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Research article

Musa acuminate seed extract attenuates the risk of obesity and associated inflammation in obese mice via suppression of PPARγ and MCP-1

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ABSTRACT

Obesity is a severe public health burden and a major component of metabolic syndrome. It is critical to identify treatment medicines for obesity and associated inflammation. We examined the anti-obesity and anti-inflammatory properties of *Musa acuminate* seeds methanol extract in high-fat diet-induced obesity. Changes in body weight, Lee index, fat mass accumulation, serum cholesterol, and serum triglyceride were monitored. Alteration in the expression of PPARγ, GLUT4, and MCP-1 at the transcript level in adipose tissue was also studied. After tabulation of our data, a significant reduction ($p < 0.05$) was recorded for body weight gain, and fat mass accumulation followed by significant changes ($p < 0.05$) in serum cholesterol, and serum triglyceride levels by the extract. In agreement with the biochemical data, the extract was capable enough ($p < 0.05$) to reduce the mRNA expression of PPARγ, and MCP-1, confirming the ability of the extract to ameliorate the risk of obesity and obesity-associated inflammation. Moreover, an in-silico study showed the high binding affinity of the reported compounds from *M. acuminate* like Delphinidin, Umbelliferon with COX-2, PPARγ, and MCP-1, supporting the notion of the risk-reducing potential of *M.acuminate* for obesity and obesity mediated inflammatory.

1. Introduction

Obesity is a significant component of metabolic syndrome and is considered an important challenge for public health globally. Excess energy accumulation in the body leads to obesity and contributes to different lifestyle diseases like cardiovascular complications, diabetes, insulin resistance, and many more [1]. During the adipogenesis process, adipocyte releases inflammation-stimulating cytokines like monocyte chemoattractant protein-1 (MCP-1) which causes monocytes to migrate into adipose tissue through the endothelial wall. Monocyte-derived macrophages then stimulate the inflammatory cascade leading to adipocyte metabolic dysfunction. A significant increase in serum MCP-1 levels has been documented to support the development of inflammation due to excess adiposity [2]. Moreover, systemic administration of MCP-1 in mice elicited the development of insulin resistance irrespective of

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Abbreviations

COX-2	Cyclooxygenase -2
GLUT4	Glucose transporter-4
HFD	High fat diet
MAPK	Mitogen-activated protein kinase
MCP-1	Monocyte chemoattractant protein-1
PGDS	Prostaglandin D synthase
PGD_2	Prostaglandin D_2
PPARγ	Peroxisome proliferator-activated receptor-γ
15d-PGJ_2	15-Deoxy-Delta-12,14-Prostaglandin J_2
Δ^{12}- PGJ_2	delta-12 Prostaglandin J_2

adipocyte inflammation [3].

Although several complex environmental, biological, behavioral, and cognitive factors are associated with the weight-loss mechanism, dietary modification and lifestyle and behavioral intervention are commonly prescribed to control obesity [4, 5]. Over the years, various medications like orlistat, lorcaserin, and liraglutide have been approved by the FDA for treating overweight and obesity, but most of the drugs are being used more carefully because of potential side effects [6]. In contrast, natural products, including dietary herbs, are now preferably used due to their effective management of overweight and obesity with fewer adverse effects [7, 8].

Musa acuminate, commonly known as 'Banana,' is a trendy and widely consumed fruit, especially in tropical and subtropical regions. It contains lots of minerals and nutrients that are beneficial to health. Banana cultivars have been recorded for their alpha-amylase and alpha-glucosidase inhibitory activities, promoting the recommendation in the management of diabetes [9]. Moreover, bananas and their flower have been documented to have antioxidant and free radical scavenging activities [10, 11, 12]. Banana flower is used in culinary in different countries of the world. The traditional benefit of the banana flower has been noted for cardiac pain, diabetes, asthma, and gastro spasm [13]. Recently, lupeol, an anti-inflammatory agent, has been reported in the ethanol extract of banana flowers [14, 15]. Besides, various plant-based extracts and compounds have been attempted to inhibit obesity and obesity-induced metabolic syndromes [16, 17]. Although different parts of *M. acuminate* have been studied for different pharmacological actions, *M. acuminate* seeds are not studied yet for obesity and related complications. Thus, here we studied the *M. acuminate* seeds, for the first time, to rationale its use for the research and development of functional food and new lead compounds for drug discovery to treat obesity and associated inflammation.

2. Materials and methods

2.1. Plant materials and extraction

M. acuminata seeds were collected from Brahmanbaria, Bangladesh. Bangladesh National Herbarium, Dhaka, Bangladesh recognized the species having a voucher specimen (DACB, 44931). The seeds were rinsed and dried at room temperature under the shed for seven days. The seeds were then ground to a fine powder using a laboratory mill and then extracted with methanol. After filtration with Whatman filter paper, a rotary evaporator was used to concentrate the crude extracts under reduced pressure at 40 °C. The crude extracts were then dried, weighed, and stored in desiccators until further use.

2.2. Experimental animals

Fifteen matured Swiss Albino mice (six weeks old, male and female) were purchased from Jahangirnagar University and were accommodated in the animal house (temperature; 22 ± 1 °C, 12-h light-dark cycle) provided with unrestricted access to food and water as well as regular cage cleaning. The institutional Ethical Committee of Noakhali Science and Technology University gave its clearance (Ref: NSTU/SCI/EC/2021/81) for handling the animals in accordance with the law.

2.3. Experimental design

High-fat diet (HFD) used in our previous study [18] was attempted with slight modification in fat percentage (30% fat, previously we used 20% fat) to induce obesity in mice. A group of mice (n = 10) were fed with HFD for four weeks to make them obese. After development of obesity, obese mice were divided into further two groups, proving extract (200 mg/kg body weight of extract, once per day by oral gavage) with HFD in one group (n = 5) for the next six weeks and another group (n = 5) continued with HFD. Another group of non-obese mice (n = 5) were given a normal diet throughout the experimental period. Bodyweight gain and Lee index [19] were monitored to confirm the HFD -induced obesity.

$$Lee\ index = \frac{Cube\ Root\ of\ Body\ weigh\ (gm)}{Nasoanal\ Length\ (cm)} \times 100$$

At the end of the study period, 24 h fasting period was maintained before the animals were euthanized by diethyl ether followed by decapitation. Biochemical and mRNA expression studies were conducted on the serum samples and the abdominal white adipose tissues respectively.

2.4. Biochemical analysis

Serum lipid profile (Triglyceride, Total Cholesterol) and serum level of liver enzymes (SGPT, SGOT) were estimated utilizing specific analytical kit available commercially (Human Diagnostics, Germany). A semi-automatic biochemistry analyzer (Mindray BA-88A, China) was employed to record the data after validating the test procedures in our laboratory setting.

2.5. mRNA extraction, quantification and qPCR analysis

Following the procedure employed in our previous study [20], total RNA from adipose tissue were extracted with Trizol T-reagent (SRL, India). After the quantification of mRNA (Colibri Micro-Volume Spectrometer, Titertek-Berthold, Germany), cDNA was synthesized from one (1) μg of total RNA with the help of Protoscript-II (BioLabs Inc. New England). The cDNA fragments were amplified by quantitative PCR (40 cycles in CFX96 Touch Real-Time PCR Detection System, Bio-Rad, US) with the specific primers (Macrogen Inc., Korea), in duplicate using Luna Universal qPCR Master Mix (BioLabs Inc. New England). Relative mRNA expression for each gene was estimated by ΔΔCT method using β-actin as control. No Template Control (NTC) in qPCR was used to avoid contamination and primer-dimer formation risks. Also, the MIQE guidelines was followed during the experiment [21].

2.6. Molecular docking

COX-2, MCP-1, and PARPγ proteins were retrieved as pdb files from the protein database (PDB IDs: COX-2:3OLT; MCP-1:1DOM and PARPγ: 5DSY). Water molecules were removed from the pdb files. The protein structures were energetically minimized using a Swiss PDB viewer [22]. The structures of ligands delphinidin, lupeol, and umbelliferone were retrieved from the PubChem database. The ligands were processed using Avogadro software [23]. The prepared ligands were docked to the proteins using Autodock vina v.1.5.6 software [24]. After docking, the results were visualized using pymol [25] and discovery studio software and analyzed for the presence of the hydrogen bonds and the docked sites.

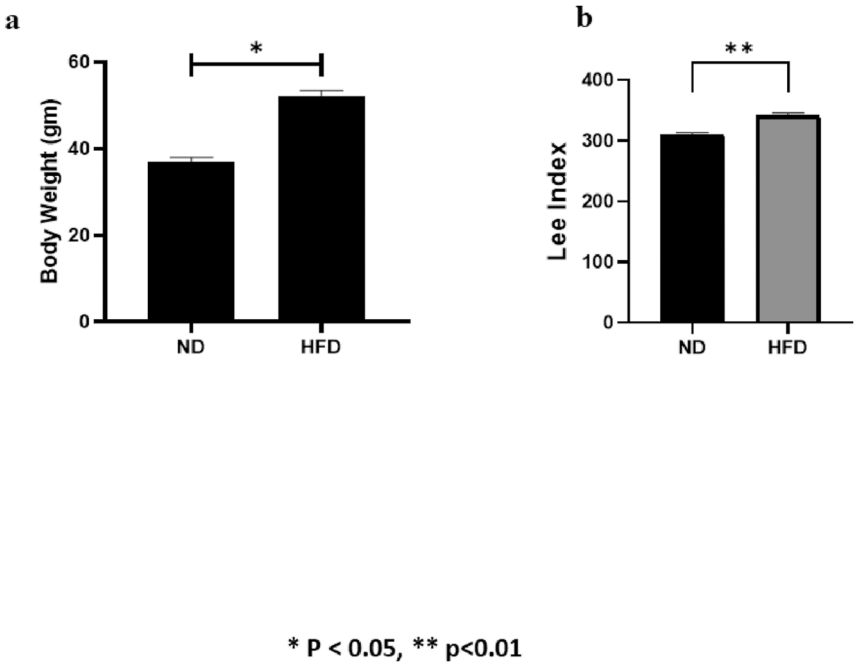

Figure 1. Development of obesity by high-fat diet in experimental mice. (a) Changes in body weight gain (b) Changes in Lee index. ND: Normal diet; HFD: High fat diet, n = 5, *p < 0.05, **p < 0.001 versus normal diet.

2.7. Statistical analysis

Results were expressed as the means ± standard error of mean (SEM). Student's t-test was applied to analyze the statistical significance of the results using GraphPad Prism software version 8.00 for Windows (GraphPad Software, La Jolla, CA, USA). Significant data had a p-value 0.05 or less and denoted as *$p < 0.05$, **$p < 0.01$.

3. Results

3.1. Development of obesity by HFD

Development of obesity was assessed by monitoring body weight gain and Lee index after feeding the mice with HFD. HFD that we used in our previous study [18] was employed with slight modification (changes in fat percentage) in this study. HFD employed in the experiment could induce obesity, as evident by the weight gain pattern and Lee index (Fig. 1). HFD increased the body weight (Fig. 1a) significantly ($p < 0.05$) by 1.5 folds compared with mice fed in the normal diet. The weight gain pattern was supported by the Lee index (Fig. 1b). A statistically significant ($p < 0.01$) elevation in the Lee index was recorded for the mice fed with HFD than that of the control. Our data satisfied the development of obesity in this experimental setting.

3.2. Effect of M. acuminate extract on body weight gain and abdominal fat mass

HFD used in this study was effective enough to increase the body weight and abdominal fat, but the extract used here rescued the elevated body weight gain (Fig. 2a) and abdominal fat (Fig. 2b) significantly ($p < 0.05$). Plant extract helped obese mice to decrease the body wright immediately after the second week of treatment and remained effective until the experiment period was over.

3.3. Effect of M. acuminate extract on serum cholesterol and triglyceride

As a biochemical marker for obesity, serum cholesterol and triglyceride in study animals were estimated. As usual, HFD increased the serum level of total cholesterol and triglyceride compared with a normal diet. However, when the extract was co-administered with the HFD, the level of the total triglyceride (Fig. 3a) and total cholesterol (Fig. 3b) significantly ($p < 0.05$) decreased as like as the body weight and fat accumulation.

3.4. Effect of M. acuminate extract on liver function

Fatty liver is a major complication linked with obesity. Liver function was assessed by estimating the SGOT and SGPT in this experimental setting. The high-fat diet was capable to increase the level of SGOT and SGPT but when the mice were treated with extract along with a high-fat diet, the phenomena were reversed significantly (Fig. 3c and 3d).

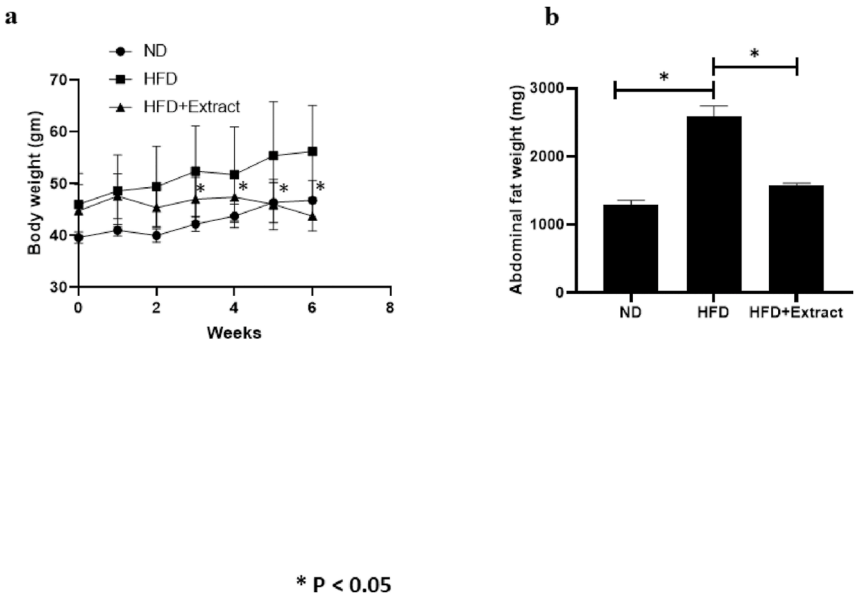

Figure 2. Attenuation of body weight gain by *M. acuminate* seeds (methanol extract) in high-fat diet-induced obese mice. (a) Changes in body weight gain pattern by *M. acuminate* seeds extract, (b) Changes in abdominal fat accumulation by *M. acuminate* seeds extract. n = 5, *$p < 0.05$ versus HFD.

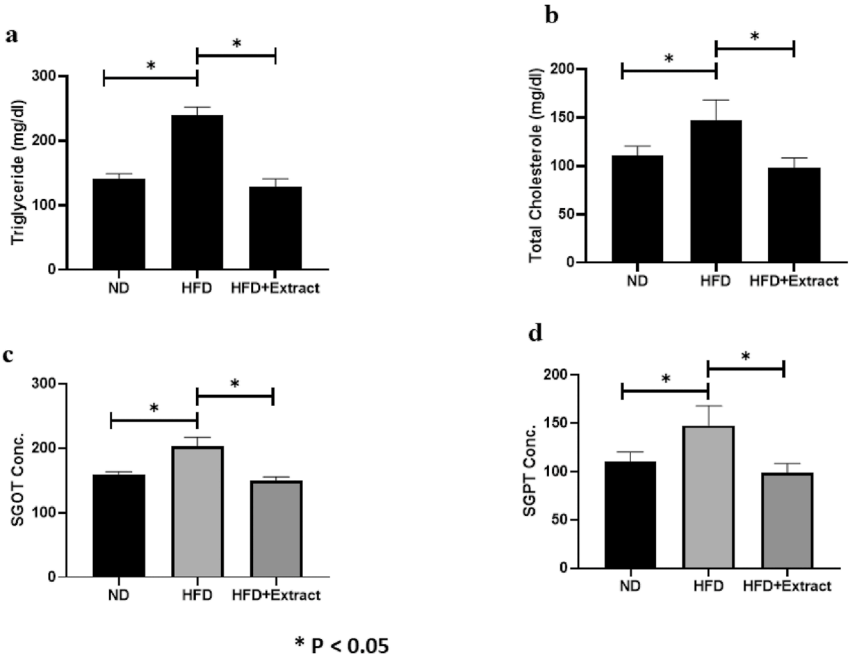

Figure 3. Effect of *M. acuminate* seeds (methanol extract) on serum obesity marker (a) Changes in serum triglyceride, (b) Changes in serum cholesterol, (c) Changes in SGOT, and (d) Changes in SGPT. n = 5, *p < 0.05 versus HFD.

3.5. Effect of M. acuminate extract on adipogenic and inflammatory marker gene expression

Based on the results obtained from the fat accumulation, triglycerides, and cholesterol level, we sought to examine the transcript level of adipogenic marker PPARγ along with GLUT4 under the control of PPARγ. Our data revealed that HFD caused a significant increase in the PPARγ at the mRNA level (Fig. 4a), however after giving the plant extract to obese mice, the phenomenon was reversed significantly ($p < 0.05$), indicating the negative role of the extract to induce adipogenesis in HFD induced obesity. Nevertheless, there were no significant changes in the case of GLUT4 expression (Fig. 4b).

Of interest, we aimed to know the effect of *M. acuminate* extract in the regulation of MCP-1, a pro-inflammatory cytokine,

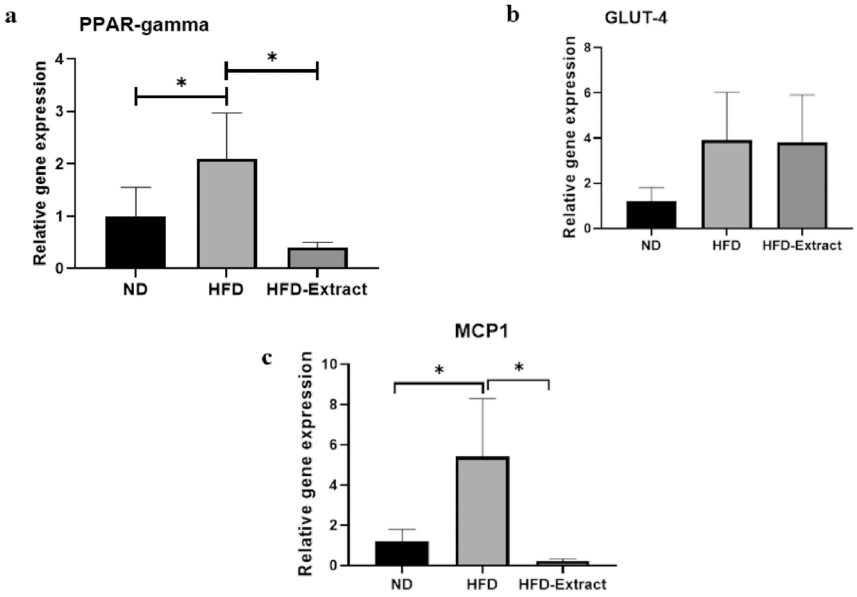

Figure 4. Effect of *M. acuminate* seeds (methanol extract) on adipogenic and inflammatory gene expression normalized to β-actin. (a) relative gene expression of PPARγ, (b) relative gene expression of GLUT4, and (c) relative gene expression MCP-1. n = 5, *p < 0.05 versus HFD.

preferentially expressed in obese adipose tissue to modulate adipocyte functions. Our data showed that plant extract was significantly ($p < 0.05$) capable of reducing the elevated expression of MCP-1 in obese mice, supporting the notion of anti-inflammatory action of *Musa acuminate* extract (Fig. 4c).

3.6. Docking analysis

M. acuminate is attributed to a wide range of bioactive secondary metabolites, among them Umbelliferone, Lupeol, and Delphinidin are most common in different parts of this plant [15, 26]. Here *in-silico* approach was considered to examine the anti-adipogenic and anti-inflammatory effects of these compounds.

Docking results have been summarized in Tables 1 and 2. Lupeol did not show any hydrogen bonds with the target proteins. On the contrary, delphinidin and umbelliferone showed a significant number of hydrogen bonds formed with target proteins.

After docking, Umbelliferone formed four hydrogen bonds with Cox-2 (Gln-204, Thr-207, Tyr-386, and His-389). Two pi-pi interactions have been also seen with Ala-203 and Leu-392. While docking with MCP-1, Umbelliferone generated two hydrogen bonds (Thr-32, Ala-40), two pi anions (Arg-30, Glu-39), and one pi alkyl bond (Pro-55). Umbelliferone forms only two pi alkyl interactions (Lys-289, Ile-290). On the other hand, Delphinidin forms six hydrogen bonds (Gln-193, Ile-350, Leu-353, Tyr-386, Gly-527, and Ser-531) and two pi interactions (Trp-388, Val-524). Two hydrogen bonds (Asn-14, Asn-17) and two pi interactions (Ile-51, Cys-52) have been formed when Delphinidin docked with MCP-1. Docking between Delphinidin and PARPγ shows three hydrogen bonds (Phe-275, Ser-370, Gln-373) and two pi interactions (Ile-290, Ile-369) are formed. Moreover, the respective binding affinity for the docked ligands is fair. Among the ligands, delphinidin and umbelliferone have formed 6 and 4 hydrogen bonds with COX-2. In addition to that, these two ligands have a higher binding affinity (−8.9 kJ/mol and -7.9 kJ/mol, respectively). Delphinidin forms 3 hydrogen bonds with PARPγ, and the binding affinity is higher enough (−7.1 kJ/mol). Based on the information, delphinidin and umbelliferone are potential inhibitors of COX-2. Besides that, delphinidin may also be a promising inhibitor of PARPγ. Docking patterns are presented in Fig. 5(a-c) and Fig. 6(a-c).

4. Discussion

Interest in obesity is gaining more attention because it is considered a significant public health burden worldwide. Along with energetic imbalance, many other factors like physical inactivity, socioeconomic condition, and environmental changes to increase food consumption are responsible for the development of obesity [27]. Obesity-induced metabolic syndrome has been attributed to the inflammatory process [28]. Thus knowing the pathological process of obesity and identifying the therapeutic target is an important issue.

The use of medicinal plants to treat obesity has been well documented [29]. Here we report the anti-obesity and anti-inflammatory activity of *M. acuminate* seeds via the suppression of PPARγ, and MCP-1 expression in HFD-induced obese mice for the first time. Although we did not determine the toxicity of extract, neither death of any experimental animal nor any other side effects were recorded with dose (200 mg/kg BW) applied in this study.

We monitored the body weight gain pattern and Lee index as the indicators for the development of obesity. A significant ($p < 0.05$) elevation in body weight and Lee index were observed in mice treated with HFD, but methanol extract of *M. acuminate* seeds was capable of reducing the body weight gain effectively ($p < 0.05$) in this study. This reduction in body weight gain was observed immediately after the second week and continued up to the end of the study period. The bodyweight reduction was supported by the changes in the Lee index (data not shown). Secondly, we measured the abdominal fat mass accumulation as a function of abdominal obesity. Along with body weight gain, compared to the mice on normal diet, animals on the HFD diet accumulated excess fat, and our extract in the presence of HFD could reverse this phenomenon significantly ($p < 0.05$). These results indicate the anti-obesity action of our extract. Moreover, no significant changes in food intake by the mice of any group were recorded attributing to the body weight loss process but the increased food efficiency ratio in high fat diet group was reduced by the treatment with the extract (data not shown). Additionally, hyperlipidemia characterized by hypertriglyceridemia and hypercholesterolemia is considered the biochemical marker of adipogenesis. We measured the serum total cholesterol and triglyceride to get insight into whether these body weight changes were linked with serum lipid profile. Once tabulated, HFD used in this experiment showed an appreciable elevation ($p < 0.05$) of triglyceride and cholesterol in mice compared with that of a normal diet, but when the mice were given the extract while receiving HFD, a substantial decreased ($p < 0.05$) in lipid accumulation was recorded, supporting further, the ability of the extract to ameliorate the development of obesity. As fatty liver is considered as obesity-related complication, and thus we measured the level of SGOT and SGPT in our experimental conditions. HFD increases the levels of these two hepatic enzymes in obese mice, but the extract reduced the levels of these enzyme significantly, ensuring the use of this extract to reduce the hepatotoxicity developed in obese mice. Although we could not compare our results with other studies directly due to the lack of available information about the anti-obesity activity of

Table-1
Binding affinity between ligands and target proteins.

Protein	Lupeol	Delphinidin	Umbelliferone
COX-2	-	−8.9 kJ/mol	−7.9 kJ/mol
MCP-1	-	−5.6 kJ/mol	−4.7 kJ/mol
PARPγ	-	−7.1 kJ/mol	−6.3 kJ/mol

Table 2
Number of hydrogen bonds formed between ligands and target proteins in molecular docking.

	Lupeol	Delphinidin	Umbelliferone
COX-2	-	6	4
MCP-1	-	2	2
PARPγ	-	3	0

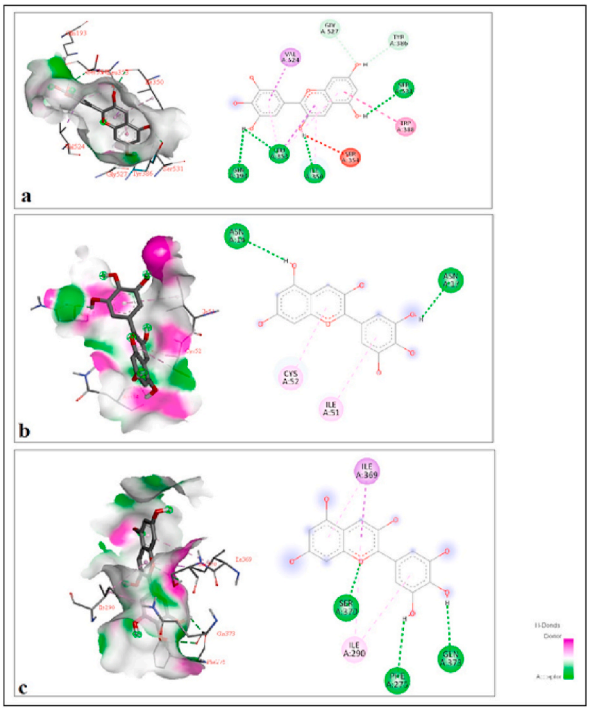

Figure 5. *In silico* approach to study the antiadipogenic and anti-inflammatory effect of Delphinidin from *M. acuminate*. (a) Docking poses of Delphinidin with COX-2, (b) Docking poses of Delphinidin with MCP-1, (c) Docking poses of Delphinidin with PARPγ.

M. acuminate seeds but different parts of *M. acuminate* like banana blossom [30], banana peels [31] have been documented to reduce the cholesterol, triglyceride level in the obese experimental animal. Recently Shidu et al. [32] reviewed the bioactive compounds in bananas and mentioned the presence of catechin, a polyphenolic compound that is known as the lipid-lowering agent. Besides, polyphenolic compounds present in different plant extracts have been noted to decrease lipid absorption by inhibiting pancreatic lipase activity [33]. Moreover, recently, Singh et al. [34] summarized the anti-obesity action of natural polyphenols associated with energy expenditure, appetite suppression, adipocyte differentiation, and gut microbiota. Furthermore, flavonoids reported as cyclo-oxygenase inhibitors [35] have been recorded in *M. acuminate*, playing anti-inflammatory action [36]. Cyclooxygenase enzymes are known to biosynthesize different prostaglandins (PG), including PGD_2 via the terminal PGDS enzyme. PGD_2, along with its degradative product 15d-PGJ_2 and Δ^{12}-PGJ_2 are considered to stimulate adipogenesis by activating PPARγ, the master regulator for adipogenesis [37]. Considering these and being not sure of a particular compound for this anti-obesity activity of *M. acuminate* seeds, we examined the effect of methanol extract of our interest in the mRNA expression pattern for PPARγ and GLUT4 in this study. GLUT4 regulates insulin-stimulated glucose take up in adipose tissue and skeletal muscle to maintain the whole body glucose homeostasis. Higher GLUT 4 activity changes the nutrient distribution and exacerbate transport of glucose in adipose tissue, therefore, increases the adipose tissue bulk [38]. Although we did not find any significant changes in GLUT4 expression in different groups of mice but provided evidence of reduced expression tendency by the extract in this experimental setting, the reduction of GLUT 4 expression might contribute partly to the lowest visceral fat gain. Although we did not study the glycemic effect of *M. acuminate* seed extract here, and failed to locate any report that described the glycemic effect of M. *acuminate* seed, but Abedyo et al [9] noted the anti-hyperglycemic effect of different cultivars of *Musa spp.*

Our data showed that obese mice had a substantial higher transcript level of PPARγ than their non-obese counterpart. However, when the mice were fed with extract in the presence of HFD, attenuated expression of PPARγ at the transcript level was observed, confirming the notion of the anti-obesity action of our extract. Our data advocated that the bioactive compounds present in *M. acuminate* seeds might suppress the expression of PPARγ directly or reduce the biosynthesis of pro-adipogenic prostanoids, involving the cyclooxygenase pathway, the natural ligand for PPARγ for exerting its anti-obesity activity. Besides, any other

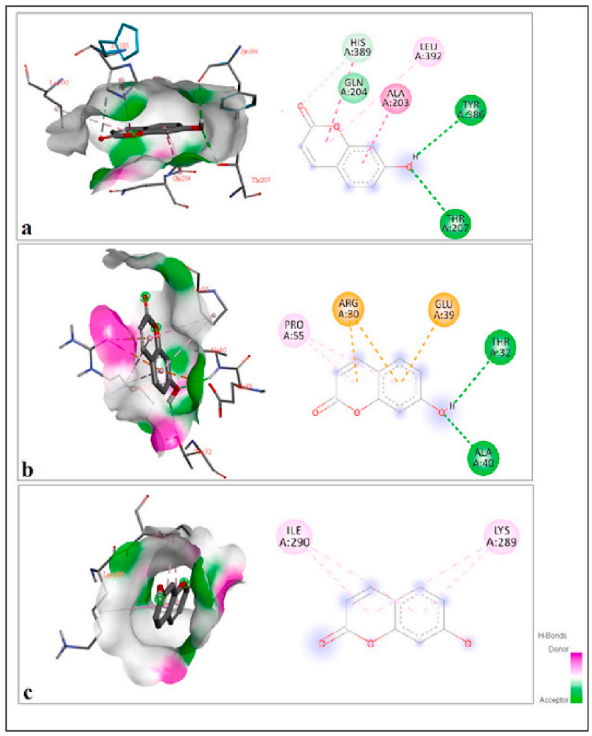

Figure 6. *In-silico* approach to study the antiadipogenic and anti-inflammatory effect of Umbelliferone from *M. acuminate*. (a) Docking poses of Umbelliferone with COX-2, (b) Docking poses of Umbelliferone with MCP-1, (c) Docking poses of Umbelliferone with PARPγ.

unidentified mechanisms involved in this process cannot be excluded to explain the role of the tested extract.

Inflammation is a complex biological event that occurs when tissues respond to harmful stimuli. Now a -days, obesity is recognized a low-grade systemic inflammation [39]. Obesity-induced metabolic syndrome and inflammation are interconnected. Understanding the link between obesity and inflammation will give a new approach to health and weight loss. Although it is not clear how exactly obesity triggers inflammation, it seems that the inflammatory condition is an immune response. Quantitative and phenotypic changes in adipose tissue macrophages are linked with the inflammatory response in adipose tissue. Macrophages, the matured monocytes, migrate to the adipose tissue with the help of MCP-1 and cause adipocyte dysfunction and promote adipocyte-specific inflammatory responses and metabolic syndrome. The noted association of MCP-1 in adipogenesis at the transcript level has been characterized in cultured matured adipocytes using 3T3-L1 cells under the control of PPARγ involving the COX pathway [40]. Here we attempted to check the expression of MCP-1 mRNA, and in agreement with our other results, our extract effectively decreased the expression of MCP-1 transcript in obese mice, showing the anti-inflammatory action in HFD-induced obese mice.

The fact that the extract studied here was capable enough to reduce the mRNA expression of adipogenic and inflammatory genes, and we did not check the effect of this extract at protein levels of these biomarkers. Although we did not isolate compounds from the seed extract, we made use of molecular docking of Delphinidin, Lupeol, and Umbelliferone, the reported compounds from *M. acuminate* [15, 26] with target proteins like COX-2, PPARγ, and MCP-1 involved in inflammatory and adipogenic responses to rationalize the use of banana for the management of obesity and inflammation. All the compounds except Lupeol showed an excellent binding affinity with the target proteins in the order of COX-2 > PPARγ > MCP-1, data presented in Table 1 and Table 2. In concert with the biochemical and gene expression data, these results revealed the anti-obesity and anti-inflammatory action of *M. acuminate*. In another study [41] delphinidin has been reported to inhibit COX-2 expression at both mRNA and protein levels by blocking the MAPK-mediated pathway in LPS-evoked macrophages. Again, the positive role of MAPK has been identified in coordinating adipocyte differentiation [42] and chemotactic responses [43]. Moreover, umbelliferone isolated from *Aegle marmelos* leaves was analyzed to counteract obesity by lipolysis in adipocytes [44]. Thus it is not unlikely that delphinidin and umbelliferone present in *M. acuminate* evoke anti-obesity and anti-inflammatory action by mimicking the similar signaling pathway in HFD-induced obese mice. Besides these, other compounds from *M. acuminate* with antioxidant activity [32] might play a vital role in this process, favoring its traditional uses to heal and treat different diseases to maintain a healthy life.

Thus, we postulate here that the bioactive compounds present in *M. acuminate* block the cyclooxygenase enzyme and eventually reduce the expression of PPARγ and MCP-1 to give the anti-obesity and anti-inflammatory action. Moreover, the effect of *M. acuminate* on TNFα, IL-6, MAPK, and SREBP-1 gene expression are warrant to find out the detailed mechanism of this activity.

5. Conclusion

Our study suggested that *M. acuminate* seeds extract possesses a potent anti-inflammatory and anti-adipogenic activity in HFD-induced obese mice. These findings validated the uses of *M. acuminate* by the indigenous people to treat and heal different diseases to lead a comfortable life. Isolation and identification of the bioactive compounds from the seeds of *M. acuminate* are of further interest.

Author contribution

SI, DRB, MTA, AFMSUD, MSH: conceived and designed the experiments; SI, DRB, SR, ASRS, MH: performed the experiments; SI, DRB, RB, SR, ASAR, MTA, MSH: analyzed and interpreted the data; AFMSUD, MSH: contributed reagents, materials, analysis tools or data; SR, RB, MH, MTA, MSH: wrote the paper.

Data availability

Data is available upon proper request.

Funding information

None.

Conflict of interest

None.

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