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ORIGINAL ARTICLE **OPEN ACCESS**

Role of *Benincasa hispida* (Thunb) on Olanzapine induced Obesity in Rats

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ABSTRACT
Olanzapine, an atypical antipsychotic medication, is used to treat bipolar disorder and schizophrenia. Obesity is the main side effect of the olanzapine, hence the goal of this study is to find out how Benincasa hispida affects Olanzapine -induced obesity in rats. Benincasa hispida comes under Cucurbitaceae family, generally called as ash gourd. It is a climbing, and widely used in India, Indochina, China and Malaya. In kusmana lehyam it is employed as a main component, in medicine of Ayurvedic system of. To evaluate the effect of Benincasa hispida on olanzapine induced obesity in rats. The rats were divided into five groups, namely, control, olanzapine control (4mg/kg), orlistat (12 mg/kg), and Benincasa hispida extract low and high dose (100 and 200 mg/kg respectively). All Wistar rats were administered with olanzapine 4mg/kg by i.p to develop obesity, with the exception of the control group. The drugs were administered for 28 days daily by oral route. During the experiment, body weight and behavior were monitored at regular intermissions. After the 28 days, blood samples were collected from experimental rats for estimation of biochemical parameters. Liver tissue was collected from the sacrificed rat and conserved in formalin (neutral) for histopathological studies. Phytochemical investigation of extract revealed the presence of flavonoids, glycosides, proteins and sacchrides. Olanzapine administered rats showed increase in body weight and food intake. Biochemical parameters such as ALB, AST, ALP, ALT, GLU, VLDL, TG and TP were increased and HDL was decreased as compared to control group. However, the LDBH and HDBH pretreated rats showed significant reduction in above parameters and increase in HDL level. Serum enzymes like amylase was significantly decreased and lipase level was significantly increased in olanzapine administered rats compared to control group, whereas rats pretreated with LDBH and HDBH showed significant increase in amylase level and decrease in lipase levels respectively. Histopathological studies exhibited, the pretreatment with LDBH and HDBH groups reduced the sinusoidal congestion, portal vein congestion and hepatic degeneration as compared to doxorubicin treated group. The biochemical and histopathological outcomes data clearly support the anti-obesity effect of ethanolic extract of Benincasa hispida, which might be attributed to its lowering lipids and enzyme levels.
Keywords: *Olanzapine, Benincasa hispida, Obesity, Rats.*

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INTRODUCTION

Obesity is major health problem throughout worldwide because it affects regular lifestyle and life span. Alarmingly, a significant proportion of the population in many countries is obese and this rate is increasing. Olanzapine is a antipsychotic drug has been using for the treatment of various mental illness. Although this drug has many beneficial effects, but also not devoid of serious side effects. [1] Pancreatic lipase is the important enzyme involved in triglyceride absorption in the intestine by inhibiting fat absorption from the diet and it is the one of the strategies to treat obesity [2]. Regular use of olanzapine causes weight gain, which makes patients less compliant and ultimately stop taking their prescription. This in turn results their earlier mental disorder. Antipsychotic medications are crucial for managing and treating a variety of mental diseases, including schizophrenia and other psychoses. They don't have any significant adverse effects despite having many positive effects.[2] Serious metabolic diseases like obesity and diabetic ketoacidosis are at risk due to the side effects of these medications. There have already been reports of patient non-compliance due to these negative effects. Obesity development is one of the most important negative effects. The type of psychiatric medication taken and how it works affect how much weight gain occurs. Typical antipsychotics cause patients to gain weight relatively slowly, however atypical medications like

olanzapine cause patients to gain weight rapidly. [3] It has been demonstrated that olanzapine's potent ability to bind and block 5-hydroxytryptamine (5- HT) and histamine (5-HT2C, 5-HT2A, and H1) receptors is directly associated to weight gain.[4]. There are very few options for treating weight gain caused by olanzapine. It has been discovered that using betahistine, metformin, and fluoxetine together provides considerable benefits.[5,6] Due to the adverse effects of these medications and patient compliance, it is also clinically problematic to include medications that treat olanzapine induced obesity. So there is a much more interest in herbal remedies which contain many bioactive compounds that play a crucial role in the treatment of numerous diseases with less side effects. In the search for a medication that can treat or manage olanzapine induced obesity, natural substances with low toxicity profiles may be been demonstrated that substances like curcumin and myricetin are efficient in reducing obesity and problems related to nutrition, as well as metabolic disorders.[7]. The *Benincasa hispida* (Thunb) Cogn. known as Ash Gourd, belonging to cucurbitaceous family and is employed as a main ingredient in kusmana lehyam, (Ayurvedic medicine). This lehyam is been used for various disorders. According to the Sanskrit texts, it is useful in insanity, epilepsy, constipation, piles, dyspepsia and other nervous diseases.[7] Some scientific studies have been carried out to reveal its Anti-ulcer[8], anti-diarrhoel[9], anti-angiogenic[10], anti-inflammatory[11], anticancer[12], antiasthmatic [13], antioxidant and angiotensin converting enzyme inhibitor[14], analgesic[15], anorectic[16], nootropics[17], prevent the withdrawal symptoms of morphine addiction[18], diuretic [19] and hypoglycemia [20] activities. The major phytoconstituents are flavonoids, triterpenoids, glycosides, sacchrides, proteins, carotenes, ß-sitosterin, vitamins, minerals and uronic acid. [21,22,23,24]. The current investigation was carried out to investigate the anti-obesity function of *Benincasa hispida* (Thunb) in the search for a secure and efficient treatment for the weight increase caused by olanzapine. on the rat weight gain brought on by olanzapine.

MATERIAL AND METHODS

Plant materials and preparation of extracts:

The species *Benincasa hispida* was collected in from local market of Hubli in Karnataka, India. Identified and authenticated by S. N. Emmi H.O.D of Botany Dept. H.S.Kotambari Science Institute, Vidyanagara, Hubli. (Ref no : KLECOPH/Plant/2021-22). The fruit of *B. hispida* was squashed using an electric mixer to get a soft mass. Hundred milliliter of fresh juice was mixed with 500ml of ethanol and kept for seven days with tight sealing at room temperature with daily occasional stirring. After seven days, mixture was filtered and the filtrate was heated below 55^0C and evaporated under reduced pressure. After that, by using rotary evaporator the extract was dried completely, brownish sticky mass was obtained, which was protected from direct sunlight. The yield of the extract was 0.688gm/100ml of the fresh juice.[25]

Chemicals and drugs:

Olanzapine was purchased from local pharmacists. Other chemicals and kits were procured from Sigma Aldrich and ERBA Mannheim India respectively.

Animals:

Wistar rats of either sex weighing between 150-200 g were used, after obtaining the ethical approval from IAEC (Institutional Animal Ethical Committee) (Ref. No. MPh/NC0220010/KLECoPH/21). All the animals were housed in a group of six under environmentally controlled room with 12 h light/dark cycle in polyprophylene cages and maintained at controlled room temperature (22 ± 2^0 C) and relative humidity of 40 to 60% with free access to standard laboratory chow (Gold Mohur Lipton India Ltd.) and water ad libitum was provided. Before the initiation of experiment, rats were acclimatized for seven days to laboratory environment.

Fixation of doses of the extraction:

Up to 2000mg/kg, no side effects or death were noted in Wister rats of ethanolic pulp extracts of *Benincasa hispida* (Thunb). Therefore, the maximum tolerated dose 2000mg/kg. was chosen for further studies. [26]

Experimental design:

The rats were divided into five groups of six animals in each.
Group I received saline 5 ml/kg body weight *p.o.*
Group II were treated with olanzapine 4 mg/kg body weight by *i.p*. [27]
Group III received orlistat 12mg/kg body weight by *i.p*.[28]
Group IV (LDBH) received 100 mg/kg body weight *p.o* of ethanolic pulp extract of *Benincasa hispida*
Group V (HDBH) received 200 mg/kg body weight *p.o* of ethanolic pulp extract of *Benincasa hispida*

Body weight, food and water:

Body weight, food and water intake were weekly measured throughout the study period, for all the animals.

Behavioral analysis: (Actophotometer and Rota rod)

The locomotor activity, immobilisation period and grip strength were measured on the pre-study and at the end of the experiment, as described previously.[29] The activity of the rats were recorded using an

actophotometer for locomotor activity with an acrylic cage and six built-in photo sensors and digital counter beams on both the X and Y horizontal axes. Individual rat activity was recorded for 10 minutes at room temperature and rota rod apparatus was used for grip strength.

Plasma lipid profile:

All of the animals' blood was withdrawn by retro-orbital sinus puncture for the estimation of total cholesterol, triglycerides, HDL, LDL and VLDL. Ratio of LDL and HDL were measured.

Biochemical parameters:

All of the animals' blood was withdrawn by retro-orbital sinus puncture for the estimation of serum markers such as total protein (TP), glucose, alkaline phosphatase (ALP), AST and albumin.

Serum bio-enzyme parameters:

Plasma amylase and lipase enzymes were determined by kinetic method using commercial kits.[30]

Histopathological studies: [31]

Liver was isolated after sacrificing the animals. The isolated liver was washed with saline, cut into pieces and preserved in 10% neutral formalin solution for two days and then pieces were washed with running water for 12 h followed by dehydration with alcohol. The liver tissue was cleaned by xylene two times for 15-20min each followed by subjecting to paraffin infiltration in automatic tissue processing unit. The hard paraffin was heated to melt and was poured in square shaped blocks in which the liver pieces were dropped quickly and permitted to cool. Microtome was used to cut the blocks to get 5µ thickness sections. These sections were taken on a microscopic slide to which sticky substance was applied and the section was dried completely before staining. The acidic stain (eosin) and basic stain (haematoxyllin) were used for staining the sections followed by observing in microscope for any changes in histopathalogical characteristics.

Statistical analysis:

The experimental data were statistically analyzed using one-way analysis of variance (ANOVA) followed by Bonferroni post hoc test by using Graph Pad Prism 5.0 software. Data were expressed as Mean ± S.E.M. Differences were considered significant at $p<0.05$.

RESULTS

Phytochemical constituents in ethanolic pulp extract of *Benincasa hispida:*

The phytochemical investigation showed the presence of saccharides, glycosides, flavonoids and proteins.

Body weight:

In olanzapine treated group, body weight was significantly increased as compared to control group ($p<0.001$). In treatment groups i.e. orlistat ($p<0.001$) and HDBH ($p<0.001$) significantly reduced the excess weight as compared to olanzapine treated group (Fig. 1).

Food and Water consumption:

In olanzapine administered group, food and water intake was increased significantly ($p<0.001$ and $p<0.001$) respectively as compared to control group. In treatment groups i.e. orlistat ($p<0.001$ and $p<0.001$) and HDBH ($p<0.001$ and $p<0.01$) respectively showed significantly decreased food and water consumption as compared to olanzapine group (Fig. 2).

Plasma Lipid profiles:

In olanzapine treated group, total cholesterol (TC) ($p<0.001$), triglycerides (TG) ($p<0.001$), LDL ($p<0.001$), and VLDL ($p<0.001$) were significantly increased and HDL ($p<0.001$) was significantly decreased as compared to control group. Whereas in treatment groups, i.e. orlistat (TC - $p<0.001$, TG - $p<0.001$, LDL- $p<0.001$, VLDL- $p<0.01$) and HDBH (TC - $p<0.001$, TG - $p<0.01$, LDL- $p<0.01$, VLDL- $p<0.01$) have significantly decreased as compared to olanzapine treated group. (Fig. 3).

Biochemical parameters (Serum markers):

Olanzapine treated rats showed significant increase in ALB ($p<0.001$), AST ($p<0.001$), ALT ($p<0.001$), ALP ($p<0.001$), and Glucose ($p<0.001$) as compared to control group. Whereas in treatment groups, i.e. orlistat ($p<0.001$, $p<0.001$, $p<0.01$, $p<0.01$ and $p<0.01$) and HDBH ($p<0.01$, $p<0.01$, $p<0.01$, $p<0.05$ and $p<0.05$) respectively decreased as compared to olanzapine treated group. (Fig. 4)

Serum bio-enzyme parameters:

In olanzapine treated rats, amylase and lipase enzymes were significantly increased ($p<0.001$, $p<0.001$) respectively as compared to control group. Whereas in treatment groups amylase and lipase enzymes were significantly decreased i.e. orlistat ($p<0.001$, $p<0.001$), LDBH ($p<0.05$, $p<0.05$) and HDBH ($p<0.01$, $p<0.01$) respectively as compared to olanzapine treated group. (Fig. 5)

Locomotor activity using Actophotometer:

In olanzapine treated rats, locomotor activity was significantly reduced in 14^{th} and 28^{th} day ($p<0.01$, $p<0.001$) compared to control group. Whereas in treatment groups locomotor activity was significantly increased in 14^{th} and 28^{th} day i.e. orlistat ($p<0.01$, $p<0.001$), LDBH ($p<0.01$, $p<0.01$) and HDBH ($p<0.001$, $p<0.01$) respectively as compared to olanzapine treated group (Fig. 6).

Muscle grip strength using Rota rod apparatus :
In olanzapine treated rats, muscle grip strength was significantly reduced in 28th day (p<0.001) compared to control group. Whereas in treatment groups muscle grip strength was significantly increased in 28th day i.e. orlistat (p<0.001), LDBH (p<0.05) and HDBH (p<0.01) respectively as compared to olanzapine treated group (Fig. 7).

Histopathological studies:
Olanzapine treated rat hepatic tissue exhibited sinusoidal congestion, portal vein congestion, fat accumulation and hepatic degeneration. Whereas normal group showed normal morphological appearances but pretreated groups i.e. LDBH showed less sinusoidal congestion, portal vein congestion, hepatic degeneration with no fat accumulation and HDBH showed only little portal vein congestion with no other changes as compared to olanzapine treated group (Fig. 8).

DISCUSSION

Presently available anti-obesity drugs are having many side effects, therefore alternative and safe natural agents from plants are needed [32].. *Benincasa hispida*, which has been used in the traditional medicine for the treatment of different ailment which including obesity.[33]. Phytochemicals are secondary metabolites obtained from different plants and produce different pharmacological or toxicological effects in man and animals and play slight role(s) in plant growth and development [34]. In the present study, *Benincasa hipida* was found to contain phytoconstituents such as, triterpenoids, flavonoids, glycosides, sacchrides, proteins, carotenes, vitamins, minerals, ß-sitosterin and uronic acid. These phytochemicals are showing synergistic effect in various activities.[35] and these metabolites have been linked with various roles in the management of obesity and other risk factors associated with obesity. [36] Olanzipine is a antipsychotic drug and it helps to manage symptoms of mental health conditions but at the same time it can induce cardiovascular disease, insulin resistance and diabetes mellitus resulting in increased morbidity and mortality.[37] Many strategies developed for the alternative therapy to reduce the metabolic abnormalities induced by olanzapine such as life style change and pharmaceutical intervention [38]. How olanzapine induces the weight gain is still completely not understood but previous literatures reported due to increase food intake and accumulation of abdominal fat including increase in the plasma TG, hepatic TG levels, plasma insulin, and hepatic SCD-1 protein levels. [39] The present study was aimed to evaluate the effect of *Benincasa hispida* on weight gain and metabolic disturbances associated with olanzapine in rats. Earlier reports confirmed the increase in weight gain after olanzapine administration in rats.[37] Olanazipine treated rats showed increase in body weight, which might be due to accumulation of body fats [40], whereas high doses of extract prevented the weight gain induced by olanzapine due to less accumulation of body fat and reduction in food and water intake. These results are similar to earlier reports[41]. It has been proposed that changes in adipocytokines secreted by adipocytes such as leptin are believed to be involved in weight gain induced by olanzapine [42]. The commonly assayed lipids from the blood or serum are cholesterol and triglycerides because of their clinical importance [43].Earlier studies reported that, Olanzapine is known to produce hypertriglyceridemia,[44,45]. But high dose of extracts prevents the hypertriglyceridemia by preventing the gut reabsorption of cholesterol and accordingly increasing the excretion of cholesterol from the body [46], this leads to lipid lowering effects. Olanzapine treatment develops about 0.2% severe liver injury but no known fatalities associated with this injury. But still we don't know the exact mechanism by which it produces liver injury.[47] Earlier studies reported the increase in the liver enzymes such as AST and ALT after chronic administration of olanzapine. Whereas high doses of extracts reduce the liver injury by reducing above mentioned enzyme levels. There is a significant increase in amylase and lipase levels in olanzapine treated animals, which are agreed with earlier studies. This might be due to blocking of muscarinic M3 receptors, because studies have revealed that the binding affinity of second generation antipsychotics to the M3 receptors is a predictor of diabetes risk.[48] In the present study, the results show that olanzapine has a prominent effect on locomotor activity, olanzapine produced a reduction in voluntary locomotor activity and it was dose-dependent with a maximum reduction of approximately on 28th day. This effect is previously observed in earlier studies after once or twice daily administration of olanzapine, this was due to decrease energy expenditure through independent effects on thermoregulation. [49] Olanzapine causes a state of sedation and motor incoordination in animals due to binding profiles of antipsychotic medications for the histamine H1 receptors [50] and to test this, Rota rod and grip tests were used to assess muscular strength, which can be influenced by sedative drugs and muscle relaxant compounds. [51] High doses of extract reduce the sedation and increases the muscle grip strength. This might be due to decreased in binding capacity and reducing the sedation of animals. In histopathalogical studies olanzapine administered rats showed changes such as congestion in sinusoidal and portal vein, accumulation of fat and damages to hepatocytes.

These are agreed with earlier reports [52] and high doses of extract produced less congestion and damage and this might be due to membrane stabilizing efect.

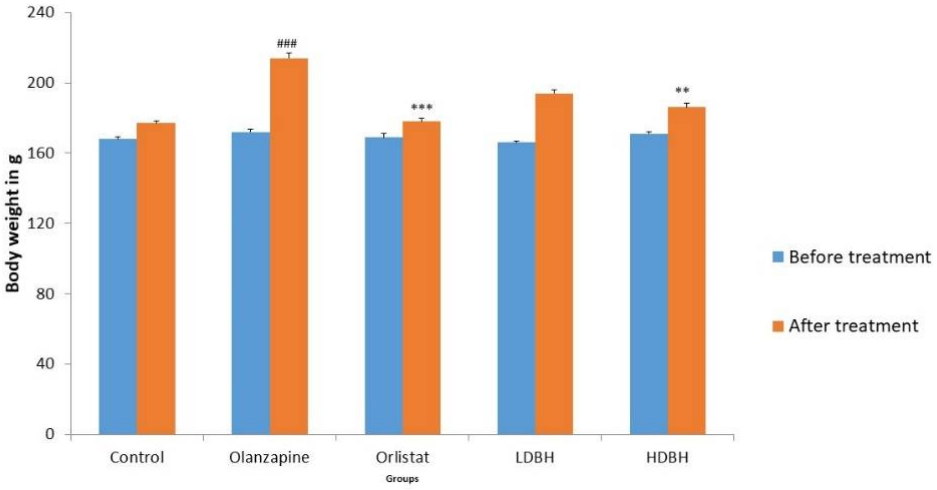

Fig 1. Effect of ethanolic pulp extract of *Benincasa hispida* on Body weight.

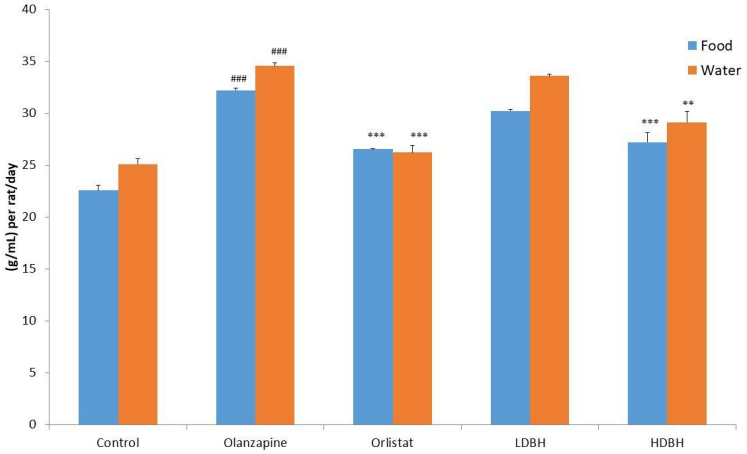

Fig 2. Effect of ethanolic pulp extract of *Benincasa hispida* on Food and Water intake.

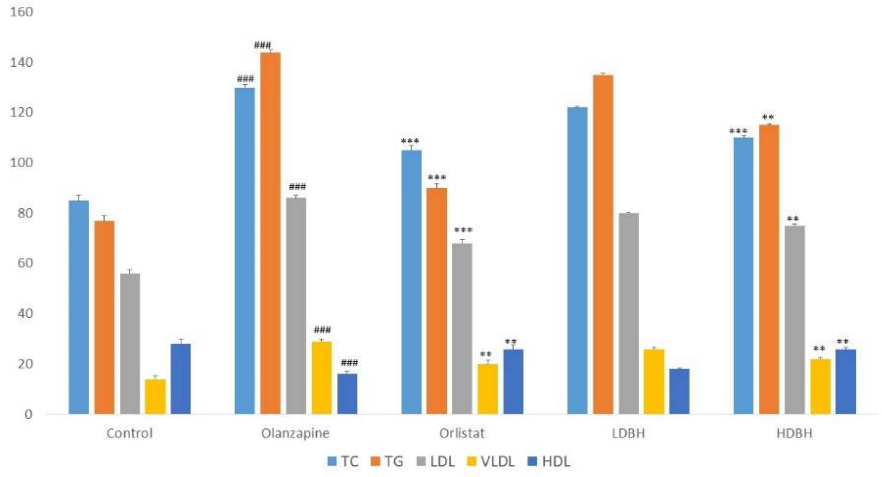

Fig 3. Effect of ethanolic pulp extract of *Benincasa hispida* on Lipid profiles.

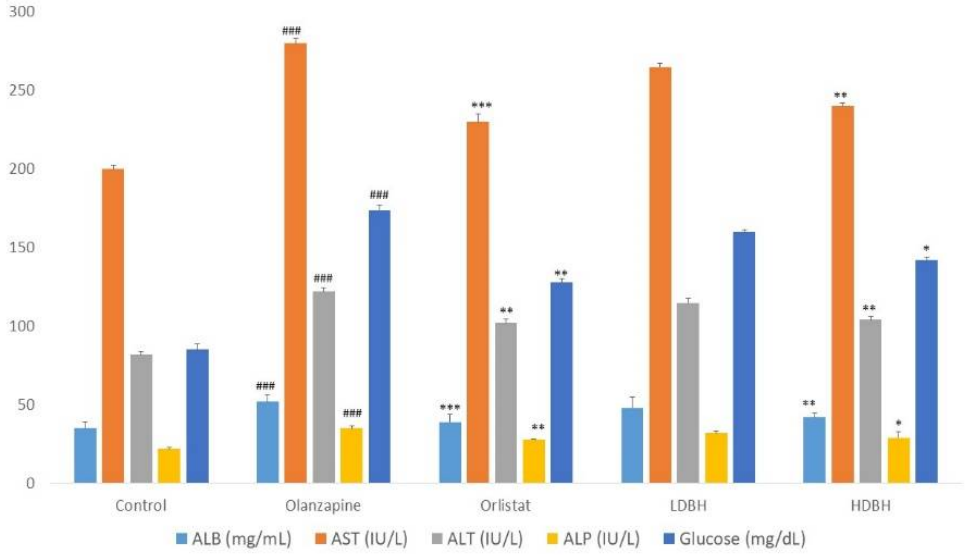

Fig 4. Effect of ethanolic pulp extract of *Benincasa hispida* on Serum markers.

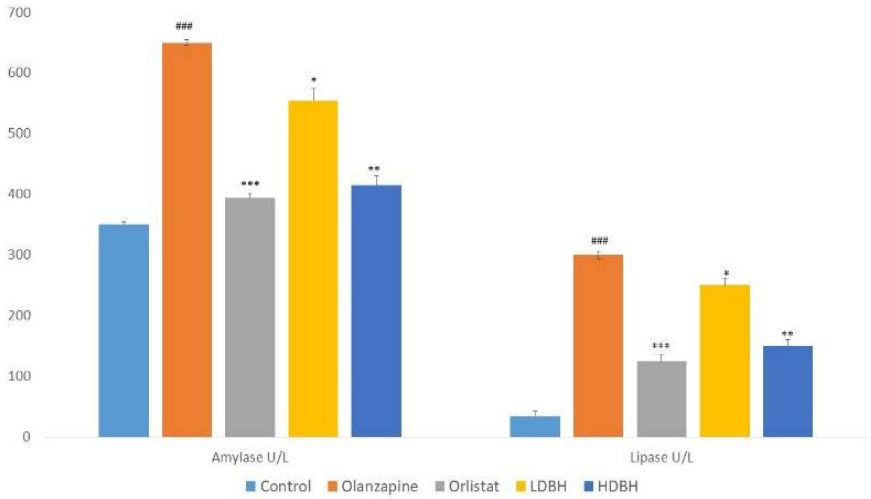

Fig 5. Effect of ethanolic pulp extract of *Benincasa hispida* on Serum bio-enzyme parameters.

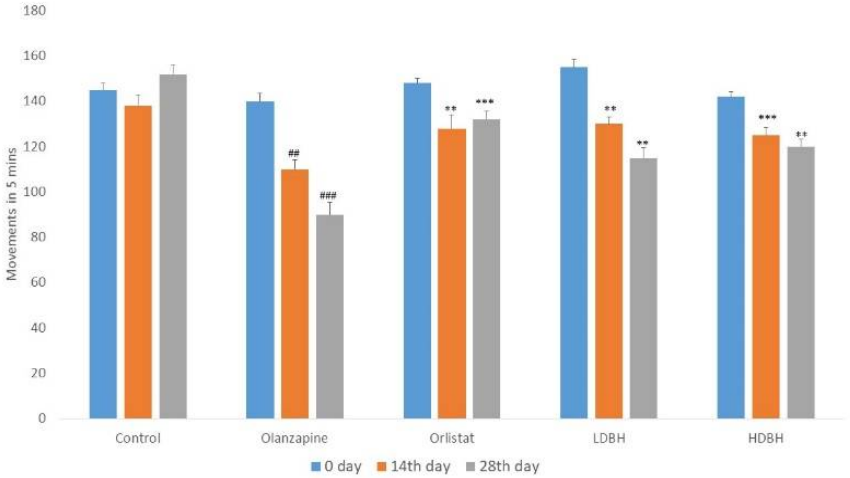

Fig 6. Effect of ethanolic pulp extract of *Benincasa hispida* on Locomotor activity.

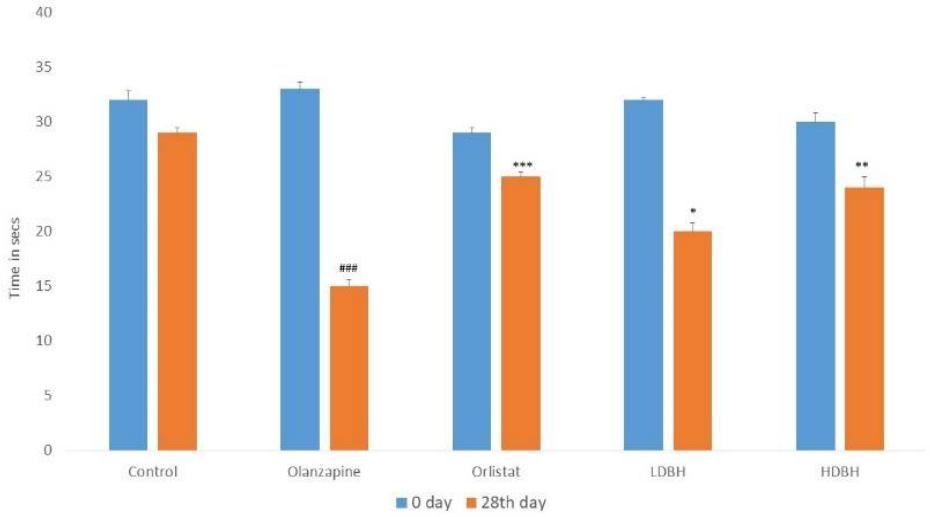

Fig 7. Effect of ethanolic pulp extract of *Benincasa hispida* on Muscle grip strength.

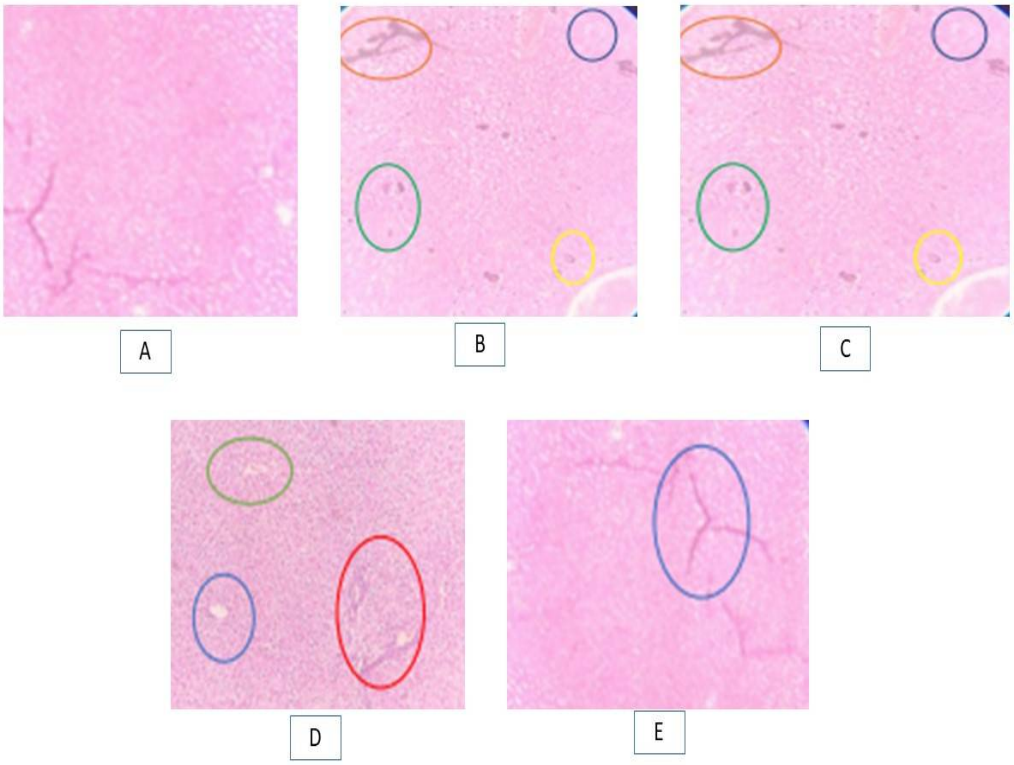

Fig 8. Effect of ethanolic pulp extract of *Benincasa hispida* on histopathalogical studies. A-Control, B-Only Olanzapine treted, C-Std drug, D- Low dose of extract, E-High dose of extract.

CONCLUSION

The present study indicates the extract of *Benincasa hispida* (Thunb) reduced the obesity induced by administration of olanzapine in rats. The study shown that extract might be considered as useful in combination with olanzapine. However, further clarification of the molecular and cellular mechanisms would provide the strong evidence for anti-obesity effects of plant extract.

DECLARATION OF COMPETING INTEREST

Authors declare that there is no conflict of interest in publishing the experimental data in this manuscript.

ETHICAL APPROVAL

Ethical committee approval (Ref no : KLECOPH/Plant/2021-22) was obtained from the Institutional Animal Ethical Committee of KLE College of Pharmacy, Hubballi, Karnataka, India.

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