THERAPEUTIC PROPERTIES OF MEDICINAL PLANTS: A REVIEW OF PLANTS WITH HYPOLIPIDEMIC, HEMOSTATIC, FIBRINOLYTIC AND ANTICOAGULANT EFFECTS (PART 1)

Ali Esmail Al-Snafi*

Department of Pharmacology, College of Medicine, Thi qar University, Iraq.

ABSTRACT

The recent studies showed that many plants possessed cardiovascular effects. This review was designed to cover the hypolipidemic, fibrinolytic anti platelet aggregating and antioxidant effects of the medicinal plants.

Key words: Medicinal plants, Cardiac, Hypolipidemic, Fibrinolytic, Anti platelet aggregating, Antioxidant.

INTRODUCTION

Plants and their secondary metabolite constituents have a long history of use in modern medicine and in certain systems of traditional medicine, and are the sources of important drugs such as atropine, codeine, digoxin, morphine, quinine and vincristine. In some cases, the active principles of plant-derived products have been isolated and characterized, and their mechanisms of action are understood. Many recent studies showed that many plants possessed hypolipidemic, fibrinolytic, anti platelet aggregating and antioxidant effects [1-46]. This review was designed to cover the hypolipidemic, fibrinolytic anti platelet aggregating and antioxidant effects of the medicinal plants.

Plant with hypolipidemic effects

*Allium porrum*

The antihypercholesterolemic effect of a hydroalcoholic extract of *A. porrum* L. bulbs was evaluated in rabbits on hypercholesterolemic diet. The extract was given in three doses, 250, 500, and 1,000 mg/kg of body weight. Plasma total cholesterol decreased in all groups treated with *A. porrum* extract in a dose-dependent fashion [47]. The antioxidant activity of *Allium porrum* ranged from 490 to 3323 μmol TE/100 g fresh weight [48]. *Allium porrum* flavonoids exerted platelet anti-aggregation activity [49].

*Allium sativum*

Garlic (1–4% in diet) and garlic protein administration in hypercholesterolemic rats induced by a high-cholesterol diet, significantly reduced serum cholesterol, triglyceride and LDL cholesterol [50-56]. Long term feeding of garlic and garlic preparations on experimental atherosclerosis induced by a high-cholesterol diet in rabbits cause statistically significant reduction in serum lipids and atheromatous lesions [57-62]. Water soluble extract of garlic inhibited the biosynthesis of cholesterol in hepatocytes. Garlic derived components are capable of binding with the sulphydryl (-SH) group. Reduced conversion of acetate into cholesterol has been observed both *in vivo* and *in vitro* [53, 63-64]. Eating of 10 g fresh garlic per day for 2 months significantly decreases (15%-28.5%) serum cholesterol levels among hypercholesterolemic patients [65]. Garlic oil caused a steady decrease in LDL and VLDL levels with concomitant increase in HDL levels [51, 66]. Intake of enteric-coated garlic powder (equal to 400 mg garlic, 1 mg allicin) twice daily in hyperlipidemic patients has significantly reduced total cholesterol, LDL-cholesterol and triglyceride and increased HDL-cholesterol [67].

The level of cholesterol, triglyceride, phospholipids and β- lipoproteins were significantly declined in the individuals consuming 10-50 g of garlic /week. These results indicate that routine consumption of garlic in the diet has a beneficial effect in maintaining the serum lipids at low or normal levels [68]. In a placebo-controlled trial of patients with stage II peripheral arterial occlusive disease, garlic powder supplements , 800 mg daily were associated with a significant increase in walking distance by 46 meters; the improvement started after the
fifth week of treatment [69]. Patients treated with 900 mg daily of standardized garlic powder showed 9-18% reduction in plaque volume, a 4% decrease in LDL levels, an 8% increase in HDL concentrations, and a 7% decrease in blood pressure [70].

Aloe vera
Aloe vera gel lowered triacylglyceride levels in liver and plasma. Histological examinations of peripipidymal fat pad showed that Aloe vera gel reduced the average size of adipocytes [71].

Five thousand patients of atheromatous heart disease, presented as angina pectoris, were studied over a period of five years. After adding the (Husk of Isabgol) and (Aloe vera) to the diet, a marked reduction in total serum cholesterol, serum triglycerides, increased HDL, decreased fasting and postprandial blood sugar level in diabetic patients were noted. Simultaneously the clinical profile of these patients showed reduction in the frequency of anginal attacks [72].

Alpinia galanga
Ethanolic extract of A. galanga 20mg/day for 4 weeks in rats exerted hypolipidemic activity, with a significant increase in the serum levels of high density lipoproteins (HDL) in rats [73]. A. galanga constituents exerted platelet activating factor (PAF) antagonists. Methanolic extract showed significant inhibitory effects on PAF with IC50 value of 5.5ug/ml in rabbit platelets [74].

Ammi visnaga
A clinical study was carried out on 20 non-obese, normolipaemic male subjects to determine the effects of orally administered 50 mg khellin four times daily for 4 weeks on the plasma lipids. Plasma total cholesterol and triglyceride remained unchanged, but high-density-lipoprotein cholesterol concentration was significantly elevated during the treatment and till one week after cessation of treatment [75]. In a comparison with glyceryl trinitrate, khellin (3 ml. Containing 150 mg of khellin, alcoholic extract standardized to contain 50 mg/ml) was used in twelve patients for prevention of angina of effort and the electrocardiographic changes that may accompany it. Khellin was less potent but longer acting than glyceryl trinitrate, and it did not cause any unpleasant side effects [76].

Anethum graveolens
The crude extract of Anethum graveolens L showed anti-hyper cholesterolamieic and anti-hyperlipidaemic activities. The crude extracts of A. graveolens L., besides having strong anti-hyperlipidaemic effects, it improved the biological antioxidant status by reducing lipid peroxidation in liver and modulating the activities of antioxidant enzymes in rats fed with high fat [77, 78]. Treatment of hyperlipidaemic rats with defatted ethanolic Anethum graveolens L. extract (single daily dose of 1 ml, equivalent to 500 mg of the plant powder) and high-fat diet for up to 10 and/or 30 days reversed the serum lipid levels compared to rats which were fed only high-fat diet. In addition, it induced significant increase in HMG-CoA/mevalonate ratio as compared to rats which were fed high-fat diet after treatment with defatted ethanolic Anethum graveolens L. extract for 30 days [79].

Apium graveolens
Many experimental studies showed that Apium graveolens significant lowered serum total cholesterol, triglycerides, LDL and VLDL and increased HDL level. Apium graveolens also reduced the formation of arterial plaques in experimental studies. However, the mechanisms suggested for lipid lowering action of Apium graveolens including inhibition of hepatic cholesterol biosynthesis, increasing faecal bile acid excretion and enhancing plasma lecithin: cholesterol acyltransferase activity and reduction of lipid absorption in the intestine. Some authors mentioned that blood lipids lowering effects was attributed to the compound 3n butylphthalaldeor (3nB) isolated from Apium graveolens, but, the active extract free from 3-n-butylphthalalide has been reported to have lipid-lowering action. Instead, thin layer chromatography indicated that polar compounds with sugar or amino acid side chains(s) could be the hypocholesterolaemic constituents of celery extract [80-85].

In evaluation of the protective effects of ethanolic extract of Apium graveolens on ritonavir (a protease inhibitor) - induced dyslipidemia. It appeared that concurrent treatment with high dose of ethanolic extract of Apium graveolens (150mg/kg) in mice with ritonavir, showed significant improvement in blood lipid profile. However, using of low dose of ethanolic extract of Apium graveolens (75mg/kg) showed no significant effects [86].

Arachis hypogaea
The effect of water soluble polyphenolic extract of peanut skin (PE) was investigated for its hypolipidemic properties and improvement of lipid homoeostasis in rats. 300mg/kg body weight of ( PE ) significantly reduced body weight and epidymidal fat. Plasma and liver triglyceride (TG) and cholesterol (TC) levels were also significantly reduced, and the faecal secretion of TG and TC was greatly increased upon PE administration. Liver mRNA expression of enzymes involved in fatty acid synthesis, such as fatty acid synthase (FAS), sterol receptor element binding protein (SREBP)-1c, acetyl-CoA carboxylase (ACC1) and lipid uptake genes, such as PPARγ, were decreased, while PPARα was up-regulated by administration of PE [87].

Feeding a high-cholesterol diet with a water-soluble peanut skin polyphenol fraction to rats reduced their plasma cholesterol level, with an increase in fecal cholesterol excretion. The hypocholesterolemic effect was greater with the lower-molecular-weight rather than higher-
molecular-weight polyphenol fraction. This effect attributed to some oligomeric polyphenols which reduced the solubility of dietary cholesterol in intestinal bile acid-emulsified micelles [88]. The effects of peanut (Arachis hypogaea) consumption on oxidant-antioxidant status and lipid profile in Streptozotocin (STZ) induced diabetic rats was investigated. Rats were given standard rat chow supplemented with 0.63 g % peanut for 12 weeks. The supplementation with peanut in the diabetic group led to significantly higher HDL-C levels and lower atherogenic index (AI) levels compared to diabetic group. Peanut consumption increased GSH levels significantly both in control and diabetic groups [89]. Most of peanet stilbenoids inhibited intracellular generation of reactive oxygen species (ROS) in PMA inducedHL-60 cells. Three stilbenoids compounds produced a strongest antioxidant effect. Twelve compounds demonstrated significantly high antioxidant properties which were comparable to those of Trolox. Although, the majority of stilbenoids demonstrated moderate cytotoxicity toward HL-60 cells, but the antioxidant effect was observed at much lower concentrations which confirmed that the antioxidant effect was not related to cytotoxic effect [90, 91].

**Asparagus officinalis**

The hypolipidemic effect of n-butanol extract from asparagus by-products was evaluated in mice fed a high-fat diet. Asparagus butanol extract significantly decreased the levels of body weight gain, serum total cholesterol and low density lipoprotein cholesterol; it dramatically increased the high density lipoprotein level when administered at three different doses (40, 80 or 160 mg/kg body weight) for 8 weeks in hyperlipidemic mice. In addition, asparagus butanol extract decreased the levels of alanine transaminase, aspartate transaminase and alkaline phosphatase in serum. Superoxide dismutase activity and the total antioxidation capacity were evidently increased; in addition, the malondialdehyde level and the distribution of lipid droplets were reduced in liver cells of asparagus butanol extract -treated mice [92-93].

**Avena sativa**

Oat β-glucan exerted cholesterol-lowering properties. The consumption of oat meal and oat bran reduced total plasma cholesterol and LDL-cholesterol levels. This effect attributed to β-glucan, it interfered with the reabsorption of bile acid in the gut and reduces cholesterol levels. The oat bran has been found to be the only fiber source that significantly lowered total and low density-lipoprotein cholesterol levels in mild hypercholesteroleemics [94].

C57BL/6J mice responded to oat bran with 19 ± 1 % (P < 0.001) lower plasma cholesterol, 40 ± 5 % (P < 0.01) higher excretion of bile acids and increased expression of the bile acid-producing hepatic enzymes CYP7A1 and CYP8B1, but none of these effects were found in C57BL/6J mice. However, on control diet, C57BL/6J mice had tenfold higher expression of CYP7A1 and levels of hepatic cholesterol esters than C57BL/6N mice. Plasma levels of fructosamine indicated improved glycemic control by oat bran in C57BL/6N but not in C57BL/6J. C57BL/6J mice had higher intestinal microbiota diversity, but lower numbers of Enterobacteriaceae, Akkermansia and Bacteroides fragilis than C57BL/6N mice. Oat bran increased bacterial numbers in both substrains. Microbiota diversity was reduced by oats in C57BL/6J, but unaffected in C57BL/6N [95].

The United States Food and Drug Administration (FDA) approved a health claim for β-glucan soluble fiber from oats for reducing plasma cholesterol levels and risk of heart disease in 1997. Similarly, in 2004 the United Kingdom Joint Health Claims Initiative (JHCI) allowed a cholesterol-lowering health claim for oat β-glucan. Studies conducted during the past 13 years support the suggestion that intake of oat β-glucan at daily doses, of at least 3 g, reduced plasma total and low-density lipoprotein (LDL) cholesterol levels by 5-10% in normocholesterolemic or hypercholesterolemic subjects. Studies also showed that oat consumption is associated with 5% reductions in total cholesterol levels [96].

The effect of oat consumption on serum lipid profiles in Thai hypercholesterolemic adults was studied. Following daily oat consumption, total cholesterol and LDL-cholesterol levels were significantly lower than baseline levels and lower than the levels observed with rice consumption. Oat consumption reduced total cholesterol by 5% and LDL-cholesterol by 10% from baseline levels. In addition, mean and percent changes were significantly different from the levels after consuming rice porridge (p < 0.05) [97].

A clinical trial was carried out to confirm the anti-obesity effect of oat. Subjects with BMI ≥27 and aged 18-65, were randomly divided into a control (n=18) and an oat-treated (n=16) group, taking a placebo or beta glucan-containing oat cereal, respectively, for 12 weeks. The result showed that consumption of oat reduced body weight, BMI, body fat and the waist-to-hip ratio. Profiles of hepatic function, including AST and ALT showed decrements in patients with oat consumption. Nevertheless, anatomic changes were not observed by ultrasonic image analysis. Ingestion of oat was well tolerated and there was no adverse effect during the trial [98].

To explored the dose-dependent effect of oat cereal β-glucan on improving metabolic indexes of obesity mice, C57BL mice were randomized to chow diet (N) group and high fat diet group and other three doses of oat β-glucan groups (low β-glucan, medium β-glucan, and high β-glucan). Energy intake, glucose, lipids, and appetite related hormones were tested. Dose-dependent relation was observed on oat β-glucan doses and body weight change, average energy intake, total cholesterol, HDL cholesterol,
plasma neural peptide Y, arcuate neural peptide Y mRNA, and arcuate neural peptide Y receptor 2 mRNA level. Oat β-glucan helped to increase plasma peptide Y-Y and intestine peptide Y-Y expression in obesity mice [99].

**Bauhinia variegata**

The ethanol and aqueous extracts of the root of *B. variegata* (200 and 400 mg/kg body weight) in rats, showed significant reduction (P ≥ 0.01) in cholesterol and significant reduction (P ≥ 0.01) in triglyceride level. The VLDL level was also significantly (P ≥ 0.05) reduced, with a significant increase in HDL [100]. The anti-hyperlipidemic activity of fractions of total methanol extract of leaves of *Bauhinia variegata* was investigated against Triton WR-1339 induced hyperlipidemia in rats. Fractions were administered at a dose of 100mg/kg orally. Butanol fraction showed significant reduction (p<0.05) in serum cholesterol, triglyceride, LDL, VLDL and increase in HDL level in comparison with standard drug fenofibrate (p<0.05) [101].

The antiobesity effect of methanolic extract of stem and root barks of *Bauhinia variegata* was examined in female rats fed with hypercaloric diet. The methanolic plant extract (200 and 400 mg/kg) exhibited a significant hypolipidemic effect with a reduction in the feed intake and body weight. Treatment of obese animals with the methanolic extract of *B. variegata* exhibited an increased brain serotonin level and high density lipoprotein with a concomitant decrease in total cholesterol, triglycerides and low density lipoprotein. Thus the antiobesity activity of methanolic extract of *B. variegata* could be attributed to tendency of the extract to reduce lipid profile and elicit the brain serotonin level[102].

**Bellis perennis**

The methanolic extract and its saponin fraction (methanol-eluted fraction) of the flowers of *Bellis perennis* were found to suppress serum triglyceride elevation in olive oil-treated mice. Among these saponins, perennisosides I and II showed inhibitory effects on serum triglyceride elevation at doses of 25-50 mg/kg orally [103]. As a result of hypolipidemic effect of saponin constituents isolated from the flowers of *Bellis perennis*, it also can be utilize as preventive drug in ischemic diseases and as an anti-obese remedy [104].

**Benincasa hispida**

Salad prepared by using 100gm of ash gourd (*Benincasa hispida*) and one gram of curry leaves (10 curry leaves) and five grams of skimmed milk powder (made into curd) and pepper and salt are added for taste. This salad was freshly prepared every day and given to hyperlipidemic diabetic patients in mid morning for a period of three months to find out the therapeutic effect of supplementation of ash gourd and curry leaves. Supplementation of ash gourd and curry leaves had significant hypoglycemic and hypolipidemic effect and it reduced the blood glucose level (both fasting and post prandial), within the period of three months [105].

**Brassica rapa**

The effect of different doses of turnip juice on blood lipid changes was studied in hypercholesterolemic rabbits. Extract was given in as 100, 200, 400 mg / kg body weight of the rabbits. The results showed that the turnip root extract can prevent the occurrence of atherosclerotic in hypercholesterolemic rabbits which may be due to flavonoids and vitamins contents [106].

Caulillexin C, indoleacetonitrile and arvelexin isolated from the root of *Brassica rapa* (at a concentration of 100 μg/ml) showed an inhibitory activity on human Acyl CoA: cholesterol transferase 2 (hACAT2) by 4.8±13.4%, 45.6±4.8% and 39.5±4.3%, respectively [107].

The influence of ethanolic extracts of *Brassica campestris* spp. rapa roots (EBR) on obesity was examined in imprinting control region (ICR) mice fed a high-fat diet (HFD) and in 3T3-L1 adipocytes. The molecular mechanism of the anti-obesity effect of EBR was investigated in 3T3-L1 adipocytes as well as in HFD-fed ICR mice. In the obese mouse model, both weight gain and epididymal fat accumulation were highly suppressed by the daily oral administration of 50 mg/kg EBR for 8 weeks, whereas the overall amount of food intake was not affected. EBR treatment induced the expression in white adipocytes of lipolysis-related genes, including beta3-adrenergic receptor (beta3-AR), hormone-sensitive lipase (HSL), adipose triglyceride lipase, and uncoupling protein 2. Furthermore, the activation of cyclic AMP-dependent protein kinase, HSL, and extracellular signal-regulated kinase was induced in EBR-treated 3T3-L1 cells. The lipolytic effect of EBR involved beta3-AR modulation, as inferred from the inhibition by the beta3-AR antagonist propranolol. Accordingly, EBR may have potential as a safe and effective anti-obesity agent via the inhibition of adipocyte lipid accumulation and the stimulation of beta3-AR-dependent lipolysis [108].

The role of turnip (*Brassica rapa*) on fructose-induced metabolic syndrome (MS) was studied in rats. MS was induced by administration of fructose as 10% solution in drinking water for 8 weeks. Three groups of rats were administered fructose as 10% solution in drinking water for 8 weeks. One served as fructose fed control while the remaining two groups were treated with metformin (10 mg/kg/day) and turnip (400 mg/kg/day) for two weeks. At the end of the experiment, blood samples were withdrawn for estimation of markers related to MS. Induction of MS was associated with increased body weight gain and elevated levels of blood glucose, MDA, nitric oxide, total triglycerides and total cholesterol. It also reduced levels of blood GSH and liver glycogen. *Brassica rapa* attenuated
most of the changes associated with MS. It reduced weight gain and blood glucose, MDA, nitric oxide, total triglycerides and total cholesterol. It also elevated blood GSH and liver glycogen [109].

**Caesalpinia crista**

The methanol extract significantly (P<0.05) decreased the levels of lipid peroxidation and significantly (P<0.05) increased the levels of GSH, superoxide dismutase and catalase, when administered at the doses of 50, 100, and 200 mg/kg body weight per day for 14 days in mice [110].

Aqueous extract in isoproterenol treated rats significantly decreased plasma total cholesterol, TC (87.45 ±1.5), triglycerides TG (91.59±2.12), LDL (67.79±1.80), VLDL (12.46±0.68), along with a significant increased in HDL level (18.67±0.72) when compared to untreated isoproterenol group. Ethanolic extract of *Caesalpinia Crista* + isoproterenol treated group showed decrease lipoproteins level except HDL of plasma. *Caesalpinia crista* aqueous extract treated group showed significantly decrement plasma TC (81.23±1.99), TG (73.82±1.34), LDL (60.34±1.56), VLDL (10.53±0.54), along with a significant (P<0.01) increased in HDL level (19.38±1.25) when compared to untreated isoproterenol group [111].

**Calotropis procera**

Serum lipid profile was measured in the diabetic rats. The extracts were significantly (p<0.001) decreased total cholesterol, triglycerides, phospholipids, LDL and VLDL cholesterol and significantly (p<0.001) increased HDL cholesterol [112].

**Capparis spinosa**

Leaves and flowers of *Capparis spinosa* were rich in either polyphenol or flavonoids, while roots are the poor ones. All extracts have anti lipid peroxidation and antioxidant effects with a dominance of flowers and leaves especially in the methanolic extracts (82.78 ± 2.64 and 80.94 ±1.57 respectively). Seeds exerted the acceptable effects followed by bud than roots [113].

**Capsicum annuum and Capsicum frutescens**

The anti-obesity effects of water extracts of seven *Capsicum annuum* L. varieties, Putgouche (Pca), Oyee gochu (Oca), Kwari putgouche (Kca), Green pepper (Gca), Yellow paprika (Yca), Red paprika (Rca) and Cheongyang gochu (Cca), were examined through the evaluation of lipoprotein lipase (LPL) mRNA expression level in 3T3-L1 cells (mouse pre-adipocytes). After capsaicin elimination by chloroform defatting, freeze-dried powder of Cca was treated to 3T3-L1 cells and anti-obesity effects were examined by determining the LPL mRNA level using the RT-PCR method. Of the primary fractions, only proven fractions underwent secondary and tertiary re-fractionating to determine anti-obesity effects. From seven different *Capsicum annuum*, there was a significant decrease of the LPL mRNA expression level of 50.9% in Cca treatment compared to the control group. A significant decrease of the LPL mRNA expression level was shown in primary fractions (Fr 5 (36.2% decrease) and 6 (30.5% decrease)) of the Cca water extracts. Due to the impurities checked by UPLC chromatography, Fr 5 and 6 were re-fractionated to determine the LPL mRNA expression level. Treatment of Fr 6-6 (35.8% decrease) and Fr 5-6 (35.3% decrease) showed a significant decrease in the LPL mRNA expression level. When analyzed using UPLC, major compounds of Fr 6-6 and Fr 5-6 were very similar. Subsequently, Fr 6-6 and Fr 5-6 were re-fractionated to isolate the major peak for structure elucidation. Treatment of Fr 5-6-1 (26.6% decrease) and Fr 6-6-1 (29.7% decrease) showed a significant decrease in the LPL mRNA expression level [114].

**Carum carvi**

The efficacy of different doses of dietary Carum carvi on tissue lipid peroxidation (LPO) and antioxidant profile in rat colon carcinogenesis was studied. To induce colon cancer, rats were given a weekly subcutaneous injection of 1,2-dimethylhydrazine (DMH) at a dose of 20 mg/kg bw for the first 15 weeks. Caraway was supplemented every day orally at doses of 30, 60 and 90 mg/kg for the total period of 30 weeks. The results showed diminished levels of intestinal, colonic and caecal LPO products, such as conjugated dienes (CD), lipid hydroperoxides (LOOH) and thiobarbituric acid reactive substances (TBARS) [115].

The hypolipidemic effect of aqueous extract of Carum carvi seeds (60 mg/kg of body weight for eight weeks) was investigated in diet induced hyperlipidemia in rats. Carum carvi and simvastatin significantly decreased lipids levels in rats. Carum carvi extract reduced lipid levels more effectively than the simvastatin. Carum carvi constituents, especially flavonoids and carvone have strong anti-oxidant activity which might be involved in hypolipidemia [116].

Oral administration of caraway to rats, 1g/kg body weight, daily caused a significant decrease in blood glucose level (p=0.001) and alleviated their body weight loss (p = 0.037). Furthermore, it caused significant decrease in total cholesterol (p = 0.036), and low-density lipoprotein cholesterol levels (p = 0.001) compared with the diabetic control rats, and with no significant changes in triglyceride and high-density lipoprotein cholesterol levels were recorded [117].

The effect of single and repeated oral administration of the aqueous extract of Carum carvi fruits at a dose of (20mg/kg) on lipid metabolism was studied in normal and streptozotocin-induced diabetic rats (STZ). After a single oral administration, Carum carvi extract produced a significant decrease on triglycerides levels in normal rats (p<0.05). In STZ diabetic rats, cholesterol levels were decreased significantly 6h after Carum carvi treatment (p<0.05). On the other hand, repeated oral administration of
Carum carvi extract exhibited a significant hypo-triglyceridemic and hypo-cholesterolemic activities in both normal (p<0.01) and STZ diabetic rats (p<0.001), 15 days after Carum carvi treatment [117].

**Carthamus tinctorius**

The effect of the extracts from safflower was investigated on cholesterol metabolism in high cholesterol fed rats. After treatment for 14 and 30 days, a significant reduction in total cholesterol and total cholesterol/HDL-cholesterol and a significant induction in HDL-cholesterol were observed in the hypercholesterolemic rats treated with the dichloromethane extract. Higher expression of SRBI and ABCA1 in the liver of the control group was observed after 4 weeks whereas no significant difference in the expression level of SRBI and ABCA1 was found in groups treated with extract after 2 and 4 weeks. The authors suggested that the expression of SRBI and ABCA1 mRNA may not be regulated by the crude extract of safflower, which may not in part explain the decrease in HDL-cholesterol and gene encoding enzymes of the cholesterol biosynthetic pathway [119].

The inhibitory effects of defatted safflower seed extract (SSE) and serotonin derivatives (N-p-coumaroyl serotonin and N-feruloyl serotonin, CS+FS), were evaluated on hypercholesterolemia and atherosclerosis, using Pulse wave velocity (PWV) in Kurosawa and Kusanagi-hypercholesterolemic rabbits. The atherosclerotic lesioned area in the aorta was significantly reduced in the SSE and CS+FS groups, without significant changes in serum cholesterol and triglyceride levels among the three groups after supplementation. Local PWV (LPWV) in the middle thoracic and distal abdominal aortas was significantly smaller in the SSE and CS+FS groups than in the control group. PWV in the entire aorta was also significantly lower in the SSE and CS+FS groups, compared with that in the control group. Pressure-strain elastic modulus, an index of wall distensibility, was significantly lower in the middle thoracic and middle abdominal aortas in the SSE and CS+FS groups than in the control group. Wall thickness was also significantly smaller in the middle thoracic aorta in the SSE and CS+FS groups compared with that in the control group [120].

**Casuarina equisetifolia**

The effect of *Casuarina equisetifolia* bark incorporated into rat feed at 10-40% on the lipid profiles and blood sugar of albino rats was investigated. The parameters studied were triacylglycerol (TGL), total cholesterol (TC), total lipid (TL), phospholipids (PHOS), high-density lipoprotein (HDL) and random blood sugar (RBS). There was no significant change (P>0.05) in the TGL levels of all the rats, including the control, as they all range between 0.18-0.22 (mg/dl). The effects on TC and TL were irregular as they did not display any dose dependence. The mean plasma PHOS levels did not change significantly (P>0.05) between the control and the rats fed on 10% feed (0.19±0.00 vs 0.18±0.00 mg/dl), but was significantly lowered (P<0.05) at 20-40% feed content. The mean HDL level rose, although insignificantly (P>0.05) with the percentage contents of the bark in the feeds; by implication, the low-density lipoprotein (LDL) was decreasing with the increase in the bark contents of the feeds. The RBS also decreased as the percentage bark contents of the feeds increased, indication that it could have anti-diabetic properties [121].

The effect of extracts of *Casuarina equisetifolia* bark on serum lipid profile, total cholesterol, triglycerides, low density, very low density and high density lipoprotein was evaluated in the diabetic and non diabetic rats. There was significant reduction in total cholesterol, LDL cholesterol, VLDL cholesterol and improvement in HDL cholesterol in diabetic rats [122].

**Plant with Hemostatic, fibrinoloytic or anticoagulant effects**

**Achillea santolina**

*Achillea santolina* crude extract induced dose-dependently inhibition in *in vitro* ADP and collagen-induced human platelet aggregation (maximal inhibition was 34.4 ± 2.9% and 78.3 ± 2.5 % respectively). This effect was mostly exerted by diethylester extract. Chloroform and ethyl acetate extracts had about half the effect, and water extract was devoid of antiaggregant effect. However, when *Achillea Santolina* extracts given to rats for 10 days (10 mg/kg/day), they produced insignificant decline in the thrombus weight [123].

**Allium cepa**

Both raw onions and the essential oil increased fibrinolysis in rabbits and humans. An increase in coagulation time was also observed in rabbits. *Allium cepa* inhibited platelet aggregation *in vitro* and *in vivo*. An aqueous extract of *Allium cepa* inhibited diphosphate, epinephrine, arachidonic acid, adenosine, and collagen induced platelet aggregation *in vitro*. Essential oil, a butanol and chloroform extract inhibited platelet aggregation in rabbits. Chloroform, ethanol, butanol extract and the essential oil 10–60 μg/ml inhibited aggregation of human platelets *in vitro* by decreasing thromboxane synthesis [124-130]. Sulfur compounds of onion oil also inhibited the formation of thromboxanes and the action of platelet activating factor (PAF) [131, 132].

The bulb juice exerted fibrinolytic effects in rabbits. The essential oil administered by gastric intubation to the rabbits at a dose of 2.0 gm/kg for 3 months, decreased fibrinolytic activity. Butanol extract and ethanol soluble fractions of the bulb (20.0 microliters) inhibited ADP-induced aggregation of platelets in human and rabbit via inhibition of thromboxane synthesis. The essential oil, at concentrations of 10 to 30 mcg/ml, produced strong antiplatelet in human adults vs ADP-induced aggregation.
Allium sativum
Garlic inhibited platelet aggregation in both in vitro and in vivo studies. A water, chloroform, or methanol extract of the drug inhibited collagen-, ADP-, arachidonic acid-, epinephrine-, and thrombin-induced platelet aggregation in vitro [134-139].

As appeared in experimental animals and clinical studies, garlic, ether extract and garlic juice and its constituents decreased cholesterol and fibrinogen, increased tissue plasminogen activator activity, increase fibrinolytic activity and blood coagulation time, and decrease in thrombocyte aggregation in blood [139-148].

Apium graveolens
Apigenin from Apium graveolens exhibited potent antiplatelet activity in vitro, inhibiting the aggregation of rabbit platelet induced by collagen, ADP, arachidonic acid and platelet aggregation factor, but not that induced by thrombin or ionophore A23187 [149].

Arachis hypogaea
There is a haemostatic principle in the peanut flour, which is said to improve the condition of haemophiliacs. It contained a protease inhibitor which act on the fibrinolytic system, primarily as an antiplasmin [150].

Aristolochia maurorum
The methanolic extracts, the acidic fractions of aerial and root parts, and the three identified compounds (aristolochic acid I, aristolochic acid II and aristolochic acid IIIa) were evaluated using an automatic platelet aggregometer and coagulation tracer (APACT 2). Pure compounds and aristolochic acid standard were tested at two concentrations, 0.20 and 0.40 mg/mL on both phase I (adhesion of platelet) and phase II (platelet aggregation), while the methanolic extracts and the acidic fractions were tested at 4.4 mg/mL. Methanolic extracts of aerial and roots parts, in addition to acidic fractions, showed 100% activity at 4.4 mg/mL. Also, 100% inhibition of platelet aggregation has been noted with aristolochic acid standard and a mixture consisting of 38% aristolochic acid I and 58% aristolochic acid II. At 0.40 mg/mL, aristolochic acid I and II exhibited 100% inhibition of platelet aggregation. 0.20 mg/ml aristolochic acid I selectively inhibited phase II with 100% activity and phase I with 39.5% inhibition while aristolochic acid II selectively inhibited phase I (adhesion) with 100% inhibition, and with less affinity towards phase II, inducing 75.8% inhibition. At 0.20 mg/ml, aristolochic acid IIIa exhibited 100% inhibition of the both phases. At 0.40 mg/ml aristolochic acid IIIa showed 85.3% and 100% inhibition of phase I and phase II, respectively (151). Both aristolochic acids, I and II, possessed good antithrombin activity [152-153].

Asclepias curassavica
The latex enzyme fraction of Asclepias curassavica exhibited strong proteolytic activity when compared to trypsin and exerted pro-coagulant action by reducing plasma clotting time from 195 to 58s whereas trypsin reduced clotting time marginally from 195 to 155s. The pro-coagulant activity of this enzyme fraction was exerted by selectively hydrolyzing A alpha and B beta subunits of fibrinogen to form fibrin clot when pure fibrinogen was used as substrate as assessed by fibrinogen-agarose plate method and fibrinogen polymerization assay. The electrophoretic pattern of latex enzyme fraction-induced fibrin clot was very much similar to that of thrombin-induced fibrin clot and mimic thrombin like action. The proteolytic activity including thrombin like activity of Asclepias curassavica latex enzyme fraction was completely inhibited by iodoaceticacid [154-156]. Cysteine proteases from Asclepias curassavica latex exhibited strong pro-coagulant action [157].

Brassica rapa
Crude extract and fractions of Brassica rapa was screened against human platelet aggregation induced by two different aggregating agents and further delineated their underlying signal transduction pathways. Furthermore, Brassica rapa was screened for the presence of calcium channel blocking potential. The results showed that Brassica rapa blocked calcium channel opening as indicated by its effects on KCl-induced contraction in guinea pig ileum and this activity was distributed into various fraction of Brassica rapa except ethyl acetate fraction which did not show any significant calcium channel blocking activity. Platelet aggregation induced by arachidonic acid (AA), platelet activating factor (PAF) and agonists of protein kinase C (PKC) and inositol triphosphate (IP3) was inhibited by various fractions of Brassica rapa with different potencies, suggesting that phyto compounds responsible for these effects are differentially concentrated in various fractions [158].

Calotropis procera
The proteins derived from the latex (LP) of Calotropis procera were evaluated for their efficacy in maintaining coagulation homeostasis in sepsis. Intraperitoneal injection of LP markedly reduced the procoagulation and thrombocytopenia observed in mice infected with Salmonella; while in normal mice, LP produced a procoagulant effect. In order to understand its mechanism of action, the LP was subjected to ion-exchange chromatography, and the three subfractions (LPPI, LPPII, and LPPIII) thus obtained were tested for their proteolytic effect and thrombin- and plasmin-like activities in vitro. Of the three subfractions tested, LPPII and LPPIII exhibited proteolytic effect on azocasein and exhibited procoagulant effect on human plasma in a concentration-dependent manner. Like trypsin and plasmin, these subfractions
produced both fibrinogenolytic and fibrinolytic effects that were mediated through the hydrolysis of the Aα, Bβ, and γ chains of fibrinogen and α-polymer and γ-dimer of fibrin clot, respectively [159].

**Canna indica**

The hemostatic effect of *Canna indica* was evaluated in mice. The bleeding time (BT), clotting time (CT) and the permeability of abdominal capillary were measured respectively. The results showed that *Canna indica* significantly reduce the BT, CT and the permeability of abdominal capillary [160].

**Capparis spinosa**

When stachydrine was given to dogs, rabbits and rats, it quickened the coagulation of blood [161].

**Capsicum annuum** and **Capsicum frutescens**

*Capsicum annuum* contained an anticoagulant that helps prevent the blood clots that can cause heart attacks [162].

An *in-vitro* thrombolytic model was used to check the clot lysis effect of *Capsicum frutescens*. A combination of honey and *Capsicum frutescens* was also investigated along with streptokinase as a positive control and water as a negative control. By using an *in vitro* thrombolytic model *Capsicum frutescens* and a combination of honey and *Capsicum frutescens* showed 57.40% and 44.54% clot lysis effect respectively [163].

Capsaicin also inhibited platelet aggregation and the activity of clotting factors VIII and IX, a property which reduce the incidence of cardiovascular diseases [164-165].

**Carthamus tinctorius**

The effects of The carthamins yellow (CY) was studied on a blood stasis model, which was obtained by placing rats in ice-cold water during the time interval between two injections of epinephrine. The results demonstrated that CY significantly decreased the whole blood viscosity, plasma viscosity, and erythrocyte aggregation index, which were increased in the blood stasis model. Hematocrit and platelet aggregation were reduced, while prothrombin time was delayed with increasing doses of CY [166].

Safflower yellow inhibited the PAF induced washed platelet aggregation and 5-HT release in a dose dependent manner. When the PAF was 2.0×10⁹ mol/l, the inhibition rate of platelet aggregation was 26.2%, 41.3%, 58.1%, 81.2%, and the inhibition rate of 5-HT release was 3.7%, 11.9%, 29.9% and 54.4% after treatment with safflower yellow at 0.21, 0.42, 0.85 and 1.69 g/l, respectively. Accordingly, safflower yellow can inhibit the PAF induced platelet aggregation, 5-HT release by platelets and elevation of free calcium in platelets [167]. Intraportaline administration of 30 mg of an aqueous extract of the flowers to mice reduced platelet aggregation induced by adenosine diphosphate (ADP) by 65% in γ-irradiated animals [168].

**Celosia cristata**

Five days after mice were given decoction of Flos *Celosiae cristatae* with the dosage of 17g/kg,they were compared with a control group. It emerged that the bleeding time(BT) was shortened greatly (P0.01). Seven days after rabbits were given the same decoction with the dosage of 1.7g/kg, it was found that the coagulation time (CT), prothrombin time (PT) and plasma recovery (PRT) were shortened (P0.05) ,and the euglobulin lysis time (ELT) was markedly shortened(P0.01)in comparison with control [169].

**CONCLUSION**

This paper reviewed the hypolipidemic, fibrinolytic anti platelet aggregating and antioxidant effects of the medicinal plants to open the door for their clinical uses as a result of efficacy and safety.

**REFERENCES**

1. Al-Snafi AE. Central nervous and endocrine effects of Myristica fragrans. 4th Arabic Conf. of Medicinal plants, Thamar Univ, Yemen 1999, 111-121.


44. Al-Snafi AE. The chemical constituents and pharmacological effects of Chenopodium album- An overview. International J of Pharmacological Screening Methods, 5(1), 2015, 10-17.
84. Le QT and Elliott WJ. Dose response relationship of blood pressure and serum cholesterol to 3-n-butylphthalide, a component of celery oil. Clin Res, 39, 1991, 750A


105. Amirhavenei M and Priya V. Hypoglycemic and hypolipidemic effect of ash gourd (Benincasa hispida) and curry leaves (Murraya koenigii). International Journal of Current Research, 3(8), 2011, 37-42.


130. Vanderhoek JY, Makheja AN and Bailey JM. Inhibition of fatty acid oxygenases by onion and garlic oils. Evidence for the mechanism by which these oils inhibit platelet aggregation. *Biochemical Pharmacology*, 29, 1980, 3169-3173.


