REVIEW

HERBAL TREATMENT FOR CARDIOVASCULAR DISEASE THE EVIDENCE BASED THERAPY

ZAFAR ALAM MAHMOOD*, MOHAMMAD SUALEH,**
SAAD BIN ZAFAR MAHMOOD* AND MAHWISH AHMED KARIM******

**Department of Pharmaceutics, University of Karachi, Karachi, Pakistan*
*** Department of Pharmacognosy, Fedral Urdu University of Arts, Science & Technology, Gulshan-e-Iqbal Campus, Karachi, Pakistan*
****Ziauddin Medical College, Ziauddin University, Karachi, Pakistan*
*******Department of Pharmacognosy, University of Karachi, Karachi, Pakistan*

ABSTRACT

More than 2000 plants have been listed in the Traditional (Herbal/Alternative) systems of medicine and some of these are providing comprehensive relief to the people suffering from cardio-vascular diseases, specially "hyperlipidemia" and "ischemic heart disease". WHO reports indicate that around eighty percent of the global population still relies on botanical drugs and several herbal medicines have advanced to clinical use in modern times. Based on these findings, present review is written to identify the "Pharmacology and Cardio-vascular Application" of four commonly used plants in Pakistan. These include, *Crataegus oxycantha, Inula racemosa, Terminalia arjuna and Commiphora mukul.* The selection of the plants in the present study is primarily based on their chemistry and pharmacological properties including toxicology reported in various research articles and reviews. Some very interesting findings have been observed and thus recorded and reported in this review.

Keywords: *Crataegus oxycantha, Inula racemosa, Terminalia arjuna, Commiphora mukul,* cardiovascular disease.

INTRODUCTION

There is little doubt that Traditional Medicines have been utilized since antiquity in the health care. However, with the advent of the pharmaceutical industry early in this century, the popularity of traditional/herbal medicine declined, in spite of the fact that twenty five percent of all prescription drugs still contain ingredients isolated from plants. The resources now do exists which can help and assist for greater understanding of the ways in which herbs can facilitate health and restore balance in disease (Murray and Pizzorno, 1991). The global herbal cornucopia represents an eclectic collection of the most authentic early medicines that even today continued to prevent and cure diseases. A major portion of the global population in developing countries still relies on botanical drugs to meet its health needs. The attention paid by health authorities to the use of herbal medicines has increased considerably, both because they are often the only medicine available in less developed areas and because they are becoming a popular alternative treatment in more developed areas. Thus herbal medicines have been given a valuable status and readily available products for primary health care, and WHO has endorsed their safe and effective use (WHO Research Guidelines, 1993).

It is one of the peculiarities of herbal drugs that their indications have for the most part been determined empirically. The reason is easily understood because most herbal drugs have been used for a long time to alleviate or cure illnesses and more especially disorders. Their introduction in therapeutics happened at a time when "Pharmacodynamics" and "Pharmacokinetics" were unknown concepts, when there was no "Medicine Act" to require proof of the quality, efficacy, and safety of herbal medicines. Today, when introducing a new medicine, extensive investigations are required in the interest of safety. To many, the requirement of the proof of activity of a drug appears to be superfluous; but nevertheless, as a representative of a scientifically oriented pharmaceutical science, one strives to pluck herbal drugs out of their present level of pure empiricism and by elucidating their active principles give their application a more secure basis (Wichtl, 1994).

In recent years much prominence has been given to the association of abnormal levels or values of lipid profile (e.g., total cholesterol, LDL, VLDL and triglycerides) with atherosclerosis and ischemic heart disease (IHD). Treatment of hyperlipidemia is preferably by the dietary factors accompanied by other natural regimes. Drug therapy is reserved for more intractable conditions (Evans, 2005). Thus, foremost in the development and management of atherosclerosis is the reduction of serum cholesterol levels. Individuals (men or women) with 33 to 44 years of age, the total cholesterol levels of 256 mg/dL or over have a 5 times greater risk of developing coronary

Corresponding author: e-mail: zamahmood@hotmail.com

artery disease than those whose levels are below 220 mg/dL (Murray and Pizzorno, 1991). It is further reported that of lipoproteins (fat-carrying proteins) can increase this risk to show that the serum levels of " Low Density Lipoproteins" (LDL) and "Very Low Density Lipoproteins "(VLDL) are directly related to risk in both men and women, while "High Density Lipoproteins" (HDL) are protective against atherosclerosis. Reduction of LDL results in a decrease in progression of atherosclerosis in humans and other primates.

The association of hyperlipidemia with the development of atherosclerotic lesion has promoted widespread search for plant based compounds which safely and effectively control the lipid profile (level of cholesterol and triglycerides) in the blood and tissues with least or no toxic effect. Though a number of plants have so far been screened, evaluated and tested against various cardiovascular disease including hyperlipidemia but very few of the findings have been presented or transformed into a suitable dosage form for proper use, either alone or in the form of compound herbal preparation, with the exception of one or two, particularly in this part of the world. A couple of compound herbal medicines are available in the local market, but most of them have a very broad and expanded indications Keeping in view of socio-economic structure, there seems to be a need rather than the desire to investigate more and more indigenous sources, specially plants for the development of useful product which can help people in reducing and maintaining their lipids (cholesterol, triglycerides, LDL and HDL) with least or no toxic manifestation.

DISCUSSION

The selection of the plants in the present review is primarily based on their chemistry and pharmacological properties including toxicology reported in various research articles and reviews. A cursory review of plants selected for detail analysis are delineated herewith as, *Commiphora mukul, Crataegus oxycantha, Inula racemosa and Terminalia arjuna.*

Commiphora mukul

Extracts (Guggul Gum), derived form the exudates has been employed for a long time in Ayurvedic system of medicine for the treatment of obesity and other weight related problems, rheumatoid arthritis and lipid disorders. The usefulness of guggul for treatment of obesity and other disorders of fat, including coating and obstruction of channels has been described in Ayurveda medical text in details. Based on these descriptions, a number of workers have conducted clinical trials to test the effectiveness of this herb for lowering cholesterol and disorders of lipid metabolism as well as lowering weight. The results of the various studies indicated guggul as a natural cholesterol lowering substance, safe and more effective than many cholesterol-lowering conventional drugs. Based on all these research activities, 1986, an approval was given to Guggulipid in India to marketing this as a cholesterol lowering medicine (Satyavati, 1988). Since then, Guggulipid is frequently used by a large group of people against hyperlipidemia and hypertension. Gum guggul is an oleo-gum-resin containing volatile oil, gum and resin. The guggulsterones are the main steroidal component isolated from the crude extract responsible for lowering elevated lipid profile. Studies indicated reduction in triglycerides and cholesterol (including both LDL and VLDL) and a raise in HDL cholesterol after its regular use. In addition, it also reported to lower the risk of coronary artery disease by reducing the stickiness of platelets (Ara derMarderosian and John, 2000).

Pharmacology and cardio-vascular application

Mechanisms of action

The two main areas of pharmacological and cardio-vascular applications have been investigated and reported by many workers (Petkov, 1979; Patel, 1982; Satyavati, 1988; Weiss, 1988; Ceriana, 1992; Singh *et al*., 1993; Leuchtgens, 1993; Schüssler *et al*., 1995; Chatterjee *et al*., 1997). These include: hypolipidemic action (which has been recognized since the vedic ages) and its anti-inflammatory effect. The hypolipidemic action was pioneered by the laboratory investigations carried out by the research workers based on the postulation of Sushruta that guggul is very useful in the treatment of obesity. It is reported that the uptake of LDL-cholesterol from the blood by the liver increases due to Guggulsterones consequently the concentration of LDL also decreases (.Satyavati, 1988). The stereo isomers E - and Z-guggulsterone have been reported as main component in Guggulipid (an antagonist ligands for the bile acid receptor farnesoid X receptor (FXR)) are responsible for hypolipidemic activity (Urizar, 2003).

Cardio protective and anti-hyperlipidemic activity

The ethyl acetate extract of *Commiphora mukul* has been reported to possess preventive activity against deteriorating changes in serum cholesterol, triglycerides, and plasma fibrinogen level in lab animals. Further, increase in plasma fibrinolytic activity has also been noted (Srivastava, et. al., 1991). The oleoresin part of guggul, at a dose of 12.5 mg/100g has been noted to produce pronounced anti-arthritic and anti-inflammatory activities (Sharma and Sharma, 1977). Few side effects such as weight loss, peptic ulcer have been noted in lab animals fed on extract against those, given betamethasone (Satyavati, 1991).

Clinical study was carried out on patients (35 in number) with rheumatoid arthritis using guggulipid and based on this study results, dose requirement side effects along with change in hematology were recorded. Results of the study were very encouraging and showed the digestive

and analgesic activity of guggulipid with no toxic or side effects (Antonio, 1999). In another study 20 patients with hyperlipidemia were given guggulipid in two different dose level and noted to decreased total cholesterol and triglyceride concentration. In addition, a gradual increase in HDL level and significant decrease in LDL and VLDL have been recorded at the end of study (Verma and Bordia, 1988). Few minor side effects, such as mild diarrhea and nausea were among patients kept on guggulipid. Other side effects, such as raise in bilirubin levels, hemolysis of blood, hepatitis, and obstruction of the biliary tract need to be confirmed (Murray, 1995).

In a double-blind placebo control study, guggulipid found to decreased the total cholesterol level by 11.7%, LDL by 12.5%, triglycerides by 12.0%, and the total cholesterol / HDL) ratio by 11.1% from the post diet levels, whereas the levels were unchanged in the placebo group. The study was carried out on 61 patients with hypercholesterolemia (31 in the guggulipid group and 30 in the placebo group) using 50 mg of guggulipid or placebo capsules twice daily for 24 weeks. However, no change was noted in both groups with respect to HDL level. It was further reported that in guggulipid group, the lipid peroxides decreased to 33.3% (Singh, 1994; Urizar and Moore, 2003).

Crataegus oxycantha

Germany is the most prominent country where Crataegus oxycantha has been extensively studied for its effect and used in cardiology (Blesken, 1992) and also it's possible application in the treatment of congestive heart failure (Weikl *et al*., 1996). During clinical studies, no major side effect was observed. Based on this, the authors concluded that Crataegus oxycantha is safe and can be an alternative therapy for congestive (Leuchtgens, 1993). It has been indicated that *Crataegus oxycantha* extracts under ischemic conditions, improves the energy dynamics of the heart muscle (Al Makdessi *et al*., 1996). In addition, animal studies indicated a highly positive effect in decreasing blood lipid (Shanthi *et al*., 1994).

Pharmacology and cardio-vascular application

Mechanisms of action

Due to inotrophic and chronotropic effects, Crataegus' reported to possess cardiovascular effects, including enhanced blood vessel integrity, and effects on coronary blood flow and oxygen utilization (Al Makdessi *et al*., 1996; Nasa *et al*., 1993).

Cardio protective and anti-hyperlipidemic activity

The oligomeric proanthocyanidin (OPC) reported in the leaves and flowers of Crataegus with respect to free radical scavenging and inhibition of human neutropils elastase (HNE) has been studied and reported. Under ischemic conditions, significantly greater number of HNE is released which may be partly responsible for myocardial damage and reperfusion along with free radicals (Ceriana, 1992). The authors, further proposed that the cardio protective activity of Crataegus may be due to radical scavenging and inhibition of HNE by the OPC. Research workers have found. The free radical scavenging effect and HNE inhibition was found maximum in the OPC fraction (Chatterjee *et al*., 1997).

Studies on monoacetyl-vitexin rhamnoside, a flavonoid from Crataegus, suggested that it has potent anti-ischemic properties. A part from phosphodiesterase inhibition, it was found to exert vasodilatory action (Schüssler *et al*., 1995). This action is related to release of lactic dehydrogenase (LDH) from isolated hearts during ischemia. The energy dynamics of the heart muscle has been reported to be improved by the Crataegus extract, especially in ischemic condition (Al Makdessi *et al*., 1996).

During a similar investigation, the investigators reported the effect of Crataegus on isolated rat hearts in ischemia and reperfusion. The results revealed comprehensive improvements on the over all function of the heart compared to controls. No increase in coronary flow was observed, indicating more efficient myocardial energy utilization (Nasa *et al*., 1993). In another study, the flavonoids from Crataegus revealed diversified action. The different flavonoid constituents have been noted to produce different effects on the heart. Some flavonoids found increasing coronary flow, left ventricular pressure, and heart rate, and others not affecting these parameters, or even decreasing them. (Schüssler *et al*., 1995). Some workers also reported flavonoids to increase coronary blood flow with decrease in oxygen consumption by the myocardium and reduction in coronary spasm (Petkov, 1979). While in a separate study, the flavonoids from have also been found to inhibit in vitro the formation of thromboxane A2 (Vibes *et al*., 1994). Further, the extract of Crataegus has also been noted to prolong the refractory phase (opposite to digoxin) thus reducing the risk of arrhythmias (Joseph *et al*., 1995; Pöpping *et al*., 1995). Some studies suggest that Crataegus might also have a positive effect on blood lipid profile and may decrease fat deposition in the aorta and liver (Shanthi *et al*., 1994; Rajendran *et al*., 1996). While in two different double-blind studies carried out on 30 and 136 patients respectively with cardiac insufficiency, the cardiac function (by PRP) was noted to be significantly improved in the Crataegus group over the eight-week period. With the progressively deterioration of PRP in the placebo group (Leuchtgens, 1993 and Weikl *et al*., 1996). However, in cases of acute angina, Crataegus does not work well and thus it is considered to be a long-term treatment (Weiss, 1988).

Inula racemosa

The plant has reported as traditional Ayurvedic medicine with a number of beneficial effects on the cardiovascular system. In Ayurvedic medicine, the root powder of this

plant is indicated for reducing cholesterol, to support healthy circulation, and to treat angina and dyspnea. The plant may have a cardio protective effect based on the results obtained when given before and after experimental myocardial infarction. A mixture of *Inula racemosa* root powder and Guggulipid granules (1:1) when administered for six months exhibited significant improvement in lipid profile physical condition of patients (Tripathi *et al*., 1984 and Singh *et al*., 1993).

Pharmacology and cardio-vascular applications
Inula racemosa has been reported as a reputable traditional Ayurvedic botanical, which has potential beneficial effects on the cardiovascular system. It is also known as Pushkarmoola. In Ayurvedic medicine, the root powder of this plant is indicated for angina and dyspnoea (Tripathi *et al*., 1984 and Ceriana, 1992).

Mechanism of action
The cardio protective effect of Inula was demonstrated in rats before and after experimental myocardial infarction. The animals indicated small increases in LDH, CPK, cAMP, cortisol, pyruvate, lactate, and glucose compared untreated control group (Patel *et al*., 1982).

Cardio protective and anti-hyperlipidemic activity
A combination of *Commiphora mukul* and *Inula racemosa* (1:1 ratio) was studied in 200 patients with ischemic heart disease. The major symptoms include chest pain, with ST-segment and T-wave changes on electrocardiogram (ECG), suggestive of myocardial ischemia in about 80% of the patients. The results were quite encouraging. Total cholesterol decreased in 39%, triglycerides in 51%, and total blood lipids in 32%. During this trial, fried foods and excessive carbohydrates have been restricted in these patients. A complete restoration of normal ECG was noted in 26% while improvement in the ECG was observed in 59% of the patients at the end of six month study period. In addition, no chest pain was recorded in 25% of the subjects, while dyspnoea fell to 32%, from a baseline 80 percent. The subjective levels of chest pain and dyspnoea also improved after treatment (Singh *et al*., 1996).

For the prevention of anginal symptoms, Inula was compared with nitroglycerin in nine subjects with ischemic heart disease. The major symptoms include, chest pain and ECG ST-segment depression, indicative of myocardial ischemia on exertion. All nine subjects showed improvement in ST-segment depression on ECG, with greater improvements seen after Inula treatment using a dose of 3 g root powder 90 minutes prior to testing (Tripathi *et al*., 1984).

Terminalia arjuna
The bark of *Terminalia arjuna* is very famous as cardio tonic and a long history (about 2500 years) of use in Ayurvedic medicine. Its usefulness is well documented in relieving anginal pain, and in the treatment of coronary artery disease, heart failure, and hypercholesterolemia including (Ram and Gupta, 1997).

Pharmacology and cardio-vascular applications
The clinical and animal studies have indicated the usefulness of *Terminalia arjuna* in decreasing hypercholesterolemia, including LDL cholesterol. This extends its application in relieving anginal pain, and in the treatment of coronary artery disease (Lucas 1977; Khanna *et al*., 1996; Ram and Gupta, 1997; Ara derMarderosian and John, 2000; Evans, 2005).

Mechanisms of action
The results of various studies suggest that the saponin glycosides are possibly responsible for the improvement of cardiac muscle function and subsequent improved pumping activity of the heart. While the flavonoids and OPCs fractions have been reported to contribute the antioxidant activity and vascular strengthening (Chevallier, 1996; Shaila, 1998).

Cardio protective and anti-hyperlipidemic activity
Clinical studies revealed reduction of anginal episodes (50%) in patients with stable and unstable angina at the end of three months with Terminalia. Reduction in systolic blood pressure in these patients was also noted along with the improvement in exercise tolerance with both the time to onset of angina and the time to appearance of ECG ST-T changes in the stable angina group. In comparison, patients with unstable angina did not experience much reductions in angina or systolic blood pressure. However, both groups showed improvements in left ventricular ejection fraction. Evaluating the over all treadmill testing results, improvement in 66% of the subjects with stable angina and 20% with unstable angina was observed at the end of three months therapy (Dwivedi and Agarwal, 1994).

Based on Terminalia's effect of increasing cardiac output, a double-blind study was conducted using 500 mg Terminalia bark extract or placebo every eight hours for two weeks for the treatment of congestive heart failure in twelve patients with severe refractory heart failure (NYHA Class IV). During whole study, all patients continued with their drug therapy which included diuretics, angiotensin-converting-enzyme inhibitors, vasodilators, digoxin, and potassium supplementation. The symptoms, such as edema, fatigue and dyspnea along with walking tolerance, stroke volume, left ventricular ejection fraction, with decreases in end-diastolic and end-systolic left ventricular volumes improved in patients who were on Terminalia therapy. Prolong use of Terminalia to complete the second phase of the study was also done and during this study patients were continued on Terminalia extract for approximately two years. Results of the study

indicated improvements in the ensuing two to three months. At the end of four months, nine patients had improved to NYHA Class II and three improved to Class III. The authors concluded these findings as significant piece of research because these patients had not responded to conventional drug therapy in earlier studies (Bharani *et al*., 1995).

Effect of Terminalia extract was also investigated against post myocardial infarction (in 10 patients) and two patients with ischemic cardio myopathy (in 2 patients), at a dose level of 500 mg every eight hours for three months. These patients were continued on their regular treatments. The symptoms of angina, left ventricular ejection fraction, and left ventricular mass were significantly reduced in the Terminalia group, whereas a control group taking only regular drugs had decreased angina only. The severity of cardio myopathy also improved from NYHA Class III to Class I in two patients during the study (Dwivedi and Jauhari, 1997).

REFERENCES

Agarwal RC (1986). Clinical Trial of Guggulipid: A new hypolipidemic agent of plant origin in primary hyperlipidemia. *Indian J. Med. Res.*, **84**: 626-634.

Al Makdessi S, Sweidan H, Mullner S and Jacob R (1996). Myocardial protection by pretreatment with Crataegus oxycantha: An assessment by means of the release of lactate dehydrogenase by the ischemic and reperfused Langendorff heart. *Arzneimittelforschung*, **46**: 25-27.

Antonio J, Colker CM and Torina GC (1999). Effects of a Standardized guggulsterone phosphate supplement on body composition in overweight adults: A Pilot Study. *Curr. Ther. Res.*, **60**: 220-227.

Ara der Marderosian and John A Beutler (2000). The Review of Natural Products, 3rd edition published by Facts and Comparisons, St. Louis, Missouri, USA, p.357.

Bharani A, Ganguly A and Bhargave KD (1995). Salutary effect of *Terminalia arjuna* in patients with severe refractory heart failure. *Int. J. Cardiol.*, **49**: 191-199.

Blesken R (1992). Crataegus in cardiology. *Fortschr Med*, **110**: 290-292.

Ceriana P (1992). Effect of myocardial ischemia reperfusion on granulocyte elastase release. *Anaesth Intensive Care*, **20**: 187-190.

Chatterjee SS, Koch E, Jaggy H and Krzeminski T (1997). *In vitro* and *in vivo* studies on the cardio protective action of *Oligomeric procyanidins* in a Crataegus extract of leaves and blooms. *Arzneimittelforschung*, **47**: 821-825.

Chevallier A (1996). Encyclopedia of Medicinal Plants, DK Publishing, New York, pp.141, 273.

Dwivedi S and Agarwal MP (1994). Antianginal and cardio protective effects of *Terminalia arjuna*, an indigenous drug, in coronary artery disease. *J. Assoc. Physicians India*, **42**: 287-289.

Dwivedi S and Jauhari R (1997). Beneficial effects of *Terminalia arjuna* in coronary artery disease. *Indian Heart J.*, **49**: 507-510.

Evans WC (2005). Plants in medicine: the origins of Pharmacognosy. In: Trease and Evans Pharmacognosy, 15th edition, published by Saunders, An Imprint of Elsevier, USA, pp 3-4.

Hanus LO, Rezanka T, Dembitsky VM and Moussaieff A (2005). Myrrh – Commiphora Chemistry, *Biomed. Papers*, **149**(1): 3-28.

Hertog MGL, Feskens EJM and Hollman PCH (1993). Dietary antioxidant flavonoids and risk of coronary heart disease; the Zutphen Elderly Study. *Lancet*, **342**: 1007-1011.

Hertog MGL, Kromhout D and Aravanis C (1995). Flavonoid intake and long-term risk of coronary heart disease and cancer in the Seven Countries Study. *Arch. Intern. Med.*, **155**: 381-386.

Joseph G, Zhao Y and Klaus W (1995). Pharmacologic action profile of Crataegus extract in comparison to epinephrine, amirinone, milrinone and digoxin in the isolated perfused guinea pig heart. *Arzneimittel-forschung*, **45**: 1261-1265.

Khanna AK, Ramesh C and Kapoor NK (1996). *Terminalia arjuna*: An Ayurvedic cardiotonic regulates lipid metabolism in hyperlipidemic rats. *Phytotherapy Res.*, **10**: 663-665.

Leuchtgens H (1993). Crataegus Special Extract WS 1442 in NYHA II heart failure. A placebo controlled randomized double-blind study. *Fortschr. Med.*, **111**: 352-354.

Lucas R (1977). Nature's Medicines, Wilshire Book Company, California, USA, pp.13-16.

Murray MT (1995). The Healing Power of Herbs (2nd Edition), Prima Publishing Murray MT and Pizzorno JE (1991). Atherosclerosis. In: Encyclopedia of Natural Medicine published by Prima Publishing, CA, pp.156-170.

Nasa Y, Hashizume H, Hoque AN and Abiko Y (1993). Protective effect of Crataegus extract on the cardiac mechanical dysfunction in isolated perfused working rat heart. *Arzneimittelforschung*, **43**: 945-949.

Nityanand S, Srivastava JS and Asthana OP (1989). Clinical trials with Guggulipid, a new hypolipidemic agent. *J. Asso. Physicians India.* **37**: 321-328.

Patel V, Banu N and Ojha JK (1982). Effect of indigenous drug (Pushkarmula) on experimentally induced myocardial infarction in rats. *Act. Nerv. Super.*, 3(Suppl.), 387-394.

Petkov V (1979). Plants with hypotensive, anti-atheromatous and coronarodilatating action. *Am. J. Chin. Med.*, **7**: 197-236.

Pöpping S, Rose H and Ionescu I (1995). Effect of a hawthorn extract on contraction and energy turnover of

isolated rat cardiomyocytes. *Arzneimittelforschung*, **45**: 1157-1161.

Rajendran S, Deepalakshmi PD and Parasakthy K (1996). Effect of tincture of Crataegus on the LDL-receptor activity of hepatic plasma membrane of rats fed an atherogenic diet. *Atherosclerosis*, **123**: 235-241.

Ram A, Lauria P and Gupta R (1997). Hypocholesterolemic effects of *Terminalia arjuna* tree bark. *J. Ethnopharmacol.*, **55**: 165-169.

Satyavati GV (1988). Gum Guggul (*Commiphora mukul*) – The success of an ancient insight leading to a modern discovery. *Indian J. Med.*, **87**: 327-335.

Satyavati GV, Dwarkanath C and Tripathi SN (1969). Experimental studies on the hypocholesterolemic effect of *Commiphora mukul*, *Indian J. Med. Res.*, **57**: 1950. Satyavati GV (1991). A promising hypolipidemic agent from gum guggul (*Commiphora wightii*). *Econ. Med. Plant. Res.*, **5**: 47-82.

Schüssler M, Hölzl J, Rump AF and Fricke U (1995). Functional and antiischemic effects of monoacetylvitexinrhamnoside in different *in vitro* models. *Gen. Pharmacol.*, **26**: 1565-1570.

Shaila H (1998). Hypolipidemic activity of three indigenous drugs in experimentally induced atherosclerosis. *Int. J. Cardiol.*, **67**(2): 119-124.

Shanthi S, Parasakthy K, Deepalakshmi PD and Devaraj SN (1994). Hypolipidemic activity of tincture of Crataegus in rats. *Indian J. Biochem. Biophys.*, **31**: 143-146.

Sharma JN and Sharma JN (1977). Comparison of the anti-inflammatory activity of *Commiphora mukul* (an indigenous drug) with those phenylbutazone and ibuprofen in experimental arthritis induced by mycobacterial adjuvant. *Arzeimittel-Forsch.*, **27**: 1455-1457.

Singh RB, Niaz MA and Ghosh S (1994). Hypolipidemic and antioxidant effects of *Commiphora mukul* as an adjunct to dietary therapy in patients with hypercholesterolemia. *Cardiovasc. Drugs Ther.*, **8**(4): 659-664.

Singh RP, Singh R, Ram P and Batliwala PG (1993). Use of Pushkar-Guggul, an indigenous antiischemic combination, in the management of ischemic heart disease. *Int. J. Pharmacog.*, **31**: 147-160.

Srivastava VK (1991). Conference of Pharmacology and Symposium on Herbal Drugs, 15th March, New Delhi, India, p.15.

Tripathi SN, Upadhyaya BN and Gupka VK (1984). Beneficial effect of *Inula racemosa* (Pushkarmoola) in angina pectoris: A preliminary report. *Ind. J. Physio. Pharmac.*, **28**: 73-75.

Urizar NL and Moore DD. (2003). GUGGULIPID: a natural cholesterol-lowering agent. *Annu. Rev. Nutr.*, **23**: 303-313.

Verma SK and Bordia A (1988). Effect of *Commiphora mukul* (Gum Guggul) in patients of hyperlipidemia with special reference to HDL cholesterol. *Indian J. Med. Res.*, **87**: 356-360.

Vibes J, Lasserre J, Gleye J and Declume C (1994). Inhibition of thromboxane A2 biosynthesis *in vitro* by the main components of *Crataegus oxycantha* (Hawthorn) flower heads. *Prostaglandins Leukot Essent Fatty Acids*, **50**: 173-175.

Weikl A, Assmus KD and Neukum-Schmidt A et al. (1996). Crataegus Special Extract WS 1442. Assessment of objective effectiveness in patients with heart failure. *Fortschr. Med.*, **114**: 291-296.

Weiss RF (1988). Herbal Medicine, 6th Ed. Gothenburg, AB Arcanum, Sweden, pp.162-168.

WHO Research Guidelines for Evaluating the Safety and Efficacy of Herbal Medicines (1993). Published by World Health Organization, Regional Office for the Western Pacific, Manila, pp.1-10.

Wichtl M (1994). Herbal Drugs and Phyto-pharmaceuticals. A handbook for practice on a scientific basis – English Edition (Editor: Norman Grainger Bisset) published by Medpharm, Stuttgart, Germany, pp.5-7.