CTE

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Review Article

Antiobesity Potential of Herbal Plant Butterfly pea flower (*Clitoria Ternatea*)

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Abstract

Obesity is a health problem with an increasing prevalence every year in many countries. Obese patients are at risk for complications related to some non-communicable diseases. The difficulty of losing weight in obese patients is due to low awareness of a good lifestyle, appropriate dietary patterns, and discipline in taking drugs to prevent complications. However, the need for drug consumption takes a long time. The risk of side effects arising from long-term drug use needs to be considered. Using herbal plants as an additional dietary intervention could be a better choice. This review was describe the benefits of the butterfly pea (Clitoria ternatea) flower in obese patients and reduce the potential for the side effects and complications. This study used the scooping review method by searching for articles in Pubmed, ScienceDirect, Cochrane, and Google Scholar journals. The keywords used are ((Clitoria ternatea) OR (Peacock Flower) OR (Butterfly nut) AND (Obesity) OR (Antiobesity)). Articles are limited by publication period from 2012 to 2022. Based on an article search, four matching reports were found. Our results showed that administration of Clitoria ternatea ectract (CTE) inhibited weight gain, reduced triglyceride (TG) levels, increased adipose lipolysis, and decreased expression of adipogenic and lipogenic proteins. There is a positive effect of CTE on obese people and prevention of complications related to dyslipidemia.

Keywords: Clitoria ternatea; Butterfly Pea Flower; antiobesity; obesity

Potensi Antiobesitas Tanaman Herbal Bunga Telang (Clitoria Ternatea)

Abstrak

Obesitas adalah masalah kesehatan dengan prevalensi meningkat setiap tahunnya di banyak negara. Pasien obesitas memiliki berisiko mengalami komplikasi berbagai penyakit non-communicable. *Sulitnya menurunkan berat badan pasien obesitas dikarenakan rendahnya kesadaran akan gaya hidup yang baik, pola diet yang sesuai, dan disiplin mengkonsumsi obat-obatan untuk mencegah komplikasi. Namun kebutuhan konsumsi obat membutuhkan waktu yang lama. Risiko efek samping yang timbul dari*

penggunaan obat jangka panjang perlu diperhatikan. Pemanfaatan tanaman herbal sebagai intervensi diet tambahan bisa menjadi pilihan yang lebih baik. Penelitian ini menggunakan metode scooping review *dengan mencari artikel di jurnal* Pubmed, ScienceDirect, Cochrane, *dan* Google Scholar. *Kata kunci adalah ((Clitoria ternatea) ATAU (Bunga Merak) ATAU (Kacang kupu-kupu) DAN (Obesitas) ATAU (Antiobesitas)). Artikel dibatasi dengan periode terbit dari tahun 2012 hingga 2022. Berdasarkan penelusuran artikel, ditemukan empat laporan yang sesuai. Hasil analisis literatur menunjukkan bahwa pemberian CTE menghambat penambahan berat badan, menurunkan kadar TG, meningkatkan lipolisis adiposa, dan menurunkan ekspresi protein adipogenik dan lipogenik. Terdapat pengaruh positif CTE terhadap penderita obesitas dan pencegahan komplikasi terkait dislipidemia.*

Kata Kunci: *Clitoria ternatea; Butterfly Pea Flower; antiobesitas; obesitas*

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INTRODUCTION

Obesity and overweight can affect health conditions due to excess accumulation of body fat. Since 1975, the obesity rate has tripled. There are 39% of adults who are overweight and 13% have been diagnosed with obesity. The mortality rate in obesity is higher than in underweight patients in various countries (Vaamonde & Álvarez-Món, 2020). The obesity prevalence in Indonesiaraised by 11.3% in a decade. Obese sufferers in 2007 reached 10.5%, and increased to 21.8% in 2018 (IMH, 2018). In fact, obesity has been declared a chronic disease with a high mortality rate and disability (Burki, 2021). However, obesity can be prevented through dietary modifications and physical activity. Various food and non-food ingredients were studied to find out their role in preventing obesity, such as butterfly pea (*Clitoria ternatea*) (WHO Regional office for Europe, 2022).

Clitoria ternatea is a subgenus of Clitoria originating from the island of Ternate (Maluku Islands, Indonesia). This flower grows in South and East Africa, India, Madagascar, and other islands in the western Indian Ocean (Oguis et al., 2019). Butterfly pea flowers have been used traditionally for health as a supplement to improve cognitive function, antipyretic, anti-inflammatory, anti-pain and anti-diabetic. This flower has two colors, white and blue, but more research has been done on blue flowers. Butterfly pea flowers are known to contain many phenolic acids and other flavonoids. The main color-producing substance in butterfly pea flower is anthocyanin, a delphinidin derivative called ternatin. Ternatin is delphinidin 3-O-(6”-O-malonyl)-β-glucoside which has the structure of 3',5'-di-O-β-glucoside in ring B (Hiromoto et al., 2013). The application of anthocyanin in food products is limited because of its stability (Vidana Gamage et al., 2021). Cyclotide is the latest active compound found in butterfly pea flowers (Nguyen et al., 2016). Cyclotide are small circular peptide or mini proteins, consisting of 30 amino acids containing six conserved cysteine residues and three disulfide bonds which form the cyclic cystine knot (CCK) thereby making it more stable againts acids, heat and proteolytic degradation (Burman et al., 2015). The structure of proline as cis or trans determines the cyclotide subfamily, Mobius (Kalata B1) has a cis-proline, and Bracelet (cycloviolacin) structure O1) has a trans-proline structure. In addition, there are minor cyclotides, which inhibit trypsin (Andrew Gould, 2017). Eliasen et al. inserted the melanocortin receptor-activation sequence into Kalata B1 to form a more stable melanocortin receptor agonist (Eliasen et al., 2012). Melanocortin-4 receptor (MC4R) is known to be an essential gene that causes obesity. Mutation in this gene cause a partial or complete loss of the ability of the MC4R to regulate dietary intake, homeostasis, and body weight (BW) (Marenne et al., 2020)(Brouwers et al., 2021). The studies on CTE effect in preventing obesity are still limited. However, there are several studies that have been carried out both

in vitro and in vivo methods. There are many useful ingredients in *CTE* which can be used to prevent diseases such as obesity and its complications. We did not find literature in the form of a review regarding the benefits of pea flowers in obesity. Therefore, we would like to conduct a scoping review to collect studies that have been conducted to improve an insight of the potential of butterfly pea flowers in preventing obesity. So that this study can provide a reference for developing further studies on the benefits of butterfly pea flowers in overcoming obesity.

METHODS

The search method in this study is a scooping review. Article searches use a database of articles from PubMed, ScienceDirect, Cochrane, and Google Scholar. The search was limited to published literature with a range of 10 years from 2012 to 2022. The types of literature used were Indonesian and English literature related to the good of the CTE in cases of obesity. The literature search strategy uses the keywords ((Clitoria ternatea) OR (Telang flower) OR (Butterfly pea) AND (Obesity) OR (Anti-obesity)). Based on the search results, four pieces of literature matched the topics to be discussed (Figure 1).

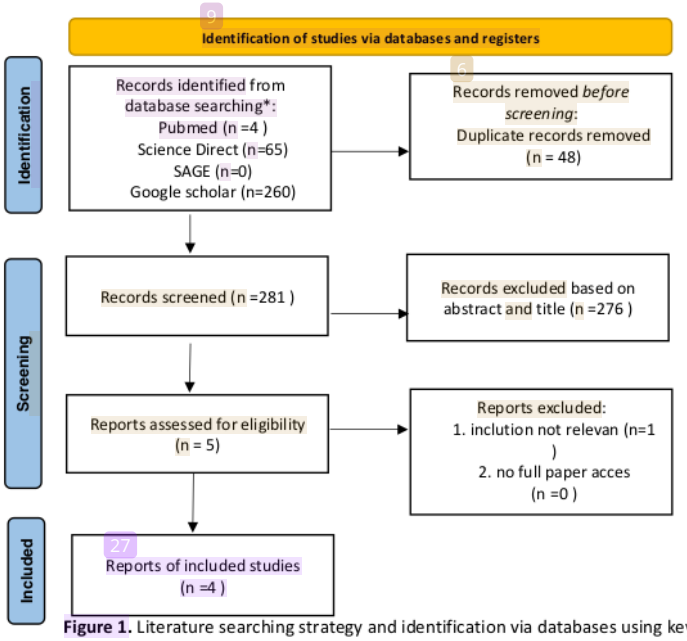

Figure 1. Literature searching strategy and identification via databases using keywords

RESULTS

In the search process, 329 articles were found, with 48 duplicate articles. The process continued with the selection of titles, relevant abstracts, appropriate inclusion and exclusion criteria, and articles

with full text until four relevant articles were obtained. Table 1 summarizes the details of each reported article.

Table 1. Summary of the *Clitoria ternatea* study

No	References	Methods	Result
1	Wang et al, 2022	In vivo study. 40 C57BL/6J mice were fed a standard diet (SD) or a high-fat, high-fructose (HFFD) diet for 16 weeks, and the HFFD-fed animals were fed at doses of 0.25%, 0.5%, and 2% (w /w) of CTE in drinking water.	Administration of high doses of AqCTE (2%) significantly inhibited weight gain, increased plasma adiponectin levels, gained levels of HDL-C, LDL-C, and FFA levels; decreased total cholesterol level.
2	Permatasari et al, 2022	In vitro study: amylase inhibition test: Incubation of dilute kombucha butterfly pea flowers (KBPF) in some concentrations with sodium phosphate buffer (500 L of 0.02 M), pH 6.9 with 0.006 M NaCl, and 0.5 mg/mL of pancreatic ÿ amylase pigs occurred for 10 minutes at 25 oC.To record the absorbance at 540 nm, dilution with distilled water (10 mL) was carried out to bring the readings within the acceptable range. This study used acarbose as a positive control. In vivo study: 40 Swiss albino male mice were weighing 21.53 ± 1.92 g (3-5 weeks old). Probiotic drinks in the form of KBPF were given for six weeks. The treatment group was given KBPF with various doses of 65 mg/kg BW and 130 mg/kg BW,	In vitro study: Acarbose produced better ÿ-amylase inhibitory activity than KBPF at doses of 150 and 200 mg/mL. The EC50 values of acarbose and KBPF were 162.6 and 160.2 mg/mL, respectively In vivo studies: A dose of 130 mg/kg BW lowers the lipid profile; increases HDL levels, lowers LDL, and lowers blood sugar levels, lowers oxidative stress levels, lowers levels of lipase & amylase, and increases levels of inflammatory markers (PGC-1α, TNFα, IL10).
3	Thilavech et al, 2021	1. Clinical study (human) 2. 19-person early recruitment: 16 people (9 overweight dan 7 obese) finished the study 3. Three groups: 4. 1. High fat meal + washout 1 week given 2gCTE+ HF meal + washout 1 week + 1gCTE+ HF meal	1. Postprandial blood sugar did not decrease significantly after treatment 2. TG levels decreased after being given 2g of CTE after 300 and 360 minutes 3. Free fatty acids (FFA) decreased significantly at 360 min postprandial at 2g CTE

		5. 2. 1gCTE+ HF meal + washout 1 week + HF meal + washout 1 week + 2gCTE+ HF meal 6. 2gCTE+ HF meal + washout 1 week + 1gCTE+ HF meal + washout 1 week + HF meal	4. levels of antioxidants (FRAP & thiols) increased followed by a significant decrease in MDA at CTE 1g and 2g 5. Glutathione peroxidase (Gpx) activity increased significantly at 2g CTE, with decreased cytokine levels IL-6 & TNFα and increased IL-1β
4	Chayaratanasin et al, 2019	Invitro: preadiposit 3T3-L1 Phytochemical profile of CTE was analyzed by *liquid chromatography & tandem mass spectrometry* (LC-MS/MS)	1. Giving CTE 500-750 µg/mL significantly lowers triglyceride levels accompanied by increased lipolysis of mature adipocytes 2.RT-PCR Akt1 (T308) phosphorylation decreased significantly at a dose of 500 µg/mL; 750 µg/mL; 1000 µg/mL CTE b. ERK1/2 phosphorylation (T202/Y204) decreased significantly at a dose of 750 µg/mL; 1000 µg/mL CTE c. PPARγ & C/EBPα mRNA expression decreased significantly at doses of 500-1000 µg/mL CTE 4. Western blot: CTE (500-1000 µg/mL) a. The expression of adipogenic protein, lipogenic PPARγ & C/EBPα, fatty acid synthase (FAS), acetyl-CoA carboxylase (ACC), decreased significantly 5. Flowcytometry No signs of toxicity up to 2000 µg/mL CTE at H1, H3, H9

DISCUSSION

Obesity is a condition caused by excessive energy intake accompanied by increased free fatty acids in adipose tissue and a lack of physical activity as a form of energy expenditure (Sundaram et al., 2019) (Misra & Shrivastava, 2013). This condition was very worrying because obesity, especially central obesity, can lead to some chronic diseases. Obese patients with dyslipidemia showed elevation of TG and FFA levels. They increased plasma concentrations of apolipoprotein (apo) B. Impaired lipolysis of triglyceride-rich triglyceride lipoproteins can occur with decreased mRNA expression of lipoproteins in adipose tissue (Adel Mehraban, et al, 2021). In managing obesity and dyslipidemia, dietary recommendations play a crucial role in pharmacological interventions to prevent the side effects of chronic hypercholesterolemia (Sundaram et al., 2019) (Misra & Shrivastava, 2013).

Clitoria Ternatea Extract might inhibit the progression of weight gain or the development of obesity. It is likely to occur because CTE can increase adiponectin levels. Adiponectin levels were inversely related to body mass index (BMI) (Senkus et al., 2022) and fat mass. (Reneau et al., 2018) The CTE-improved energy balance by adiponectin is likely due to several mechanisms that align with the results of the four studies above. Clitoria Ternatea Extract reduce total cholesterol, LDL cholesterol (Wang et al.,

2022), triglycerides (Thilavech et al., 2021), plasma glucose (Permatasari et al., 2022) and mature adipocyte lipolysis. (Chayaratanasin et al, 2019)

Adiponectin is a protein class hormone mainly produced by white adipose tissue. It contains 247 amino acids with a molecular weight (for humans) of 28kDa, consisting of four parts, namely the signal region; variable region specific to the species; collagenous domain; and globular domains. (Da Silva Rosa et al., 2021) Several studies state that adiponectin plays a role in energy homeostasis and lipid and carbohydrate metabolism. (Halah et al., 2018) Adiponectin increases the efficiency of energy use because it plays a role in increasing glucose tolerance & insulin sensitivity, and reducing energetic expenditure. (Cisternas et al., 2019) Insulin sensitivity rise because adiponectin reduces hepatic glucose production and improve hepatic insulin sensitivity. (Bao et al., 2014) Adiponectin can gain the expression of gluconeogenesis enzymes, phosphoenol-carboxykinase, and glucose-6-phosphatase in the liver. (Qin et al., 2022) Pancreatic beta cells treated with adiponectin showed improvement in insulin exocytosis and Pdx-1 and MafA gene expression, both co-activators of insulin gene transcription. (Li et al., 2020) Adiponectin elevate glucose consumption by stimulating GLUT4 membrane translocation in muscle cells and adipocytes after AMPK phosphorylation. (Wang et al., 2017) It is because the APPL1 protein activates the Rab5 protein. Rab5 is a GTPase enzyme involved in endosome biogenesis and a key in GLUT4 translocation from the endosome to the plasma membrane. (Karvela et al., 2020) Adiponectin also inhibits the formation of glucose and glycogen. This is because it reduces the expression of the enzyme glucose-6-phosphatase and PEPCK, reducing glycogenolysis and gluconeogenesis in liver cells. (Tang et al., 2022) Because of its role in AMPK activation, adiponectin also reduces glycogen production in muscle cells. (Sung et al., 2022)

Increased adiponectin expression raised adipocyte differentiation, insulin sensitivity and TG accumulation in adipocytes. (Su et al., 2021) Visceral lipid deposits will be destroyed and stimulate the formation of new adipocytes in the subcutaneous tissue more sensitive to insulin. (Yang et al., 2018) This situation is also related with increased FFA levels. Adiponectin stimulates the expression of fatty acid translocase enzyme, so it also increases the transport of fatty acids to muscle cells. Several enzymes involved in the β-oxidation process also increase in number and activity due to adiponectin, so fatty acid catabolism also increases. (Ye et al., 2014) AMPK phosphorylation that occurs will inactivate ACC so that malonyl CoA production decreases and CPT-1 inhibition does not occur. CPT-1 is a transport protein that carries fatty acids to mitochondria, so it can be said that adiponectin increases fatty acid movements to mitochondria which β-oxidation enzymes will then degrade. (Ida Malandrino et al., 2015) Adiponectin elevates the expression of PPARγ so that it also influences the transcription of many genes involved in lipid catabolism. (Zheng et al., 2014)

The development of the herbal plant Clitoria ternatea provides hope for a safer additional dietary intervention for patients with obesity. Many studies have demonstrated the anti-obesity potential of leaf, root, and flower extracts from the butterfly pea flower plant. A study by Chayaratanasin et al. (2019) showed a positive effect of CTE on 3T3-L1 preadipocytes. It inhibited the proliferation and cell cycle retardation. Expression of the phospho-Akt and phospho-ERK1/2 signaling pathways was also repressed. In addition, inhibitory activity was also shown in the late stages of cell differentiation through decreased PPARÿ and C/EBPÿ. Furthermore, there was a process of downregulation of fatty acid synthase and acetyl-CoA carboxylase, which also caused a decrease in triglyceride levels. Another benefit generated by the administration of Clitoria ternatea extract is increased catecholamine-induced lipolytic activity in adipocytes. These results indicate that CTE effectively attenuates adipogenesis by controlling cell cycle progression and decreasing adipogenic gene expression (Chayaratanasin et al., 2019).

A study was carried out by Permatasari et al. (2022) said that the CTE (130 mg/kg BW) significantly relieved metabolic disorders caused by a high-fat diet. It also increased HDL levels, reduced LDL, TG, fasting blood glucose (FBG), and cholesterol levels. The addition of 65 and 130 mg/kg BW significantly

decreased the activity of the lipase and amylase enzymes (Permatasari et al., 2022). Wang et al. (2022) conducted a study on obese rats. C. ternatea aqueous extract significantly inhibited high-fat diet-induced weight gain in rats. Supplementation of Clitoria ternatea improved high-fat-induced increases in plasma insulin, leptin, and HOMA-IR levels and significantly increased plasma adiponectin levels in rats. In addition, mice treated with CT-H showed a significant reduction in liver weight compared to mice fed a high-fat diet (Wang et al., 2022).

Thilavech et al. (2021) demonstrated the role of CTE in postprandial glycemic and lipemic responses, antioxidant status, and pro-inflammatory markers in overnutrition men after consuming a high-fat meal. Administration of 2 g of CTE to obese patients has been shown to reduce serum triglycerides and postprandial serum free fatty acids 360 minutes post eating HF food. It significantly improved plasma antioxidant status by gained plasma FRAP and thiol levels. The plasma Gpx activity was significantly higher at 180 min after the HF meal with 2 g of CTE ingestion. This study supports that CTE can be used as an alternative natural agent to reduce postprandial lipemia and improve antioxidant status in overnutrition men after consuming HF foods (Thilavech et al., 2021). Very few studies, especially in humans, have looked at the role of CTE on adiponectin levels. Therefore, it needs future study explores how CTE can reduce adiponectin to support the development of CTE as an alternative therapy to support obesity.

CONCLUSION

Based on the review of the literature studies conducted, it was concluded that the extract of the butterfly pea flower (Clitoria ternatea) has benefits in treating patients with obesity. In addition to losing weight, Clitoria ternatea also has a role in preventing obesity complications associated with dyslipidemia by improving HDL, LDL, total cholesterol, and amylase and lipase levels closer to normal.

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