



## Obesity-alleviating capabilities of *Acalypha indica*, *Pergularia ademia* and *Tinospora cordifolia* leaves methanolic extracts in WNIN/GR-Ob rats

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### HIGHLIGHTS

- *Acalypha indica*, *Pergularia ademia* and *Tinospora cordifolia* medicinal plants traditionally used in India for the management and treatment of diabetes mellitus ailments.
- We evaluated the efficacy of *Acalypha indica*, *Pergularia ademia* and *Tinospora cordifolia* leaves consumption against genetically mutant obesity rats.
- AP, PA and TC leaves supplementation to genetically mutant obese rats altered body composition.
- *Acalypha indica*, *Pergularia ademia* and *Tinospora cordifolia* is potent nutraceuticals, an alternative to synthetic drugs in obese model.

### ARTICLE INFO

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### ABSTRACT

The present study was intended to assess the anti-obesity efficiency of methanolic extracts of leaves of *Acalypha indica*, *Pergularia daemia* and *Tinospora cordifolia* in WNIN/GR-Ob rats. Leaves of three plants were extracted with methanol by using soxhlet apparatus and flash evaporated. WNIN/GR-Ob rats were taken for this study and plant extracts were supplemented to rats in the form of handmade pellets along with standard diet for 30 days. We evaluated the effects of plant extracts on body and organ weights, blood glucose, and lipid profiles, body composition by TOBEC and DXA and histopathological analysis as well. In the current study, we found that decreased body and organ weights, blood glucose and increased bone mineral density and bone mineral concentration were noticed. We also observed that decreased lipid levels and altered body composition parameters were restored to near normal in treated obese rats when compared to untreated rats. Histopathological study confirmed that these three plant extracts significantly reduced the pathological changes in treated groups caused by obesity. Hence, these results suggest that plant extracts of methanolic extract of *A. indica*, *P. daemia* and *T. cordifolia* (200 mg/kg BW) may be consider in the treatment of obesity.

### 1. Introduction

Obesity is one of the momentous threat factors for metabolic disorder and syndrome of energy equilibrium and basically well thought-out as a disarray of lipid metabolism, which includes hyperlipidaemia and hypertension, potentially leading to type 2 diabetes mellitus, non alcoholic fatty liver disease and cardiovascular diseases [1]. Obesity is categorized by too much fat deposition in adipose tissue and other internal organs like heart, skeletal muscle, liver and pancreatic islet, fundamentally in retort to a state of optimistic energy balance that occurs when intake surpasses energy disbursement. In the current-circumstances obesity remains as a foremost universal communal

health problem for the reason that of its pervasiveness, cutting across all age groups, race and sex. Globally about 1.9 million adults are fatty and 600 million of them are clinically obese. Studies by the World Health Organization (WHO) indicated that at least 2.8 million people pass away each year as a result of being obese [2]. Metabolic disarrays of the liver, lung, kidney and spleen are reflection to be the central causes of obesity by practitioners of Oriental medicine. In particular, the disturbed metabolism in the stomach and spleen caused by heavy hyperphagia, lycorexia, drinking and predilection for junk food cause dampness-phlegm [3].

Choosing the preeminent management for obesity depends on the accurate diagnosis. There are abundant complementary and integrative

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practices, including physical activity, surgical interventions, behavioral therapy, dietary programs, lifestyle modification, medicinal therapies, hypnosis, acupuncture, drug addiction treatments and the use of medicinal plants [4]. Among the options available for the treatment of obesity, the most used ones are regular physical exercises; drug treatments, balanced diets and ranging from lipase inhibitors to anorectics. As occurrence and cruelty of obesity and related co-morbidities are mounting there is an urgent need to develop effective and safe drugs for its treatment. Only a single drug named Orlistat was at presently permitted by Food and Drug Administration for long term obesity management. But it has adverse side effects like nephrotoxicity, respiratory infection, oily stools, dyspepsia, abdominal pain, flatulence, psychiatric and menstrual disorders [5]. Therefore, finding new targets and safe remedial agents is a crucial point for fighting this outbreak. Phytotherapy, more than predilection to synthetic drugs for obesity management is considered as a corresponding approach for treating and preventing disease. At present, the prospective of natural products for the handling of obesity has been explored and it can be a tremendous substitute for the development of safe anti-obesity and anti-diabetic agents [6,7]. A large number of native drugs have been claimed to possess anti-obesity effect in the Indian system of medication [8].

*Acalypha indica* Linn is a herb belonging to family Euphorbiaceae. The twigs and leaves of *A. indica* possess flavonoids, catechols, alkaloids, saponins, volatile oil, fatty acids, phenolic compounds and steroids [9]. *Pergularia daemia* is dispersed right through the hotter parts of India. It has a plays an important role in diverse folk medicines including the Ayurveda system and is supposed to boost defence against various diseases [10]. *Tinospora cordifolia* is deciduous climbing juicy shrub, usually originate in hedges belongs to the family Menispermaceae. It has been recognized for long in the Ayurvedic literature as a vitalizer and tonic and as an antidote for diabetes and other metabolic disorders [11]. There is no scientific evidence of anti-obesity action of these three medicinal plants. Hence, in this study we made an endeavour to evaluate the ameliorative potentials of *A. indica*, *P. Daemia* and *T. cordifolia* against obesity in WNIN/GR-Ob rats.

## 2. Materials and methods

### 2.1. Collection of plant samples (kindly include vouchers numbers)

The plants *A. indica*, *P. Daemia* and *T. cordifolia* were collected from the Herbal garden, Hyderabad, Telangana and India. We are authenticated plant materials with Dr JB Naik, Assistant Professor, Department of Botany, Nizam Collge, Osmania University, Hyderabad. India.

### 2.2. Extraction of plant samples

From the above plants, leaves were collected dried under shade and extracted with methanol by using soxhlet apparatus. The methanolic extracts were flash evaporated and used for the experiment.

### 2.3. Animals

In the present study healthy WNIN/GR-Ob rats were used. Rats weighing 180–230 g were obtained from the National Centre for Laboratory Animal Sciences (NCLAS), National Institute of Nutrition (NIN-ICMR), India. Experimental rats were kept under standard laboratory conditions (moistness; 40–60%; temperature;  $22 \pm 2^\circ\text{C}$ ), and permitted food and water *ad libitum*. The animals were fed with standard rodent diet and provided water *ad libitum*. After one week of adaptation the animals were used for the further experiments. Approval from the Institutional Animal Ethical Committee for the usage of animals in the experiments was obtained as per the Indian Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA) guidelines.

### 2.4. Experimental design

The rats were alienated in to 4 groups (n = 6). Extracts were mixed with powdered standard diet and handmade pellets were prepared. Every day in the morning this handmade pellet (containing test compound) was given to animals and after 1-h 15 g of pelleted diet was weighed and given to each animal. Obese control groups only received pelleted diet. The treatment schedule was continued for 30 days.

Group I: Obese control

Group II: Obese + *A. indica* methalonic extract (200 mg/kg body weight (BW))

Group III: Obese + *P. daemia* methalonic extract (200 mg/kg BW)

Group IV: Obese + *T. cordifolia* methalonic extract (200 mg/kg BW)

At the end of the experiments, all the animals were anaesthetized using low doses of phenobarbitone and sacrificed by cervical decapitation. Blood samples were collected into tubes containing 2% sodium oxalate as an anticoagulant. The samples were centrifuged at  $250 \times g$  for 5 min at  $4^\circ\text{C}$ , and then the plasma was immediately removed and stored at  $-20^\circ\text{C}$  until analyzed.

### 2.5. Body weights and organ weights

Body weights were measured and at the end of the experimental period animals were sacrificed according to the ethical committee (IAEC) guidelines and dissected liver, kidney, brain, spleen and washed in ice cold PBS buffer and taken organ weights.

### 2.6. Body composition by Total Body Electrical Conductivity (TOBEC)

At the end of the experiment body composition which includes leanmass, fat free mass, fat %, total fat (g) content were measured in all experimental groups by TOBEC using small animal body composition analysis system (EM-SCAN, Model SA-3000 Multi detector, Springfield, USA) as described by Refs. [12,13].

### 2.7. Estimation of bone mineral concentration (BMC) and bone mineral density (BMD) by DXA

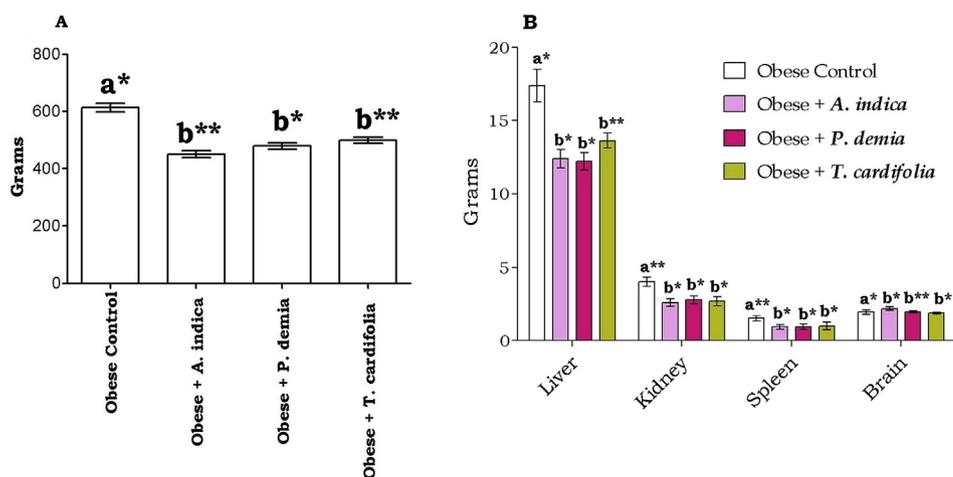
Body composition of experimental animals was assessed at the end of experiment by Dual-X ray absorptiometry (DXA), using body composition analysis system (halogen 1000 series). DXA data were used to compare levels of body adiposity, BMC and BMD between the control and experimental groups, calculations were made according to manufacturer's protocols.

### 2.8. Estimation of biochemical markers

Blood samples were centrifuged at 4000 rpm for 10 min to separate plasma for analyzing biochemical parameters. Blood glucose level was determined by using Span Diagnostic kit, Mumbai, India. The levels of low density lipoprotein (LDL), high density lipoprotein (HDL), triglycerides (TGs) and total cholesterol (TC) were determined using commercially available kits. Fasting plasma glucose and insulin levels were measured using a radioimmunoassay kit as per manufactures protocol Stangen immunodiagnosits, Hyderabad, India.

### 2.9. Histopathological studies

Harvested liver and adipose tissues from the sacrificed animals were fixed in 10% neutral buffered formalin solution, dehydrated in ethanol and embedded in paraffin. Sections of  $5 \mu\text{m}$  thickness were prepared using a rotary microtome and stained with hematoxylin and eosin (H&E) dye for microscopic observations.



**Fig. 1.** Effect of *A. indica*, *P. daemia* and *T. cordifolia* extracts on (A) Body weights (B) Organ weights in control and experimental obese rats. Values are expressed as Mean  $\pm$  SD for 6 animals in each group. Values are statistically significant at \* $p < 0.05$ , \*\* $p < 0.001$ , <sup>a</sup>Significantly different from treated obese control, <sup>b</sup> Significantly different from untreated obese control.

### 3. Results

Fig. 1(A and B) depicts the changes in body and organ weights in the obese control and treated groups during the experiment. The body weights of the obese group was significantly ( $p < 0.05$ ) higher than that of the treated groups. There is a significant reduction in the body weights of animals treated with the all three plant extracts. Among the all three plant extracts *A. indica* shown noteworthy reduction in the body weights of obese rats. There were increased weights of liver, kidney and spleen and decreased weights of testis and brain in obese groups. On the other hand, animals treated with all three plants groups do not shown any significant changes in their organ weights.

There was no observable changes in food intake in obese rats but significant reduction in appetite found in obese rats treated with *A. indica*, *P. daemia* and *T. cordifolia*. Supplementation of plant extracts produces significant decrease in lean body mass, fat-free mass and fat percentage in obese rats when compared to untreated obese rats (Table 1).

Fig. 2 depicts the BMC and BMD levels in control and treated obese rats. Obese rats showed a substantial decrease in BMC and BMD (Fig. 2.1A-2.1D). However, administration of three plants extracts for 30 days, caused significant ( $p < 0.05$ ) increase in BMC (Fig. 2.2) and BMD (Fig. 2.3) when compared to untreated obese rats.

There was a significant ( $p < 0.05$ ) elevation in blood glucose level in obese rats and administration of *A. indica*, *P. daemia* and *T. cordifolia* caused reduction in blood glucose levels when compared to the untreated obese rats (Fig. 3). Obese rats showed increased TC, LDL-cholesterol, TG levels and decrease levels of HDL. Supplementation of *A. indica*, *P. daemia* and *T. cordifolia* demonstrated considerable reduction in the TC, LDL-cholesterol, TG levels and concomitant increase in HDL levels in obese rats (Table 2). Supplementation of *A. indica*, *P. daemia* and *T. cordifolia* demonstrated considerable changes in levels of glucose and insulin in obese rats (Table 3).

**Table 1**

TOBEC analysis and food intake in control and experimental obese rats.

|                    | Obese Control                     | Obese + <i>A. indica</i>          | Obese + <i>P. daemia</i>         | Obese + <i>T. cordifolia</i>      |
|--------------------|-----------------------------------|-----------------------------------|----------------------------------|-----------------------------------|
| Food Intake(g)     | 261.42 $\pm$ 9.16 <sup>***</sup>  | 202.8 $\pm$ 16.57 <sup>b**</sup>  | 198.66 $\pm$ 18.92 <sup>b*</sup> | 215.16 $\pm$ 15.07 <sup>b**</sup> |
| Lean body mass (g) | 302.58 $\pm$ 28.42 <sup>***</sup> | 258.60 $\pm$ 37.99 <sup>b**</sup> | 289.90 $\pm$ 19.19 <sup>b*</sup> | 271.73 $\pm$ 25.43 <sup>b*</sup>  |
| Fat (g)            | 355.41 $\pm$ 16.61 <sup>a*</sup>  | 299.72 $\pm$ 29.51 <sup>b*</sup>  | 309.42 $\pm$ 10.2 <sup>b*</sup>  | 321.92 $\pm$ 33.97 <sup>b**</sup> |
| Fat (%)            | 55.8 $\pm$ 0.79 <sup>a*</sup>     | 48.86 $\pm$ 1.04 <sup>b*</sup>    | 45.86 $\pm$ 1.04 <sup>b**</sup>  | 51.20 $\pm$ 0.78 <sup>b**</sup>   |

Values are expressed as Mean  $\pm$  SD for 6 animals in each group.

Values are statistically significant at \* $p < 0.05$ , \*\* $p < 0.001$ .

<sup>a</sup> Significantly different from treated obese control.

<sup>b</sup> Significantly different from untreated obese control.

#### 3.1. Histopathological analysis

In Fig. 4 histological examination, rats showed signs of hepatic steatosis with severe swelling of hepatocytes and fat accumulation. Interestingly, the liver sections made from *A. indica*, *P. daemia* and *T. cordifolia* (200 mg/kg BW) treated rats did not show intense changes as that of control rats indicating its protective effect on them, though insufficient. On the same lines, the histology sections of adipose tissue of control obese rats showed hypertrophy and hyperplasia of adipocytes when compared with treatment groups. Supplementation of *A. indica*, *P. daemia* and *T. cordifolia* decreased fat cell size and volume, with the maximum therapeutic effect being observed at 200 mg/kg BW *A. indica*, as can be seen in Fig. 4 indicating the antiadipogenic activity of *A. indica*.

### 4. Discussion

Obesity is a clinical state in which unusual or extreme fat accumulates in the body to the extent that the health is worst. The international incidence of obesity is mounting drastically and consequently there is a necessity of safe and long term efficient drugs to control obesity [14]. Several models are accessible which bear a resemblance to the human obesity and among all models mutant models such as WNIN/GR-Ob is advantageous model for experimental obesity. WNIN/GR-Ob is a mutant obese rat strain with altered glucose tolerance developed at the National Institute of Nutrition (NIN), Hyderabad, India, from the existing 80 year old Wistar rat (WNIN) stock colony. WNIN/GR-Ob mutant was result of across between euglycaemic obese WNIN/Ob, and lean WNIN/GR showing glucose tolerance trait at four months of age [15]. WNIN/GR-Ob mutants had high growth, polydipsia, polyuria, glycosuria, hyperphagia, higher fat mass and lower lean body mass. These mutants, at around two months of age can exhibit unusual response to glucose load, hyper insulinaemia, hyper cholesterolaemia, hyper leptinaemia and hyper triglyceridaemia [13,16]. Therefore, in

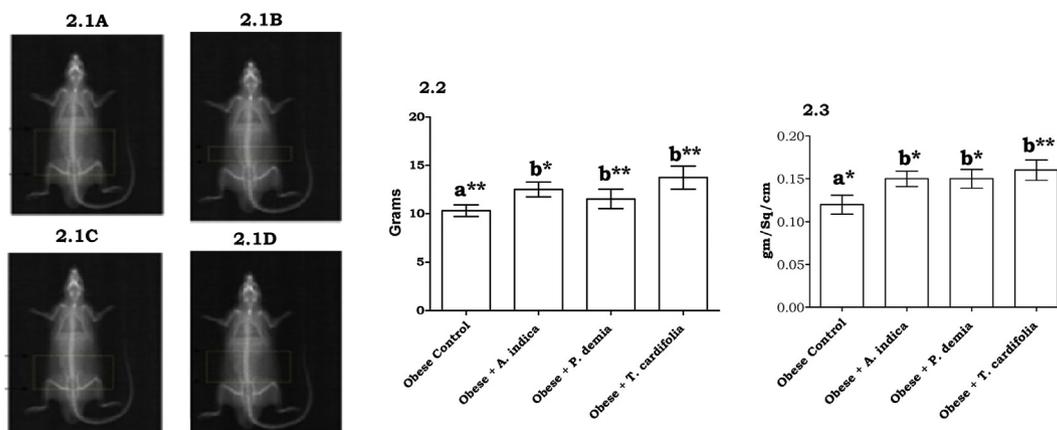


Fig. 2. Effect of *A. indica*, *P. daemia* and *T. cordifolia* extracts on (2.1)DXA (2.2) BMC (2.3) BMD in control and experimental obese rats. Values are expressed as Mean  $\pm$  SD for 6 animals in each group. Values are statistically significant at \* $p < 0.05$ , \*\* $p < 0.001$ , <sup>a</sup>Significantly different from treated obese control, <sup>b</sup> Significantly different from untreated obese control. 2.1A: Obese control, 2.1B: Obese + *A. indica*, 2.1C: Obese + *P. demia*, 2.1D: Obese + *T. cordifolia*.

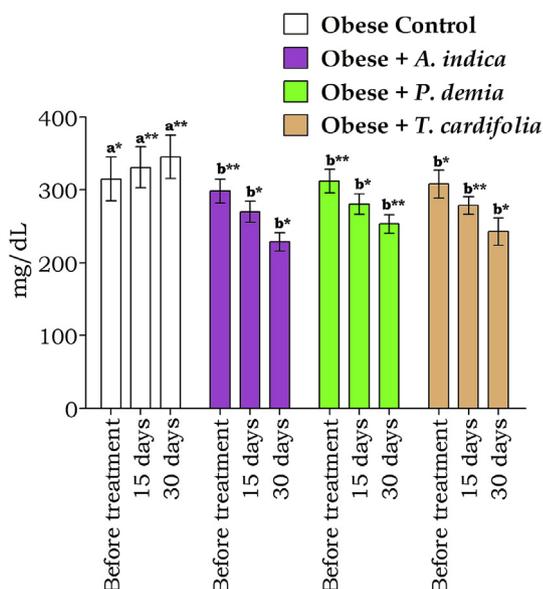


Fig. 3. Effect of *A. indica*, *P. daemia* and *T. cordifolia* extracts on blood glucose in control and experimental obese rats. Values are expressed as Mean  $\pm$  SD for 6 animals in each group. Values are statistically significant at \* $p < 0.05$ , \*\* $p < 0.001$ , <sup>a</sup>Significantly different from treated obese control, <sup>b</sup> Significantly different from untreated obese control.

the current study we have taken WNIN/GR-Ob rats to evaluate the anti-obesity potential of *A. indica*, *P. daemia* and *T. cordifolia*.

There is an excellent relationship between body weight and its composition in relation to organ weights and the peril of metabolic disorders [17]. Obesity and overweight are also distinct as undue or abnormal fat accumulation triggered by discrepancy in energy

expenditure and intake. The elevation in body weight might be due to increase in energy intake foremost to augmented fat deposition and Lee-index of animals. In the present study, we found that the body weights were markedly reduced in the obese groups treated with *A. indica*, *P. daemia* and *T. cordifolia*. On the other hand, we found that the feeding of *A. indica*, *P. daemia* and *T. cordifolia* for 30 days controlled the increases in organ weights of the heart kidney, liver and spleen. Similarly, it is reported that the obese state leads to increase in weight of body organs such as liver, heart, spleen and both kidneys [18]. The diminution in the weights of the animals and recommended a probable mechanism of action based on the reticence of glycosidases and lipases. In our study, results showed that medicinal plants such as *A. indica*, *P. daemia* and *T. cordifolia* may having digestive enzyme inhibitors in their extracts and might be constructive for restraining the assimilation of carbohydrates and fat of the diet, ensuing in weight loss [19].

Hyperphagia, a distinctive characteristic of all hereditary and non-genetic models was apparent in 28 days of age, irrespective of the gender. Even though, hyperphagia is an attribute of all the foremost obese mutants, it require not be a prerequisite to the progression of obesity [16]. The usual daily food expenditure by the animals was observed in this study. The treatment with the plant extracts showed a significant effect, plummeting food consumption, thus was efficient in tumbling the hunger, which characterized an anorexigenic action by an unknown mechanism, and these changes could be related to the weight loss observed for this treatment. TOBEC and DXA analysis of the present study, WNIN/GR-Ob showed differences in lean body mass, total body fat, fat %, BMD and BMC. The data suggest that the elevated fat content contributed to the noticed higher weights observed in obese rats. After treatment with *A. indica*, *P. daemia* and *T. cordifolia* considerably improved the BMC and BMD in obese rats. These actions may be due to the presence of secondary metabolites present in the plant extracts. Secondary metabolites have been reported for their hunger-suppressant assets [20,26]. From this study we are forecasting that secondary

Table 2

Effect of *A. indica*, *P. daemia* and *T. cordifolia* extracts on lipid profile in obese control and treated rats.

|                      | Obese Control                     | Obese + <i>A. indica</i>          | Obese + <i>P. demia</i>          | Obese + <i>T. cordifolia</i>      |
|----------------------|-----------------------------------|-----------------------------------|----------------------------------|-----------------------------------|
| Cholesterol (mg/dL)  | 122.38 $\pm$ 12.58 <sup>a*</sup>  | 89.16 $\pm$ 20.06 <sup>b**</sup>  | 110.41 $\pm$ 31.07 <sup>b*</sup> | 98.93 $\pm$ 27.8 <sup>b**</sup>   |
| Triglyceride (mg/dL) | 314.19 $\pm$ 45.84 <sup>a**</sup> | 205.03 $\pm$ 19.74 <sup>b**</sup> | 251.84 $\pm$ 15.09 <sup>b*</sup> | 190.60 $\pm$ 17.2 <sup>b*</sup>   |
| LDL (mg/dL)          | 175.36 $\pm$ 13.56 <sup>a**</sup> | 120.26 $\pm$ 9.55 <sup>b*</sup>   | 138.10 $\pm$ 10.25 <sup>b*</sup> | 128.50 $\pm$ 17.52 <sup>b**</sup> |
| HDL (mg/dL)          | 42.59 $\pm$ 9.52 <sup>a*</sup>    | 95.25 $\pm$ 12.22 <sup>b**</sup>  | 81.22 $\pm$ 9.25 <sup>b**</sup>  | 74.58 $\pm$ 10.74 <sup>b**</sup>  |

Values are expressed as Mean  $\pm$  SD for 6 animals in each group.

Values are statistically significant at \* $p < 0.05$ , \*\* $p < 0.001$ .

<sup>a</sup> Significantly different from treated obese control.

<sup>b</sup> Significantly different from untreated obese control.

**Table 3**Effect of *A. indica*, *P. daemia* and *T. cordifolia* extracts on insulin levels in obese control and treated rats.

|                  | Obese Control  |                              | Obese + <i>A. indica</i> |                              | Obese + <i>P. daemia</i> |                              | Obese + <i>T. cordifolia</i> |                              |
|------------------|----------------|------------------------------|--------------------------|------------------------------|--------------------------|------------------------------|------------------------------|------------------------------|
|                  | Initial        | After treatment              | Initial                  | After treatment              | Initial                  | After treatment              | Initial                      | After treatment              |
| Glucose (mg/dl)  | 121.36 ± 4.33  | 145.78 ± 5.69 <sup>a*</sup>  | 132.89 ± 9.58            | 99.31 ± 5.13 <sup>b**</sup>  | 141.89 ± 9.25            | 114.11 ± 10.2 <sup>b*</sup>  | 139.99 ± 10.58               | 106.21 ± 8.2 <sup>b*</sup>   |
| Insulin (µu/mol) | 154.89 ± 25.68 | 169.38 ± 37.58 <sup>a*</sup> | 152.31 ± 20.45           | 139.16 ± 17.06 <sup>b*</sup> | 157.12 ± 25.41           | 141.41 ± 31.07 <sup>b*</sup> | 155.76 ± 24.25               | 141.93 ± 17.8 <sup>b**</sup> |

Values are expressed as Mean ± SD for 6 animals in each group.

Values are statistically significant at \* $p < 0.05$ , \*\* $p < 0.001$ .

<sup>a</sup> Significantly different from treated obese control.

<sup>b</sup> Significantly different from untreated obese control.

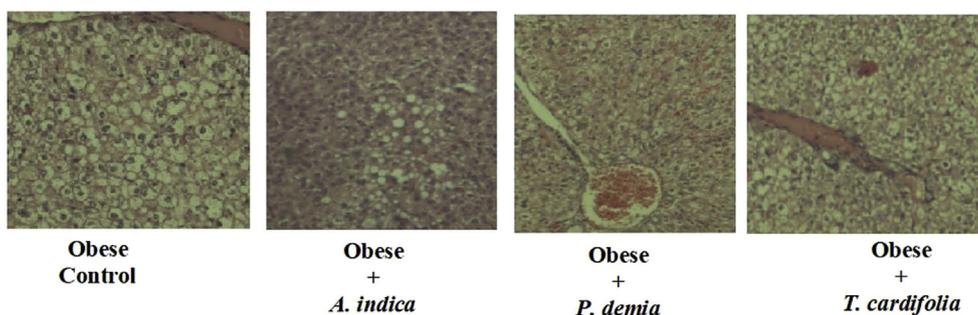


Fig. 4. Effect of *a indica*, *P. daemia* and *T. cordifolia* extracts on liver obese control and treated rats.

metabolites may standardize the food intake and energy spending which may also engage in the smouldering of fats.

Several reports have exposed that an experimental obese animal leads to hyperlipidemia along with hyperglycemia. In the present study, experimental animals established the hyperglycemic condition. It might be due to the energy in the form of saturated fats and its deposition in various body fat pads leads to excessive growth of adipose tissue ensuing in obesity which includes two growth mechanisms: hypertrophy and hyperplasia of adipose tissue [13]. Under physiological conditions, insulin inhibits lipolysis and enhances lipogenesis (Saltiel and Kahn, 2001) foremost to augmented circulating levels of lipids and glucose resulting in altered glucose entused insulin secretion. Supplementation of plant extracts radically lowered plasma glucose in treated rats compared with obese control rats. This might be due to plant extracts may endorse insulin sensitivity lowering insulin resistance and diminish glucose level in obese rats probably by sinking free fatty acids or regulating cell energy metabolism [21]. Anti-obesity and *anti*-hyperlipidemic effects in humans and animals have turn into a vital concern for food and molecular nutrition research. The noteworthy increase of lipid profile in obese rats may be due to rise in both *de-novo* cholesterol and TGs synthesis and intestinal lipid uptake [22]. Supplementation of *A. indica*, *P. daemia* and *T. cordifolia* significantly lowered TC, TGs, and LDL and increased HDL in obese rats. HDL cholesterol concentration elevation may be due to increase in lipolysis, decrease in lipogenesis, dropping lipid absorption and suppressing appetite [23]. Several studies have shown that supplementation of plant-based compounds or plant extracts to obese animals' leads to a hypolipidemic state by diminishing cholesterol assimilation from the intestine which leads to lowered accessibility of free fatty acids to the liver [1,24,25]. Hence, these results suggest that the *A. indica*, *P. daemia* and *T. cordifolia* leaf extract have the anti-hyperglycemic and *anti*-hyperlipidemic potentials.

## 5. Conclusion

The results of the current study portray that the methanolic extracts of leaves of *A. indica*, *P. daemia* and *T. cordifolia* have a promising role in treatment to obesity. This effect was renowned by the diminution in the increase in body weight, blood glucose, and fat percentage and increased BMC and BMD in obese rats' supplemented with the plant

extracts for 30 days. This was also supported by the histopathological analysis. Therefore, this study suggests that supplementation of *A. indica*, *P. daemia* and *T. cordifolia* that has the prospective to be developed as medicinal ingredients for impediment and management of obesity and other metabolic diseases.

## Conflicts of interest

Authors do not have any potential conflict of interest.

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## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jnim.2019.02.001>.

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