ORIGINAL ARTICLE

Evaluation of Cardiovascular Safety of Herbal Cough Syrup

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ABSTRACT

Background: Herbal medicine or phytotherapy is the science of using herbal remedies for the treatment of diseases. Nowadays increasing number of people are using herbal medicines because of lower level of side effects and toxicity associated with them. Pharmacologists must be knowledgeable about their safety. Present study was carried out to evaluate the cardiovascular safety of herbal cough syrup. The syrup contains Glycerrhiza glabra, Piper longum, Adhatoda vasica, Viola odorata, Hyssopus officinalis, and Alpinia galanga. All these ingredients are said to have antitussive properties without any cardiovascular toxic effects.

Objective: To evaluate cardiovascular safety of herbal cough syrup.

Methods: Twenty eight rabbits of either sex, weighing 670g–1200g were divided into four groups, with 7 rabbits in each group. Group I was the control group & received 0.3 ml of water, group II, III & IV received herbal syrup normal dose (0.57ml/kg), moderate dose (5ml/kg),and high dose (10ml/kg) respectively once daily, orally for a period of 45 days following which blood samples were collected through cardiac puncture, centrifuged & serum was analyzed on Vitalab eclipse automatic analyzer for cardiac & lipid profile.

Results: In comparison to control group there were no significant changes in cardiac and lipid profile of all groups. Overall results did not reveal any significant toxicity.

Conclusion: The Herbal Syrup is safe as an antitussive and reveals no significant cardiovascular toxicity.

KEY WORDS: *Herbal, Cough, Cardiovascular Safety.*

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INTRODUCTION

Plants are used as healing agents since time immemorial in both organized (Ayurveda, Yunani) and unorganized (folk, tribal, native) form.[1] The use of conventional medicine and medicinal plants in most developing countries, as a normative basis for the maintenance of good health, has been widely observed.[2] The alternative medicines in a number of countries have been disqualified owing to toxicity due to improper processing of the components and lack of quality control standards. As a result there is a need for the development of reliable standardization tools for effective utility of these traditional medicines.[3]

Plants play a major role in the discovery of new therapeutic agents and have received much consideration as sources of biologically active substances including antioxidants, hypoglycemic and hypolipidemic agents.[4] Many medicinal plants such as *Ocimum Sanctum*[5], *Adhatoda Vasica*[6,7] and *Glycyrrhiza Glabra*[8] have been reported to have antitussive activity. The successful health-care system in most developing countries has been due to the support granted by traditional medicine. The World Health Organization estimates, that up to 80 per cent of the world's population relies mainly on herbal medicine for primary health care.[9] Similar to medicinal agents, herbal products are viewed as having the same potential for adverse effects as patented drugs. A review of randomized controlled trials evaluating herbal medicine discovered that only 15% of studies provided information on safety or side effects.[10] According to the World Health Organization (WHO), 4 billion people (80 percent of the world's population) use herbal remedy for some aspect of primary health care.[11] Prolonged use of a substance usually offers testimony of its safety.[12]

Cardiovascular disease remains the major cause of death in both developed and developing countries, accounting for roughly 20% of all worldwide deaths per year.[13] Myocardial infarction, the most dreaded among ischemic heart diseases, is consistently followed by several biochemical alterations, such as lipid peroxidation, free radical damage, hyperglycemia, hyperlipidemia etc. leading to qualitative and quantitative changes of myocardium.[14] It is now well established that the hyperlipidemia signify a major risk factor for the early development of atherosclerosis and its cardiovascular manifestations.[15,16]

This herbal cough syrup is a polyherbal preparation which includes piper longum, adhatoda vasica, glycerrhiza glabra and hyssopus officinalis. Up till now, no study has been carried out for the cardiovascular safety of herbal cough syrup. Therefore, the present study was undertaken to evaluate its cardiovascular safety.

METHODOLOGY

The animal study was conducted in the Department of Pharmacology, Faculty of Pharmacy, University of Karachi after obtaining approval from Board of Advanced Study and Research (BASR) University of Karachi.

Twenty-eight healthy rabbits of either sex, weighing 670g–1,200g were equally divided into four groups, seven animals in each group. Group I served as control, while remaining three groups received herbal syrup normal dose (Group II), moderate dose (Group III) and high dose (Group IV). Before administration of drugs, the apparent health of these animals was monitored during the conditioning period under the laboratory environments for a week specifically noticing symptoms of gross toxicity like loss of hair, diarrhea, edema, skin ulceration and loss of activity.

Herbal cough syrup was administered daily in normal dose animals at 0.57 ml/kg, (prescribed dose 10 ml 3 to 4 times a day), 5 ml/kg moderate dose and 10 ml/kg high dose for a period of 45 days orally. Each dose was tested on 7 animals and compared with control group. The control group received normal saline orally equivalent to the volume of respective doses administered to test animals according to their body weight.

The cardiac puncture technique was used to collect blood samples of approx. 7cc from these animals after completion of dosing period on 46th day to carry out biochemical tests. The blood samples for cardiac and lipids parameters were collected prior to cardiac puncture from marginal veins in the rabbit ears.

Serum were immediately separated out by centrifuging (Heraeus, Christ Labofuge A) blood samples at 4000 rpm for about 8 minutes and parameters were analyzed within 3 hours of sample collection on Vitalab eclipse automatic analyzer (Merck) at 37° C using standard reagent kits supplied by Merck.

All the values expressed as the means and standard error to the mean (SEM.). Student significance 't' test was performed and the p values were observed.[17] Results were considered significant if p value were less than 0.05.

RESULTS

Table 1 presents the comparison of CPK, LDH & SGOT at normal (Group II), moderate (Group III) and high (Group IV) doses.

Animals of group II, III and IV showed insignificant rise in CPK i.e. 413.57±108.48 U/I, 512.43±231.31 U/I and 503.29±127.34 U/I respectively as compare to group I i.e. 407.43±87.57 U/I. Animals of group II, III and IV showed insignificant increase in LDH i.e. 544.43±26.05 U/I, 628.43±122.26 U/I and 511.85±114.41 U/I respectively as compared to group I i.e. 362.14 ±87.47 U/I. Animals of group II and IV showed an insignificant decrease in SGOT i.e. 51.00±3.69 U/I and 41.85±6.12 U/I respectively with respect to group I i.e. 64.28±19.22 U/I. However animals of group III showed an insignificant increase i.e. 132.57±51.52U/I.

Table 1: Comparison of cardiac profile following administration of herbal cough syrup (45 day dose)

	Animal Groups			
Para-meters	**Group I**	**Group II**	**Group III**	**Group IV**
CPK (U/l)	407.43 ±87.57	413.57 ±108.48	512.43 ±231.31	503 ±127.34
LDH (U/l)	362.14 ±87.47	544.43 ±26.05	628.43 ±122.26	511.85 ±114.41
SGOT (U/l)	64.28 ±19.22	51.00 ±3.69	132.57 ±51.52	41.85 ±6.12

n=7; Average values ± SEM
*p<0.05 (significant compared to control)

Table 2 depicts the comparison of cholesterol, triglycerides, HDL, VLDL and LDL following the administration of herbal cough syrup at normal (Group II), moderate (Group III) and high (Group IV) doses.

Table 2: Comparison of lipid profile following administration of herbal cough syrup (45 day dose)

	Animal Groups			
Para-meters	**Group I**	**Group II**	**Group III**	**Group IV**
Cholesterol (mg/dl)	94.28± 9.21	99.71±10.00	83.00±97.71*	77.00±20.4*
Triglycerides (mg/dl)	71.85± 12.42	68.28±11.05	94.85±27.34	77.85±22.31
HDL (mg/dl)	58.85± 17.71	26.28±4.50	38.57±11.48	24.00±2.30
VLDL (mg/dl)	14.37± 2.48	13.65±2.21	16.97±6.12	6.57±0.84
LDL (mg/dl)	49.91± 11.58	57.77±11.80	39.45±91.62*	37.20±19.74*

n=7; Average values ± SEM
*p<0.05 (significant compared to control)

Animals of group II showed insignificant increase in cholesterol i.e. 99.71±10.00 mg/dl. While animals of group III and IV showed significant decrease in cholesterol i.e 83.00±97.71mg/d and 77.00±20.4 mg/d respectively with respect to group I i.e.94.28±9.21 mg/dl. Animals of group III and IV showed insignificant rise in triglycerides i.e. 94.85±27.34 mg/dl and 77.85±22.31 mg/dl respectively in comparison to group I i.e. 71.85±12.42 mg/dl. The animals of group II showed insignificant decrease i.e. 68.28±11.05 mg/dl in comparison to control animals. Animals of all groups showed decrease in HDL. The serum levels of HDL in animals of group II, III and IV were 26.28±4.50 mg/dl, 38.57±11.48 mg/dl and 24.00±2.30 mg/dl respectively. Animals of group III showed insignificant increase in VLDL i.e 16.97±6.12. While animals of group II and IV showed decrease in VLDL i.e.

13.65±2.21 mg/dl and 6.57±0.84 mg/dl respectively in comparison to group I i.e. 14.37±2.48 mg/dl. Animals of group II showed rise in LDL i.e. 57.77±11.80 mg/dl. While animals of group III and IV showed significant decrease in LDL i.e. 39.45±91.62 mg/dl and 37.20±19.74 mg/dl with respect to group I i.e. 49.91±11.58 mg/dl.

DISCUSSION

Medicinal plants have been used in almost all cultures as a drug source. The practice of traditional medicine is common in China, India, Japan, Pakistan, Sri Lanka and Thailand. In China about 40% of the total medicinal utilization is attributed to traditional tribal medicines. In Thailand, herbal medicines make use of legumes encountered in the *Caesalpiniaceae*, the *Fabaceae*, and the *Mimosaceae*. In the mid-90s, it was estimated that revenue of more than US$2.5 billion has resulted from the sales of herbal medicines. In Japan, herbal medicinal preparations are more in demand than majority pharmaceutical products.[18]

Like many other developing countries of the world, the practice of herbal treatment is well recognized in pakistan.[19] In Pakistan, people frequently use herbal products especially in the rural areas, because of accessibility, affordability and safety.[20]

Pharmacological properties of many plants have been studied in various laboratories. However there are many limitations concerning safety and efficacy of these preparations. Information about active principals of herbal remedies is not cleared and information on toxicity and unwanted effects of these formulations are deficient. The danger of untested and unregulated remedies should be made known to the general public. Selection of plant material based on quality, standardization of preparation methods, and enforcement of regulation regarding proper labels are all measures which can increase the quality and adequacy of herbal preparations as therapeutic agents.[21]

The market range of synthetic and natural drug for curing cough, cold and sore throat is increasing gradually. Cough, cold and sore throat products range from single-entity to combination, with a wide variety of dosage forms, and include those established to be effective as well as those of unidentified efficacy and/or safety.[22] *Adhatoda Vasica* has also been traditionally included in preparations for the relief of cough, asthma and bronchitis suggested by Ayurvedic physicians for the treatment of various types of respiratory disorders.[23]

The prophylactic and therapeutic effects of plant foods and extracts in reducing cardiovascular disease has been evaluated.[24] Non-nutrient phytochemicals are gradually being recognised as potential health promoters in decreasing the risks of cardiovascular disease and atherosclerosis. Prominent herbs identified were *Achillea Millefolium* (yarrow), *Allium Sativum* (garlic), *Convallaria Majalis* (lily of the valley), *Cratageus Laevigata* (hawthorn), *Cynara Scolymus* (globe artichoke), *Gingko Biloba* (gingko) and *Viburnum Opulus* (cramp bark).[25]

In our study no cardiac toxicity was found. Animals of group II, III and IV showed insignificant increase in CPK level. Animals of group II, III and IV showed insignificant increase in LDH levels. Animals of group II and IV showed insignificant decrease and animals of group III showed insignificant increase in SGOT levels.

Study of lipid profile demonstrates abnormalities in drug induced lipoprotein levels. Animals of group III and IV showed significant decrease in serum cholesterol levels. Animals of group IV showed significant decrease in LDL levels. However there were no significant changes in triglycerides, VLDL and HDL levels. Changes in lipid profile are dose dependent and consistent therefore it might be concluded that these changes could be drug induced. In 2008, Chanda documented that a herbal preparation Trikatu showed no changes in biochemical parameters such as SGOT, total cholesterol, LDL, HDL cholesterol and triglycerides.[26] In another study, the PlrAqe significantly reduced the TC, TG, LDL-C and VLDL-C levels with an increase of HDL-C in treated diabetic rats compared to untreated diabetic rats.[27]

The aim of this research is to make people aware about the cardiovascular safety of commonly used herbal cough syrup. This study was carried out due to lack of investigations with regards to cardiovascular safety of the herbal cough syrup. The present investigation demonstrates that the plants combination used

in this herbal preparation are safe and effective as an antitussive. In this study, the observed cardiovascular safety of different plant combinations administered to healthy rabbits could be related to the presence of herbs such as piperlongum, which already known to have antihyperlipidemic[28] and cardioprotective[29] effects. The traditional use of Adhatoda Vasica as herbal medicine, which is one of the ingredients of herbal cough syrup, has been very well documented. It is one of the most frequently used medicinal plants for upper respiratory tract problems especially cough. The drug has been used for a long period of time with no serious documented adverse effects.[30]

Presently all three experimental groups showed no significant changes in cardiac and lipid profile.

CONCLUSION

The study indicates higher cardiovascular safety for herbal cough syrup, as observed from the results of cardiac and lipid profile. Overall results did not reveal any significant toxicity. Data collected during this study was however, insufficient to reach at a definite conclusion and requires further studies on large number of animals.

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