RESEARCH ARTICLE

Hypolipidemic Effect of *Portulaca oleracea* and *Salvia officinalis* Comparing to Atorvastatin in Rats

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ABSTRACT

Non-communicable diseases (NCD), mainly cardiovascular diseases, are considered the major reason of mortality universally. A high blood level of lipid, which also is known as hyperlipidemia, is mostly the main etiological factor in those diseases. Therefore, there is a persistent need to develop a strategy to cure this symptomless killer. Consequently, we aimed to investigate the effect of *Portulaca oleracea P. oleracea* and *Salvia officinalis* leaves ethanolic extract in mitigating hyperlipidemia in the rat. To achieve this aim, we divided 30 Wistar albino rats into 5 groups as follow; negative control group (-ve) received no treatment, positive control group (+ve) received 100mg/kg BW of triton, 1st treatment group (T1) received atorvastatin, 2nd treatment group (T2) received *P. oleracea* 200 mg/kg BW, 3rd treatment group (T3) received *S. officinalis* L. extract 200 mg/kg BW. All treatments were given orally. The results reveal that the tested plant extracts show significant hypolipidemic effect, which is statistically equal to that of the atorvastatin. In conclusion, this study suggests employing such herbal remedies to deal safely with hyperlipidemia instead of relying on chemical medicines.

Keywords: Atorvastatin, Hyperlipidemia, *Portulaca oleracea*, *Salvia officinalis,* Rats

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INTRODUCTION

Hyperlipidemia and more specifically hypercholesterolemia is characterized as one of the most riskiest sign of many lethal diseases such as cardiovascular diseases. According to the world health organization (WHO) during their Global Status Report on the non-communicable diseases, there was about 2.6 million case of death annually between 2008 to 2013 as a result of heart disease and stroke that resulted from hyperlipidemia. It is critically important to detect hyperlipidemia as early as possible to avoid the consequences.[1] It is confirmed that high level of high density lipoprotein (HDL) level protects against atherosclerosis, while high level of low-density lipoprotein (LDL) is a valid risk factor of atherosclerosis that is in turn a predisposing factor for cardio vascular diseases.[1,2] Therefor measuring the markers of hyperlipidemia including levels of total cholesterol, total triglycerides and LDL cholesterol is a routine test in clinics. In addition, the test includes measuring HDL as a good marker of healthy level of cholesterol. Hyperlipidemia is a poor health feature that is also connected to other conditions like type 2 diabetes, hypertension, atherosclerosis, coronary heart disease, cerebral vascular accidents, and metabolic syndrome.[1] At the cell level, the hyperlipidemia is a causative factor in increasing non enzymatic glycosylation that synchronizes with glucose oxidation. This resulted in high level of oxygen free radical production which is one of the risk factors of cardiac diseases.[3] Hypolipidemic agents such as synthetic drugs are very expensive and the treatment usually accompanied with high risk due to fatal side effects. For example, atorvastatin has been used to reduce the risk of NCD due to its hypolipidemic effect.[4] The mechanism by which the drug works is investigated to be through lowering cholesterol level which in turn enhance life span.[5,6] Nevertheless, atorvastatin has been showing deleterious side effects that limit its applications including muscular toxicity which ends up with therapy discontinuation.[7,8] In view of the above, studying of alternative approaches is been investigated, and one of the elected approaches is the plant remedies. *Portulaca oleracea* (*P. oleracea*)is traditionally used to treat lung, urinary tract, and gastrointestinal tract infections,[9] and this plant is considered to be safe as well.[10] In addition, *Salvia officinalis L.* (*S. officinalis*) has been used to rectify dyspepsia and inflammation.[11]

P. oleracea or as known as verdolaga, red root, or parsley is widely known herb for being used regularly in food recipes. Several studies attributed the medicinal features of the plant to its chemical composition. This includes alkaloides, flavonoids, terpenoides, organic acids such as oxalic acid, ω-3 and ω-6 fatty acids, and coumarins[12] but also as a traditional medicine

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for alleviating a wide spectrum of diseases. It is a well-known plant in the European Traditional Medicine. PA is mentioned by Dioscorides (40–90 CE,[9,13]). Recently many studies have been conducted to investigate the medicinal benefits of this plant. The researchers established that *P. oleracea* has an antioxidant, anti-bacterial, anti-hyperglycemia, anti-hyperlipidemia, and anti-proliferative functions,[12,14,15] but also as a traditional medicine for alleviating a wide spectrum of diseases. It is a well-known plant in the European Traditional Medicine. PA is mentioned by Dioscorides (40–90 CE). In addition, phenolic compounds of *P. oleracea* were found to have scavenging and antioxidant properties that were proven in vitro by inhibiting human low-density lipoprotein oxidation[16] 1-diphenyl-2-picrylhydrazyl (DPPH). Polyphenols delay lipid oxidative degradation to prevent food spoilage what makes it of essential value to the food Industry.[17,18] Similarly, flavonoids were found to function as free radical scavengers and antioxidants in other studies.[19]

S. officinalis as known as sage has been used in food recipe and has several medicinal features due to its chemical composition. Those include, alkaloids, saponins, phenolic compounds such as coumarins, flavonoids, and tannins, fatty acids and waxes.[20] Ethanolic and aqueous extracts of this plant are rich in flavonoids such as rosmarinic acid and phenolic compounds that include caffeic acid.[21]

According to the traditional claims that reported hypolipidemic function of *P. oleracea* and *S. officinalis* L., the proven antioxidants and free radical scavenging properties, and to produce relatively inexpensive and safe hypolipidemic therapy, we designed the present study. Herein we propose to evaluate those plants leaf extract effects in lowering the levels of bad cholesterol including LDL and increasing the good cholesterol that is the HDL in blood of hyperlipidemic rats.

MATERIALS AND METHODS

Animals

Wistar albino rats of both sexes of 150-225g body weight, were obtained from the animal house of the College of Veterinary Medicine , University of Al-Qadisiyah, Iraq. The animal were grouped and housed in polypropylene cages (38x 23x 10 cm) with not more than six animals per cage and maintained under standard laboratory conditions (room temperature 25+2^{o}C) with dark and light cycle (14/10 hour). They were allowed free access to standard dry pellet diet and water ad libitum. The rats were acclimatized to laboratory condition for 10 days before commencement of experiment.

Plants extraction

The dried leaves of *P. oleracea* and *S. officinalis* L. were obtained from the local market in Al-Diwanyia city, Iraq. Weight of about 100g of each plant by itself was exposed to extraction using 500mL ethanol (96%) in a Soxhlet apparatus for 48–72 hours. When the extraction was completed, the solvent was filtered and evaporated by Rotary evaporator. The percentage yields of the extracts were 26% and 34% for *P. oleracea* and *S. officinalis* L. respectively. The obtained *P. oleracea* and *S. officinalis* L. alcoholic extracts were stored at –4^{o}C until use. Each extract was suspended in distilled water to give 40mg of extract/ ml of the suspension and administered orally through stomach tube. The volume of the administrated extract was approximately 1 mL for each animal and according to its weight.

Experimental model for hyperlipidemia induced in albino rats

Hyperlipidemia was induced in Wistar albino rats by single intraperitoneal (ip) injection of freshly prepared solution of Triton-X-100 (100 mg/kg) in physiological saline solution after overnight fasting that lasted for 18 hrs.

Grouping of rats and experimental design

Thirty Wistar albino rats were randomly divided into five groups (6 rats each) and fed on standard rodents diet. The rats grouped into control negative (–ve) group received only the vehicle given orally. The other groups were injected with single dose of triton X100 (100 mg/kg ip) in physiological saline solution after 72 hrs of triton injection. Those groups were as follow; untreated control positive (+ve) , and 1st treatment group (T1) received standard atorvastatin (10 mg/kg BW) in 3 ml of normal saline daily, 2nd treatment group (T2) received *P. oleracea* 200 mg/kg BW, 3rd treatment group (T3) received *S. officinalis* L. extract 200 mg/kg BW. All treatments were given in stock solution by stomach tube along the period of the experiment. The study lasted for 7-day after inducing of the hyperlipidemia.

Blood collection

On the 8th day after the induction of hyperlipidemia, the blood was collected in test tubes by Retero-orbital sinus puncture method that was done under mild ether anesthesia. The collected samples were left for coagulation then centrifuged for 15 minutes at 3000rpm. Then serum samples were then collected into test tubes to analyze serum Total Cholesterol (TC), Triglycerides (TG), high density lipoprotein-cholesterol (HDL-C) that were measured by using ERBA diagnostic kits. In addition to measuring low density lipoprotein-cholesterol (LDL-C) and very low density lipoprotein-cholesterol (VLDL-C) that were calculated according to Friedewald formula as follow:

VLDL-C (mg/dl) = TG ÷ 5

LDL-C (mg/dl) = TC – (HDL + VLDL).

Moreover, Atherogenic index (AI) was calculated according to the formula given below:

AI = TC – total serum HDL-C/total serum HDL-C

Finally, the coronary artery risk index (CRI) was calculated according to the formula given below:

CRI = TC/HDL-C

Statistical Analysis

The obtained results were analyzed using statistical package for the social sciences (SPSS) program (version 23) and expressed as mean and standard error (SE). Statistical significance

($p < 0.05$) among the groups was determined by one-way ANOVA with least significant differences (LSD).

RESULTS

The results of the current study showed that oral gavage of triton to the +ve control group showed significantly (P<0.05) high levels of total cholesterol (TC), triglycerides (TG), low density lipoprotein- cholesterol (LDL-C), atherogenic index (AI), and the coronary artery risk index (CRI) compared to the -ve control as well as the T1, T2, and T3 groups as shown in Figures 1 to 7. The results also showed the unwanted significant (P < 0.0.5) effect of triton in lowering the high density lipoprotein- cholesterol (HDL-C) level (Figure 3). The results also revealed the positive effects of the atorvastatin, *P. Oleracea*, and *S. Officinalis* ethanolic extracts in curing the hyperlipidemic effect of triton in the +ve group, as those groups showed a significant respond to the plant extracts treatments (Figures 1 to 7).

DISCUSSION

An estimation of 12 million people per year die around the world due to NCDs and more specifically the cardiovascular

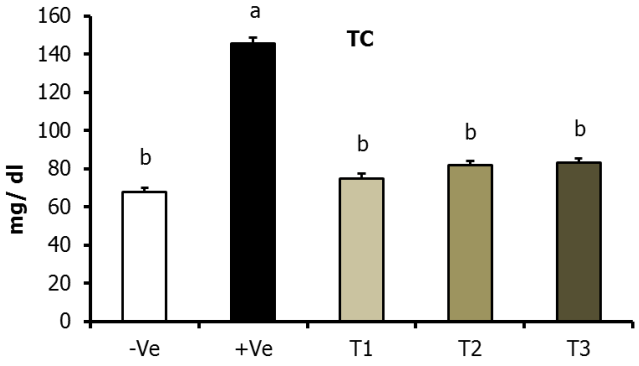

Figure 1: TC levels in blood measured in mg/dl in the groups of rats, n = 6 rats per group. Means with different letters are significantly different at p < 0.05.

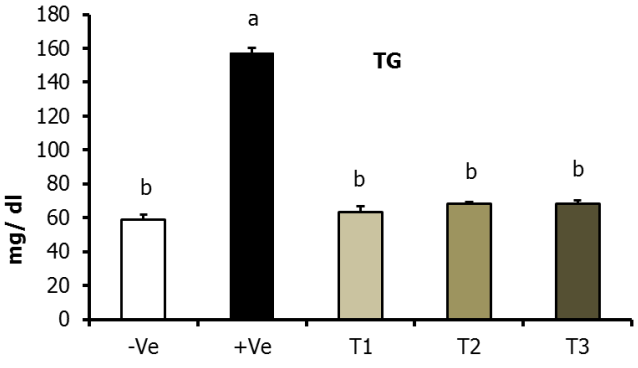

Figure 2: TG levels in blood measured in mg/dl in the groups of rats, n = 6 rats per group. Means with different letters are significantly different at p < 0.05.

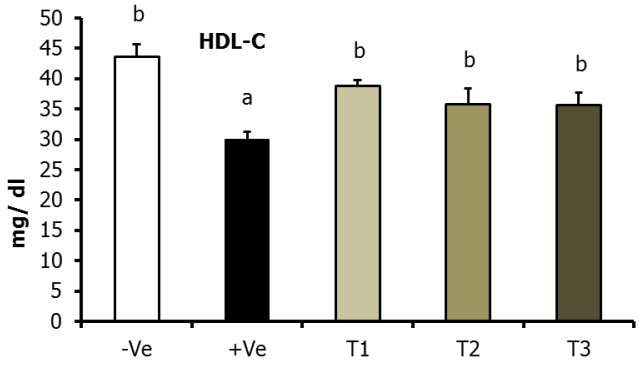

Figure 3: HDL-C levels in blood measured in mg/dl in the groups of rats, n = 6 rats per group. Means with different letters are significantly different at p < 0.05.

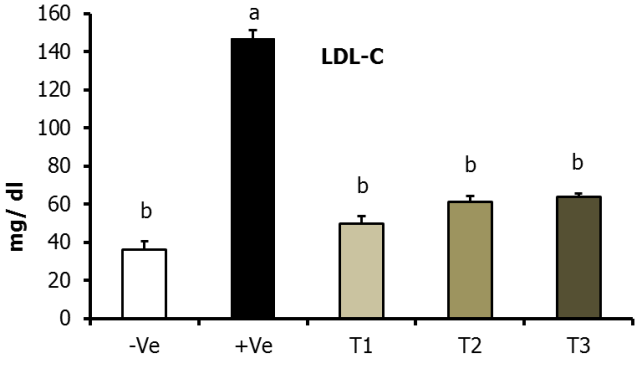

Figure 4: LDL-C levels in blood measured in mg/dl in the groups of rats, n = 6 rats per group. Means with different letters are significantly different at p < 0.05.

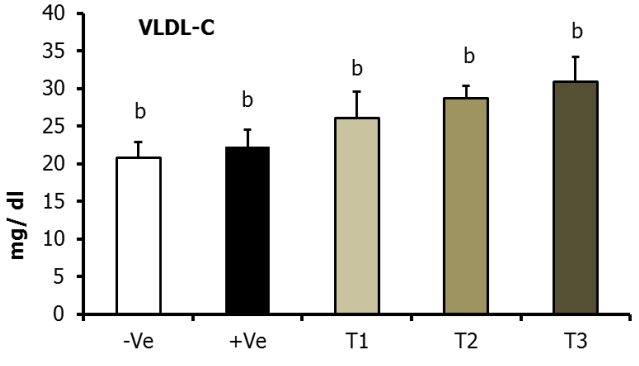

Figure 5: VLDL-C levels in blood measured in mg/dl in the groups of rats, n = 6 rats per group. Means with different letters are significantly different at p < 0.05.

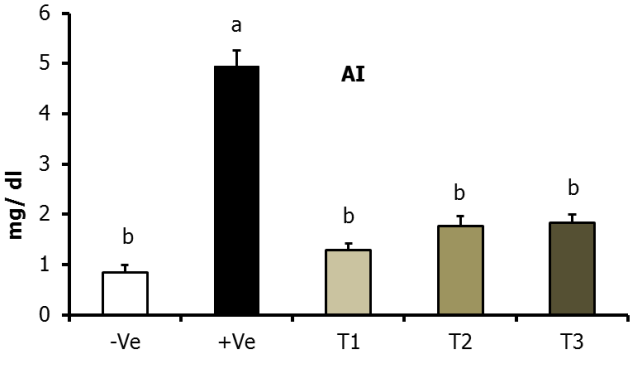

Figure 6: AI levels in blood measured in mg/dl in the groups of rats, n = 6 rats per group. Means with different letters are significantly different at p < 0.05.

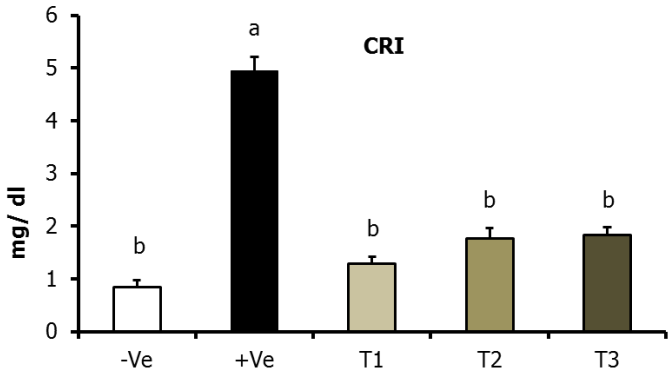

Figure 7: CRI levels in blood measured in mg/dl in the groups of rats, n = 6 rats per group. Means with different letters are significantly different at $p < 0.05$.

diseases according to the WHO.[22] Hyperlipidemia, including high levels of LDL and VLDL, is one of the main causes of the NCDs that have been growing problem worldwide. Our results showed that atorvastatin treatment was able to lower bad cholesterol and enhance good cholesterol levels. Atorvastatin ability to lower the bad lipid is attributed to the effect of this medicine in increasing proprotein-convertase-subtilisin-kexin-type9 (PCSK9), that is responsible for lowering LDL level in blood and lipid metabolism generally.[23] Herb remedies have been proven to be less toxic in addition to their availability and low-priced relatively. *P. oleracea* plant is well-known in folk medicine to treat diabetes, hypertension, heart diseases and many others. In the current study we found that the *P. oleracea* leaf extract significantly lowered the TC, TG, LDL-C, AI, and CRI in the treatment group. Shanker and Denbath, 2016 showed similar results when fed *P. oleracea* leaves aqueous extract to high cholesterol-diet rats.[24] The latter study showed that the *P. oleracea* extract also reverse the adverse effect of feeding cholesterol to the rats. Our results also agreed with what other study that showed that the phenolic compounds of leaf extract have significant role in improving the lipid profile of female rats.[25] In addition to the flavonoids, *P. oleracea* also contains considerable amounts of organic acids that were proven to aid in correcting the lipid profile and increasing the HDL-C level in hyperlipidemic animals.[26] Despite the fact that flavonoids are known to bring up the HDL level in the blood, but the mechanism still ambiguous. Baba et al., 2007 reported that flavonoids trigger the gene expression of the main HDL component that is called apolipoprotein A_1 which lead to increase the HDL production.[27] Moreover, it was suggested that flavonoids increase the HDL level through activation of lecithin acyl transferase that converts part of the free cholesterol into HDL.[28] Literatures postulated that phenols, flavonoids, and terpenoids components affect blood levels of LDL-C, HDL-C, and VLDL-C through different mechanisms.[29] Furthermore, the hypolipidemic effect of P. oleracea and S. officinalis is also attributed to the antioxidant properties of the plants.[30,31] This activity might be related to the presence glycine in the plant extract, which is considered the building unit of glutathione that blocks lipid peroxidation due its radical scavenging function[32] a principle bioactive component of Curcuma longa L, is well known for its anti-hyperlipidemia effect. However, no holistic metabolic information of curcumin on hyperlipidemia models has been revealed, which may provide us an insight into the underlying mechanism. In the present work, NMR and MS based metabolomics was conducted to investigate the intervention effect of curcumin on hyperlipidemia mice induced by high-fat diet (HFD). Also, the high activity of *P. oleracea* as an antioxidant belongs to the high content of linolenic-omega-3 fatty acid,[33] which is also implicated in the hypolipidemic function of the plant since it decreases the LDL cholesterol level in blood.[24] The antioxidants polyphenols and flavonoids components of plants grabbed lots of attention due to their ability to inhibit oxidation and peroxidation of lipids. Studies have showed that the *S. officinalis* effect in decreasing blood lipids related to the high content of flavonoids in the plant extract as mentioned above. This role is anchored mainly to the rosmarinic acid that was implemented in lowering triglycerides and cholesterol levels in blood in high fat diet-rats.[34] Moreover, rutin, the other flavonoid might work as hypolipidemic factor as it was found to reduce lipid content of adipose tissues and body weight[35] despite equivalent energy intake ($p < 0.05$). It is worth to know that the oxygen species are involved in hypercholesterolemia that is risk factor for many diseases. It was found that the *S. officinalis* water extract inhibits the superoxide anion formation.[34] Taurine and glycine as components of *S. oficinalis* were postulated to be the constituents that play fundamental role in reducing the cholesterol level in the blood of hypercholesterolemic rats.[36] The researchers suggested that the ability of those elements is owing to their antioxidant properties.[37] Taurine functions to alleviate lesions that resulted by hypercholesterolemia through lowering the atherogenic LDL and VLDL cholesterol, in addition to increasing the antiatherogenic HDL cholesterol.[38]

CONCLUSION

NCDs such as cardiovascular disease are one of the most fatal diseases with an incidence of 50% in the developed world and the range is also growing in the developing countries. Hypolipidemic medicines are not only high-priced but also with detrimental side effects. Using *P. oleracea and S. officinalis* leaves extracts in this study proved that those

remedies are highly effective in lowering the bad cholesterol levels in the blood. The study showed that all the animals that were hyperlipidemic and then treated with the mentioned leaf extracts exhibited normal levels of LDL, VLDL, and triglycerides. On the other hand those animals had high level of HDL in the blood. Those results indicate that those plants are strongly recommended to cure hyperlipidemia and might have promising role in the future NCDs treatment strategies.

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