A COMPREHENSIVE REVIEW ON ANTI-OBESITY POTENTIAL OF *CYPERUS ROTUNDUS* IN EXPERIMENTAL ANIMALS

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ABSTRACT

Worldwide, obesity and the illnesses it causes have become serious health issues, and obesity is today the fifth most common cause of death. According to research, there were 641 million obese adults worldwide in 2014. This review was based on detailing of obesity, BMI ranges, anti-obesity potential and signalling pathways of Cyperus rotundus. It covered extensive literature survey from the studies published in PubMed, Elsevier, Google Scholar etc. A member of the Cyperaceae family, Cyperus rotundus grows naturally in tropical and temperate climates and has long been used to heal mental and digestive issues. In order to determine the effectiveness and safety of Cyperus rotundus rhizome extract (CRE), which is standardised to contain Piceatannol, Scirpusin A, and Scirpusin B (5 percent total Stilbenoids), in overweight people, studies have been conducted. Cyperus rotundus has shown dietary enzyme inhibitory action when observed. It significantly lowered the level of all three enzymes i.e., Lipase, Alpha-amylase and Alpha- glucosidase. Changes in cell shape and the concentrations of cytoskeletal and extracellular components signal the beginning of adipogenesis. As a result of this process, CCAAT-enhancerbinding proteins (C/EBP) and peroxisome proliferator-activated receptors (PPAR) that are predicated on adipogenicity begin to express themselves. In overweight people, the extract proved successful in lowering body weight and BMI. CRE might prevent obese mice from gaining weight and demonstrated anti-adipogenic effect in differentiated 3T3 L1 adipocytes in-vitro. In conclusion, many current studies have proved for its anti-obesity and lipid lowering potential in various animal or human models. It would be great change towards human use if it is developed into any suitable dosage form for better bioavailability.

Keywords: *Cyperus rotundus, anti-obesity, anti-hyperlipidaemic, rats, human*

INTRODUCTION

Worldwide, obesity and the illnesses it causes have become serious health issues, and obesity is today the fifth most common cause of death. The World Health Organization (WHO) further explains that "the basic reason of obesity and overweight is a caloric imbalance between calories ingested and calories spent when defining obesity as an abnormal or excessive fat build-up that may damage health (Salvador & Ruppel, 2017).

Types of obesity, BMI ranges and associated risk

The following table depicts the types of obesity on the basis of their severity. Body Mass Index (BMI) ranges and risk of complications.

Table 1. Types of obesity, BMI ranges and associated risk of complications

Classification	BMI (kg/m^2)	Risk of co-morbidities
Underweight	<18.5	Low
Normal weight	18.5- 24.9	Average
Overweight	25.0- 29.9	Mildly increased
Obese	≥30	
Obese I	30.0- 34.9	Moderate
Obese II	35.0- 39.9	Severe
Obese III	≥40	Very severe

According to research, there were 641 million obese adults worldwide in 2014, up from just 105 million in 1975 (Zhang et al. 2018), a startling increase (Hoda & Acosta, 2017). Numerous studies have shown that obesity is not a straightforward issue but rather a complicated health condition caused by a confluence of personal factors (genetics, learnt habits) and underlying causes (Syahrul et al. 2015). Despite its genetic and epigenetic implications, the majority of researchers also concur that obesity is a "acquired" condition that mainly depends on lifestyle variables including low rates of physical activity and persistent overeating. Asthma, cancer, diabetes, hypercholesterolemia, and cardiovascular disorders are among the chronic conditions and diseases that have been linked to various forms of obesity, including abdominal obesity, according to research (Lihua et al. 2017).

The considerable clusters of obesity seen in particular geographic areas and contexts also reflect the impact of socioeconomic and environmental factors in "obesogenic" environments (Xiao et al. 2020). Some genetic and lifestyle factors influence an individual's chance of adult obesity. Due to the aforementioned added challenges, understanding the origins and determinants of obesity is essential to devising successful policy and practical preventative strategies.

Numerous studies have also linked insufficient or infrequent exercise to obesity, as well as a person's degree of education (Akira et al. 2020; Helen & Furnham, 2013). Researchers also

demonstrated that obesity may resemble a heterogeneous chronic illness, in which a variety of factors interact to cause an energy imbalance that results in a rise in body weight. Therefore, obesity is determined by biological, environmental, and behavioural variables. As a result, many behavioural and environmental factors, particularly rising calorie consumption and declining physical activity, could have an impact on disparities in the prevalence of obesity among diverse population groups (Sartorius et al. 2015).

The causes of obesity are also depicted in Fig 1. as below-

Fig 1. Depiction of causes of obesity

A member of the Cyperaceae family, Cyperus rotundus Lin. grows naturally in tropical and temperate climates and has long been used to heal mental and digestive issues (Peerzada et al. 2015). Additionally, it has been utilised for analgesic, antimalarial, anti-inflammatory, anti-diarrheal, antidiabetic, wound-healing, and antioxidant actions (Kamala et al. 2018). The plant is described as a medicine that can "de-fat" adipose or muscular tissues in ancient Ayurvedic texts (Mohamed, 2015). An anti-obesity efficacy of *C. rotundus* crude aqueous extract in rat models was previously described. According to reports, methyl 3,4-dihydroxybenzoate, ipolamiide, 6-hydroxyipolamiide, and rutin were all present in the rhizome's methanol extract. While the essential oil from the rhizome of *C. rotundus* was said to include -Cyperone, other investigations have found the presence of phenolic glycosides (Rotundusides) in the n-BuOH fraction (38.46 percent) (Hu et al. 2017).

Anti-obesity potential

There are some researchers who have been evaluated the anti-obesity potential of *Cyperus rotundus* in animal or human models, in recent months & years.

In order to determine the effectiveness and safety of Cyperus rotundus rhizome extract (CRE), which is standardised to contain Piceatannol, Scirpusin A, and Scirpusin B (5 percent total Stilbenoids), in overweight people, studies have been conducted. In vitro adipocytes and a diet-induced obesity mouse model were used to assess the mechanism of activity. In a randomised, double-blind, parallel-group, placebo-controlled research, 30 obese people with a BMI of 30 to 40 kg/m2 underwent 90 days of CRE administration to assess its effectiveness, safety, and acceptability. The therapeutic efficacy was assessed in obese mice created by a high-fat diet, and in vitro research was conducted in differentiated 3T3 L1 adipocytes. The results of the pilot clinical trial revealed a drop in body weight together with a significant reduction in waist size and BMI. Individuals receiving CRE treatment demonstrated a significant improvement in their serum lipid profile. No side effects were noted at the conclusion of the study, and the extract was well tolerated. With an IC50 value of 9.39 g/mL, CRE demonstrated a dose-dependent reduction in adipogenesis in vitro, and oral treatment of CRE decreased weight gain in diet-induced obese mice. Leptin, corticosteroids, and blood cholesterol levels were all lowered in mice, and there were no negative side effects. CRE possesses anti-adipogenic qualities, is safe for consumption by humans, and efficiently controls hypercholesterolemia and weight in overweight people (Majeed et al. 2022).

Previous study indicated the impact on Liver Function and Serum Lipid Profile Triglycerides, total cholesterol, HDL, and VLDL levels all significantly decreased as a result of CRE's effects on blood lipid levels. Surprisingly, there was no discernible decrease in LDL cholesterol levels. Despite the enzymes being decreased in CRE-treated rats, statistical significance was not reached. Additionally, there was no significant gonadal fat decrease reported. Hematological and clinical indices, as well as the weight of the important organs, were determined to be comparable to those of control animals. The fact that no deaths or negative effects were recorded throughout the entire research suggests that rodents were able to handle CRE.

Total cholesterol, triglycerides, serum LDL, HDL, and VLDL were all significantly lower in people who took CRE supplements, indicating that the extract had an effect on dyslipidemia. Additionally, a sizable rise in serum HDL levels was seen in conjunction with the therapy. According to Fischer et al, obesity-related hyperlipidemia is a recognised risk factor for both atherosclerosis and CVD (Fischer et al. 2015). The decreased circulating lipid levels are a result of increased fat metabolism and decreased fat accumulation in the body, suggesting that overweight patients may experience cardiovascular advantages. The remaining clinical and haematological markers stayed within normal ranges with no noticeable alterations, indicating the extract's safety.

In the in vivo investigation, supplementing mice receiving HFD with Cyperus extract considerably decreased their weight gain by 30-46 percent. Along with weight loss, the CRE-treated rats' blood total cholesterol and triglycerides were decreased. The lipids in HFD-fed mice, including HDL, were higher than in the control group. It has been noted that mice made obese by diet showed an increase in HDL (Yin et al. 2015). Rodents carry more HDL than LDL cholesterol than humans do, which may account for the disparity in HDL levels between human and animal research (Bergen & Mersmann, 2005).

A study done in 2014 reported anti-obesity potential of *C. rotundus*. In which obese rats given a high-fat cafeteria diet (HFCD) were examined to determine the anti-obesity potential of Cyperus rotundus L.'s aqueous tuber extract (ATECR). Methods: Rats of the Wistar albino strain were separated into six groups of six each. Groups III, IV, and V animals received ATECR at dose levels of 100, 200, and 300 mg/kg bw along with HFCD for 40 days, while Group VI served as the standard drug control and received Orlistat at a dosage of 50 mg/kg bw along with HFCD. Group I served as the normal control fed with normal pellet chow. Group II served as the disease control fed with high fat cafeteria diet. Results: When experimental rats received HFCD for 40 consecutive days, their body weight, organ and fat pad weights, serum total cholesterol, LDL cholesterol, VLDL cholesterol, triglycerides, and glucose levels all increased significantly in comparison to the control group while their HDL cholesterol levels decreased. While using ATECR demonstrated a dose-dependent increase in HDL cholesterol, a substantial reduction in body weight gain, weight of fat pads, liver, kidney, and spleen weight, and levels of serum triglycerides, total cholesterol, LDL cholesterol, and VLDL cholesterol. Additionally, the serum of obese rats had higher levels of liver indicators such aspartate transaminase (AST), alanine transaminase (ALT), and alkaline phosphatase (ALP). also returned to normal after receiving therapy with various ATECR doses. Additionally, consuming ATECR increased the levels of glutathione (GSH), glutathione peroxidase (GPx), super oxide dismutase (SOD), and catalase in the hepatic tissue of obese rats who had undergone HFCD-induced weight gain. This lowered oxidative stress. Conclusion: These findings clearly show that oral administration of Cyperus rotundus L. tuber aqueous extract repeatedly can cause a robust anti-obesity response (Athesh et al. 2014).

Fathima et al. (2018) revealed that obesity is a troubling global problem that reduces life expectancy due to the excessive build-up of body fat. Its multiple causes include pathophysiological, environmental, and hereditary factors. It causes metabolic syndrome, which is characterised by type 2 diabetes, heart disease, fatty liver, hyperlipidaemia, and other conditions. Using the inhibitory effect on lipid and carbohydrate metabolising enzymes as markers, we screened hydroalcoholic extracts of seven plants for anti-obesity efficacy in this work. We next tested these plants in the 3T3 L1 cell line for suppression of adipogenesis. *Cyperus rotundus* and Citrus limon displayed the strongest inhibitory action when compared to the other plants out of the seven plants that were screened. Additionally, the plants displayed antioxidant activity. Additionally, the effects of these plants on adipogenesis and lipolysis in 3T3-L1 cells were studied. At 125 g/mL, *Cyperus rotundus* and Citrus limon demonstrated triglyceride accumulation inhibition and lipolysis promotion. Overall, a preliminary invitro screening investigation found that *Cyperus rotundus* and Citrus limon demonstrated strong anti-obesity efficacy, suggesting that these plants could be used as an alternative herbal treatment for obesity (Fathima et al. 2018).

Effects on enzymes and cholesterol & triglycerides

Cyperus rotundus has shown dietary enzyme inhibitory action when observed. It significantly lowered the level of all three enzymes as below-

- Lipase
- Alpha- amylase
- Alpha- glucosidase

The use of plant extracts appeared to promote lipolysis, indicating that these plants are effective at combating obesity. Triglyceride content in the cell lysate was used to quantify adipogenesis, and free glycerol release in the medium to measure lipolysis. *Cyperus rotundus* medium at 125 g/mL displayed decreased triglyceride content and enhanced lipolysis as measured by free glycerol release.

Another study by *Lemaure et al. (2007)* demonstrated the lipid-lowering and anti-obesity activity of *C. rotundus*. An Indian medicinal plant known as *Cyperus rotundus* has been shown to have a number of positive effects on health. The objective of the current study was to examine the biological effectiveness of *C. rotundus* tubers extract in regulating weight in Zucker rats that were obese. It was proven that giving Zucker rats 45 or 220 mg/kg/day of the hexane extract of C. rotundus tubers for 60 days resulted in a significant decrease in weight gain without influencing food intake or producing toxicity. The ability of this extract to promote lipolysis in 3T3-F442 adipocytes in vitro suggests that this plant's therapeutic properties include -adrenoreceptor activators. The *C. rotundus* tubers extract's ability to consistently and potently bind to the rat 3-AR isoform, known to stimulate thermogenesis, was established by the binding assay. These findings imply that the effect of *C. rotundus* tubers extract on weight gain may be at least partially mediated by activation of the 3-AR. Finally, *C. rotundus* tubers extract shows promise as a novel herbal supplement for body weight management, especially in 3-AR sensitive species (Lemaure et al. 2017).

Pandey et al. (2022) stated that due to its numerous medicinal properties, Cyperus rotundus, popularly known as "Nutgrass," has been employed in Ayurvedic and Traditional Chinese medicine. Given that obesity is a significant contributor to the rise in complications linked to the metabolic syndrome. We gave mice a high-fat diet and a methanolic extract of Cyperus rotundus. Cyperus rotundus provided high fat diet shown considerable weight loss along with decreased triglycerides and cholesterol levels when compared to only high fat diet group. When Cyperus rotundus was given to mice along with a high-fat diet, it also had an anti-inflammatory effect and decreased TNF alpha levels. This was similarly related to the degree of COX-2 mRNA expression reduction in the mice's visceral fat (Pandey et al. 2022).

Wongchum et al. (2022) also performed the anti-obesity activity of *Cyperus rotundus.* As a model organism, Drosophila is used to ascertain the anti-obesity properties of hydroethanolic C. rotundus extract (HECE). We looked into how C. rotundus extract inhibited lipase activity in vitro. Drosophila given a high-fat diet were used to test the effects of C. rotundus extract on obesity-related traits such body weight, triglyceride content, and lifespan extension (HFD). Drosophila antioxidant assays were used to determine in vivo the effect of the extract on the decrease of oxidative stress related to obesity. Results: In vitro, HECE reduced lipase activity with an IC50 of 128.24±3.65 g/mL. In vivo lipase inhibition studies revealed that feeding Drosophila 10 mg/mL HECE or 2 M orlistat decreased lipase activity by 21.51 ($P<0.05$) and 42.86 percent ($P<0.01$), respectively, and triglyceride levels by 20.67 ($P<0.05$) and 28.39 percent ($P<0.01$) compared to those of the untreated group. In comparison to flies fed an HFD, the mean survival rate increased after supplementation with 10 mg/mL HECE or 2 M orlistat (10.54 ($P< 0.05$) and 13.90 percent ($P<0.01$), respectively, and the capacity to climb increased (25.03 ($P< 0.01$) and 28.44 percent ($P<0.01$). According to the paraquat and H2O2 challenge tests, flies fed HECE in a mixed HFD had a higher survival rate than flies fed an HFD. This study shows the positive benefits of dietary HECE supplementation on reducing oxidative

stress, triglyceride levels, and pancreatic lipase activity, which lengthens the lifespan of Drosophila fed an HFD (Wongchum et al. 2022).

Yadav & Mani (2022) carried-out the screening of anti-obesity effect of Nagarmotha in animal models that was procured from the Moradabad area and verified by the botanist. The calibration curve was initially plotted. Animals were sourced from the animal facility run by the faculty of pharmacy at IFTM University in Moradabad, IN. Animals had unlimited access to water and pellet chow meal. Prior to slaughtering the mice, they were housed for one week in accordance with CPCSEA guidelines while fasting continuously. There were 6 groups of 6 rats apiece in the rat population. Groups 1: Normal Diet Control, Group 2: High Calorie Diet Control, Group 3: HCD + Orlistat (5 mg/kg), Group 4: HCD + EEN (100 mg/kg), Group 5: HCD + EEN (200 mg/kg), and Group 6: HCD + EEN (300 mg/kg) are all included. After the continuous treatments, each rat was assessed for a variety of factors, including body weight and food intake, Total Body Electrical Conductivity (TOBEC), blood glucose levels, an oral glucose tolerance test, histopathological studies of the liver and adipose tissue, RNA Extraction and Semi-Quantitative PCR Analysis, and tests for the functions of the liver and kidneys. Results showed that Ethanolic Extract of Nagarmotha (EEN) significantly reduced cholesterol levels in all parameters when compared to the standard group treated with orlistat and control or high-calorie diet animals at all three doses—100 mg/kg, 200 mg/kg, and 300 mg/kg. As the dose was increased, the effects were seen in a dose-dependent manner and in increasing sequence. EEN is a possible anti-lipidemic agent, it can be concluded. In order to establish the method of action—at which receptor subtype binding occurs—his research advises characterising and isolating the primary moiety responsible for its pharmacological activity (as an anti-obesity agent) (Yadav & Mani, 2022).

Signalling pathway of anti-obesity

Changes in cell shape and the concentrations of cytoskeletal and extracellular components signal the beginning of adipogenesis. As a result of this process, CCAAT-enhancerbinding proteins (C/EBP) and peroxisome proliferator-activated receptors (PPAR) that are predicated on adipogenicity begin to express themselves. The important transcriptional regulators of adipogenesis are C/EBP and PPAR, which are necessary for the production of many functional proteins associated with adipocytes. The expression of PPAR and C/EBP is upregulated downstream, although C/EBP is also upregulated. Numerous research has shown that Cyperus rotundus prevents weight gain without changing food intake or causing any negative effects. 250 micro/mL of this extract was able to stimulate lipolysis in 3T3 fibroblasts in the in-vitro research.

F442 adipocytes indicating that this medicinal plant contains beta-adrenoceptor activators. It has been proven that giving Zucker rats hexane extract from C. rotundus tubers at doses of 45 or 220 mg/kg/day for 60 days reduced weight growth significantly without altering food intake or causing toxicity. Pre-adipocytes do not begin to exhibit lipolytic activity until they have undergone differentiation into mature adipocytes.

Peroxisome proliferator activated receptor (PPAR) family control mechanism in relation to phytoconstituents in plants. The PPARs are the primary nuclear receptors that are ligand-induced or active for all three isoforms of PPAR. They are activated by a variety of fatty acids and its derivatives, in addition to acting as regulators in the biosynthesis, storage, and

metabolism of fats. Therefore, PPAR ligands have demonstrated the significance of these receptors in terms of controlling the equilibrium of lipids and glucose (Pandey et al. 2021).

CONCLUSION

Previous studies demonstrated that a Cyperus rotundus extract standardised for 5% total stilbenoids had anti-obesity properties (Piceatannol, Scirpusin A & Scirpusin B). In overweight people, the extract proved successful in lowering body weight and BMI. CRE might prevent obese mice from gaining weight and demonstrated anti-adipogenic effect in differentiated 3T3 L1 adipocytes in vitro. This is the first observation of the action of an extract comprising piceatannol and the dimeric stilbenoids scirpusin A & scirpusin B, despite the fact that stilbenes have been proven to have anti-obesity activity in vitro and in animal models. In conclusion, many current studies have proved for its anti-obesity and lipid lowering potential in various animal or human models. It would be great change towards human use if it is developed into any suitable dosage form for better bioavailability.

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Nil.

CONFLICT OF INTEREST

None.

REFERENCES

1. Akira Ishida, Yushuang Li, Osami Matsuda, Emiko Ishida. Factors affecting adult overweight and obesity in urban China. Pertanika J. Soc. Sci. Human., 28 (1) (2020): 503-513.
2. Athesh K, Megha M Divakar, Pemaiah Brindha. Anti-obesity potential of Cyperus Rotundus L. aqueous tuber extract in rats fed on high fat cafeteria diet. Asian Journal of Pharmaceutical and Clinical Research 7(2):88-92.
3. Bergen WG, Mersmann HJ. Comparative aspects of lipid metabolism: impact on contemporary research and use of animal models. *J Nutr*. 2005;135(11):2499–2502. Environ. Res. Lett., 15 (4): (2020), Article 044009.
4. Fathima A, Khanum F and Ilaiyaraja N: In-vitro anti-obesity efficacy of selected plants in 3T3-L1 cell line. Int J Pharm Sci & Res 2018; 9(11): 4666-73.
5. Fischer S, Schatz U, Julius U. Practical recommendations for the management of hyperlipidemia. *Atheroscler Suppl*. 2015;18:194–198.
6. Helen Cheng, Adrian Furnham. Personality traits, education, physical exercise, and childhood neurological function as independent predictors of adult obesity. PloS One, 8 (11) (2013), Article e79586.
7. Hoda C. Kadouh, Andres Acosta. Current paradigms in the etiology of obesity. Tech. Gastrointest. Endosc., 19 (1) (2017), 2-11.

8. Hu Q-P, Cao X-M, Hao D-L, Zhang -L-L. Chemical composition, antioxidant, DNA damage protective, cytotoxic and antibacterial activities of cyperus rotundus rhizomes essential oil against foodborne pathogens. *Sci Rep*. 2017;7(1):45231.
9. Kamala A, Middha SK, Karigar CS. Plants in traditional medicine with special reference to Cyperus rotundus L: a review. *3 Biotech*. 2018;8(7):309.
10. Lemaure Bernard, Andre Touch, Irene Zbinden, Julie Moulin, Didier Courtois, Katherine Mace, Christian Darimont. Administration of *Cyperus rotundus* tubers extract prevents weight gain in obese Zucker rats. Phytotherapy Research, 2007;21(8):724-730.
11. Lihua Hu, Xiao Huang, Chunjiao You, Juxiang Li, Kui Hong, Ping Li, Yanqing Wu, Qinhua Wu, Zengwu Wang, Runlin Gao, Huihui Bao, Xiaoshu Cheng. Prevalence of overweight, obesity, abdominal obesity and obesity-related risk factors in southern China. PloS One, 12 (9) (2017); e0183934.
12. Majeed Muhammed , Kalyanam Nagabhushanam, Beena Bhat, Mohammad Ansari, Anjali Pandey, Sarang Bani, and Lakshmi Mundkur. The Anti-Obesity Potential of *Cyperus rotundus* Extract Containing Piceatannol, Scirpusin A and Scirpusin B from Rhizomes: Preclinical and Clinical Evaluations. Diabetes Metab Syndr Obes. 2022; 15:369-382.
13. Mohamed GA. Iridoids and other constituents from Cyperus rotundus L. rhizomes. *Bull Fac Pharm Cairo Univ*. 2015;53(1):5–9.
14. Pandey Nikhil, Priyanka M, Yamini B T. Cyperus Rotundus and its Anti-Obesity Effect in Swiss Albino Mice. Ann Rev Resear. 2022; 7(2): 555707.
15. Pandey Nikhil, Priyanka Mishra, YB Tripathi. Cyperus Rotundus in the Management of Metabolic Syndrome Benefit in the Treatment of Metabolic Syndrome. J Clin Chem Lab Med., 2021; 4(7):651.
16. Peerzada AM, Ali HH, Naeem M, Latif M, Bukhari AH, Tanveer A. Cyperus rotundus L.: traditional uses, phytochemistry, and pharmacological activities. *J Ethnopharmacol*. 2015;174:540–560.
17. Salvador Camacho, Andreas Ruppel. Is the calorie concept a real solution to the obesity epidemic? Glob. Health Action, 10 (1) (2017), 1289650.
18. Sartorius Benn, Lennert J. Veerman, Mercy Manyema, Lumbwe Chola, and Karen Hofman. Determinants of obesity and associated population attributability, South Africa: empirical evidence from a national panel survey, 2008-2012. PloS One, 10 (6) (2015), Article e0130218.
19. Syahrul Sazliyana Shaharir, Abdul Halim Abdul Gafor, Mohd Shahrir Mohamed Said, C. Norella, T. Kong. Steroid-induced diabetes mellitus in systemic lupus erythematosus patients: analysis from a Malaysian multi-ethnic lupus cohort. Int. J. Rheum. Dis., 18 (5) (2015), 541-547.
20. Wongchum Nattapong, Ananya Dechakhamphu, Panatda Panya, Somchai Pinlaor, Sitthisak Pinmongkhonkul, Alongklod Tanomtong. Hydroethanolic *Cyperus rotundus* L. extract exhibits anti-obesity property and increases lifespan expectancy in *Drosophila melanogaster* fed a high-fat diet. J Herbmed Pharmacol. 2022; 11:296-304.

21. Xiao Zhang, Mei Zhang, Zhenping Zhao, Zhengjing Huang, Qian Deng, Yichong Li, An Pan, Li Chun, Zhihua Chen, Maigeng Zhou, Chao Yu, Alfred Stein, Peng Jia, Lim in Wang. Obesogenic environmental factors of adult obesity in China: a nationally representative cross-sectional study
22. Yadav Rita, Munesh Mani. Pharmacological Investigation of Anti-obesity Effect of Cyperus Rotundus. *Journal of Pharmaceutical Research International*, 2022;19-33.
23. Yin W, Carballo-Jane E, McLaren DG, et al. Plasma lipid profiling across species for the identification of optimal animal models of human dyslipidemia. *J Lipid Res*. 2012;53(1):51–65.
24. Zhang Chunlan, Jingjing Zhang, Zhenqi Liu, Zhiguang Zhou. More than an anti-diabetic bariatric surgery, metabolic surgery alleviates systemic and local inflammation in obesity. Obes. Surg., 28 (11) (2018), 3658-3668.