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Effects of soy isoflavone genistein on lipid profile and hepatic steatosis in high-fat-fed Wistar rats

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ABSTRACT

Background: Hyperlipidemia is a major cause of atherosclerosis-induced conditions such as coronary heart disease, ischemic cerebrovascular disease, and peripheral vascular disease. Due to various adverse effects with the current pharmacological therapy, many plant-derived compounds are being tested to lower serum lipid levels. Genistein, a soy isoflavone, showed promising results in several studies. **Aims and Objectives:** The study aimed to evaluate the effectiveness of genistein on serum lipid profile and its hepatoprotective activity in hyperlipidemic male albino Wistar rats. **Materials and Methods:** Thirty-six male Wistar rats were randomly divided into six groups. Animals were given high cholesterol diet (0.75% cholesterol + 1.5% bile salt) to induce hyperlipidemia. The animals were treated with atorvastatin (10 mg/kg oral) and genistein (1 mg/kg oral and 5 mg/kg oral) once daily for a period of 30 days. Blood samples were collected for biochemical analysis of lipoproteins and a portion of liver tissue was taken for histopathological examination. Statistical analysis was performed by one-way analysis of variance test followed by *post hoc* Dunnett's multiple comparison test. $P < 0.05$ was considered statistically significant. **Results:** Oral administration of genistein showed a significant reduction in serum total cholesterol, triglycerides, and low-density lipoprotein levels. Histopathological examination of liver showed a significant reduction in hepatic steatosis ($P < 0.001$) with no inflammatory changes as compared to high cholesterol-treated rats. **Conclusion:** The present study demonstrated significant hypolipidemic and hepatoprotective activities of genistein at a dose of 5 mg/kg in the experimental rats.

KEY WORDS: Genistein; Hypolipidemia; Hepatic Steatosis; High-fat Diet

INTRODUCTION

Cardiovascular disease (CVD) is one of the leading causes of death and disability in the developing nations. There is an estimated 31.8 million people living with coronary artery disease (CAD) in India alone.[1] The age-standardized estimates for disability-adjusted life years lost due to CAD are 3 times higher in India than in developed countries. Dyslipidemia refers to the derangements of one or many of the lipoproteins; elevations of total cholesterol (TC), low-density lipoprotein (LDL) cholesterol and triglycerides (TGs), and/or low levels of high-density lipoprotein (HDL) cholesterol. A strong association exists between hyperlipidemia and CAD, cerebrovascular stroke, and peripheral vascular disease.[2]

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The causes of hyperlipidemia are due to primary genetic defect or secondary to diet (diet rich in saturated fat), drugs (isotretinoin and protease inhibitors), and diseases (diabetes, nephrotic syndrome, hypothyroidism, etc.). The pharmacotherapy of dyslipidemia includes statins, fibrates,

niacin derivatives, bile acid-binding resins, and cholesterol absorption inhibitor. Chronic use of these drugs often associated with various adverse effects such as myopathy, hepatic dysfunction, gastrointestinal symptoms, and rashes.[3] This warranted the search for newer hypolipidemic drugs with minimal adverse effects. Genistein is an isoflavone compound extensively found in soybean extracts. It has been gained special focus due to its remarkable estrogenic activity, hence, the name phytoestrogens. Genistein was found to be a potential agent for its multidirectional action in the live cell for the prophylaxis and treatment of cancer and other chronic conditions such as osteoporosis, diabetes, postmenopausal syndrome, and CVD.[4] Moreover, cellular studies have also provided direct evidence that soy isoflavones affect peroxisome proliferator activator receptor (PPAR)-directed gene expression and exert a beneficial effect on lipid and glucose metabolism. Suppression of hepatic lipid synthesis may be accounted as one mechanism for the lipid-lowering action of genistein.[5] The role of genistein as an antiatherogenic agent in preventing and treating the conditions such as atherosclerosis, acute coronary syndromes, pulmonary hypertension, heart failure, and myocardial infarction has been reported.[6] Hence, our study was designed to evaluate the effect of genistein on lipid profile and hepatoprotective activity in hyperlipidemic male albino Wistar rats.

MATERIALS AND METHODS

Experimental Animals

Laboratory-bred adult male albino Wistar rats (10–12 weeks old) having body weight in the range of 180–250 g were purchased from Tamil Nadu Veterinary and Animal Sciences University, Chennai, Tamil Nadu. They were kept in the animal house under controlled conditions of illumination (12 h light/12 h darkness) and temperature 20–25°C (air-conditioned room) for 1 week before and during the experiments. They were maintained on standard pellet diet and water *ad libitum* throughout the experimental period. All procedures in the study were reviewed and approved by the institutional animal ethical committee (IAEC – Code No: 14/17/10/2013). The animals were taken care as per guidelines of the Committee for the Purpose of Control and Supervision of Experiments on Animals. Experiment was conducted based on good laboratory practice.

Drugs and Chemicals

Standard pellet diet – Pranav Agro Industries, India; hypercholesterolemic diet – 0.75% cholesterol + 1.5% bile salt (Yucca Industries, Mumbai); and atorvastatin, solvents – polyethylene glycol (PEG), dimethylsulfoxide (DMSO) (Subra Scientific, Puducherry), genistein (Sigma-Aldrich Company, USA), cholesterol reagent kit and triglyceride reagent kit were procured from JEEV Diagnostics Pvt. Ltd., India, and HDL cholesterol reagent kit was procured from Agappe Diagnostics Ltd., India, were used.

Experimental Procedure

Thirty-six adult male albino Wistar rats were divided randomly into six groups consisting of six animals in each group. This study was conducted over a period of 1 month.

Grouping of Animals

- Group 1 – Standard pellet diet + Vehicle (PEG)
- Group 2 – Standard pellet diet + Vehicle (DMSO)
- Group 3 – High cholesterol diet
- Group 4 – High cholesterol diet + Atorvastatin 10 mg/kg oral
- Group 5 – High cholesterol diet + Genistein 1 mg/kg oral
- Group 6 – High cholesterol diet + Genistein 5 mg/kg oral.

Doses were selected based on the previous studies.[7] Atorvastatin was dissolved in PEG and genistein was dissolved in 0.5 mL of 30% DMSO.

Animals were given high cholesterol diet (0.75% cholesterol + 1.5% bile salt) and drugs daily orally along with the standard pellet diet for a period of 30 days. On the 31st day after overnight fasting, blood samples were collected from orbital sinus for biochemical analysis of lipoproteins. Later, the animals were sacrificed with high dose of pentobarbitone. A portion of liver tissue was removed and sent for histopathological examination.[7]

Parameters Measured

I. Serum lipid profile:
   1. Cholesterol levels (Cholesterol peroxidase method)
   2. Estimation of TGs (Glycerol kinase – peroxidase method)
   3. Estimation of HDL (Liquichek test kit)
   4. Estimation of LDL and very LDL [VLDL] (LDL = TC−(HDL+VLDL), by Freidewald's formula
   5. Estimation of VLDL (VLDL = TG/5).

II. Histopathological examination of liver:
   A portion of liver tissue was separated and placed in 10% neutral buffered formalin for fixation. After regular processing, tissue was embedded in paraffin wax and then sectioned (4–5 μm) using a microtome. Sections were stained using hematoxylin and eosin. Histopathological changes were observed under light microscope and tissue morphology; presence of steatosis, inflammation, and ballooning degeneration was examined. The severity of steatosis was graded as the percentage of parenchymal cells containing fat as follows: 0 = <5% of hepatocytes containing fat, 1 = <33% of hepatocytes containing fat, 2 = 33–66% of hepatocytes containing fat, and

3 = more than 66% of hepatocytes containing fat.[8] The grading of portal inflammation as follows: 0 indicates no inflammation, 1+ indicates <1/3rd of portal triad, 2+ indicates 1/3rd–2/3rd of portal triad, and 3+ indicates >2/3rd of portal triad. The grading of lobular inflammation as follows: 0 indicates no foci of inflammation, 1+ indicates 1–2/foci, 2+ indicates 3–4/foci, and 3+ indicates >4/foci. Photomicrographs were taken on an Optika 4083.B5 microscope (Italy).

Statistical Analysis

Data were entered and analyzed using SPSS software version 16.0 by one-way analysis of variance (ANOVA) and results were expressed as mean ± standard deviation. Significance of difference between groups was further analyzed with Dunnett's test for *post hoc* comparisons. $P < 0.05$ was considered statistically significant.

RESULTS

Effect of Genistein on Serum Lipid Profile in Experimental Animals

As depicted in Table 1, the mean serum lipid profile of vehicle-treated animals was 82.23 ± 4.26 (TC), 123 ± 4.73 (TG), 36.66 ± 5.04 (HDL), 21.56 ± 1.72 (LDL), and 24.6 ± 0.94 (VLDL). The values did not differ significantly between the vehicle-treated animals.

High cholesterol diet treated animals showed a significant increase in the serum levels of TC, TG, HDL, VLDL, and LDL (161.16 ± 9.66, 230.0 ± 15.50, 54.83 ± 4.57, 46.0 ± 3.10, and 60.33 ± 3.80, respectively) as compared to vehicle (both) treated animals indicating the development of hyperlipidemic state. Oral dose of atorvastatin (10 mg/kg, oral) treated animals showed a significant reduction in the levels of TC, TG, VLDL, and LDL 109.83 ± 14.79, 150 ± 9.63, 30 ± 1.92, and 37.83 ± 15.95, respectively.

Oral administration of genistein in a dose of 1 mg/kg caused a significant decrease in the serum levels of TC (122 ± 17.57), TG (143.83 ± 12.12), and VLDL (28.76 ± 2.42), whereas LDL levels do not show a significant decrease when

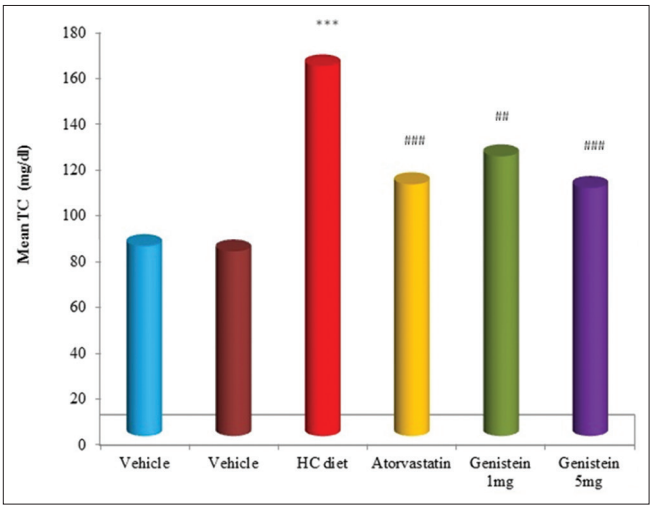

Figure 1: Effect of genistein on serum total cholesterol levels in experimental animals. ***$P < 0.001$ as compared with vehicle (polyethylene glycol and dimethylsulfoxide) treated groups. ##$P < 0.01$, ###$P < 0.001$ as compared with high cholesterol group

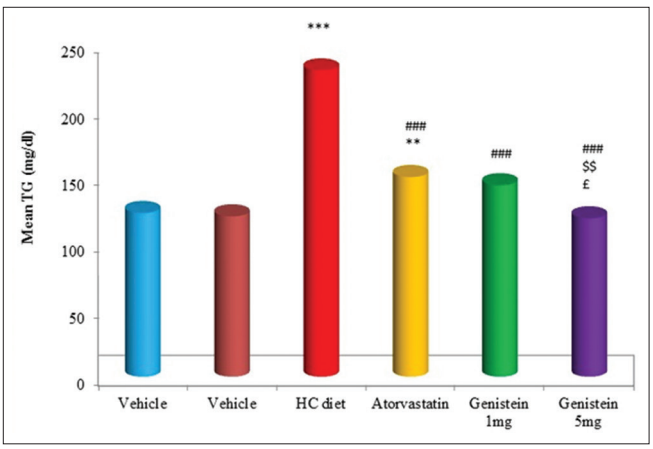

Figure 2: Effect of genistein on serum triglyceride levels in experimental animals. **$P < 0.01$, ***$P < 0.001$ as compared with both vehicle (polyethylene glycol and dimethylsulfoxide) groups. ###$P < 0.001$ as compared with high cholesterol group. $$$P < 0.01$ as compared with atorvastatin group. £$P < 0.05$ as compared with genistein 1 mg/kg group

Table 1: Effect of genistein on serum lipid profile in experimental albino Wistar rats

Groups	Treatment (mg/kg, oral)	TC (mg/dl)	TG (mg/dl)	HDL (mg/dl)	VLDL (mg/dl)	LDL (mg/dl)
I	Vehicle (PEG)	82.23±4.26	123.0±4.73	36.66±5.04	24.6±0.94	21.56±1.72
II	Vehicle (DMSO)	80.51±9.22	120.52±2.06	35.29±3.67	20.90±6.81	22.91±2.85
III	HC diet	161.16±9.66***	230.0±15.50***	54.83±4.57***	46.0±3.10***	60.33±3.80***
IV	HC diet+Atorvastatin (10)	109.83±14.79###	150.0±9.63###**	42.0±3.34	30±1.92**###	37.83±15.95###
V	HC diet+Genistein (1)	122±17.57##	143.83±12.12###	40.5±9.56	28.76±2.42###	52.73±10.52**
VI	HC diet+Genistein (5)	108.17±15.98###	119±10.46###$$≤	40.5±6.22	23.8±2.09###$$≤	33.87±17.52###≤≤

Values are expressed as mean±SD for all six groups (n=6 in each group). *P<0.05, **P<0.01, ***P<0.001 as compared with both vehicle (PEG and DMSO) groups. #P<0.05, ##P<0.01, ###P<0.001 as compared with high cholesterol group. $$$P$<0.01 as compared with atorvastatin group. ≤P<0.05, ≤≤P<0.01 as compared with 1 mg/kg genistein group. Comparison was done by one-way analysis of variance followed by *post hoc* Dunnett's test. LDL: Low-density lipoprotein. TC: Total cholesterol. TG: Triglyceride. HDL: High-density lipoprotein. HC diet: Hypercholesterolemic diet. PEG: Polyethylene glycol. DMSO: Dimethylsulfoxide. SD: Standard deviation

compared to high cholesterol-treated animals. High-dose genistein (5 mg/kg, oral) caused a significant reduction in TC, TG, and VLDL 52.73 ± 10.52, 119 ± 10.46, and 23.8 ± 2.09, respectively ($P < 0.001$), and LDL (33.87 ± 17.52, $P < 0.01$) levels as compared with high cholesterol-treated group [Figures 1 and 2]. However, no significant changes in serum HDL levels were noticed in all the drug-treated animals.

A dose-dependent decrease in LDL ($P < 0.01$), and TG and VLDL ($P < 0.05$) levels was observed with high-dose genistein (5 mg/kg) compared to low-dose genistein (1 mg/kg) treated animals. Moreover, a significant decrease in TG and VLDL levels was noticed with high-dose genistein-treated animals and effects on TC and LDL levels were similar when compared to atorvastatin-treated animals.

Histopathological Examination of Rat Liver

With hematoxylin and eosin staining, the hepatic accumulation of lipid was observed by light microscopy in rat liver tissue. Histopathological examination showed preservation of liver cell architecture with no significant steatosis and inflammatory cell infiltration in vehicle-treated animals. In high cholesterol-treated animals, varying degree of hepatic steatosis (2 + [33–66%]) and mild lobular inflammatory infiltration of lymphocytes (1+) were observed [Figures 3a and b]. The area of hepatic steatosis observed in atorvastatin-treated group was reduced (1+B [10–15%]) associated with mild inflammatory cell infiltration with lymphocytes (1+) in the portal triad when compared with high cholesterol-treated animals [Figure 3c].

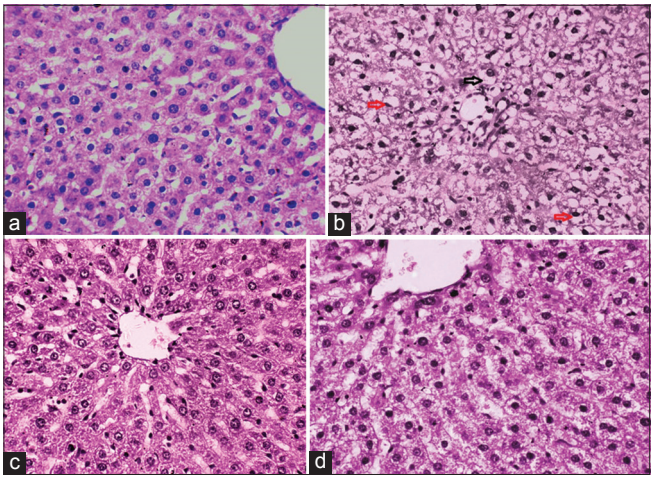

Figure 3: Photomicrographs of liver sections (hematoxylin and eosin staining – original × 400). (3a) Normal diet-fed rats – the hepatocytes in livers show normal architecture. (3b) High cholesterol-fed rats – the hepatocytes show microvesicular steatosis and feathery degeneration (arrows). (3c) Atorvastatin-treated rats – moderate reduction in steatosis in hepatocytes with few inflammatory cells. (3d) Genistein (5 mg/kg)-treated rats – marked reduction in steatosis in hepatocytes

Genistein-treated (5 mg/kg) animals showed a marked decrease in hepatic steatosis changes (1+A [5–10%]) with no lobular/portal inflammation [Figure 3d]. Low-dose genistein (1 mg/kg) treated animals also showed mild reduction in hepatic steatosis (1+C [15–33%]) with no inflammatory changes [Table 2].

DISCUSSION

In the present study, experimental animals fed with high cholesterol diet evidenced a significant increase ($P < 0.001$) in serum TC, TG, VLDL, and LDL levels than rats fed with normal diet. It was observed that genistein in two different doses (1 and 5 mg/kg) decreased serum TC, TG, VLDL ($P < 0.001$), and LDL ($P < 0.01$) levels significantly when compared with high cholesterol diet treated animals. The effect of genistein-treated animals on TC and LDL levels was comparable with atorvastatin-treated group, whereas TG and VLDL levels were significantly reduced ($P < 0.01$) when compared with atorvastatin-treated animals. In the present study, rats fed with high cholesterol diet showed fatty changes as evidenced by accumulation and deposition of abundant fat droplets in hepatocytes which occupied the entire cell cytoplasm described as hepatic steatosis caused by oxidative damage in liver. Moderate hepatic steatosis (2+, 33–66%) with mild lobular and portal inflammatory changes with lymphocyte infiltration was observed in high-fat diet-fed animals. Genistein (5 mg/kg) treated animals showed a marked improvement in hepatic steatosis (1+, 10–15%) with no portal and lobular inflammation when compared to high

Table 2: Effect of genistein on liver morphology of experimental animals

Groups	Treatment (mg/kg, oral)	Hepatic steatosis	Lobular inflammation	Portal inflammation
I	Vehicle (PEG)	0	0	0
II	Vehicle (DMSO)	0	0	0
III	HC diet	2+	1+	0
IV	HC diet+Atorvastatin (10)	1+B	0	1+
V	HC diet+Genistein (1)	1+C	0	0
VI	HC diet+Genistein (5)	1+A	0	0

Portal inflammation: 0: None, 1+: <1/3rd of portal triad, 2+: 1/3–2/3 of portal triad, 3+: >1/3rd of portal triad. Hepatic steatosis: 0: <5%, 1+A: 5–10%, 1+B: 10–15%, 1+C: 15–33%, 2+: 33–66%, 3+: >66%. Lobular inflammation: 0: No foci, 1+: 1–2/foci, 2+: 3–4/foci, 3+: >4/foci. DMSO: Dimethylsulfoxide, PEG: Polyethylene glycol

cholesterol-treated group. Moreover, in atorvastatin-treated animals, there was moderate steatosis (1+, 15–33%) with mild portal inflammation.

A study done by Yao *et al.* showed a significant reduction in serum TC and TG levels in genistein-treated group compared to high cholesterol-treated animals.[9] Another study done by Kim *et al.* demonstrated genistein supplementation (4 g/kg diet) showed reduced serum TC, LDL, and triacylglycerol levels in experimental animals.[10] However, the present study conflicts those of Kim who reported that genistein had no effect on serum TC and TG in diabetic mice.[11] The hypolipidemic effects of genistein could be ascribed to reduced cholesterol synthesis and esterification; reduced cholesterol and bile acid absorption from gastrointestinal tract; increased bile acid excretion; inhibition of hepatic glucose conversion to lipids; increase in hepatic LDL receptor activity; and expression due to upregulation of hepatic catabolic genes (liver fatty acid catabolism genes) including sterol regulatory element binding protein 2 (SREBP-2) regulated genes.[12] Transactivation of PPARγ is associated with adipocyte differentiation, insulin sensitization and further promotes adipogenesis and lipid storage in subcutaneous adipose tissue which results in redistribution of visceral fat mass to subcutaneous tissue.[13] The exact role of genistein on liver X receptor (LXR)/SREBP-1c remains controversial with different concentrations. A study done by Kim *et al.* suggested that genistein (2 and 4 g/kg) inhibited the expression of LXRα-RXRα-SREBP1-c genes or activation of adiponectin genes.[10] Genistein has exhibited an inhibition of adipogenesis at low concentrations and an enhancement of adipogenesis at high concentrations.[14] According to two-hit hypothesis, accumulation of fat in the liver triggers hepatic steatosis and increased susceptibility of liver to inflammatory cytokines, mitochondrial dysfunction, and oxidative stress which contributes to necroinflammation and fibrosis in liver.[15] However, studies showing marked improvement in hepatic steatosis, inflammatory changes induced by genistein were comparable with our study.[9,10] The possible mechanism is through upregulation of PPARγ and reduced expression of TNFα at both pre- and post-translational levels.[16] Genistein also acts by modulating estrogen receptors in alleviating oxidative stress.[17,18] Based on the previous studies, another possible explanation could be due to high plasma-free fatty acid-induced expression of liver cytochrome P450 2E1 (CYP2E1), production of reactive oxygen species, peroxidation of phospholipids on cell membranes with resultant cell damage, or an inflammatory response which leads to progression of hepatic steatosis. Soy protein containing genistein may prevent oxidative damage in the liver by lowering plasma-free fatty acids and decreasing CYP2E1 expression.[19] Genistein also has been reported to prevent LDL oxidation, radical scavenging action, activation of antioxidant enzymes, and suppression of oxidative DNA damage.[20]

The strengths of the present study were that it has been done in two different doses of genistein. Furthermore, the hyperlipidemia of rats was induced by diet alone and drugs are also given orally so that the study can be extrapolated in humans in future. However, the limitations include, the duration of the study was short and combination effect of genistein with atorvastatin was not studied.

CONCLUSION

The present study showed that genistein effectively attenuated raised serum TC, LDL, VLDL, and TG levels with remarkable reduction in hepatic steatosis and inflammation. Thus, genistein, a soy isoflavone, in a dose of 5 mg/kg has beneficial effect on serum lipid profile with hepatoprotective activity in hyperlipidemic male albino Wistar rats.

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