MEDICINE TESTED BY SCIENCE:
AN EFFECTIVE BOTANICAL TREATMENT FOR CIRCULATORY INSUFFICIENCY DUE TO ATHEROSCLEROSIS

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TIBETAN
ABSTRACT

The botanical formula originates in Tibetan medicine. Its historical and contemporary use provides an instructive example of a nutraceutical evolving from an ancient concept into a contemporary application through a scientific research. This developmental pathway led to a standardized 25 ingredients nutraceutical with clinically proven efficacy in the treatment of a form of atherosclerosis i.e. PVD. The systematic scientific research started in the 1970’s in Switzerland and resulted in six double-blind studies conducted in various European counties on cardiovascular use of the formula. The mechanism of the formula has been described in Tibetan tradition based on the formula’s three groups of botanical ingredients: main acting ingredients, supporting main action ingredients and the components to offset action of the first two groups and facilitate gastrointestinal absorption of the formula relevant to alleviation of the pathomechanism of PVD have been discussed, e.g. increase in threshold for platelet aggregation, lowering total blood cholesterol, lowering the low density lipoproteins (LDL), while increasing the high density lipoproteins (HDL), and preventing blood lipids per oxidation. Recent studies also show that the formula can exert its action as a biological response modifier alleviating vascular inflammation in experimental animals. The latter mechanism may be particularly important in view of the immunological theory of atherosclerosis.

INTRODUCTION

One of the important discussions of the future of medicine is on what bonds and what separates Allopathic medicine and the unconventional medical systems, particularly that of Indian Ayurveda, Tibet, China and Japanese Kampo. The allopathy and ancient systems are obviously to provide the best medical treatments according to their respective theoretical and practical knowledge. Contrary to the fact that there has been lack of systematic preservation of traditional knowledge, the time accumulated wisdom and knowledge has to be on the side of ancient traditions. The fact that certain medical practices and treatments withstood tests of hundreds or thousands of years in maintaining healthy existence of ancient cultures, makes them especially suitable in preventive medicine and for the treatment of chronic diseases. On the other hand, in emergency and life-threatening situations and in the invasive medical treatments, the technological advancement of mainstream medicine provides a clear advantage. Thus, the differences and similarities between the two systems advocate not an exchange of one system for another, but a beneficial process of reciprocal studying and learning. This process substantiates what is recognized as the body of Complementary Medicine, which effectively replaces too often one sided Alternative Medicine.

The relatively recent recognition given to ancient medical traditions has acted like a catalyst of a
change from the current medical system into a more complete, complementary health care system of the future. The emerging laboratory and clinical research of the unconventional medical systems begins to demonstrate results that shed new light on communicating these ancient theories to health professionals without risking a ridicule or, on the other hand, distortion of the original concept.

The different historical, sociological, and cultural contexts of allopathic and unconventional medicines are nowhere more obvious than in the design of multi-component herbal and mineral formulae used prominently in Tibetan medicine. Nowhere, is the importance of translation through science more relevant that in the case of Tibetan pharmacology. This paper provides a 20 year account of the research derived in Tibetan tradition on a multi-component herbal-mineral formulation.

**A Formula Used in the Treatment of Peripheral Vascular Disease (PVD)**

When the formula was introduced into Switzerland in the 1960's, its purported effects on the circulatory system attracted the attention of physicians, mostly because of the lack of effective pharmacological treatments of vascular pathology. Dr. Werner Bubb, the then Vice President of the Swiss Medical Society, initiated efforts to conduct a controlled clinical trial of this formula in the treatment of peripheral vascular disease (PVD). The personal experience and enthusiasm of Dr. Bubb recruited Dr. Franz Huerlimann, a Zurich based angiologist. Dr. Hurlimann was the first to conduct a double-blind clinical trial with this formula.* He used the formula and the matching placebo in form of capsules, which is unlike in the traditional form of the uncoated tablets. The study was carried with 24 ambulatory patients (17 men and 7 women, 50-70 years of age) who presented with a history of PVD, confirmed radiologically as the pelvic/femoral artery occlusion type. Clinically PVD was classified according to Fontaine classification as stage II-B i.e. the pain-free walking distance did not exceed 200 meters. Of the 24 patients 12 reported night cramps and paresthesia. The patients were randomized. Thirteen patients were assigned to the active treatment group, and 11 were assigned to the placebo group. Each patient received three capsules twice daily for the period of three months.

The treated group showed a statistically significant ($p<0.02$) 56% increase in the pain-free walking distance measured on treadmill, as compared to a 6% increase in the placebo group. Up to 70% of those patients who had nocturnal leg cramps and paresthesia prior to the treatment reported complete relief from the symptoms with this formula.

Hurlimann also carried an open-field study on a group of 10 patients, 8 men and 2 women, 55 to 68 years old, with the advanced PVD - Fontaine classification stage III and IV of the disease. Those patients, the subjective feeling of pain during walking and at rest, disappeared or was significantly reduced to a tolerable levels in 7 out of 10 patients. The formula was found compatible with other pharmacological therapy received by some of the patients, such as anticoagulants, anti-diabetics, anti-hypertensives, anti-lipemics and cardiac glycosides. In conclusion of this study the formula could be useful as an additive to PVD therapy together with anticoagulants.
Hurlimann published his results in 1978 in Proxis (Swiss Medical review).* The report stimulated much interest in the medical community as well as the public at large. Shortly thereafter, the Swiss Food and Drug Administration known as IKS (interkantonalle) approved the formula as an over-the-counter drug for treatment of early stages of PVD. The official introduction of the botanical treatment for the serious medical condition polarized the Swiss medical community: many physicians were convinced of the effectiveness of the formula derived from clinical evidence as well as their own experience from medical practice. Others criticized Hurlimann’s study as lacking a proper design, and they also remained skeptical because of the botanical nature of the compound, with too little of the active principle(s) to exert the therapeutic effect.

Further evidence of the effectiveness of the formula came from a double blind study performed at the University of Bern by Schrader as her doctoral thesis. The study was conducted during a two year period, 1982 to 1984. Schrader designed her study based on the previous experience of Hurlimann, and concentrated on patients with stage II PVD. The following criteria for inclusion of patients were selected: clinical diagnosis of the disease with at least 8 months of duration, maximal walking distance not exceeding 250 m, age of patient above 50 years old and expected good compliance with the guidelines of the study. Subjects were randomly assigned to the treatment and placebo groups. After a treatment-free interval of 14 days, 23 patients were treated for 4 months with this formula 3 x 2 capsules a day, and 20 patients were administered the matching placebo in form of lactose containing capsules.

As a result of the 4 month treatment, subjects who received the active formula increased their pain-free walking distance on average by 66 m (100%; \(p<0.002\)) as compared to the placebo group which showed an average increase in walking distance by 30 m (46%; \(p<0.01\)). The maximal walking distance in the group receiving active treatment increased on average by 124 m (98%; \(p<0.002\)), as compared with the placebo group by 27 m (21%). Schrader also measured the difference between the systolic pressures of the upper arm and the ankle, which reflects the degree of PVD caused by arterial occlusion. The pressure difference at rest decreased significantly in the active treatment group, on average from 71 mmHg to 55 mmHg \((p<0.03)\), as compared to a non-significant increase in the placebo group. None of the patients had to discontinue either active or placebo treatment, due to side effects or poor tolerance. The reported side effects were randomly distributed amongst the both treatment groups, and were minor and transient in nature: 4 patients reported stomach aches, and 3 patients reported a skin rash.

As a result of positive outcome of Hurlimann and Schrader studies, this formula became a popular herbal drug used in several European countries for the treatment of PVD. Subsequently clinical studies were done in Europe, outside of Switzerland. The double blind study of this formula in PVD patients was conducted in 1984 by Samochowiec and his colleagues at the department of Clinical Pharmacology of Medical Academy in Szczecin, Poland. The criteria for patients inclusion into this study group were maximal walking distance of less than 159 meters, and duration of the disease of more than eight months. One hundred patients with PVD were randomly assigned to the treatment groups with 19 women and 36 men assigned to receive this
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formula and 18 women and 27 men assigned to receive the placebo. The average age of the participants in the active treatment group was 46 years and 57 years in the placebo. After a two-week introductory period with no treatment, patients received active treatment or placebo in the form of capsules, 2 capsules 2 times daily for 4 months.

In the course of the 4-month treatment, the average maximum walking distance for patients receiving the formula increased by 78 meters (93% increase over the baseline; whereas, no significant change occurred in the maximum walking distance in the placebo group. The biochemical tests showed that the active treatment resulted in a significant reductions in the levels of cholesterol, triglycerides, and beta lipoproteins, as compared to the placebo receiving group. The active treatment also resulted in a significantly increased threshold for blood platelet aggregation. The entire population of patients completed the study, with no reports of side effects.

Denmark was another major European country where this formula was studied. In 1993 by Drabaek and colleagues from the Department of Clinical Physiology and Clinical Chemistry, Frederiksberg, Denmark conducted another double-blind study of the formula on PVD patients. The Drabaek study included 36 patients, 18 women and 18 men, with an average age 66 years, with median duration of PVD of five years, clinical steady state of the disease for more than six months, maximum walking distance between 50 and 300 meters, and ratio between systolic blood pressures at the ankle and the upper limb lower than 0.85. The 36 patients were randomly assigned to receive either an active treatment in form of capsules or matching placebo, two tablets, 2 times daily for four months.

As a result of the 4-month treatment, patients receiving this formula increased the pain-free walking distance on average from 52 meters to 86 meters (65% increase over the baseline), and the maximum walking distance from 115 meters to 227 meters or by (97% increase over the baseline). The group receiving placebo did not show any significant changes in either the pain-free or the maximal walking distance. Unlike in Schrader study, Drabaek could not demonstrate any significant changes in the ankle systolic pressure as a result of the treatment. No side effects or dropout cases are reported in the study.

The most recent double-blind, randomized clinical trial to determine the efficacy of the formula for PVD, was carried out by Smulski and Wojcicki from the Department of Internal Medicine, Szczecin District Hospital, Poland. This study included 100 patients between the ages of 35 and 65 with clinically diagnosed PVD. The subjects were randomly assigned to the placebo and active treatment groups: 50 patients received active treatment, 50 received matching placebo. Inclusion criteria was based on anamnesis, positive physical examination, maximum walking distance of less than 250 m, and a minimum of 6 month’s duration of the disease. Exclusion criteria were advanced PVD (Fontaine stages III, IV) and diseases affecting walking ability other than PVD. Patients received two capsules twice daily for 16 weeks.

The results of this study further confirmed the efficiency of the formula in treatment of PVD. Patients receiving the formula increased their maximum walking distance from the average 87.5 m to 187.5 m (114% increase). Most of this increase occurred in the second half of the
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trial, particularly in the 4th month. Placebo recipients showed an insignificant increase in walking distance, on average from 75.0 m to 87.5 m. Five placebo patients dropped out, due to newly diagnosed unrelated to PVD medical conditions. Of the 49 patients receiving active treatment, 36 patients showed a clinically improvement, defined as more than 50% increase in the maximum walking distance. In a subjective self-evaluation, 40 out of the 49 patients on active treatment, assessed the effectiveness of their treatment as good or very good, compared with 7 out of 44 of the placebo patients. The LDL, and total lipid levels improved significantly in the active formula receiving group.

This data summarized from 6 clinical studies done on ethnically and culturally different populations of the patients in Europe, point out to a solid clinical evidence of the formulas effectiveness in PVD. It is therefore important to compare the levels of effectiveness to the data obtained with synthetic pharmaceutical drugs tested in similar clinical trials. As a parameter for the comparative evaluation, a percent of increase in maximum walking distance due to carious treatments has been chosen. Based on the comparison of one parameter, the maximum walking distance, the formula emerges as a superior therapeutic modality vs. the cited pharmaceutical drugs in improving PVD condition (Table 1).

<table>
<thead>
<tr>
<th>Duration of treatment of the formula</th>
<th>percent increase of maximal walking distance</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 weeks (Hurlimann)</td>
<td>54%*</td>
</tr>
<tr>
<td>16 weeks (Schrader)</td>
<td>98%</td>
</tr>
<tr>
<td>16 weeks (Samochowiec)</td>
<td>93%</td>
</tr>
<tr>
<td>16 weeks (Drabaek)</td>
<td>97%</td>
</tr>
<tr>
<td>16 weeks (Wojcicki)</td>
<td>103%</td>
</tr>
<tr>
<td>16 weeks (Smulski)</td>
<td>112%</td>
</tr>
<tr>
<td>24 weeks (Porter)'</td>
<td>58%</td>
</tr>
<tr>
<td>4 weeks (Volker)</td>
<td>40%</td>
</tr>
<tr>
<td>24 weeks (Porter)'</td>
<td>33%</td>
</tr>
<tr>
<td>8 weeks (Bojan)</td>
<td>47%</td>
</tr>
<tr>
<td>24 weeks (Lindgrade)15</td>
<td>50%</td>
</tr>
<tr>
<td>90 days (Chacon-Quevedo)16</td>
<td>25%</td>
</tr>
<tr>
<td>24 weeks (Phole)11</td>
<td>70%</td>
</tr>
<tr>
<td>23 weeks (Maass)12</td>
<td>54%</td>
</tr>
<tr>
<td>12 weeks (Trubestein)13</td>
<td>97%</td>
</tr>
</tbody>
</table>
The formula in the treatment of other than PVD cardiovascular conditions.

The formula was also evaluated in a double-blind study in angina pectoris. This study was conducted by Wojcicki and colleagues, who had previously evaluated the formula in the treatment of PVD. The group of patients consisted of 36 men and 14 women, 40 to 69 years old, with a clinically diagnosed stable form of anginal attacks. All patients had at least a 6 month history of anginal attacks, with an average of seven attacks per week. The clinical trial lasted 6 weeks, and two tablets of either placebo or active treatment were administered twice daily. During the first two weeks, all patients received placebo tablets, in the following two weeks the formula tablets, and during the next two weeks placebo tablets. The purpose of the trial was explained and all patients were given the option of self-administering nitroglycerine tablets throughout the study when needed for symptom-relief.

The number of anginal attacks during the two initial weeks of placebo administration amounted to 37.5. This number was reduced to 11.5, or by 69%, during the next two weeks with the formula. The number of attacks increased again on an average of 28.7 in the next two weeks when placebo was reinstated. The heart rate and systolic blood pressure measured during the exercise test were lowered significantly, as compared between the initial two weeks of placebo administration and the following two weeks on active treatment. The number of self administered nitroglycerine tablets required by patients while receiving the formula, was on average, three times less than those receiving placebo.

Blood biochemistry data showed that total lipids and triglycerides were significantly decreased as a result of treatment with the formula. In addition, ADP platelet aggregation decreased two-fold after two weeks of treatment with the verum.

The apparent effectiveness of the formula, and angina pectoris, patients pointed to the direction for further research into vascular disease due to atherosclerosis, i.e. cerebrovascular insufficiency. The former Director of Merck Research and Development Panjwani studied the formula in 34 elderly patients who suffered from gradually deteriorating mental acuity. The elderly patients with median age, 59 years old, had been seen in a physician’s office for a number of years, all of them with complaints of worsening mental functions due to the cardiovascular and cerebral insufficiency. The patients were evaluated at the beginning of the study and then on a monthly basis. Six clinical indicators of cerebral function were used: memory, mental clarity and orientation, overall energy, alertness, general mental attitude including depression, sleep
patterns, and the patient’s general mental attitude including depression, sleep patterns, and the patient’s general subjective sense of well-being. The patients took two tablets daily, of the formula half an hour before breakfast and dinner. The study was carried out for six months, with a monthly evaluation of each participant. Of the 34 patients, 21 complied fully with the regimen throughout 6 months of the study (Table 2).

**TABLE 2. EFFECT OF CAMPHOR COMBINATION ON THE MENTAL AND EMOTIONAL WELL-BEING OF ELDERLY PATIENTS WITH CEREBROVASCULAR INSUFFICIENCY.**

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>-2</th>
<th>-1</th>
<th>0</th>
<th>+1</th>
<th>+2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Memory</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>14(67%)</td>
<td>7(33%)</td>
</tr>
<tr>
<td>Mental clarity</td>
<td>0</td>
<td>0</td>
<td>2(10%)</td>
<td>7(33%)</td>
<td>12(57%)</td>
</tr>
<tr>
<td>Vital energy</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>15(71%)</td>
<td>6(29%)</td>
</tr>
<tr>
<td>Sleep pattern</td>
<td>0</td>
<td>0</td>
<td>1(5%)</td>
<td>8(38%)</td>
<td>12(57%)</td>
</tr>
<tr>
<td>Attitude</td>
<td>0</td>
<td>0</td>
<td>2(10%)</td>
<td>12(57%)</td>
<td>7(33%)</td>
</tr>
<tr>
<td>General well-being</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>10(48%)</td>
<td>11(52%)</td>
</tr>
</tbody>
</table>

Rating scale:  
"+2" considerable improvement  
"+1" some improvement  
"0" no change  
"-1" some deterioration  
"-2" considerable deterioration

The Panjwani study showed that the majority of the patients treated with the formula, benefited noticeably from taking the formula continuously for 6 months, as evaluated by self-rating of memory (2 1/2 1 improved), mentally clarity (19/2 1 improved), vital energy (2 1/2 1 improved), sleep pattern (20/2 1 improved), attitude towards daily adversities (19/21 improved), and a general well being status (21/2 1 improved). None of the 2 1 patients who completed the study reported any side effects of the treatment or deterioration of the primary testing points. Of the 13 patients who did not complete the study, none reported side effects as the reason for earlier termination of the treatment. In conclusion of his report, Panjwani stated that if the preliminary results were confirmed by a placebo-controlled, double-blind trial, then the formula could represent an important advance in gerontologic care for the aging population.

**Mechanism of action of the formula**

The underlying mechanism of the formula was evaluated in the 1970’s based on the formula’s hypothesized anti-thrombotic activity. Concurrent with the clinical trial by Hurlimann, the platelet aggregation studies were performed with the formula in the Laboratory of Experimental Surgery, Davos, Switzerland (personal communication). The formula was fed to healthy rabbits.
After 1 to 1.5 tablets daily for seven days, and after a week regimen the ADP, thrombin, and collagen induced platelet aggregation tests were performed. The platelet aggregation tests with ADP and thrombin were not affected by treatment with the formula. However, the test performed with collagen showed a considerable degree of inhibition\(^{20}\). The effect of the formula on platelet aggregation was later studied by Wojcicki and colleagues\(^*\). Two weeks of administration of the formula to patients with angina pectoris increased the platelet aggregation threshold from 0.65 mmol\text{mol} to 1.47 mmol of ADP, i.e. by 125\%. During the 16 weeks administration of the formula to PVD patients, the threshold for the ADP dependent platelet aggregation, increased by 100\% (p<0.00 1).

The effect of the formula on blood lipids was studied. The formula was administered to rats fed with a high fat diet (HFD)\(^{21}\). The HFD consisted of cholesterol 4 gm, hydrogenated coconut oil 10 gm, and cholic acid 0.2 gm/kg per 24 hours. The formula was administered by gauge in a dose of 30 mg/kg per day for 12 weeks. At the termination of the experiment, blood levels of total cholesterol, malondialdehyde (MDA) as a major metabolite of oxidized plasma lipids, triglycerides, and lipoproteins, were examined in the treated and control groups of animals.

As compared to the untreated animals, the formula receiving rats had significantly reduced total cholesterol, triglycerides, and markedly increased the relative content of alpha-lipoproteins. In addition, the levels of lipid endoperoxides, as measured by levels of MDA were reduced more than two-fold by the feeding of the formula. MDA appears to be specifically produced through the action of the arachidonic acid, metabolizing enzyme cyclooxygenase, and its formation occurs in equimolecular amounts to formation of a prostaglandin Thromboxane A2, a potent vasoconstrictor. MDA formation also correlates positively with lipid per oxidation, which may play an important role in free radical or oxidative damage to the arterial wall. The free radical damage to the vascular endothelial lining may initiate the atheromatous plaque formation.

The biochemical evaluation of cardiovascular patients receiving the formula in clinical studies by Wojcicki and colleagues indicated that this formula may exert regulatory effects on lipid metabolism. Subsequently Wojcicki investigated an effect of the formula on oxidation of palmitic acid in Wistar rat\(^{22}\). Palmitic acid administered to rats may, similarly to other blood lipids, be oxidized to carbon dioxide and eliminated from the organism with exhaled air, or may be absorbed into the body and accumulated in the adipose tissue or the blood serum. A single dose administration of the formula to Wistar rats increased oxidation and elimination of the palmitic acid, and its deposition in the adipose tissue and blood serum correspondingly decreased.

The mechanism of the formula was also studied in vitro and in vivo experiments which measured the immune and inflammatory parameters relevant to degenerative conditions like atherogenesis\(^{34}\). In vitro it was found that water extract from the formula selectively increased T lymphocyte rosette formation, and increased the mitogenic response to Concanavalin A induced T cells from human peripheral blood leukocytes. In this vitro effect it was significant when the formula was applied in a T cell rosette test and the mitogen stimulation test. In the vivo evaluation of the formula, it was done on an experimental allergic encephalomyelitis (EAE) model in SJL mice. This model of inflammatory conditions in the brain showed that the formula
fed to mice resulted in a significantly lower mortality rate in animals with EAE as treated compared to untreated controls. This therapeutic effect occurred in a dose dependent fashion.

In accordance with Tibetan theory, this formula contains three categories of herbal and mineral ingredients which consist of main acting ingredients, supporting the main action and preventing any undesirable effects arising from the pharmacologic action of the first two groups of ingredients. Only this combined mechanism is traditionally credited with a broad safe and effective activity of the formula. One of the paradoxes of the formula often brought up by the skeptics, is that none of the individual ingredients of the formula has been used in a meaningful pharmacological dose. In view of an apparent clinical efficacy of the formula, it is possible that it may differ from the effective dose dependent mechanism which operates with the formula. A possible explanation could be that sub-therapeutic doses of the individual ingredients are summarily able to activate the body’s natural defense against the disease. This mechanism is possible in view of Tibetan perception that none of the techniques devised by man against any disease would be as helpful as the body’s own means of fighting the disease. This hypothetical mechanism of action is particularly interesting in explaining a report among broad clinical effectiveness of the formula. For example in clinical experience, the formula has been used in conditions with radically different imbalances: specifically some disease due to immune suppression as well as others due to over stimulation of the immune system. The therapeutic effect of the formula is acting as an adaptogen or, newly defined, bioprotectant - a substance that protects homeostasis by the action of prevention and intervention against the pathology caused by free radicals. The formula should be regarded as a classic example of an adaptogen or bioprotectant, and a paradigm of a safe and effective medicine.

Advantages learned from studying this formula:

1. three group design, 2. additive action, 3. need for new definition of pharmacological action

References


