# Studies on Anti-obesity activity of Methanolic extract of *Gardenia resinifera* in High Fat diet induced obesity

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**Abstract:**

In the present research, we aimed to assess *Gardenia resinifera's* ability to prevent obesity in rats that had been given a high-fat diet (HFD). The methanolic extract of *Gardenia resinifera* (MEGR) was prepared and evaluated at various doses (50 mg/kg, 100 mg/kg, and 4 mg/kg), and its effectiveness was compared to that of the standard anti-obesity medication orlistat (20 mg/kg b.wt). Despite slightly increased food intake, MEGR treatment significantly decreased weight gain in HFD-fed rats. When MEGR was given along with HFD, serum levels of total cholesterol (TC), triglycerides (TG), low-density lipoproteins (LDL), and very low-density lipoproteins (VLDL) were all significantly (*P* 0.05) decreased, while high-density lipoproteins (HDL) increased. Based on our findings, we show that MEGR has potential anti-obesity activity.

**Keywords:** *Gardenia resinifera*, high fat diet, progesterone, lipid level, obesity.

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## Introduction

In developed countries like Europe, the United States of America (USA), and Japan, obesity is the most prevalent health issue to become epidemic on a worldwide scale, increasing the risk of morbidity and mortality. The World Health Organization (WHO) defines obesity as an excess fat accumulation that affects human health. An increase in adipose tissue mass has also been used to identify obesity [1]. Additionally, obesity has been linked to several diseases, including osteoarthritis, hypertension, cardiovascular disease, diabetes mellitus type 2, atherosclerosis, and several cancers [2]. The prevalence of obesity among children aged 6 to 19 in the USA is up to 16.5 %, and it has also risen in countries like Europe, Asia, Africa, and South America. This is a significant public health concern. Primary and secondary prevention efforts have generally been disappointing, despite increased attention being paid to overweight and obesity by virtually every significant body concerned with public health, including the National Institutes of Health (NIH), the Centers for Disease Control, the United States Department of Agriculture [3], and the World Health Organization. Many elements of society are affected by obesity. For instance, it costs society money, lowers the quality of life, and raises the chance of developing several morbidities [4]. Extreme obesity is thought to shorten young adults' lives by 5 to 20 years.

For the treatment of obesity, several drugs are used, such as phentermine, fluoxetine, orlistat, sibutramine, and rimonabant, as well as dietary changes and even surgery. It is impossible to ignore the accompanying side effects of nausea, vertigo, sleeplessness, diarrhea, dyspepsia, and constipation. Maintaining a healthy lifestyle can be challenging and surgery is only an option for people with extreme obesity. As a result, scientists are concentrating on the demand for novel natural treatments and innovative strategies to battle obesity. Due to their antiadipogenic characteristics, plant extracts containing phytochemicals such as polyphenols, curcumin, resveratrol, and prostaglandins have gained popularity in recent years [5–6]. Herbal remedies have been employed to manage weight and treat obesity. For instance, the hydroxycitric acid-containing fruit extract from *Garcinia cambogia* has been used regularly to manage weight without causing any hazardous side effects [7].

Gardenias are members of the *Madder* or *Rubiaceae* family. The tropical regions of Southeast Asia and the Pacific islands, as well as South Africa, India, China, and Japan, are where Gardenias are most common. Over 200 different Gardenia species, primarily hybrids, are still in existence today. The plant *Gardenia resinifera Roth*, often known as Dikamal, is a member of the *Rubiaceae* family. It grows up to 6-7.5 m high and is a big, glabrous shrub or small tree that can be found throughout India's hills and Ghati regions. Different phytoconstituents found in this plant are utilized to treat a variety of ailments, including bronchitis pain relief, vomiting, liver disorders, constipation, and cutaneous diseases [8-12].

Considering potential phytoconstituents present in *Gardenia resinifera*, the current work has been undertaken to establish the anti-obesity effect of methanolic extract of this plant in high-fat diet-induced obesity.

## Materials and methods

### Plant collection and identification

The leaves of the plant *Gardenia resinifera* were collected from the local areas of Mumbai, India from January to March 2019. Identification of the plant was confirmed by Blatter Herbarium, St. Xavier's College, Mumbai (Voucher Number T-617).

### Preparation of methanolic plant extract

The leaves of *Gardenia resinifera* Roth were washed under tap water and dried in the air under

the shade at room temperature and converted to a coarse powder and stored in an airtight container. The coarse powder of the leaves was successively extracted with methanol by using the soxhlet apparatus. The extracts were concentrated under reduced pressure using a rotary flash evaporator, and the residues were dried in desiccators [13].

### Preliminary Phytochemical Screening

Phytochemical screening of leaves of the *Gardenia resinifera* methanol extract was subjected to preliminary phytochemical screening for plant constituents [14]. Alkaloids, flavonoids, phenolic compounds, carbohydrates, tannins, proteins, and free amino acids, saponins, steroids, and triterpenoids, glycosides were traced in the methanolic extract by the qualitative phytochemical study as per standard procedures.

### *In Vivo* anti-obesity evaluation

For this study, mature, nulliparous, female Wistar rats weighing 180-220 g were housed in cages maintained for 12 hours light and 12 hours dark cycle. The feed and water were provided *ad libitum*. All experiments were performed following the principles and guidelines of the CPCSEA. Rats were acclimatized for 7 days before initiation of the study.

### Acute oral toxicity study

An acute oral toxicity study was performed as per the OECD (Organization for Economic Co-operation and Development) guidelines 425. Healthy, mature, nulliparous female Wistar rats were taken. The limit test was performed for 2000mg/kg to ascertain the toxicity of the extract [15].

### High Fat Diet (HFD) induced Obesity

HFD-induced obesity method was performed to measure various physical, biochemical, and histopathology parameters for evaluation of the anti-obesity effect of methanolic extract of *Gardenia resinfera* leave in HFD-induced obesity in rats. The composition of the high-fat diet was as follows (per 1000 gm) in **table 1**. A freshly prepared diet was given to them.

Female Wistar rats were divided into five groups, with each group consisting of six animals. The treatment was given as follows [16, 17].

**Group I** received standard pellet chow and placebo treatment.

**Group II** received HFD throughout the study (8 weeks, or 56 days).

**Group III** received HFD (throughout the study) and received Orlistat 20 mg/kg p.o. from day 43 to day 56 as a standard drug.

**Group IV** received a high-fat diet (throughout the study) and received a methanolic extract of *Gardenia resinifera* leaves at 50 mg/kg p.o. from day 43 to day 56.

**Group V** received a high-fat diet (throughout the study) and received a methanolic extract of *Gardenia resinifera* leaves at 100 mg/kg p.o. from day 43 to day 56.

Animals were subjected to freshly prepared HFD from group II to group V along with the treatment mentioned above, and group I was subjected to standard pellet chow. On the 56$^{th}$ day of the study, the blood was collected by retro-orbital for estimation of glucose and serum parameters such as lipid profile (triglycerides, total cholesterol, HDL-Cholesterol, LDL-Cholesterol, VLDL, atherogenic index) and liver profile (SGPT, SGOT), etc. Physical parameters such as body weight, abdominal circumferences, and body mass index were also identified during treatment. On the 56$^{th}$ day, the animals were sacrificed for estimation of tissue parameters of the liver, lipid peroxidation, glutathione peroxidase, and histopathology of adipose tissue and liver.

### Statistical analysis

The results were reported as mean + SEM (n = 6). Statistical analysis was performed using a one-way analysis of variance (ANOVA) followed by Tukey's Kramer test. *P<0.05, **P 0.01, ***P 0.001, $^{ns}$P0.05 when compared to the HFD control group.



## Results

### Phytochemical screening of leaves extract

*Gardenia resinifera* leaves methanol extract demonstrated the presence of flavonoids, saponin, tannin, quinone, and steroid/triterpenoid during preliminary phytochemical screening. The bioactivities of phytoconstituents are complex. Therefore, the complex pharmacological activity of the phytoconstituents found in the extract may be responsible for the anti-obesity effect.

### Physical parameters (body weight, BMI, and abdominal circumferences):

Body weight (**Table 2**) was significantly increased (p<0.05) in week 2, (p < 0.01) in weeks 3 and 4, and (p < 0.001) from week 5 to week 8 in group II when compared to the normal control group. In groups IV and V, the mean body weight was significantly decreased (p<0.01) in week 7 and (p < 0.001) in week 8. The reference standard was more potent and showed a significant reduction in body weight (p < 0.01) in weeks 1 and (p < 0.001) from weeks 2 to 8.

The abdominal circumference and BMI (**Table 3**) were significantly (P<0.001) increased in HFD treated group-II whereas these parameters were significantly decreased (P<0.001) from week 5 to week 8 of the study in reference standard as well as ME treated groups. Effect of methanolic extract of *Gardenia resinifera* leaves on Body Weight in High Fat Diet-induced obesity in Wistar rats shown in **Figure 1**.

Table 1: Preclinical evaluation of methanolic extract of *Gardenia resinfera* leaves (ME) on Body Weight in High Fat Diet-induced obesity in Wistar rats

| week | Group I Normal Control | Group II HFD Control | Group III Standard Orlistat 20 mg/kg p.o. | Group IV ME 50 mg/kg p.o. | Group V ME 100 mg p.o. |
|---|---|---|---|---|---|
| **1** | 183.33±2.108 | 188.33±4.014$^{ns}$ | 173.33±2.108** | 203.33±2.108$^{ns}$ | 208.33±3.073$^{ns}$ |
| **2** | 189.33±2.011 | 200.17±3.851$^{\#}$ | 181.5±1.945*** | 214.83±1.815$^{ns}$ | 216.33±2.044$^{ns}$ |
| **3** | 196.83±2.242 | 211.83±4.094$^{\#\#}$ | 190.5±2.045*** | 223.33±1.667$^{ns}$ | 227.83±1.327$^{ns}$ |
| **4** | 206.5±2.592 | 222.5±4.380$^{\#\#}$ | 200.17±1.939*** | 229.17±1.869$^{ns}$ | 232±1.033$^{ns}$ |
| **5** | 211.67±2.431 | 233.67±4.161$^{\#\#\#}$ | 210.67±4.626*** | 233.83±1.797$^{ns}$ | 240±1.317$^{ns}$ |
| **6** | 218.33±1.909 | 245.5±4.372$^{\#\#\#}$ | 219.83±1.905*** | 238±1.897$^{ns}$ | 246.83±1.276$^{ns}$ |
| **7** | 224±1.693 | 256.5±4.470$^{\#\#\#}$ | 227.67±2.246*** | 241.83±2.007** | 240.33±2.028** |
| **8** | 230±1.461 | 267±4.397$^{\#\#\#}$ | 236±1.949*** | 246.33±2.140** | 233.17±3.371*** |

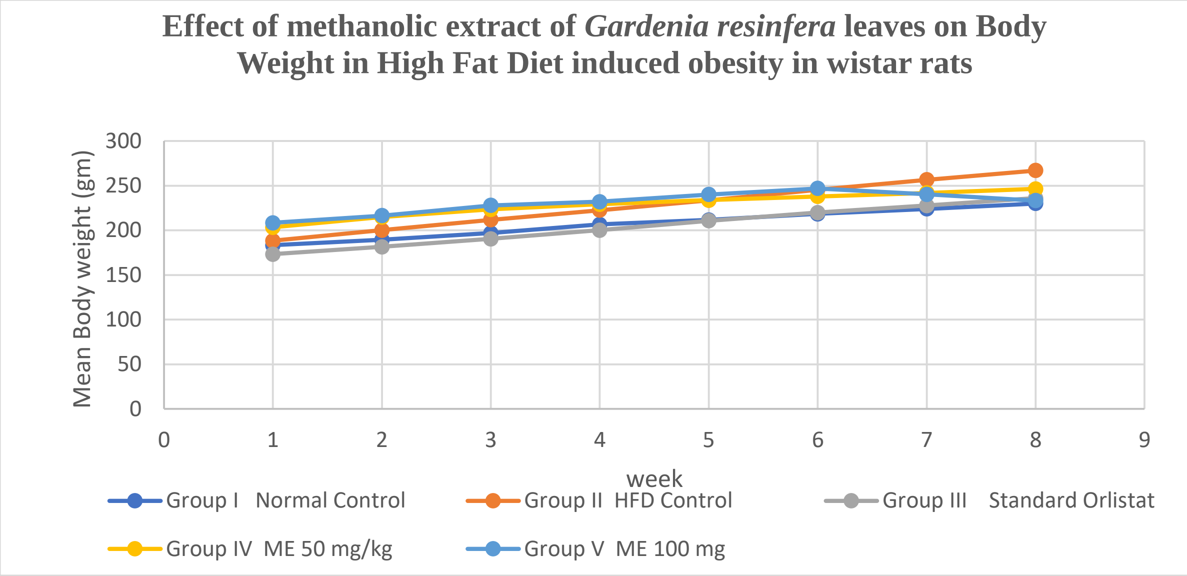
Values are the mean ± S.E.M. of six rat /treatment nsP>0.05, $^{\#}$p<0.05, $^{\#\#}$p<0.01, $^{\#\#\#}$p<0.001 when compared to normal control group Significance $^{ns}$P>0.05, *P<0.05, **P<0.01, ***P<0.001, compared Vs. HFD control

Table 2: Preclinical evaluation of methanolic extract of *Gardenia resinfera* leaves on Abdomen circumference and BMI in HFD-induced obesity in Wistar rats

| Groups | Abdomen circumference (cm) | | | BMI (gm/cm2) | | |
|---|---|---|---|---|---|---|
| | Week 1 | Week 5 | Week 8 | Week 1 | Week 5 | Week 8 |
| Normal control | 13.13±0.15 | 14.26±0.05 | 15.31±0.1 | 0.77±0.01 | 0.81±0.02 | 0.83±0.01 |
| HFD control | 13.28±0.07$^{\#\#\#}$ | 16.38±0.12$^{\#\#\#}$ | 19.3±0.08$^{\#\#}$ | 0.84±0.02$^{ns}$ | 1.019±0.02$^{\#\#\#}$ | 1.09±0.03$^{\#\#\#}$ |
| Std Orlistat 20 mg/kg p.o. | 13.48±0.13$^{ns}$ | 14.33±0.06*** | 15.53±0.09*** | 0.81±0.018$^{ns}$ | 0.9329±0.008* | 0.838±0.01*** |
| ME 50 mg/kg p.o. | 13.26±0.07 $^{ns}$ | 14.38±0.07*** | 13.9±0.14*** | 0.78±0.013$^{ns}$ | 0.885±0.012*** | 0.777±0.01*** |
| ME 100 mg/kg p.o. | 13.4±0.11$^{ns}$ | 14.18±0.07*** | 13.91±0.14*** | 0.86±0.009$^{ns}$ | 0.989±0.015$^{ns}$ | 0.745±0.02*** |

Values are the mean ± S.E.M. of six rats/treatment. $^{ns}$P>0.05, $^{\#}$p<0.05, $^{\#\#}$p<0.01, $^{\#\#\#}$p<0.001 when compared to normal control group Significance $^{ns}$P>0.05, *P<0.05, **P<0.01, ***P<0.001, compared Vs. HFD control

Figure 1: Effect of methanolic extract of *Gardenia resinfera* leaves on Body Weight in High Fat Diet-induced obesity in Wistar rats




**Effect of methanolic extract of *Gardenia resinfera* leaves on Blood glucose level in rats at week 8**

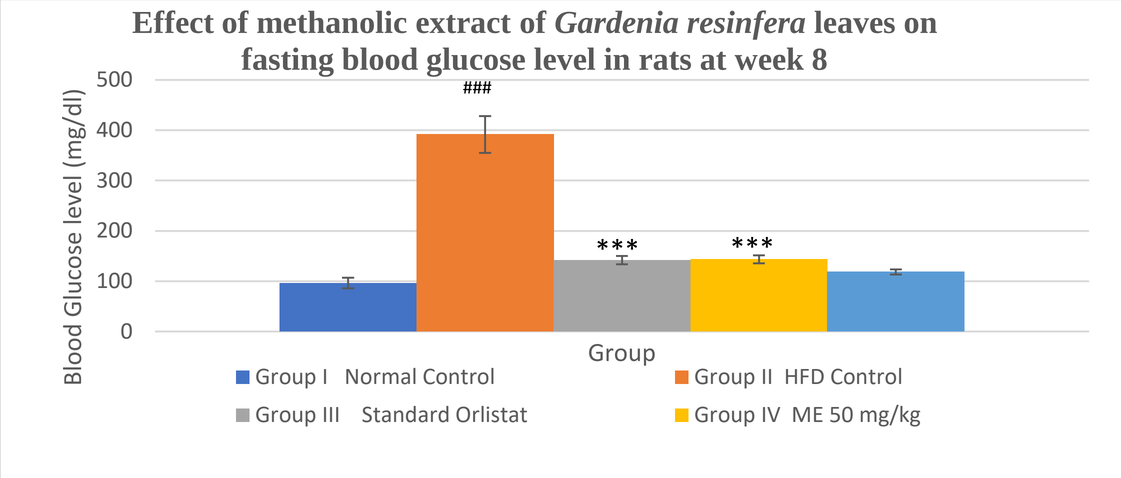
The glucose level was significantly increased (p< 0.001) in the high-fat diet treated group when compared to the normal control group and was significantly decreased (p< 0.001) in the Orlistat treated group and methanolic extract of *Gardenia resinfera* leaves (ME) treated group as compared to high-fat diet treated group. Results are shown in **Table 4** and **Figure 2** shows the effect of methanolic extract of *Gardenia resinfera* leaves on fasting blood glucose levels in rats at week 8.

Table 3: Effect of methanolic extract of *Gardenia resinfera* leaves on Blood glucose level in rats at week 8

| **Group I Normal Control** | **Group II HFD Control** | **Group III Standard Orlistat 20 mg/kg p.o** | **Group IV ME 50 mg/kg** | **Group V ME 100 mg** |
|---|---|---|---|---|
| **96.33±10.407** | 391.5±36.623### | 141.83±8.076*** | 143.5±8.028*** | 118.33±5.09*** |

Values are the mean ± S.E.M. of six rats/treatment. nsP>0.05, #p<0.05, ##p<0.01, ###p<0.001 when compared to normal control group Significance nsP>0.05, *P<0.05, **P<0.01, ***P<0.001, compared Vs. HFD control

Figure 2: Effect of methanolic extract of *Gardenia resinfera* leaves on fasting blood glucose level in rats at week 8




### Effect of methanolic extract of *Gardenia resinfera* leaves on Lipid profile in rats at week 8

The lipid profile parameters such as total cholesterol, triglyceride, LDL-cholesterol, VLDL, and atherogenic index were significantly ($p<0.001$) increased in the high-fat diet treated group as compared to the normal control group. All these lipid profile parameters were significantly decreased ($p<0.001$) in the orlistat treated group and methanolic extract treated group as compared to the high-fat diet treated group. **Table 5** shows the HDL-cholesterol was significantly ($p < 0.001$) decreased in the high-fat diet treated group as compared to the normal control group and was significantly increased ($p<0.001$) in the orlistat treated group and methanolic extract treated group as compared to the high-fat diet treated group. **Figures 3 to 8** show respective lipid profile results.

Table 4: Effect of methanolic extract of *Gardenia resinfera* leaves on Lipid profile in rats at week 8

| **Group/ Treatment** | **Cholesterol (mg/dl)** | **Triglyceride (mg/dl)** | **HDL (mg/dl)** | **LDL (mg/dl)** | **VLDL (mg/kg)** | **Atherogenic Index** |
|---|---|---|---|---|---|---|
| Normal Control | 17.11±0.39 | 51.66±1.49 | 45±0.86 | 33.87±5.12 | 10.33±0.12 | 0.054±0.04 |
| HFD control | 140.27±8.69### | 143.49±2.34### | 18.3±1.31### | 85.27±7.37### | 28.69±0.46### | 0.899±0.03### |
| Std Orlistat 20 mg/kg p.o. | 31.43±0.69*** | 57.54±6.07*** | 38.54±1.98*** | 27.94±0.70*** | 11.51±1.21*** | 0.165±0.03*** |
| ME 50 mg/kg p.o. | 16.51±0.17*** | 56.22±4.01*** | 38.38±0.83*** | 29.93±1.09*** | 11.25±0.80*** | 0.166±0.01*** |
| ME 100 mg/kg p.o. | 16.14±0.34*** | 50.2±1.08*** | 40.04±0.68*** | 31.15±1.14*** | 10.04±0.22*** | 0.092±0.04*** |

Values are the mean ± S.E.M. of six rats/treatment. $^{ns}P>0.05$, $^{\#}p<0.05$, $^{\#\#}p<0.01$, $^{\#\#\#}p<0.001$ when compared to normal control group Significance $^{ns}P>0.05$, $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$, compared Vs. HFD control

Figure 3: Effect of methanolic extract of *Gardenia resinfera* leaves on Cholesterol in rats at week 8

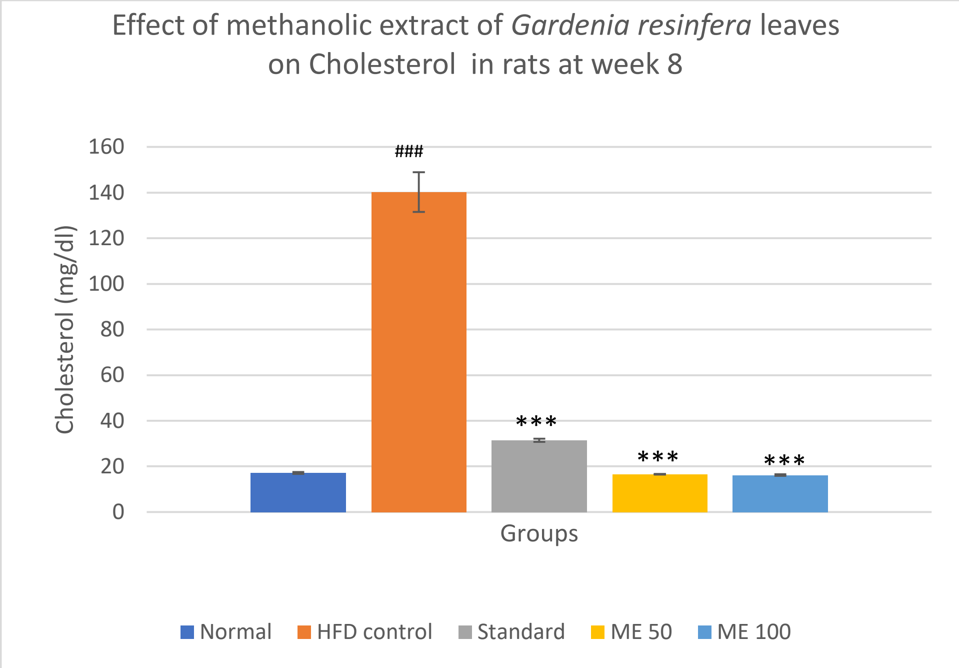





Figure 4: Effect of methanolic extract of *Gardenia resinfera* leaves on Triglyceride in rats at week 8

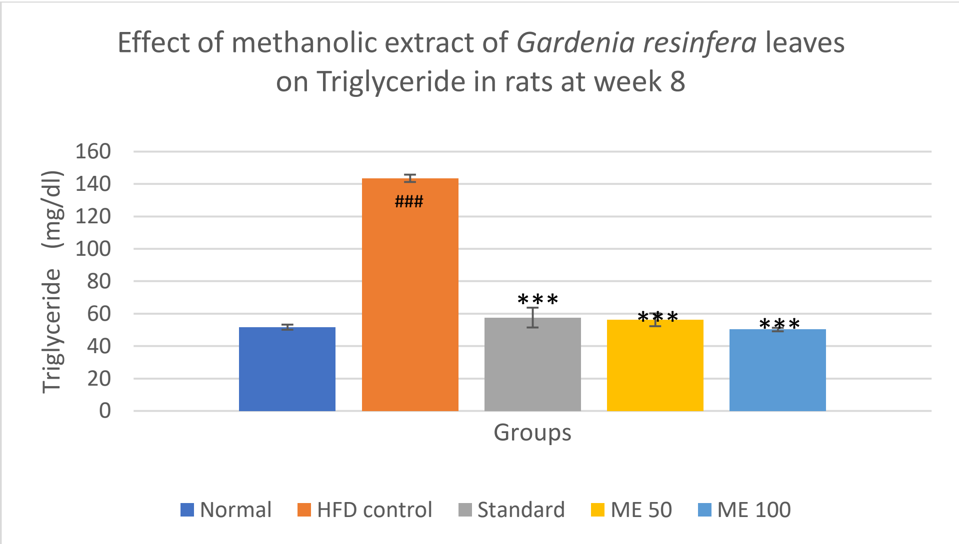


Figure 5: Effect of methanolic extract of Gardenia resinfera leaves on HDL in rats at week 8

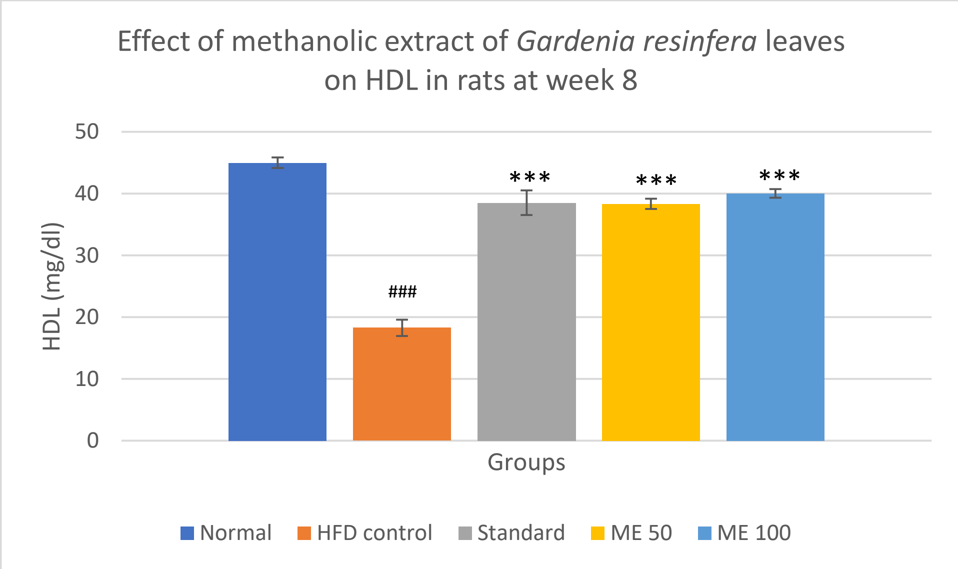





Fig 6: Effect of methanolic extract of *Gardenia resinfera* leaves on LDL in rats at week 8

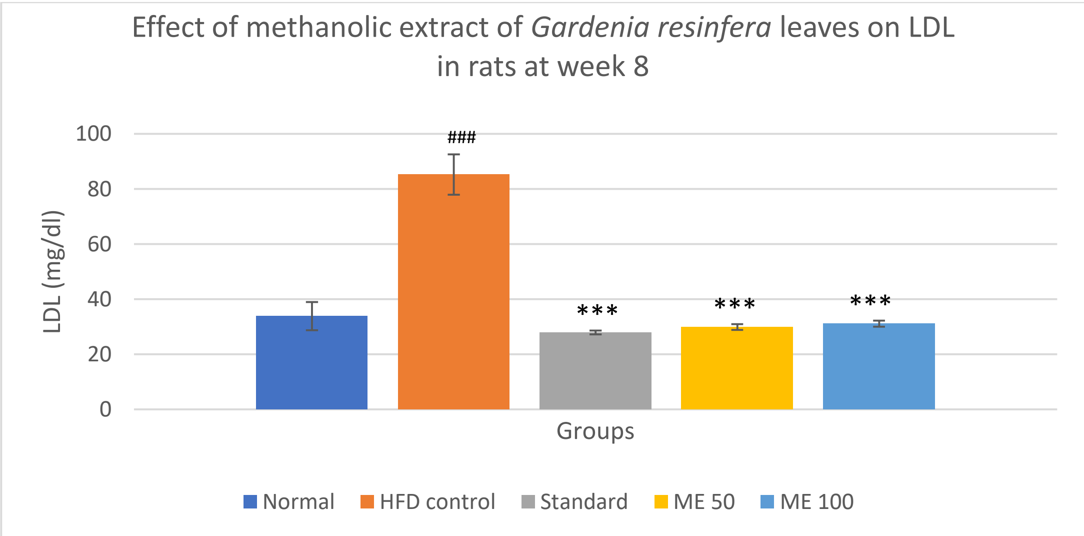


Figure. 7: Effect of methanolic extract of *Gardenia resinfera* leaves on VLDL in rats at week 8

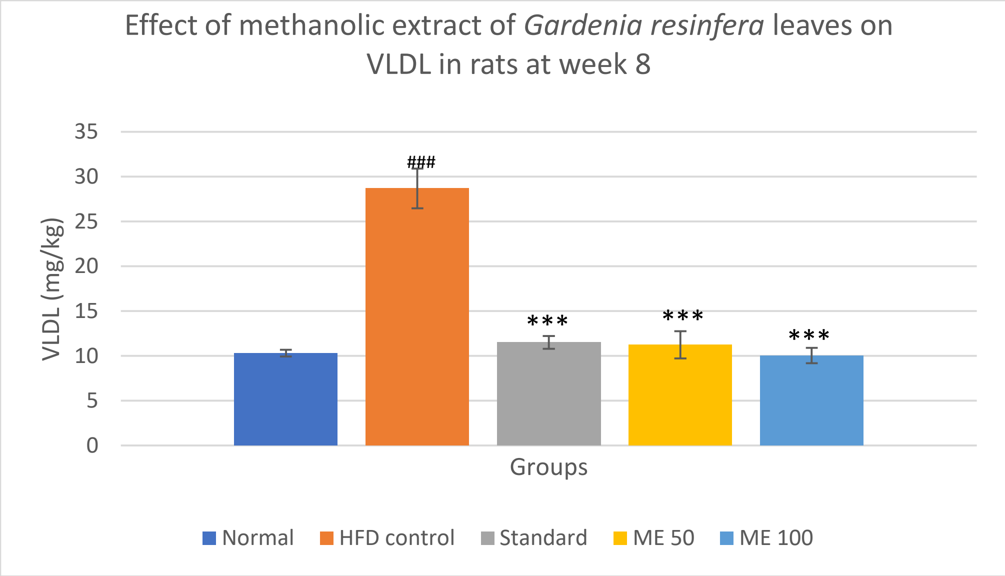
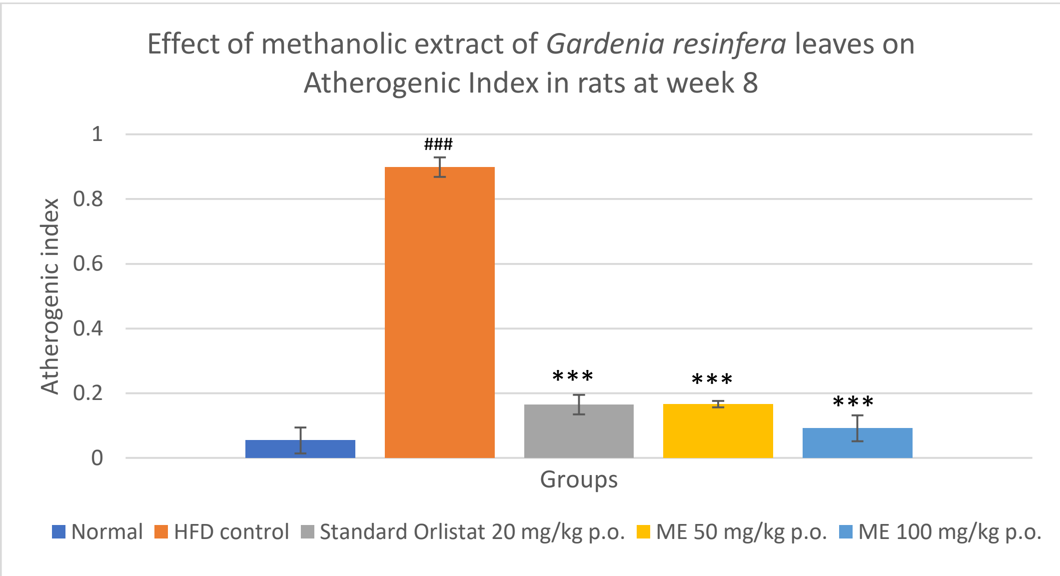



Figure 8: Effect of methanolic extract of *Gardenia resinfera* leaves on Atherogenic Index in rats at week 8




## Histopathological studies

### Effect of methanolic extract of *Gardenia resinfera* leaves on histopathological studies HFD induced in rats at week 8.

All the animals were euthanized by CO2 asphyxiation, for collection of liver and Adipose tissue. Organs were collected in 10% neutral buffered formalin. Tissues were trimmed to suitable size and thickness for proper penetration of reagents while processing. The tissues were processed routinely and embedded in paraffin. The sections of 3-5µm thickness were cut, stained with Hematoxylin and eosin stain, and examined microscopically.

### Effect of methanolic extract of *Gardenia resinfera* leaves on the histopathology of liver

Histopathological observation of the liver from the HFD group revealed moderate lipid accumulation in hepatocytes, minimal focal necrotic foci, and increased sinusoidal space, indicating that whereas lipid accumulation and hepatocellular degeneration were lower in Group III, IV, and V, they had comparable regenerative effects on histopathological changes of the liver (**Figure 9**).

**Effect of ME of *Gardenia resinfera* leaves on the histopathology of Adipose tissue**

Histopathological observation of adipose tissue from the HFD group revealed increased size and coalescence of adipocytes and mild perivascular infiltration of polymorphonuclear cells, whereas the size of adipocytes was reduced in groups III, IV, and V, indicating that Std and ME can suppress the development of adipose tissue induced by an HFD (**Figure 10**).

## Discussion

A chronic metabolic disease called obesity is brought on by an unbalanced energy intake Sedentary lifestyle, white-collar occupations, lack of exercise, psychological problems, and consumption of energy-rich meals are the main ones among the many elements that contribute to its etiology [18]. It is characterized by enlarged fat mass and elevated lipid concentration in blood [19]. More than 1.1 billion people worldwide are overweight, 312 million of who are obese. The International Obesity Task Force estimates that at least 155 million children globally are overweight or obese. With 1.7 billion people classed as overweight, this task force and the World Health Organization (WHO) have revised the definition of obesity to adjust for ethnic differences. This definition may therefore indicate an even larger prevalence [20]. The Phytochemical tests with the methanol extract of *Gardenia resinifera* indicated the presence of carbohydrates, alkaloids, tannins, terpenoids, saponins, proteins, and amino acids. Hyperlipidemia is associated with heart disease, which is the leading cause of death in the world. The lowering of the levels of harmful lipids to satisfactory values has been confirmed by several experimental animal and interventional studies indicating lowered morbidity and mortality in coronary heart diseases [21]. The results are discussed under the lipid profile in serum. Lipid profile in serum with high triglyceride (TG) and cholesterol levels was significantly reduced by treatment of *Gardenia resinifera.* The acute toxicity studies of the ME of *Gardenia resinifera* were found to be non-lethal up to the dose of 2000 mg/kg body weight of the animals so that 1/5th and 1/10th were selected for further investigations. When compared to normal and control groups the body weight observed was higher in HFD-induced obese animals. MEGR treated group exhibited significant activity by reducing the body weight as mentioned in **Table 2** and the values are comparable to the standard drug. The glucose levels were increased after HFD and the values are mentioned in **Table 4**. When the animals were treated with methanolic extract at 50mg/kg,100mg/kg showed a significant reduction in glucose levels. The values are comparable with the standard drug Orlistat 20mg/kg. Total cholesterol, triglycerides, LDL, and VLDL levels were significantly increased in HFD-induced animals to control rats. The results are shown in **Table 5**. The *Gardenia resinifera* markedly lowers the levels of serum cholesterol and other serum lipids. The decrease in cholesterol may indicate increased oxidation of mobilized fatty acids of inhibition or lipolysis [22]. The present investigation shows that all HFD-induced animals displayed hyperlipidemia as shown by their elevated levels of serum and liver cholesterol, triglyceride, VLDL, and LDL level. It can be concluded that *Gardenia resinifera* treatment was effective in the reduction of cholesterol, TG, VLDL, and LDL in a dose-dependent manner. Histopathological studies revealed that the control group showed normal architecture; (b) the HFD group had Moderate lipid accumulation in hepatocytes (Yellow arrow) and increased sinusoidal space; (c) the Orlistat group showed negligible cytoplasmic fatty infiltration and granular degeneration; (d) group treated with 50mg/kg extract showing minimal sinusoidal congestion and congested. Central vein and group treated with 100mg/kg extract showed mild cytoplasmic fatty infiltration and mild to moderate granular degeneration.

## Conclusion:

According to the results of the study, *Gardenia resinifera* can decrease cholesterol, which makes it valuable for preventing cardiovascular disorders. It lowers the levels of plasma lipids, particularly triglycerides and low-density lipoproteins. In the HFD-induced obese mice receiving treatment with MECA (50 mg/kg and 100 mg/kg), the lipid levels are reduced. When compared to the normal and control groups, histopathological investigations demonstrated that the *Gardenia resinifera* extract treatment group displayed minor cytoplasmic fatty infiltration and mild granular degeneration. Therefore, it may be inferred that treatment with *Gardenia resinifera* extract at doses of 50 mg/kg and 100 mg/kg will reduce cholesterol, TG, VLDL, and LDL in a dose-dependent manner. It will be necessary to do more thorough research on this herb to determine the precise mechanism of action of the plant extract, which will be extremely helpful in treating obesity and hyperlipidemia, two conditions that increase the risk of developing several illnesses.

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