AYURVEDIC AND COLLATERAL HERBAL TREATMENTS FOR HYPERLIPIDEMIA: A SYSTEMATIC REVIEW OF RANDOMIZED CONTROLLED TRIALS AND QUASI-EXPERIMENTAL DESIGNS

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Background • Ischemic heart disease (IHD) is a leading cause of morbidity and mortality in both developing and developed countries. An underlying cause of IHD involves retention and deposit of serum lipids in coronary arteries, decreasing blood flow. Drugs (conventional and herbal) are used to lower levels of serum cholesterol to help prevent IHD. The Ayurvedic medicine pharmacopoeia identified herbs that might contribute to a decrease in cholesterol and therefore reduce the risk of IHD.

Methods • Literature searches were conducted at 3 points: 2003, 2004, and 2007. Databases searched included PubMed, the National Library of Medicine, the National Center for Complementary and Alternative Medicine, Ovid, and EBSCO Information Services, and other search strategies also were used. Each article was assessed for quality by 3 people, and discrepancies were resolved by arbitration using a fourth person, who also read and scored each article. Additional assessments of safety using a scale and determination of reported efficacy/effective-

ness of the randomized controlled trials (RCTs) and quasi-experimental designs (QEDs) were made.

Results • RCTs generally received high quality scores and improved by decade of publication. More than 50% of garlic, more than 80% of guggul, and 100% of Arjuna RCTs reported product effectiveness. Safety scores did not improve by decade. The QEDs received medium and high quality scores, and 93% of them reported effectiveness. The QEDs had a higher mean score for safety reporting than the RCTs.

Conclusions • Many studies received high quality scores and noted safety information and reported effectiveness or efficacy in a clear manner. This finding was not consistent with other systematic reviews that have found the highest reported efficacy/effectiveness in studies of poorer quality. Ayurvedic herbs reviewed here should be considered by physicians when trying to manage hyperlipidemia in their patients.

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Ischemic heart disease (IHD), which includes angina, myocardial infarction, chronic postischemic cardiac failure, and sudden ischemic death, is one of the leading causes of morbidity and mortality in developed and developing countries.[1,2] It is currently considered a world epidemic.[3-5] The underlying mechanism of IHD involves the deposition and retention of serum lipids consisting of low-density lipoprotein (LDL) cholesterol in the coronary arteries, resulting in decreased blood flow to heart muscles.[6,7] The treatment is based on the hypothesis that reduced cholesterol biosynthesis will lead to lower blood levels of cholesterol. Most of the drugs (statins) available today are inhibitors of 3-hydroxy-3-methylgluatarylcoenzyme A reductase, which is involved in cholesterol biosynthesis in the liver.[8,9]

Although statins have been found to be effective in lowering the serum low-density lipid levels by as much as 21% to 43%, they have been found to cause many adverse side effects. Statins are basically enzyme inhibitors, so it is likely that they may be inhibiting other critical enzymes in the body that have not been investigated so far, causing serious adverse side effects. Statins are ingested on a long-term basis to produce and maintain the desirable effect; therefore, there may be a risk of chronic toxic effects, including carcinogenic, teratogenic, and mutagenic, over a lifetime of use.[7,10-13] In this study, we evaluated the clinical data on Ayurvedic and collateral herbal cholesterol-lowering products to

determine whether the studies are methodologically sound, their conclusions are valid, and whether herbals offer a safe alternative to conventional drugs.

AYURVEDA

Ayurveda, a combination of the Sanskrit words *ayu* (longevity) and *veda* (knowledge), is the traditional medical system that has been practiced in India for more than 5000 years.[14] In Ayurveda, *kapha* imbalance (atherosclerosis) is an underlying mechanism of heart diseases. In Ayurvedic texts, the treatment for heart diseases is offered to promote biofire (*agni*) and to clear the channels by *panchakarma* as well as through the use of natural herbs that have hypolipidemic and antistress activity.[15] Because Ayurveda relies on a pragmatic, individualistic approach,[16] it is a challenge to understand systematically the true benefit of Ayurvedic herbals in a Western medicine schema.

OBJECTIVES

This study's focus was to look at both randomized controlled trials (RCTs) and quasi-experimental designs (QEDs) of Ayurvedic herbals and commonly used collateral herbals that are available over the counter for the treatment of hyperlipidemia. It was important to include QEDs in this review because RCTs, though generally the literature of choice for systematic reviews, do not represent the full knowledge base on which clinical decisions should be made. A rating form for QEDs that has been used in 4 other published systematic reviews was used, along with a quality review form that includes 21 items in addition to the 5 items in the Jadad scale for RCTs. This scale covers a wider breadth of content areas, which are important for high-quality studies.

This systematic review has 3 aims: (1) to evaluate the quality of existing clinical literature on Ayurvedic and collateral herbals for hyperlipidemia, primarily available through easily accessible electronic databases and using standard literature search methods; (2) to report the effectiveness or efficacy of these products as stated in the articles; and (3) to report the safety data reported for herbals used in these articles and to evaluate the quality of the safety data using a standardized scale developed for that purpose.

This systematic review was 1 of 5 systematic reviews conducted by this team on Ayurvedic herbals found in the Ayurvedic pharmacopoeia and other commonly used herbs in this medical tradition for specific diagnoses. This reported systematic review was concerned with hyperlipidemia as the focus diagnosis. As this work is not a literature review or a monograph of specific herbs, only articles that addressed the 3 points noted above in either an RCT or QED structural clinical design were reviewed.

METHODS
Search Methods

A search of multiple databases was conducted in September 2003, February 2004, and January 2007. Even after the last search, few articles meeting the search criteria had been published, though a number of case studies, pre-clinical studies, and dose-finding studies, for example, had been conducted between 2004 and 2007. Consulting the Indian Pharmacopoeia and consulting with several Ayurvedic physicians found relevant Ayurvedic herbals. The Ayurvedic physicians held MD degrees in Ayurveda from government-approved schools in India and terminal degrees (PhDs) earned in US universities. The terms *Ayurvedic, herbal,* and *hyperlipidemia,* were exploded as Medical Subject Headings (MeSH) terms and searched as text words. The terms *garlic, guggul, Terminalia arjuna, Abana,* (a combination herbal remedy that contains *Terminalia arjuna*) *guar gum,* and *fenugreek* had no MeSH terms and were therefore searched only as text words. The search was tightened to include only articles that were published after 1970 and before February 2004, and another search was done of articles published after 1970 and before January 2007. In addition to PubMed, other online databases searched included the National Library of Medicine (NLM), the National Center for Complementary and Alternative Medicine (NCCAM), Ovid, and EBSCO. A web search also was conducted to locate sites that sold Ayurvedic herbals, and the sites were searched for articles on these herbals. For example, 6 articles were procured from the website www.himalayahealthcare.com. After selecting the articles to be reviewed, we used the footnotes to locate additional articles. Footnote tracking of meta-analyses and other systematic reviews was used as well.

Inclusion/Exclusion Criteria

All studies in this systematic review had to test an Ayurvedic herbal or collateral herbal for efficacy/effectiveness in the treatment of hyperlipidemia. Herbs used in traditional Chinese medicine (TCM) were not included in the scope of the study due to financial limitations, though some may show promise for further research. Although some shun garlic use, it was important to include this herb, as it has the potential to be used widely because it is so easily accessible. Studies that used standard allopathic treatments as "positive controls" were included, as were placebo-controlled studies. Trials that tested herbals for related conditions (hypertension, diabetes) were included only when the primary outcome measure was serum lipid levels. There was no exclusion based on a study's country of origin, but because of limited resources, articles had to be written in English. The authors hope that funds will be available in the future to evaluate the literature published in languages other than English.

Once articles were located, abstracts were reviewed for suitability. A total of 432 articles were found. Articles were excluded if they were conducted on animals (64), not written in English (56), on TCM (63), duplicates of other articles (132), or review articles or mechanism of action studies rather than clinical trials (117). Fifty-five articles met the inclusion criteria. During review, 4 more articles were excluded: 1 because it was a systematic review and 3 because lipid levels were not the primary outcome measure. Overall, 51 articles were reviewed.

Herbals Reviewed

Of the 51 articles, 26 were on garlic: 21 RCTs and 5 QED

studies. There were 10 guggul articles: 7 RCTs and 3 quasi-experimental studies. There were 7 *Terminalia arjuna* articles: 6 RCTs and 1 QED. There were 3 guar gum articles: 1 RCT and 2 QEDs. There were 5 herbals in the miscellaneous category that had only 1 article each: Maharishi Amrit Kalash, a proprietary formula by Maharishi Ayurveda with many ingredients, including Indian gooseberry, winter cherry, and heart-leaved moonseed; *Arogyavardhini*, a traditional ayurvedic formula indicated for liver disorders, with ingredients including *Terminalia chebula* and *Phyllanthus emblica*; silymarin, the active ingredient in milk thistle, commonly used for liver problems; fenugreek, commonly used for hypertension and non–insulin-dependent diabetes mellitus (NIDDM); and *Coccinia grandis,* or ivy gourd. Because we found only 1 RCT on guar gum and 1 QED on *Terminalia arjuna,* these articles were included under the miscellaneous herbal cat-

gory, for a total of 7 miscellaneous herbs.

Review Methods

As this study reviewed both quality and safety, 3 forms were used: the Singh RCT Quality Scale,[17] the Singh QED Quality Review Scale,[17] and the safety assessment score for clinical trials (SAS-CT).[18] The Singh RCT Quality Scale, which evaluates the quality of RCTs, had a total of 26 questions and 26 possible points. Questions included the 5 Jadad Scale questions plus 21 others, allowing for greater content validity of the assessments by covering a larger set of criteria for a well-structured and -conducted RCT (Table 1). All quality questions answered in the affirmative equaled 1 point. The scoring range was as follows: 0-9 = low, 10-17 = medium, and 18-26 = high. The Singh QED Quality Review Scale, which is used to evaluate the quality of QEDs or

No	Question	Garlic	Guggul	Other Herbs	Overall Score

TABLE 1 Question-by-Question Analysis of Quality Scoring for Randomized Controlled Trials

No	Question	Scores, in Percentages			
		Garlic	Guggul	Other Herbs	Overall Score
1	Was the study described as randomized?	95	71	50	80
2	Was the randomization scheme appropriate?	95	57	34	71
3	Was the study described as double blind?	90	57	34	71
4	Was the method of double-blinding appropriate?	90	43	17	66
5	Were patients reported as blinded?	90	57	17	71
6	Was the outcomes assessor reported as blinded?	95	57	17	71
7	Was there a description of dropouts and withdrawals?	100	86	34	86
8	Were co-interventions avoided or controlled for?	90	57	67	80
9	Was compliance satisfactory?	45	57	34	51*
10	Was the study population adequately homogenous?	100	100	100	100
11	Was the therapeutic time equivalent between groups?	100	100	100	100
12	Was there a proper review of literature on disease or treatment?	100	100	100	100
13	Was the optimum dose used?	100	86	0	86
14	Was the dose justified?	100	86	0	86
15	Was a power calculation used?	20	29	0	14*
16	Were there sufficient numbers recruited?	60	100	34	60
17	Was there a sufficient description of treatment or procedure?	100	100	100	100
18	Was there a description of demographics?	85	86	34	74
19	Was there a description of diagnosis-related information?	100	100	100	100
20	Were the outcome measures clearly stated?	100	100	100	100
21	Was the validity of outcome measures established?	100	100	100	100
22	Were the data reported consistent with data tables?	100	100	100	100
23	Was attention paid to possible biases in design?	55	43	67	54*
24	Were there no significant biases or flaws in operationalization of design?	80	71	34	71
25	Was there a comparison of dropouts vs completers?	45	43	17	46*
26	If findings are not consistent with similar studies, was there an adequate explanation of different findings?	100	86	100	97

*Only 50% of articles reviewed reported these items.

outcome studies, has a total of 15 questions and 15 total possible points. This scale is designed to evaluate the quality of QEDs from which RCTs are often constructed and, until RCTs and other rigorous designs are executed, may make up the bulk of research on effectiveness of an herbal treatment (Table 2). The scoring range was as follows: 0-5 = low, 6-10 = medium, and 11-15 = high. The SAS-CT is used to evaluate the safety reporting of articles, and it has 6 areas of inquiry, with a total of 100 possible points. The 6 areas of inquiry are (1) adverse events not related to the intervention, (2) serious adverse events definitely not related to the intervention, (3) adverse drug reactions, (4) dropouts due to adverse events, (5) serious adverse events definitely not related to the intervention, and (6) dropouts due to adverse drug reactions/ serious adverse drug reactions. The scoring range was: 0-28 = poor, 29-68 = medium, and 69-100 = high. Three independent reviewers scored for quality, with inconsistencies resolved by discussion with and arbitration by a fourth reader. Safety was assessed by 2 members of the team using the SAS-CT and checked for consistency by a third.

RESULTS
Quality, Efficacy, and Safety of Randomized Controlled Trials

In general, RCTs of all herbals had high quality scores. Scores improved by decade. Only 1 RCT of garlic and 1 RCT of guggul had a medium score. The Arjuna group consistently had medium scores for all RCTs in the decade of the 1990s. The scores did improve by decade, as all of the articles in the 2000s had high scores. RCT quality scores for all herbals ranged from 11 to 26 (Table 3).

Most of the RCT articles indicated product efficacy. Garlic RCTs were 53% positive; guggul RCTs were 86% positive; and

Arjuna RCTs were 100% positive. The total RCT efficacy percentage was 71% positive. In the case of the RCTs, "positive" indicates significant between-group differences. For QEDs, "positive" means that study participants improved significantly over the duration of the study.

Interestingly, reported safety scores showed no correlation to decade, meaning safety reporting did not improve by decade. This may indicate a bias in how herbals are considered—that is, they may be assumed safe because they are not "drugs," and therefore safety and tolerance are not reported even as researchers become more aware of the importance of such information. Twenty-one (58%) of the RCTs had a high score on safety and tolerance. Fifteen (42%) of the 36 RCTs had poor safety scores. The mean score for all RCTs was 58.61 out of 100 possible points. The mean safety scores broken down by herbals were garlic, 62.71; guggul, 71; and Arjuna, 20.17. The Arjuna articles had poor safety scores, as most of the articles failed to mention side effects.

Quality, Effectiveness, and Safety of Quasi-experimental Designs

All QEDs had medium or high quality scores. One guar gum outcome study had a medium score. Two miscellaneous outcome studies had a medium score. All quality questions answered in the affirmative equaled 1 point. The scoring range was as follows: 0-5 = low, 6-10 = medium, 11-15 = high. The garlic outcome studies mean was 12.2; guggul outcome studies mean was 12.34; and guar gum outcome studies mean was 11. The total mean score for all herbal outcome studies was 11.66 of 15 possible points (Table 4).

In general, most QEDs had high effectiveness. Ninety-three percent of all QEDs were positive. Garlic, guggul, and guar gum

No	Question	Garlic	Guggul	Guar Gum	Overall Scores
		Scores, in Percentages			
1	Demonstrates adequate knowledge of disease/condition/treatment	100	100	100	100
2	Optimum dose used	75	100	50	64
3	Dose justified	75	100	50	64
4	Power calculation done	0	0	0	0*
5	Sufficient number recruited	100	34	50	57
6	Sufficient description of product/procedure	100	100	100	100
7	Description of demographics	100	67	100	93
8	Description of diagnosis related information	100	100	100	100
9	Outcome measures clearly stated	100	100	100	100
10	Validity and reliability established of primary outcome measure(s)	100	100	100	100
11	Data reported consistent with data tables	100	100	100	100
12	Attention paid to possible biases in design	100	67	50	79
13	No significant biases/flaws in operationalization of design	100	67	50	64
14	Comparison of dropouts vs completers	75	100	100	79
15	Adequate explanation if findings are not consistent with earlier studies	100	100	100	100

TABLE 2 Question-by-Question Analysis of Quality Scoring for Quasi-experimental Designs

*No article reported power calculation.

TABLE 3 Quality, Safety, and Efficacy of Randomized Controlled Trials

Author's Name	Quality Score*	Safety Score**	Efficacy†
Garlic Studies			
Bhushan et al, 1979	18	0	+
Plengvidhya et al, 1988	22	0	-
Auer et al, 1990	24	100	+
Mader et al, 1990	23	100	+
Vorberg et al, 1990	24	0	+
Holzgartner et al, 1992	23	100	+
Jain et al, 1993	23	100	+
Kenzelmann et al, 1993	23	100	+
Simons et al, 1995	25	100	-
Neil et al, 1996	26	100	-
Steiner et al, 1996	22	9	+
Adler et al, 1997	25	100	+
Berthold et al, 1998	21	99	-
Bordia et al, 1998	15	0	+
Isaacsohn et al, 1998	24	100	-
McCrindle et al, 1998	23	100	-
Superko et al, 2000	23	0	-
Zhang et al, 2000	24	9	-
Gardner et al, 2001	21	0	-
Kannar et al, 2001	21	100	+
Tanamai et al, 2004	21	100	-
Guggul Studies			
Malhotra et al, 1977	13	100	+
Kuppurajan et al, 1978	21	11	+
Kotiyal et al, 1980	21	100	+
Verma et al, 1988	18	0	+
Nityanand et al, 1989	20	99	+
Singh et al, 1994	23	100	+
Szapary et al, 2003	17	87	-
Arjuna Studies			
Tiwari et al, 1990‡	11	100	+
Tiwari et al, 1990‡	11	0	+
Tiwari et al, 1990‡	10	0	+
Tiwari et al, 1991	12	0	+
Gupta et al, 2001	18	0	+
Venkataramaiah et al, 2002	21	21	+
Miscellaneous Studies			
Khan et al, 1981	24	100	+
Prasanna et al, 2000	16	75	+

*Quality scores were calculated using the Singh RCT Scale: 0-9=low, 10-17=medium, 18-26=high.

**Safety scores were calculated using the SAS-CT Safety Scale: 0-28=poor, 29-68=medium, 69-100=high.

†Plus sign indicates significant improvements; minus sign indicates no significant positive change.

‡The order of the 1990 studies by Tiwari et al matches that in which they appear in the Appendix.

had 100% positive effectiveness. One miscellaneous outcome study, which investigated silymarin, was negative.

Interestingly, the QEDs had a higher safety mean score than the RCTs. Eight (57%) of the QEDs had high scores for safety and tolerance. Six (43%) of the 15 QEDs had low scores. The mean score for all QEDs was 54. Safety scores broken down by herbal were garlic, 43.8; guggul, 66.67; and guar gum, 96.

Results of Overall Side Effects Reported

Of the 28 of 51 articles that reported side effects and tolerance, 7 (25%) reported no side effects. Side effects that were reported were generally gastrointestinal and transient in nature: belching, bloating, flatulence, cramping, nausea, upset stomach, or diarrhea. These symptoms were reported for placebos as well as herbals. Other side effects were headaches, weakness, and rashes. In all studies, most side effects did not require withdrawal from the study.

Results of Question-by-Question Analysis of Randomized Controlled Trials and Quasi-experimental Designs

In all RCTs, not using a power calculation to adequately estimate the numbers needed for the study sample was a weakness in the studies. Only 14% of the articles reviewed used a power calculation. However, in spite of this obvious procedural problem, for those studies for which "back calculation" by the biostatistician was possible, 60% had recruited enough participants into the study. Back-calculation was conducted by the team biostatistician if appropriate descriptive data before and after intervention was reported for each study group (control and treatment). Similarly, compliance reporting was an issue, as only 51% of RCTs addressed this methodological issue. When there were dropouts, many articles did not show a comparison between the dropouts and study completers. Design biases also were a problem, as only 54% of the studies addressed these potential problems (Table 1). For example, in the Arjuna group, dosing was not explained or justified.

For QEDs, power calculations were not used in any of the studies. But through back-calculation, it was noted that only 57% of the articles recruited enough participants. Dropouts were mentioned in 86% of articles. Compliance reporting in QED articles also was poor—only 51% of articles reported compliance rates. However, 64% attempted to justify dosage choice or used the optimum dose. Biases in the operationalization of the design were addressed by only 64% (Table 4).

CONCLUSIONS

This systematic review attempted to appraise the quality, efficacy/effectiveness, and safety of Ayurvedic and collateral herbals used to treat hyperlipidemia. It indicated that there are herbals that have shown positive results via clinical trials for the treatment of hyperlipidemia that are available on the market today. However, it should be remembered that the 3 score ranges used in this review are arbitrary, so the percentage of total possible score is important to note. This review also pointed to the

need for study improvements, such as sample size calculation, compliance reporting, dropout appraisal, and structural design bias. Additionally, issues of safety and tolerance reported in the studies may not be comparable to the standards used in conventional medicine. Although reported side effects have been mild, greater attention needs to be paid to tolerance and safety data.

The relatively low numbers of articles that investigated efficacy or effectiveness in treating hyperlipidemia limited this systematic review of clinical trials. Animal studies, mechanism-of-action studies, and review articles/monographs made up a large proportion of the literature searches on "Ayurvedic herbs" related to hyperlipidemia published in English. To increase the number of articles, it is important to do a focused search and retrieval of Ayurvedic herbal clinical trials written in other languages as a supplement to this work. As a result, this work is a limited initial foray into the literature on this topic and is therefore not definitive.

Acknowledgments

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APPENDIX: ARTICLES REVIEWED

Garlic Studies

Adler AJ, Holub BJ. Effect of garlic and fish-oil supplementation on serum lipid and lipoprotein concentrations in hypercholesterolemic men. *Am J Clin Nutr*. 1997; 65(2): 445-50.

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