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Role of Goldenberry in the Management Of Obesity-induced Cardiac Disorder in Wistar Rats

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Abstract
Obesity is a common disease of dietary habits, with consequences such as heart disease and coronary artery disease. Cardiac disease is a serious problem because obesity alters the structure and function of the heart, causing heart failure and atrial fibrillation with a significant risk of mortality. We aspired to study the therapeutic effect of goldenberry against induced cardiac changes in obese rats. This study attempted to lessen the danger of cardiac disease in obese rats with extracts of the natural product known as goldenberry fruit with husk extract (GB) at two doses (200 and 400 mg/kg). There was a marked amelioration in the lipid profile and obesity hormones compared to the obese group. Administration of GB extract lowered cardiac markers, troponin I, creatine phosphokinase-MB (CK-MB), lactate dehydrogenase (LDH), cardiac tissue iron content, cardiac copper content, and malondialdehyde (MDA) in either blood plasma or heart tissue. Treatment with GB extracts decreased plasma levels of monocyte chemoattractant protein-1 (MCP-1), resistin, Epithelial neutrophil-activating protein 78 (ENA-78), tumour necrosis factor-alpha (TNF-α), interleukin 6 (IL-6) and C- reactive protein (CRP). The histopathology of the heart and aorta showed better repair of cardiomyocytes and fewer inflammatory cells. The results showed a positive correlation between body mass index (BMI) and MDA, MCP-1, CK-MB, and LDH. In conclusion, it appears that GB is useful in the treatment of cardiovascular disease in obese rats via reductions in oxidative stress, cardiac iron accumulation, insulin resistance, and inflammatory markers.

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Keywords: goldenberry; obesity; cardiac markers; inflammatory markers; heart; aorta

1. Introduction

Obesity, diabetes, and cardiovascular disease (CVD) have all become serious global health issues due to unbalanced dietary intake. Large numbers of deaths occur worldwide due to obesity, diabetes, and atherosclerosis, which are increasing daily [1]. As cholesterol levels rise, it disrupts the normal flow of blood through the veins. Common causes of male morbidity and death include myocardial infarction, hypertension, coronary cardiac disease, and dyslipidemia [2, 3]. Notably, in vascular illnesses such as atherosclerosis, atherogenic plaques are produced owing to the accumulation of lipids and fibrous materials in the subendothelial region ofmajor arteries and the subsequent creation of lesions inside the coronary and cerebral arteries. Atherosclerosis develops due to a combination of risk factors, both adjustable and not, and this process takes a long time. Atherosclerosis is a complex chronic illness marked by substantial changes in the blood lipid profile and inflammation in the artery wall. Lipid peroxide in low-density lipoprotein (LDL) is recognized to play a critical role in atherosclerosis and atherosclerotic disorders. Therefore, prompt prevention and treatment of atherosclerosis are required to limit the chance of acquiring its clinical symptoms [4, 5].

Epidemiological studies have established a substantial connection between plasma cholesterol

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levels and coronary heart disease (CHD) risk [6]. A high- cholesterol diet increases atherosclerotic plaque development through increased blood LDL levels and oxidative stress. People with CHD have thicker or harder arteries in their heart muscles**.** The search for more potent and safer hypolipidemic medications led researchers to the discovery of natural substances. The lower danger of coronary heart disease has been linked to a diet substantial in fruits and vegetables, according to epidemiological research [7].

Heart and metabolic conditions may respond to or be prevented with the use of plant-based medicines [8]. Antioxidants found in plants may be particularly helpful in warding off atherosclerosis and other cardiovascular problems. As a result of its ability to mop up harmful free radicals, including it in your diet may have a revitalizing effect on your health. Considering their high antioxidant content, botanical natural goods are a significant source for multi-ingredient treatments that are less toxic, more effective, and safer. Some fruit-based anti-obesogenic treatments are considered useful in lowering the metabolic effects linked to overweight and obesity. Certain metabolic abnormalities related to diet that have caused obesity can be avoided with dietary therapies that include nutraceutical supplements [9, 10]. These fruits are similar in that they all contain a high polyphenol content provided by phenolics, which have more impressive antioxidant and anti-inflammatory properties [11].

Humans have noticed the health benifits of natural compounds due to the presence of secondary metabolites in medicinal plants. The secondary metabolites have modifying effects in different disorders. The natural compounds have fewer side effects. Obesity is a usual underrated health disorder but is now reflected a serious public health problem worldwide, which results in the emergence of further chronic health disorders [12].

Goldenberry is rich in phenolic ingredients such as “coumarin, kaempferol, quercetin, and ascorbic acid” that have a wide range of biological actions. One of them is protecting against metabolic abnormalities linked to obesity [13-14]. However, the use of GB extract (the fruit with the husk) against heart disorders caused by obesity has not yet been elucidated. Therefore, we aimed to search for the therapeutic effect of the goldenberry against the cardiac disorders induced by obesity.

2. Materials and Methods

2.1. Plant material

Goldenberry fruits, complete with husks, were purchased in Cairo, Egypt in February/March 2021. Identification of the plant was done by the “Herbarium in the Department of Botany, Faculty of Science at Cairo University”. Egyptian voucher specimens were housed at the “National Research Centre Herbarium in Cairo”.

2.2. Preparation of extract

5 kg of unprocessed fruit and husks were washed in regular tap water in the lab, blended at high speed, soaked in 70 percent methanol, heated at 40 °C, and filtered into another sterile container. There were three rounds of extraction procedures performed at 40ºC. The resultant liquid was then collected, filtered then concentrated by evaporating it at 45ºCin a rotary evaporator “Heidolph, Germany”. After that, lyophilization was used to turn the crude extract into a powder with a yield of sixty grams.

2.3. Phytochemical screening

Five fractions were obtained after applying a concentrated methanol extract from the fruit of GB to a polyamide column and eluting it with water then by different ratios of water and methanol. These fractions were then purified through a series of fractionation on a Sephadex LH-20 column and preparative paper chromatography, yielding phenolic acids including gallic acid, p-hydroxy benzoic acid, caffeine, and o-Coumaric acid.

2.4. Reagents

Folin-Ciocalteu and AlCl3 reagents were purchased from Sigma.

2.5. Estimation of total phenolics content (TPC) and total flavonoids content (TFC)

Estimation of total phenolics and flavonoid contents Folin-Ciocalteau colorimetric test was used to calculate the total phenolics content of the fruits from the *Physalis Peruviana* species, including the husk [15] with slight adjustment to use gallic acid as the reference. The data was analysed by comparing the concentrations of gallic acid (2 to 50µg/mL-1) to a standard curve. The phenol content was reported in milligrammes of gallic acid equivalent (mg GAE) per milligramme of plant extract.

Amounts of total flavonoids in the extract were detected with an AlCl3 colorimetric assay [16]. Flavonoids were measured in terms of their total concentration in the extract using the method qualified by Kumaran and Joel [17]. Each plant extract was given a value in milligrammes of rutin equivalents per gram of TFC (mg RE/g).

2.6. Animals and oral administration doses

Twenty-eight adult male Wistar rats weighing 175-200g from the "Animal house of National Research Centre, Egypt" were placed in ambient conditions with an equal day/ night cycles and add *libitum* to food pellets and drinking water. After a week, the animals had adapted to their new surroundings. To induce obesity, we fed some rats a high fat diet and tap water plus 25% sucrose for sixty days, while keeping seven animals as normal control. "The high fat diet (HFD) contains carbohydrate (42.3%), protein (17%), fat (22.50%), fiber, (3.2%), minerals (5%), and moisture (10%)" [18]. At the same time, the control rats were fed normal feed pellets. Animal handling was according to the recommendations of the "Institute of Health Guide for Care and Use of Laboratory Animals". "The Research Ethics Committee approved the National Research Centre of number 19161".

The rats were separated into four groups (Seven rats each):

Group-I: Control normal rats received vehicle for 3 months with normal feed pellets.

Group-II: Obese group fed on HFD diet with 25% sucrose in drinking water for 3 month to induce obesity

Group-III: Low dose GB group; rats fed similar to obese group and were daily administered GB (200mg/kg, orally) for two months.

Group-IV: High dose GB group; rats fed similar to obese group and were daily administered GB (400mg/kg, orally) for two months.

2.7. Determination of body mass index (BMI)

Rats in both the control and experimental groups had their body mass and nose-anus lengths (NALs) measured at the outset of the study and again at 15, 30, 45, and 60 days. The body mass index was calculated by dividing the square of the subjects' weight (g) and nose-anus length (cm).Thus, a body mass index of 0.68 or above was used as the cutoff for classifying individuals as obese, as outlined by Novelli et al. 2007 **[**19]. After 3 months, any experimental rats that had not gained enough weight were to be discarded. However, all the rats in the experimental group obtained the goal BMI and were all included.

2.8. Samples collection

Blood was drawn from the tail vein three months later while the subjects were sedated with ketamine. The plasma was collected by centrifuging the sample. The collected supernatant was iced in an 80 °C freezer for more analysis. The animals were put down while under the effects of ether anesthesia, and their hearts and aortas were removed for histopathological examinations.

The plasma levels of leptin and adiponectin were estimated by immunoassay method "ELISA, Sunlong Biotech Co. Kit, China", Cat numbers E-CL-R0416, E-OSEL-R0006. Cholesterol, triglycerides (TG), high density lipoprotein (HDL), and low density lipoprotein (LDL) were evaluated colorimetrically using kits manufactured by the Salucea Company, Netherlands. The atherogenic index was calculated with the formula = log (TG/HDL-C).

2.9. Plasma and cardiac oxidative stress parameters

Malondialdehyde (MDA), superoxide dismutase (SOD) and glutathione (GSH) were determined in plasma and heart tissues were evaluated colorimetrically using Biodiagnostic kits, Egypt.

2.10. Plasma inflammatory markers

TNF-α, MCP-1, IL6, ENA-78, resistin, and CRP concentrations were evaluated by the ELISA assay "Sunlong Biotech Co. Kit, China".

2.11. Trace element analysis

Fe, Zn, and Cu ions were determined using an "Agilent 5100 Synchronous Vertical Dual View (SVDV) ICP-OES, with an Agilent Vapor Generation Accessory VGA 77". Nitric acid was used to degrade all cardiac tissue samples prior to metal determination because it provides a sufficient matrix for consistent metals recovery using the chosen analytical method [20].

2.12. Insulin resistance parameters

Blood glucose was detected by using calorimetric method following instruction of "Salucea Company kit. Plasma insulin was assayed by immunoassay (ELISA) according to instruction of Sunlong Biotech Co. Kit (China). Insulin resistance index was determined with the aid of this calculation: - Insulin resistance "(HOMA-IR) = fasting glucose (mg/dl) x fasting insulin (mIU/ml)/ 405".

2.13. Plasma biomarkers for myocardial function

Troponin I was evaluated with an immunoassay technique according to instruction of Sunlong Biotech Co. Kit (China). Creatine phosphokinase-MB and lactate dehydrogenase activities were determined as kinetic (Centronic-gmbh Company, Germany).

2.14. Histopathological Examinations of Heart and Aorta

The cardiac muscles and aorta were kept in 10% buffered formalin, dehydrated in graded ethanol, and inserted in paraffin using standard procedures of control, obese, and treated rats. For histopathological

examination, sections of thickness 5µm light microscope were stained with hematoxylin and eosin.

2.15. Statistical Analysis

Differences between groups were examined for significance by using Analysis of Variance (ANOVA) followed by LSD comparison test estimated by SPSS software. Values were declared as mean ± S.E. for 28 rats. The level of statistical significance was $P<0.05$.

3. Results

3.1. Total phenolics and flavonoid contents

The total contents of phenolics and flavonoids of GB extract consisting of both the husk and the fruit are presented in Table 1. TPC is calculated as gallic acid equivalent (GAE)/g plant extract and the TFC is calculated as rutin equivalent (RE)/ g of dried extract.

Table 1 : Total contents of phenolics and flavonoids in GB extract

***Physalis peruviana* fruit with husk extract.**	**Concentration (M±SE)**
Total phenolics content (mg GAE/g of dried extract)	**136.8 ± 5.401**
Total flavonoids content (mg RE/g of dried extract)	**46.9±4.503**

Values were presented as the mean (M) of triplicates± Standard Error (S.E.)

3.2. Effect of goldenberry on Anthropometric measures of obese rats

In our study, there were variable changes in body weight, BMI, Naso-anal length, and waist in different experimental groups, i.e., these previous parameters were increased significantly in the obese group along 15, 30, 45, 60 days when compared to the control. After ingestion of GB at low and high doses, the above parameters decreased, particularly in the high doses group relative to the obese group ($P<0.05$) (Table 2).

Table 2: Effect of GB extract on anthropometric measurements of obese rats.

Parameters \ Groups / Time		Control	Obese	Obese+ Low dose of GB	Obesity+ High dose of GB
Body weight(g)	**Basal**	188±4.6	443±26.6*	357±13$^{@}$	324±9.1$^{@}$
Waist (cm)		14.9±0.43	18.14±0.56*	16.6±0.26	16.14±0.41$^{@}$
Naso-anal length (cm)		16.46±0.6	24.22±1.12*	26±0.9	25.12±0.91
BMI		0.7±0.05	0.78±0.09	0.54±0.05$^{@}$	0.53±0.051$^{@}$
Body weight(g)	**15 days**	191.4±4.5	439.4±29.9*	344±14.4$^{@}$	304±7.5$^{@}$
Waist (cm)		14.9±0.31	18.1±0.4*	16.7±0.25$^{@}$	16±0.32$^{@}$
Naso-anal length (cm)		16.9±0.67	23.8±1.16*	26.22±0.9	25.6±0.91
BMI		0.69±0.06	0.8±0.091	0.51±0.034$^{@}$	0.47±0.044$^{@}$
Body weight(g)	**30 days**	194.2 ± 4.74	449 ± 28.3*	336 ± 14.35$^{@}$	288.8 ± 7.17$^{@}$
Waist (cm)		15.08 ± 0.333	18.96 ± 0.35*	16.2 ± 0.29$^{@}$	15.38 ± 0.26$^{@}$
Naso-anal length (cm)		17.26 ± 0.7	23.68 ± 1.07*	26.54 ± 0.82	25.9 ± 0.85
BMI		0.66 ± 0.056	0.82 ± 0.087	0.48 ± 0.031$^{@}$	0.44 ± .041$^{@}$
Body weight(g)	**45 days**	199.2 ± 3.83	456.2 ± 26.16*	325 ± 17.02$^{@}$	284.6 ± 6.97$^{@}$
Waist (cm)		14.68 ± 0.29	19.34 ± 0.29*	15.98 ± 0.27$^{@}$	15.06 ± 0.27$^{@}$
Naso-anal length (cm)		17.32 ± 0.7	23.48 ± 1.01*	26.62 ± 0.78$^{@}$	25.98 ± 0.84
BMI		0.67 ± 0.052	0.85 ± 0.083*	0.46 ± 0.031$^{@}$	0.43 ± 0.039$^{@}$
Body weight(g)	**60 days**	202 ± 3.37	465 ± 23.55*	295.4 ± 14.32$^{@}$	279.8 ± 6.94$^{@}$
Waist (cm)		14.52 ± 0.3	20 ± 0.158*	15.52 ± 0.27$^{@}$	14.52 ± 0.2$^{@}$

Values were presented as the mean (M) of triplicates± Standard Error (S.E.)

3.3. Effect of goldenberry supplementation on adipocyte hormones and lipid profile of obese rats

In table (3), there was a marked increase in serum triglyceride in the obese group represented by an impairment of their lipid profile level, total cholesterol, and LDL, and a significant decrease in serum HDL levels compared to the normal group (P<0.05). In contrast, there was a significant decrease in serum triglyceride, total cholesterol, and LDL, accompanied by a considerable increase in HDL levels in rats that received low and high doses of GB, compared to the obese group (P<0.05). In rats exposed to a high dose of GB, the levels of triglyceride, total cholesterol, LDL, and HDL were close to those in the control group. In addition, there was a significant decrease in adiponectin levels and an increase in leptin levels in the obese group relative to the control. Moreover, in low and high doses groups, there was an improvement in the level of these two hormones compared to the highly significant obese (P<0.05).

Table 3: Effect of GB extract on adipocyte hormones and lipid profile of obese rats.

Groups / Parameters	Control	Obese	Obese+Low dose of GB	Obese+ High dose of GB
Triglyceride (mg/dl)	46.4±1.633	197.9±4.61*	113.8±5.99@	65.2±4.57@
Total cholesterol (mg/dl)	78.65±2.585	166.4±4.61*	117.6±4.34@	90.02±3.26@
HDL (mg/dl)	65.44±2.735	21.2±1.28*	38.8±1.84@	55.8±1.99@
LDL (mg/dl)	18.5±0.776	167.1±2.74*	76.58±3.07@	46.45±1.88@
Atherogenic index	0.21±0.056	7±0.54*	2.06±0.15@	0.63±0.09@
Leptin(µg/L)	5.3±0.4	21.9±1.6*	10.08±0.45@	6.9±0.37@
Adiponectin (µg/L)	196±5.1	47.4±4.1*	101±2.44@	149±9.3@

All data are expressed as mean ± SE, (* vs control group and @ vs obese group) at p<0.05.

3.4. Impact of goldenberry supplementation on antioxidant and oxidative parameters of obese rats

Fig. 1 showed plasma antioxidant and oxidative stress parameters in obese, low, and high doses of GB compared to control groups. Our results indicated a significant decrease in blood or cardiac tissue GSH and SOD levels of the obese group, and a significant increase in MDA of the two tissues (Fig.1). The blood GSH and SOD levels in low dose or high dose of GB groups significantly increased while MDA significantly decreased compared to control value (Fig 1). There was a positive correlation between both BMI and MDA. Moreover, there was a negative correlation between BMI and GSH, and SOD (Fig. 5).

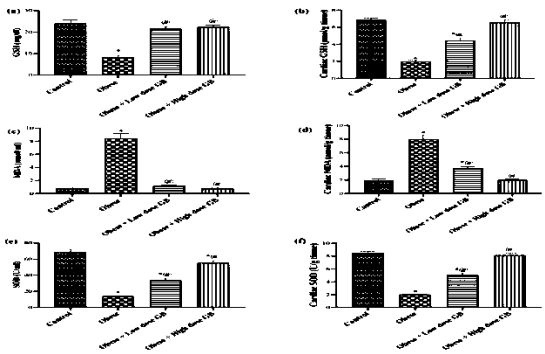

Figure 1: Effect of GB extract on Plasma and cardiac tissue antioxidant and oxidative stress parameters of obese rats. All data are expressed as mean ± SE, (* vs control group and @ vs obese group) at p<0.05.

3.5. Influence of goldenberry extract on plasma cardiac markers in obese rats.

Figures 2 and 3 displayed some plasma cardiac and inflammatory markers in four experimental groups. There was a significant increase in cardiac functions such as CK-MB, LDH, and Troponin in the obese group compared to those of the normal group (P<0.05). Also, an increase in all inflammatory markers (TNF-α, IL-6, CRP, resistin, ENA-78, and MCP-1) in the obese group was observed contra the control group. Similarly, in both doses of GB especially at higher doses of GB, there were significant improvements in cardiac functions and inflammatory markers versus the obese groups (P<0.05). Moreover, both cardiac and inflammatory markers showed a positive correlation with BMI as shown in fig. (5).

3.6. Influence of goldenberry extract on cardiac content iron, zinc and copper in obese rats.

The iron (Fe) and copper (Cu) in the cardiac tissue of obese rats increased significantly while zinc content decreased significantly compared to the control (Table 4.). Further, the obese rats supplemented with GB had significantly improved all trace elements when compared to both the control and obese groups.

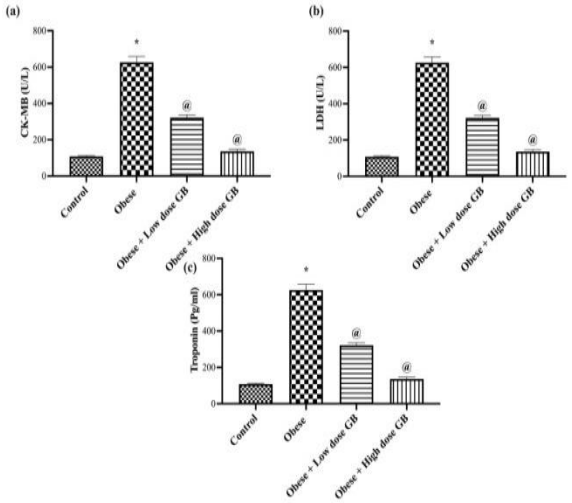

Figure 2: Action of GB extract on biomarkers of Cardiac enzymes of obese rats. All data are expressed as mean ± SE, (* vs control group and @ vs obese group) at p<0.05.

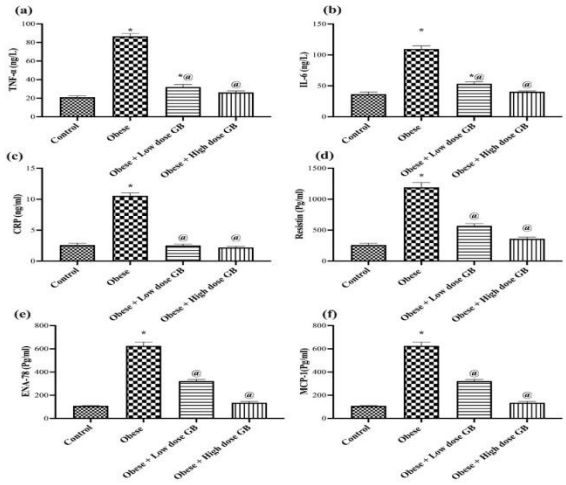

Figure 3: Inflammatory indicators in the plasma of obese rats and their response to GB extract. Each bar indicates the mean ± SE. (* vs control group and @ vs obese group) at p<0.05.

Table 4: Effect of GB extract on trace elements of cardiac tissue in obese rats

Parameters / Groups	Zn (µg/g tissue)	Fe (µg/g tissue)	Cu (µg/g tissue)
Control	9.04 ± 0.46	11.86 ± 0.77	4.66 ± 0.28
Obese	2.2 ± 0.25*	40.38 ± 1.7*	28.44 ± 1.5*
Obese+ low dose of GB Extract	4.26 ± 0.29@	22.66 ± 1.4@	17.8 ± 2.11@
Obese+ high dose of GB Extract	8 ± 0.47@	14.28 ± 1.1@	7.92 ± 0.5@

Each value indicates the mean ± SE. (* vs control group and @ vs obese group) at p<0.05.

3.7. Influence of goldenberry extract on insulin resistance parameters in obese rats.

The impact of GB on insulin resistance measures in obese rats was depicted in Figure 4. Low- and high-dose treatment of obese rats with GB extract reduced increases in plasma insulin and glucose concentrations and the insulin resistance index (Fig. 2). Higher doses of GB extract have been shown to dramatically reduce insulin levels compared to lesser doses.

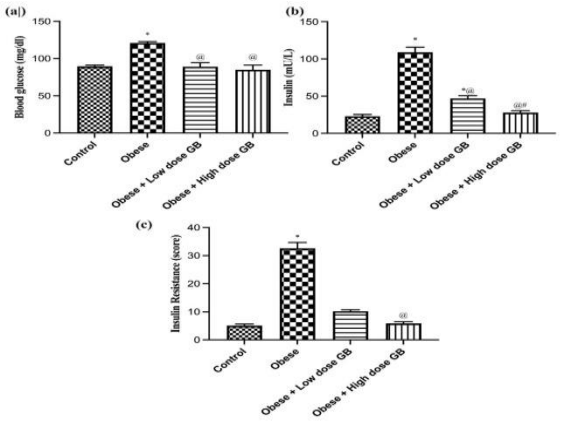

Figure 4: Insulin resistance measures of obese rats affected by GB extract. Each bar indicates the mean ± SE. (* vs control group and @ vs obese group) at p<0.05.

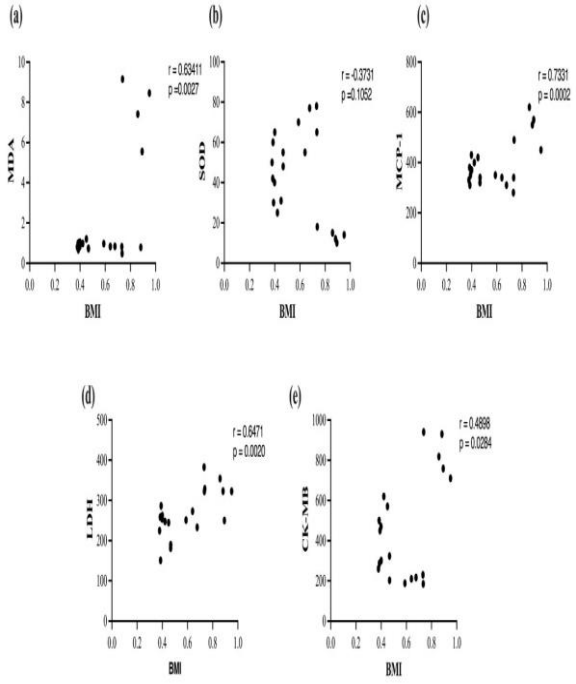

Figure 5: Correlation of BMI with plasma MDA, SOD, MCP-1, LDH, and CK-MB

3.8. Effectiveness of goldenberry supplementation on the histological investigation of the Heart and Aorta

The myocardium of the control group is striated, arranged in a linear array with muscle fibers branching across the striation, and the centrally located vesicular nuclei are joined together by intercalated discs. Besides, the cardiac muscle fibers are separated by a delicate layer of connective tissue with well-evidenced myocardial blood capillaries (Fig .6A). The obese group of rats revealed more pronounced alterations in the form of cardiac myofibril degeneration and disorganization together with sarcoplasmic vacuolation, deposition of fat degenerated, and hyalinization of muscle fiber. Noticeable congestion and dilation of the myocardial blood vessel have been shown, with diffused/focal inflammatory infiltrate and pyknotic nuclei (Figs6B&C&D). Similarly, the obese group treated with the low dose of GB extract still had severe damage to the heart tissue in the form of marked dilatation and congestion of blood capillaries with hypertrophic of muscle fiber, hyalinization, and vacuolation (Fig.6E). The group of obese rats treated by the high dose extract exhibited a recognizable recovery and restoration of the normal histological appearance of the muscle fibers with few tiny inflammatory cells still present (Fig.6F).

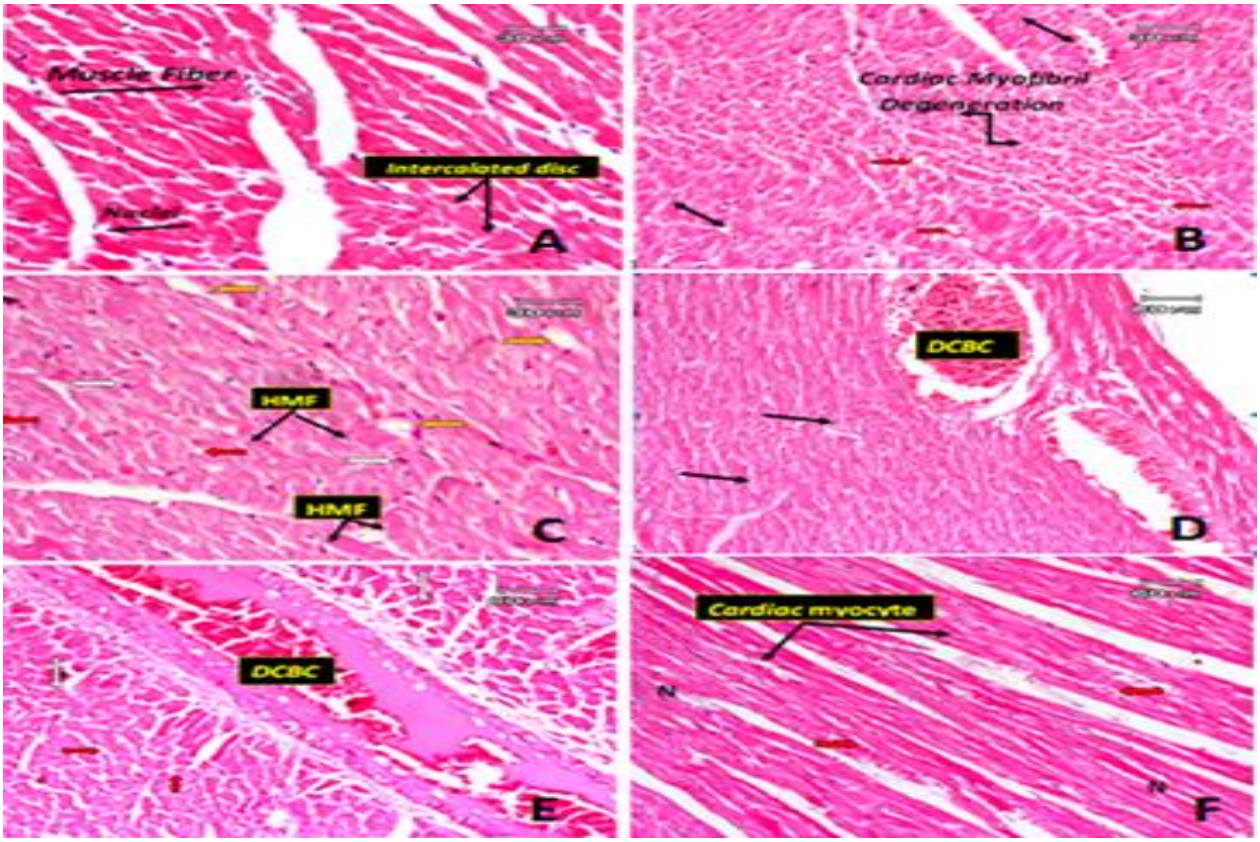

Figure 6: Photomicrographs of the heart of rat (A) normal control showing normal branching striated cardiac myocyte with the intercalated disc (black arrow), acidophilic sarcoplasm and centrally-located nuclei, (B) cardiac muscle section of obese rats showing cardiac myofibril degeneration and hemorrhage (black arrow), sarcoplasmic vacuolation (red arrow) and red blood cells in between muscle fibers (black arrow), (C) cardiac muscle section of obese rats (another filed) showing damaged myocytes architecture, hypertrophy with loss of cellular organization, sarcoplasmic vacuolation (red arrow), deposition of fat degenerated muscle fibers (yellow arrow) and pyknotic nuclei (white arrow), muscle fibers hyalinization (HMF), (D) cardiac muscle section from obese rats (another filed) showing dilatation, the congestion blood vessel of cardiac (DCBC), diffuse/focal few inflammatory infiltrate (black arrow), (E) cardiac muscle section of obese rats treated with a low dose of GB extract show severe heart tissue damage which was still present in the form of marked dilatation and congestion of blood capillaries (DCBC) with hypertrophic of muscle fiber, hyalinization (white arrow) and vacuolation (red arrow), (F) the cardiac muscle section of obese rats treated with high dose extract of GB exhibited noticeable recovery and restoration of the normal histological architecture of the cardiac myocyte, normal nuclei (N), but very few inflammatory cells (red arrow) still exists.

Histological examination of the sections of the aorta in the control group revealed that the tunica intima was intact with a thin wavy corrugated endothelium, normal subendothelial layer, and wavy corrugated internal elastic fibers. The tunica media is comprised of elastic fibers and smooth muscle. The outermost layer is the tunica adventitia and consists of loose connective tissue (Fig.7A). In obese rats, the aortic section showed an absence of corrugation with bulge formation in the tunica intima, degeneration of endothelial cells, and inflammatory cells infiltration. Fat vacuoles were noticed in the intimal, the subendothelial layer, and the tunica media. Also, there was degeneration of the muscle elastic fiber and edema in adventitia with fewer elastic fibers in both the tunica intima and tunica media (Figs7B&C). At the same time, obese rats subjected to GB extract with a low dose revealed thickening of the tunica intima with protrusion of intima into the lumen and the appearance of an extended thickening of the tunica media. Vacuolation was also recorded in intima and media (Fig, 7D). Obese rats were given a high dose of GB showed normal histological features of the tunica intima, tunica media, and tunica adventitia (Fig.7E).

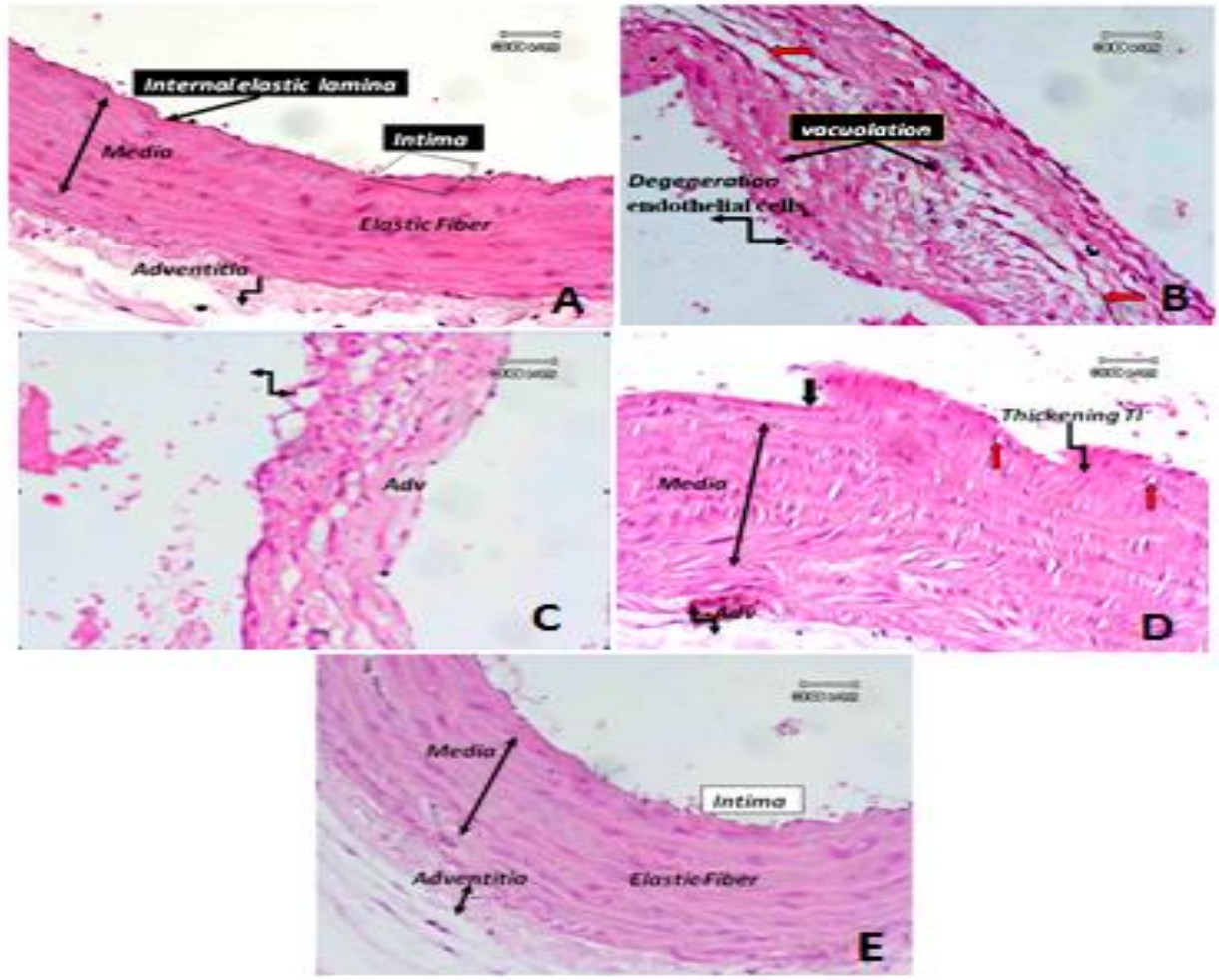

Figure 7: Photomicrographs of the aorta of a rat (A) Normal control showing normal tunica intima, facing the lumen. Elastic fibers and smooth muscle make up the tunica media. The normal amount of collagen fibers and connective tissue were exhibited in the tunica adventitia (wavy arrow), (B) aorta section of obese rats showing absence of corrugation with bulge formation in the tunica intima and degeneration of endothelial cells.., inflammatory cells (wavy arrow), and degeneration or loss of smooth elastic fiber (red arrow)(C) section of the aorta of obese rats (another filed) showing inflammatory fat vacuoles forming foam cells were noticed in the intimal subendothelial layer and edema in the adventitia(Adv), (D) a section of the aorta of obese rats exposed to a low dose extract showing thickening of tunica intima with protrusion of intima into the lumen (black arrow) and vacuolation in the subintimal layer (red arrow), media thickening , and vacuolation, (E) a section of the aorta of obese rats treated with the extract (G berry) at high dose exhibited normal histological feature (Tunica intima, Tunica media, and Tunica adventitia).

4. Discussion

Heart disease and lifestyle factors are markedly connected with a high degree in all obesity indicators [21]. Excess fat or lipids accumulated in bodily tissues due to extended eating of fat-rich meals and a hereditary abnormality cause CVD. The main target of CVD, myocardial infarction, and stroke is hyperlipidemia. It's a severe disease that causes problems with lipid levels and redox balance in the body. Natural products are essential since they can prevent metabolic and CVD. [4, 22]. This study clarifies the role of goldenberry (GB) fruit and husk extract in the treatment of CVD brought on by obesity in experimental rats at doses of 200 mg/kg and 400 mg/kg.

High body mass index can lead to myocardial dysfunction even in the nonexistence of any CVD or risk factors. Additionally, a higher degree of body mass index confers an increased risk and portends the presence of subclinical myocardial dysfunction [23]. In this study, some anthropometric measurements were performed at 0, 15, 30, 45, and 60 days along with the experiment for different groups of rats (normal control, high fat fed obese rats in addition to low and high doses of GB), and there was a significant increase in body weight, BMI, waist, and naso-anal length in the obese group in contrast to the control group. On the other hand, low and high doses of GB extract improved the anthropometric parameters.

Cholesterol is always a problem since blood total cholesterol and LDL are closely linked to coronary heart disease [6]. Results showed an improvement in lipid profiles after administration of GB extract, especially at a high dose. Phytosterols in GB extract lower total cholesterol and LDL concentrations in plasma. Our results are in agreement with those in references 24-28.

In addition, this work evaluated two markers of obesity (leptin and adiponectin); the results illustrated that obese rats had a high concentration of leptin and a low concentration of adiponectin when compared to the control, and in contrast, these two hormones improved in their levels after being exposed to additional goldenberry extract at low or high doses when compared to obese group ($P<0.05$) [29, 30].

Moreover, GB has indirect mechanisms to mitigate cardiac pathology in obesity, such as a reduction in insulin resistance, dyslipidemia, and leptin levels or restoration of adiponectin concentration [31]. Moreover, insulin resistance observed in the present obese rats may be involved in CVD. It can provoke hyperglycemia, which triggers oxidative stress and an inflammatory response that leads to cell damage. Flavonoids and phenolics in goldenberry have higher radical scavenging and anti-lipid peroxidation activity. Therefore, GB was considered to have antihyperlipidemic and cardioprotective activity [22, 32].

Oxidative stress and inflammation markers were raised, and antioxidant concentrations were reduced in the obese subjects [33]. Our results indicated a significant increase in glucose, cholesterol, triglycerides, leptin, blood pressure, and inflammatory markers that may result in oxidative stress. The possible sources of oxidative stress in obesity include hyperglycemia [34], hypercholesterolemia [35, 36], chronic inflammation [37], and hyperleptinemia [38]. There is an abnormal increase in adipose tissue because of hypertrophied and poorly oxygenated adipocytes in obese people. Inflammatory cytokines such as tumour necrosis factor alpha, interleukin 6 and monocyte chemoattractant protein-1 are often secreted by this defective adipose tissue. Pro-inflammatory adipokines are secreted by hypertrophic adipocytes in obesity, which attract macrophages and increase inflammatory signals [39, 40]. Other possible contributors to oxidative stress in obesity are the high cardiac iron content, higher copper level, and decreases in zinc concentration observed in the actual work. The results of these study were consistent with Sachinidis et al. [41].

Goldenberry extract can be applied as a nutritional antioxidant to delay aging and act as a protector from diseases caused by ROS by reducing oxidative damage in tissues [42,43]. The effects of goldenberry in reducing the damage of oxidative stress parameters in obese rats could be related to its high concentrations of polyphenols and flavonoids, which lead to an improvement in the procedure of renewal by free radicals annihilation [44-46]. GB extract has been proven to possess antioxidant activities [47] and anti-inflammatory activities [48].

Our findings elucidate that obese rats treated with GB caused a reduction in the pathological alterations observed in the cardiomyocytes. The reduction in pathological changes may be referred to as the direct effect of GB as an antioxidant, which is deduced from a lowering of cardiac MDA and iron contents or enhancement of cardiac GSH and SOD. The antioxidant properties of GB were reported [49-51]. The presence of ascorbic acid (vitamin C) and phenolics in goldenberry may contribute to the high concentration of antioxidant ability and free radical scavenging agent [52]. The juice of goldenberry was effective in decreasing systolic blood pressure in hypertension. Hypertension is a common advanced

disturbance that causes several chronic diseases such as CVD [53].

Another significant role of GB in alleviating CVD was affirmed by combating the increase in troponin and creatine phosphokinase observed in obese rats, which are routinely used as diagnostic tools for myocardial injury and coronary syndrome [54, 55]. Treatment of obese rats with GB inhibits the progression of endothelial dysfunction, as evidenced by a reduction in plasma levels of MCP-1, resistin, and CRP. MCP-1, an efficient chemoattractant for monocytes, drives mononuclear phagocytes that accumulate in the newly formed atheroma, which plays an essential role in early atherogenesis [56]. It was found that CRP directly harms the endothelial cells and correlates with atherosclerosis [57].

This study estimated some cardiac and inflammatory biomarkers in obese rats compared to controls and also in rats given low and high doses of GB extract (orally administered daily). The data showed that there were increased levels of CK-MB, LDH, troponin-I, TNF-α, IL-6, CRP, ENA-78, resistin, and MCP-1 in obese rats compared to controls, but after oral administration of GB extract, there was a highly significant reduction and improvement of cardiac and inflammatory biomarkers. Our results were in accordance with Kanda et al., Charradi et al., DeMartini et al., and Feriani et al. [58-61].

In our study, the histopathological examination of the cardiac muscle and aorta of rats that received a high dose of GB showed significant improvement, approaching the normal group, and recovery. On the other side, the pathology of the aorta displayed that, at low doses of goldenberry, tunica intima and media thickness increased, but at higher doses, they revealed a normal histological feature of the aorta. Here, the cardiac muscles of obese rats showed myofiber swelling, vacuolation, scattered hyper-eosinophilia, loss of striation, fragmentation, and sometimes rupture of the myofibers. The pathological changes in the heart muscle of obese rats may be attributed to an elevation in cardiac oxidative stress. Malondialdehyde is a product of lipid peroxidation and is linked with oxidative stress-associated cardiac dysfunction [62-66].

5. Conclusion

Cardiovascular disease is one of the most hazardous obesity complications. The current study offered goldenberry extract as a safe edible natural product to improve cardiac functions, obesity hormones, lipid profiles, organ inflammation, and fat accumulations in the arteries. Glodenberry improves pathological changes in the heart and aorta due to the scavenging of free radicals which, leads to lipid peroxidation, and ferrous reducing agents,which reduce lipid peroxidation. Ultimately, we strongly encourage the use of goldenberry to treat obesity-related cardiac complications as a safe, healthy, and inexpensive natural product.

6. References

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List of abbreviations

BMI	Body mass index
CHD	Coronary heart disease
CK-MB	Creatine phosphokinase-MB
CRP	C- reactive protein
CVD	Cardiovascular disease
ENA-78	Epithelial neutrophil-activating protein 78
GB	Goldenberry
GSH	Glutathione
HDL	High-density lipoprotein
HFD	High fat diet
IL-6	Interleukin 6
LDH	Lactate dehydrogenase
LDL	Low-density lipoprotein
MDA	Malondialdehyde
NALs	Nose-anus lengths
SOD	Superoxide dismutase
TFC	Total flavonoids content
TG	Triglycerides
TNF-α	Tumour necrosis factor-alpha
TPC	Total phenolics content