formula on problem solving at 10 months of age. *Lancet* 1998; **352**: 688-91.
37. Haller GA, Benowitz NL. Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. *N Engl J Med* 2000; **343**: 1833-8.
38. Fugh-Berman A. Herb-drug interactions. *Lancet* 2000; **355**: 134-8.
39. Veith I. *The Yellow Emperor's Classic of Internal Medicine*. University of California Press, California, USA, 1966. ■

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