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Effect of TCM-derived extracts on cataract development in the elderly: a pilot study

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Titolo
Effetto degli estratti derivati dalla Medicina Tradizionale Cinese sullo sviluppo della cataratta in anziani: uno studio pilota

Key words
Cataract, TCM/Traditional Chinese Medicine, GFDHW, Kampo, Nidek EAS-1000, elderly

Parole chiave
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Summary
As life expectancy increases worldwide, the incidence and prevalence of age-associated cataract do and impair the daily activities of millions. Correction is poor and surgery remains the most common solution, albeit out of reach for the vast majority of (poor) mankind. Reports on the efficacy of traditional Asian medicines (Chinese = TCM; Japanese = kampo) prompted us to evaluate a widely available/affordable TCM formula (GFDHW) in aged (≥ 60) subjects recruited from the Optometry Clinic of HKPU; 30 were enrolled and 22 completed the course. These subjects presented with mild cataract without any other significant health problem. After 90 days of GFDHW we did not observe any effect on the development and/or progression of cataract. However, a number of subjects reported improvement in areas of their "quality of life". A pronged, placebo-controlled and comparative (e.g. *Bawei Dihuang*) study seems warranted.

Riassunto
Così come l'aspettativa di vita sta aumentando in tutto il mondo, anche l'incidenza e la prevalenza della cataratta correlata all'età si diffonde e compromette l'attività quotidiana di milioni di persone. La correzione è scarsa e la chirurgia resta la soluzione più comune, anche se fuori dalla portata della stragrande maggioranza delle persone (classi più povere). I rapporti sull'efficacia delle Medicine Tradizionali Asiatiche (Cinese = TCM; Giapponese = kampo) hanno portato a valutare una formulazione della TCM (GFDHW), ampiamente disponibile/accessibile, in soggetti di età compresa o superiore ai 60 anni reclutati dalla Clinica Optometrica dell'Università Politecnica di Hong Kong; dei 30 arruolati per lo studio, 22 lo hanno completato. Questi soggetti presentavano una leggera cataratta senza altri significativi problemi di salute. Dopo 90 giorni di GFDHW non è stato osservato alcun effetto sullo sviluppo e/o sulla progressione della cataratta. Tuttavia, un certo numero di soggetti ha segnalato miglioramenti nella loro "qualità della vita". Sembra pertanto giustificato uno studio placebo-controllato e comparativo (ad esempio Bawei Dihuang).

Abbreviations:
TCM: Traditional Chinese Medicine; HKPU: Hong Kong Polytechnic University; GFDHW: *Gui Fu Di Huang Wan*; VA: visual acuity; SD: Standard Deviation; OTC: over-the-counter.

Introduction

Cataract decreases transmission of light through the eye lenses. Quantification of amount of light reflected back from the retina through the lens has been made possible with the use of an anterior eye segment analysis system, the EAS-1000 Nidek (1). Garrett et al. showed that measurement of lens opacity from EAS-1000 images using automated standard analysis had high repeatability (2). It is now possible to measure objectively the amount of light reflected through the crystalline lens *in vivo*. In addition, size, location and type of cataract can also be verified and measured with this instrument in conjunction with clinical assessment.

Associated with this reduced transmission of the crystalline lens is a corresponding reduction in the mean visual acuity within each age group, in spite of corrective lenses for refractive errors. When an acuity reduction to 20/25 or worse was considered as a criterion for the diagnosis of cataract, a prevalence of from 2.1% to 8.5% was found in the 45 to 64 year old age group (3). In the 65 to 75 year old group, a prevalence of 21.6% to 39.1% was found (3). All demographic studies identify cataract as an age-related ocular condition, and a substantial cause of reduced acuity (and activity) among the elderly. Visual acuity can be regarded as a subjective index for reduction of vision.

Animal (rat) studies have confirmed the efficacy of some Traditional Chinese Medicine (TCM) herbs on the development and/or progression of cataract on rats, e.g. *Rehmannia* Eight Formula, or *Bawei dihuang wan* (4-6). Kampo medicine was reported to be helpful in the treatment of diabetic women with cataract (7). A number of herb formulations are readily available for human cataract treatment. Their effects, however, have not been reported in the scientific, peer-reviewed literature. In Hong Kong, *Rehmannia* Eight Formula is not available. We selected an over-the-counter TCM available in Hong Kong that has the same ingredients as *Rehmannia* Eight Formula. Quality and safety controls for this TCM were conducted at the laboratory in the Hong Kong Polytechnic University Shenzhen Research Institute and the Shenzhen Institute of Drug Inspection. Microbiological testing (bacteria, molds & yeasts, *E. coli*, etc), quantitative analysis (loganin & paeonol), heavy metals and residual pesticides' content were assayed. The results were reported (Appendix I), showing that this TCM was safe to use in our subjects.

The aim of this pilot study was to measure objectively and subjectively the effects of the OTC TCM herb formulation *Gui Fu Di Huang Wan** (GFDHW, see appendix II) on the development of cataract.

Subjects

30 aged (≥60) subjects with mild, recent cataract were recruited from our Optometry Clinic. They included 7 male and 23 female cataract subjects of mean age 66.03 (SD 4.6) years. All subjects met the following criteria:

Ocular Criteria for Recruitment:

I. Mild cataract
II. No posterior synechia of the iris
III. Intra-ocular pressure less than 22 mmHg
IV. No indication of closed anterior angle
V. No history of ocular trauma, cataract surgery
VI. No ocular anomalies

Other Criteria for Recruitment:

I. Age >60 at time of recruitment
II. Compliant: regular intake of TCM (GFDHW)
III. Available for follow-up on day 90
IV. Exclusion of all other TCM herbal remedies during the 90-day study
V. No systemic conditions: e.g. diabetes, severe hypertension

* **Ingredients:**
Radix Rehmanniae preparata, Fructus Corni, Cortex Moutan, Rhizoma Dioscoreae, Poria, Rhizoma Alismatis, Cortex cinnamomi, Radix Aconiti lateralis preparata

and other cardiovascular conditions

VI. No history of prolonged use of any TCM

VII. Non-smoker

All subjects were screened by a TCM practitioner from our Integrated Health Clinic at the Hong Kong Polytechnic University. The purpose of the visit was to ensure that the subjects were suitable to participate in the study. Before being enrolled in the study, all subjects completed a standard informed consent form (in Chinese) complying with the Declaration of Helsinki.

Methods

Each subject's monocular habitual visual acuity (VA) was measured by using ETDRS chart at a testing distance of 4 m. Intra-ocular pressure was measured by using Nidek NT-4000. After measuring the intraocular pressure, slit lamp biomicroscopy was performed to assess the anterior angle and any anterior segment ocular abnormalities. One drop of proparacaine and one drop of tropicamide were instilled into the subject's eyes. After the pupils were dilated, the transparency of the crystalline lens was measured by using Nidek EAS-1000. Reflectance of the amount of light through the crystalline lens was recorded in percentages. Vials of TCM (GFDHW) pills were dispensed. All subjects were required to return for another image recording session 90 days after the initial visit, at which time the same procedures were repeated. A short questionnaire (see appendix III) was administered to evaluate each subject's responses to the treatment.

Table 1 - Mean VA and mean transparency of crystalline lens of the subjects in pre-treatment and post-treatment sessions

	Mean VA (SD)		Mean Transparency (SD)	
	OD	OS	OD	OS
Pre-treatment	0.07 (0.13)	0.04 (0.10)	0.875 (0.15)	0.897 (0.11)
Post-treatment	0.09 (0.18)	0.04 (0.13)	0.874 (0.17)	0.896 (0.10)

Results

8 subjects dropped out. 7 male and 15 female cataract subjects of mean age 65.86 (SD 4.5) years completed the treatment protocol and were subjected to another image recording session. 16 out of 22 subjects were found to have mild cortical cataract. The remaining 6 subjects had mild nuclear cataract. Table 1 shows mean VA and mean transparency of crystalline lens of the subjects in pre-treatment and post-treatment sessions.

Visual acuity and transparency of crystalline lens were normally distributed (One-sample Kolmogorov-Smirnov Test: $p>0.08$). The data on visual acuity and transparency of right and left eye were pooled. There was no significant difference in visual acuity and transparency between visits (Paired t-test: $p>0.36$).

Seven out of 22 subjects reported that no change in the items listed in the questionnaire (see appendix III). However, the remaining 15 subjects reported that there was slight change in some of the items listed in the questionnaire (Table 2). Decrease in the frequency of nocturnal urination was the most commonly reported response after taking the pills for 90 consecutive days. Only 3 subjects reported that there was a slight improvement in vision. 2 out of 3 subjects reported that only near vision was better. One subject reported that only vision of left eye was better.

Discussion

Our results showed that subjects' mean right visual acuity was worse by log unit 0.02 (one letter mis-

Table 2 - Frequency distribution of responses to the questionnaire after treatment (GFDHW)

	Frequency
Better vision	3
Better quality of sleep	6
Better appetite	2
Softer faeces	1
Harder faeces	1
Feeling better	4
Feeling worse	1
Feeling warmer	4
Increase in fart	6
Decrease in frequency of nocturnal urination	8
Less painful in knee joints	2

sing) and the subjects' mean left visual acuity remained the same. The mean transparency of crystalline lens was worse by 0.1% for each eye. In regard to visual acuity and transmissibility of the crystalline lens, taking GFDHW for 90 consecutive days appeared to have no effect on the development and/or progression of cataract.

Cataract may appear in different areas of the lens such as cortical, nuclear and posterior subcapsular, etc. Over 70% of our subjects suffered from mild cortical cataracts. Since cortical cataract affected the periphery lens areas, visual acuity was therefore only mildly affected. Most subjects did not notice the change in their vision when there were increases in cortical cataracts. This observation was made by 21 out of 22 subjects. They reported that distance vision remained the same although the transmissibility of the lens had changed.

Table 2 shows that most of the reported feelings were not related to vision. *Gui Fu Di Huang Wan* did not seem to affect vision. A Japanese study (8) stated that senile cataract is commonly treated with *Bawei dihuang wan* in Japan. Improvement in subjective symptoms such as eyesight and cognition was reported, whereas objective symptoms were hardly improved. That could explain why some of our subjects who reported positive feelings although the transmissibility of their crystalline lenses did not have significant change. The results of Kamei et al. study on rats (4) could mean that ingredient(s) of *Gui Fu Di Huang Wan* could delay the progressive rate of lens opacification. Another study by Kamei et al. (5) showed indirectly that the ingredient of *Gui Fu Di Huang Wan* could delay cataract appearance. The dosage in both studies depended on body weight of the rats. In our study on human subjects, it had no significant effect on the development and/or progression of cataract. The causes of cataract in senior (>60) subjects are potentially many: diabetes, smoking, heavy drinking unhealthy/unbalanced diet, dehydration, medication (e.g. long-term corticosteroids), previous eye injuries were not present in our subjects. Ultraviolet exposure in inter-tropical Hong Kong might be a factor.

Outrageous claims are made on all printed media, the Internet, and even medical journals on "miracle" cures or "total prevention" of cataracts in the elderly. A recent search on PubMed/Medline concludes that: supplementation with vitamin C, lutein, zeaxanthin, or a multivitamin may help certain populations, but is unlikely to affect the progression of cataracts in most patients (9); data from a large trial of apparently healthy female health professionals with 9.7 years of treatment and follow-up indicate that 600 IU natural-source vitamin E taken every other day provides no benefit for age-related cataract or subtypes (10); additional phyto-

chemicals of emerging interest, like green tea catechins, anthocyanins, resveratrol, and *Ginkgo biloba*, shown to ameliorate ocular oxidative stress, deserve more attention in future clinical trials (11). Positive results in rodents or *in vitro* studies have not shown-so far- any significant positive correlation in humans. Our subjects enjoy a diversified healthy diet, are physically active and fit, benefit from a comprehensive, extensive health coverage and social programs, have a structured solid familial and social life, and do not consume unnecessary medications; these beneficial characteristics are not these of most American or European subjects.

We also understand that this study has many major limitations: being a pilot study with very limited funding, we did not include a negative control (placebo) group or a positive (known active e.g. *Bawei dihuang wan)*; ninety days is possibly too short to notice significant changes in age-associated cataract in relatively young healthy subjects; we did not conduct a meticulous food and nutritional investigation that would have shown (probably) that our subjects ingest daily large amounts of antioxidants and other beneficial trace elements that result in slowing the degeneration of their ocular lens.

We intend to apply for further support and investigate the possible benefits of TCM formulas and other natural medications in slowing the development of age-associated cataract in placebo- and proven medication-controlled studies.

Conclusion

Twenty-two subjects completed this study and absorbed GFDHW daily for 90 consecutive days. There appears to be no effect on the development and/or progression of their cataract. Decrease in the frequency of nocturnal urination was the most obvious positive change after treatment. It is worth noting that 12 out of 22 subjects reported "feeling better" after this treatment.

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Appendix I

Jinkui Shenqi Pill (*Gui Fu Di Huang* Pill)

The tests conducted for Jinkui Shenqi Pill *(Gui Fu Di Huang* Pill, Lanzhou Foci Pharmaceutical Ltd.; batch no: 2007049) were divided into two stages. The first one was the safety profile analysis, and the other was the quantitative analysis of the components.

Safety Profile Analysis

In the safety profile analysis, the sample was tested for three categories: heavy metals content, residual pesticides content and microbiological contamination. According to the test report from the Shenzhen Institute of Drug Inspection, the sample passed all these tests (i.e. every test proved negative).

Quantitative Analysis of Components

In the China Pharmacopoeia 2005 version (CP 2005), there are referenced levels of two markers (active components), loganin and paeonol, for various dosages forms of this compound formula. The reference levels are the minimum that the specific dosage form should meet to be a "qualified drug". According to CP 2005, the reference levels are:

Dosage form	Reference level (mg/g)	
	Loganin	Paeonol
Large honey bolus	3.40	5.40
Small honey bolus	0.38	0.60
Water-honey bolus	0.53	0.80

The sample that was submitted belongs to another dosage form, not specified in CP 2005, which is called condensed pill. The analysis showed that it contained **1.48 mg of loganin and 1.05 mg of paeonol per gram of sample**, which is somewhere between small honey bolus and large honey bolus. This can be a reference level for future testing using the same dosage form and for checking the consistency of the product.

Appendix II

The composition of the GFDHW:

1. *Radix Rehmanniae preparata*	29.63%
2. *Fructus Corni*	14.83%
3. *Cortex Moutan*	11.11%
4. *Rhizoma Dioscoreae*	14.81%
5. *Poria*	11.11%
6. *Rhizoma Alismatis*	11.11%
7. *Cortex Cinnamomi*	3.7%
8. *Radix Aconiti lateralis preparata*	3.7%

Appendix III

Subjective grading:

	Better	Little better	No Change	Little worse	Worse
1. Vision	1	2	3	4	5
2. Sleep	1	2	3	4	5
3. Appetite	1	2	3	4	5
4. Faeces	1	2	3	4	5
5. Spirit	1	2	3	4	5
6. Feeling warm	1	2	3	4	5
7. Others: _____	1	2	3	4	5