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Effect of *Alhagi Maurorum* or *Gloularia Alypum* on lipid profile of experimentally induced hypercholesteremic rats and on blood pressure of experimentally induced hypertensive rats

Ghazala O. Othman [1], Khalid Elfsei [2], Aisha M. Alfituri [1], Abdelhakim A.G. Ali [3], Ashref El-Buri [1] Abdulkader H. El-Debanin [1], Fathi M. Sherif [4] and Awad G. Abdellatif [1 *]

[1] Department of Pharmacology, Faculty of Medicine, [2] Faculty of Pharmacy, University of Benghazi, Benghazi, Libya
[3] Faculty of Pharmacy, University of Alexandria, Alexandria, Egypt, [4] Department of Pharmacology, Faculty of Pharmacy, University of Tripoli, Tripoli, Libya
[*]Author to whom correspondence should be addressed

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Abstract: In some countries, a high percentage of the population relies on traditional plants for treating certain diseases. This study aimed to investigate the effect of G. alypum extract (GAE) and Alhagj marorum extract (AME) on lipid profiles in experimentally induced hypercholesteremic rats and on the blood pressure of experimentally induced hypertensive rats. Male Wistar rats weighing 200-300 g were divided into five groups: group one received a normal diet (negative control), group two received a high lipid diet containing coconut oil (10 g/kg/day), cholesterol (4 g/kg/day) and cholic acid (0.20 g/kg/day) (positive control), group three received a high lipid diet together with clofibrate (50 mg/kg/day), group four received a high lipid diet together with AME (200 mg/kg/day) and group five received GAE (200 mg/kg/day). The experiment continued for two weeks, then the rats were sacrificed and blood samples were collected to estimate of cholesterol, triglycerides, high-density lipoprotein and low-density lipoprotein. To induce hypertension, rats were divided into two groups (n=8 in each group). Group one received normal saline (control) and group two received dexamethasone (0.40 mg/kg, i.p.) for seven consecutive days. Later, the rats were anesthetized using thiopental and the carotid artery was cannulated for recording blood pressure. AME (40 mg/kg) or GAE (40 mg/kg) were injected through a cannula placed into the internal jugular vein at a dose volume of 0.1 ml. Systolic and diastolic blood pressure were measured before and after plant extract administration. The results showed that clofibrate GAE extract and ANE extract significantly decreased cholesterol, triglycerides, low-density lipoprotein and high-density lipoprotein compared to high-lipid diet-treated rats. Data also indicated that administration of GAE or AME extract significantly reduced systolic and diastolic blood pressure in experimentally induced hypertensive rats. In conclusion, GAE and AME have antihyperlipidemic and antihypertensive activities and further investigation is needed to clarify the mechanism of these effects.

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Introduction

Traditional medicine has remained the most affordable and easily accessible source of treatment in the primary healthcare system among communities unable to get modern medication [1]. According to a WHO report, about 80.0% of the world's population, especially in the developing world, relies on traditional medicines for curing different health disorders and diseases [2]. The World Health Organization (WHO) reported that approximately 21,000 plant species have the ability to be used as medicines or medicinal plants. According to available data, more than three-quarters of the worldwide population relies primarily on plants and plant extracts for their health-care needs. And over 30.0% of all plant species have been used for medical purposes at some point in their history [3]. It has been estimated that two-thirds of all plant species on the planet have medicinal properties [4]. Medicinal plants are a significant source of molecules with medicinal properties. Because of the nature of their phytochemical constituents, medicinal plants are valuable for treating human diseases and play an important role in healing. Natural and unique medicinal plants are used to treat various diseases and illnesses as well as produce wealth [5].

Medicinal chemists use the classical or traditional method to change bioactive compounds found in natural sources. The active components in most existing medications come from these natural compounds [6]. Some of the plants have been found to possess significant antibacterial, antifungal, anticancer, antidiuretic, anti-inflammatory, and anti-diabetic properties [7, 8]. Hypercholesterolemia is a condition characterized by very high levels of cholesterol in the blood [9]. Hypercholesterolemia is a problem faced by many societies and a cause of concern for the health professionals [10]. The continuous ingestion of high amounts of fat seems to be directly related to hyperlipidemia in humans. It has consequently been tried to induce hyperlipidemia in laboratory animals, in order to better understand the relationship between disorders in cholesterol metabolism and atherogenesis and to test possible treatments for the reduction of circulating cholesterol levels [11]. Hyperlipidemia is considered one of the most important risk factors for cardiovascular disease. Its major role in the pathogenesis of atherosclerosis has been implicated in several clinical and epidemiological studies [12]. Dietary cholesterol and aging are major risk factors that accelerate the oxidation process for developing hypercholesterolemia; they promote development of obesity and atherosclerosis which are associated with chronic metabolic inflammation [13]. It is established that long-term consumption of a high-fat diet accelerates the development of coronary heart disease (CHD). Therapeutic agents that control the levels of serum cholesterol have proven to be effective in the treatment of CHD [14, 15]. Dietary cholesterol can increase the level of serum cholesterol to levels that can place an individual at increased risk for the development or exacerbation of atherosclerosis [16, 17]. CHD increases dramatically as the plasma concentration of LDL cholesterol increases [6]. Consequently, the development of methods for lowering LDL cholesterol levels has become a major focus of medical research. According to the estimate of the WHO, hypertension is a highly prevalent risk factor for the development of cardiovascular disease, affecting 1.13 billion people in the world [18]. Cardiovascular diseases (CVDs) kill 17.9 million people per year, and by 2030, it is predicted that more than 22.2 million people will die annually from CVD [19]. Hypertension, along with dyslipidemia, is known as one of the major risk factors for CVD. Previous research has shown the coexistence of abnormalities in the lipid profile and hypertension in patients with coronary heart disease [20]. Dyslipidemia is more common in untreated hypertensive than in normotensive and lipid levels increase as BP increases [4, 5]. Though no specific pattern of dyslipidemia has been consistently reported among hypertensive individuals, many studies have shown that total cholesterol (TC), triglycerides (TG) and virtually all fractions of lipoproteins tend to be more frequently abnormal among hypertensive patients than in the general population [21-24]. It is something worth searching for a plant that treats

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high blood pressure and a high lipid profile at the same time. Therefore, this study aims to investigate the effect of GA and AM extracts in experimentally induced hypertensive and hyperlipidemic animals.

Materials and methods

Experimental animals: In this study, male Albino Wister rats weighing 250-300 gm were used. Rats were obtained from the local Central Animal House, University of Benghazi, Benghazi, Libya. Rats were kept in standard laboratory conditions (12 hours of light, 12 hours of darkness, and 22±2.0^{0}C). The rats were fed standard commercial laboratory chow and were allowed to adapt to new housing environment conditions for one week before treatment.

Preparation of plant extract: Aerial parts of the plant were collected from the Gabal al Khater area and identified by the Department of Botany, Faculty of Science, University of Benghazi, Benghazi, Libya. The plant parts were washed, dried, powdered and extracted with different solvents, starting with non-polar ones and ending with polar ones (petroleum ether, chloroform, ethyl acetate, ethanol and water using the Soxhlet apparatus). The ethanolic extract was used during experiments.

Effect of camel thorn on the serum lipid level: Rats were divided into five groups, the first group received a normal diet and water *ad libitum* (negative control), the second group received a high-lipid diet containing coconut oil (10 g/kg/day), cholesterol (4 g/kg/day) and cholic acid (0.2 g/kg/day) (positive control), the third group received a high-lipid diet together with clofibrate (50 mg/kg/day) in water; the fourth group received a high-lipid diet together with AME (200 mg/kg/day) in water and the fifth group received GAE (200 mg/kg/day) in water. The experiment continued for two weeks, then the animals were sacrificed for blood collection and estimation of cholesterol, triglycerides (TG), high-density lipoproteins (HDL) and low-density lipoproteins (LDL) [25].

Effect of GAE and AME extracts on blood pressure of hypertensive rats: To induce hypertension, rats were divided into two groups, each of eight rats, the first group received normal saline (control), the second group received dexamethasone (0.4 mg/kg i.p.) and for seven consecutive days later, they were anaesthetized using thiopental. The carotid artery was cannulated and a pressure transducer displayed on the Washington 400 MD was used to record blood pressure. AME (40 mg/kg) or GAE alypum (40 mg/kg) were injected through a cannula placed into the internal jugular vein in a dose volume of 0.1 ml. Systolic and diastolic blood pressure were measured before and after plant extract administration.

Statistical analysis: Data were expressed by using descriptive analysis as means±standard error of the mean. A test of significance was carried out using a one-way analysis of variance (ANOVA). The degree of significance was determined by using Less Significant Difference (LSD) and a student *t*-test for the dependent sample. A $p<0.05$ was considered significant.

Results

Data presented in **Table 1** showed that the level of cholesterol was significantly decreased ($p<0.05$) in the animals that received, high lipid diet plus clofibrate, high lipid diet plus GAE (200 mg/kg/day) and a high lipid diet plus AME (200 mg/kg/day), respectively, as compared to the animal that received high-lipid diet alone. The level of TG was significantly ($p<0.05$) decreased in animals that received a high-lipid diet plus GAE and a high lipid diet plus AME, respectively, as compared to the control group, and the effect of the clofibrate-treated group on TG level was more pronounced.

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The low-density lipoprotein (LDL) and high-density lipoprotein (HDL) were significantly lower ($p<0.05$) in all groups as compared to the group receiving the high-lipid diet alone. The ratios of HDL/LDL in the control group, the high-lipid diet, the high lipid diet plus clofibrate, the high lipid diet plus GAE, and the high-lipid diet plus AME were 3.4, 1.4, 1.41, 3.4 and 3.8, respectively. Data shows that this ratio was significantly higher ($p<0.05$) in the control group (3.4), the high lipid diet plus GAE treated animals (3.4) and the group receiving high lipid diet plus AME (2.8), respectively, as compared to the high lipid group (1.41) and high lipid diet plus clofibrate treated animals (1.41).

Table 1: Lipid profile in high lipid diet, high lipid diet plus clofibrate, high lipid diet plus G. alypum extract and high lipid diet plus alhagi marorum extract treated rats

Treatment	Cholesterol	Triglycerides	LDL	HDL	HDL/LDL
Control	40±2.8	38±3.0	10.5±0.4	36±3.1	3.4[j]
High lipid diet	146±7.8[a]	220±17.0[c]	60±6.1[f]	84±4.6[i]	1.4
High lipid diet plus clofibrate	65±6.1[b]	50±3.5	34±3.2[g]	48±3.5	1.41
High lipid diet plus G. alypum (200 mg/kg/day)	70±5.7[b]	112±9.0[d]	18±1.5[h]	62±5.2	3.4[j]
High lipid diet plus alhagi marorum (200 mg/kg/day)	63±5.4[b]	177±8.0[e]	17±1.2[h]	48.8±3.5	2.8[j]

[a]Significantly higher as compared to all corresponding groups ($p<0.05$), [b]Significantly higher than control ($p<0.05$), [c]Significantly higher from all the corresponding groups ($p<0.05$), [d]Significantly higher than control and the group received high lipid diet plus clofibrate ($p<0.05$), [e]Significantly higher than corresponding control and group received high lipid diet ($p<0.05$), [f]Significantly higher than all other corresponding groups ($p<0.05$), [g]Significantly higher than all other corresponding groups ($p<0.05$), [h]Significantly higher than control group ($p<0.05$), [i]Significantly higher than all groups ($p<0.05$). [j]Significantly higher than a high lipid diet and the group received a high lipid diet plus clofibrate ($p<0.05$).

Data in **Table 2**, showed the systolic blood pressure (BP) before and after treatment with dexamethasone (0.4 mg/kg), daily was 115±4.0 and 165±7.0. This indicates a significant increase in systolic blood pressure due to the administration of dexamethasone ($p<0.05$). Data in **Table 2,** showed that treatment of rats with dexamethasone (0.40 mg/kg/day) causes a significant increase in systolic and diastolic blood pressure ($p<0.05$). The systolic blood pressure before and after the administration of dexamethasone were 115±4.0 and 165±7.0 mmHg, respectively, whereas the diastolic blood pressure before and after the administration of dexamethasone was 65±3.0 and 116±6.0 mmHg, respectively. Results of **Table 3** indicated that administration of GAE (40 mg/kg, IV) or AME (40 mg/kg, IV), significantly ($p<0.05$) lowers the systolic and diastolic blood pressure.

Table 2: Systolic and diastolic blood pressure before and seven weeks after treatment with dexamethasone

Blood pressure	Before administration of dexamethasone (Control)	Seven weeks after dexamethasone administration
Systolic	115±4.0	165±7.0*
Diastolic	065±3.0	116±6.0*

*Significantly higher as compared to the corresponding control ($p<0.05$)

Table 3: Effect of G. alypum extract and alhagi marorum on the systolic and diastolic pressure of experimentally induced hypertensive rats

		Treatment	
	Before treatment (control)	G. alypum extract	Alhagi Marorum extract
Systolic blood pressure	165±7.0	130±5.0*	120±5.0*
Diastolic blood pressure	116±6.0	71±4.0*	70±4.0*

*Significantly different from the control group ($p < 0.05$)

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As indicated in **Table 4**, the percentage of the decrease in systolic blood pressure was 27.27% and 21.21% after administration of GAE or AME, respectively. Whereas, the percentage of the decrease in diastolic blood pressure was 39.65% and 38.8% in the animal treated with GAE or AME. The decrease in diastolic blood pressure was more pronounced than the decrease in systolic BP.

Table 4: Effect of G. alypum extract and alhagi marorum extract on systolic and diastolic pressure of experimentally induced-hypertensive rats

Treatment	% of decrease in systolic blood pressure	% of decrease in diastolic blood pressure
G. alypum extract	27.27	39.65
Alhagi marorum extract	21.21	38.80

Discussion

Hyperlipidemia is considered one of the major risk factors contributing to the development of coronary heart disease. This is a medical condition where abnormally high levels of plasma lipids, including triglycerides, cholesterol, cholesterol esters, and phospholipids, are found in the blood. This medical condition is also called hypercholesterolemia or hyperlipoproteinemia [26]. LDL is often called the "bad cholesterol," which is produced by the liver and transported to different parts of the body like, muscles, tissues, organs, and the heart. The high LDL indicates an elevated level of cholesterol in the bloodstream and leads to a buildup of cholesterol in arteries, which increases the risk of heart disease. Moreover, it is evident that lowering LDL cholesterol reduces the risk of CVDs [27, 28]. The formation of atherosclerotic plaque involves the accumulation of LDL in the intima, the oxidation of LDL and the uptake of oxidized LDL by macrophage scavenger receptors, the influence of macrophages on foam cells, and the stabilization of plaque. Inflammatory cytokines are involved in all steps and make this process a chronic inflammatory disease [29-31]. Antihyperlipidemic drugs such as statins and fibrates are extensively used in the treatment of elevated plasma lipids. But these drugs are cursed with side effects. In the last few years, there has been a rapid growth in the use of medicinal plants, which is gaining popularity in developing and developed countries as it possesses minimal side effects. Medicinal plants carry various bioactive secondary metabolites and these metabolites are responsible for showing different properties useful for medicinal purposes [32, 33]. As presented in this present study, the levels of cholesterol, TG, LDL, and HDL in rats that received a diet rich in lipids were significantly decreased by GAE or AME, indicating the antihyperlipidemic activity of both plants. Several studies have shown that many medicinal plants have antihyperlipidemic activity in experimentally induced hyperlipidemia using a diet rich in lipids. Kalita et al. [32], revealed that 25 plant species found in northeast India have anti-hyperlipidemic properties. Various anatomical parts (leaf, flower, root, bark and whole plant) were useful for the treatment. Different bioactive compounds present in these plants are responsible for the anti-hyper-lipidemic activity. This study only describes a few of these precious plant species from northeast India that have antihyperlipidemic activity. The detailed study of these plant resources of NE India and the characterization of the bioactive compounds present in them can open the doors of pharmaceutical companies, and we will get better life-saving medicines in the future. Solanki and Jain [34]. observed that oral administration of the hydro-alcoholic extract of C. ternetea (roots and seeds) showed a significant reduction in serum TC, TG, VLDL, and LDL. Treatment with the extract also normalized the atherogenic index and the HDL/LDL ratio in diet-induced hyperlipidemic rats. Our data also indicated that GAE or AME normalized the HDL/LDL ratio in rats that received a diet rich in lipids; however, clofibrate failed to normalize the HDL/LDL ratio.

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Medicinal plants have always been considered a healthy source of treatment due to their therapeutic effect and safety. Different medicinal plant remedies were used to treat hyperlipidemia, it decreased blood lipids by many mechanisms, including inhibition of the expression of fatty acid synthase, decreasing free fatty acid release, inhibition of HMG-CoA reductase, increasing the fecal excretion of fat and cholesterol, inhibition of the activity of pancreatic lipase, and inhibition of cholesterol absorption [35-37]. Plants have hypolipidemic activity, which means they can significantly lower total lipid levels, total cholesterol levels, LDL levels, TG levels, and raise HDL levels. Demand is increasing in the world for the use of natural plants as medicine with hypoglycemic and hypolipidemic effects on patients. We should adopt a new approach to studying plant components that are phytochemically active and study their molecular interactions with diseases. The hypolipidemic activity that is present in most Medicinal plants is strongly associated with new drug development which will be used for high lipid profiles and cardiovascular diseases [38]. Medicinal plants are extensively used in traditional folk medicine. Hypertension, or high blood pressure, is a medical condition that accounts for 9.4 million deaths all over the world every year. High blood pressure is associated with the risk of cardiovascular diseases and many other serious health complications resulting from them, which is a major concern for morbidity and mortality in the health sector. The use of diuretics, angiotensin-converting enzyme inhibitors, beta-adrenergic receptor antagonists (beta blockers), alpha-adrenergic receptor antagonists (alpha-blockers), calcium channel blockers, etc. is not efficient enough to cure hypertension. Side effects from these medications cause intolerance, impaired disease control and therapy mismanagement. As a result, the approach to quenching new potent therapeutic compounds from medicinal plants is gaining attention [39, 40]. According to El-debani et al. [41], a 0.4 mg daily dose of dexamethasone for seven days was required to induce hypertension in rats experimentally. Findings in this study showed that treatment of rats with 0.4 mg/kg of dexamethasone, significantly increased systolic and diastolic blood pressure. Our results also showed that GAE or AME significantly decreased the systolic and diastolic blood pressure, and the percentage of the decrease in diastolic blood pressure was more pronounced than the decrease in systolic. The mechanism of these plants' antihypertensive activity is unknown, as many other plants have antihypertensive activity. Sultana and Asif [40] reported that many secondary metabolites in these medicinal plants, such as flavonoids, alkaloids, tannins, and terpenoids, have been found in vivo to have antihypertensive effects.

Conclusion: This study concludes that both GLE and AME may have antihyperlipidemic and antihypertensive effects and further studies are recommended to determine the mechanism behind these effects.

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