

LITERATURE REVIEW

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A Systematic Review of Butterfly Pea Flowers (*Clitoria ternatea* L.) in Reducing Body Weight and Improving Lipid Profile in Rodents with Obesity

Tinjauan Sistematis: Bunga Telang (*Clitoria ternatea* L.) dalam Menurunkan Berat Badan dan Memperbaiki Profil Lipid pada Mencit dan Tikus dengan Obesitas

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ABSTRACT

Background: Butterfly pea flowers (*Clitoria ternatea* L.) are edible plants found in Asian countries that have several phytochemical compounds that have potential anti-obesity and anti-dyslipidemia. From several in vivo studies, the administration of various extracts of butterfly pea flowers has different effects to reduce body weight (BW) or body mass index (BMI), and lipid profiles.

Objectives: To analyze systematically the effects of butterfly pea flowers on BW or BMI and lipid profiles in rodents with or without obesity.

Methods: This study used the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and bias risk using the Systematic Review Centre for Laboratory Animal Experimentation (SyRCLs). Original articles were from Google Scholar, PubMed, ResearchGate, and Science-Direct with criteria: randomized control trial (RCT), published from 2019 to 2023, rodents, and research outcomes (BW and lipid profiles).

Results: Four original articles met the research criteria. Giving 1,000 mg/kg BW of the aqueous extract of butterfly pea flower for seven days reduced BW. Another study reported that giving 130 mg/kg BW butterfly pea flowers kombucha inhibited weight gain. Doses of 0.25 and 0.50% of the aqueous extracts of butterfly pea flowers for 15 weeks did not affect BW but the dose of 2% prevented weight gain.

Conclusions: Butterfly pea flowers have beneficial effects on reducing BW and improving lipid profiles in rodents with several diets although vary in animal models, diet types, extraction methods, and research design. This study becomes important evidence for further study.

INTRODUCTION

Obesity is a metabolic disease with multifactorial etiologies, becomes a public health problem since its prevalence has increased rapidly. According to the World Obesity Atlas (2023), the prevalence of obesity globally is predicted to increase from 38% in 2025 to 51% in 2035, while in the south-east region, the prevalence of obesity is estimated to increase from 20% in 2020 to 53% in 2035¹. In Indonesia, the prevalence of obesity in adults also increased from 14.8% in 2013 to 21.8% in 2018, and in children from 10.3% in 2013 to 17% in 2018². Obesity pathogenesis is characterized by excessive fat accumulation either in local or systemic distribution, which results in increasing body weight and

dyslipidemia. Obesity is the main risk factor for some cardiometabolic diseases such as diabetes mellitus, hypertension, stroke, coronary heart disease, and kidney failure^{3,4}. Therefore, early diagnosis and proper management of obesity are required to reduce obesity complications.

In general, the standard management of obesity without complications is diet and physical activity. The most popular diet for obesity is a low-energy diet, which has similarities with the balanced diet but the total energy intake is lower (500-1,000 kcal per day) than the balanced diet. Implementation of this diet is expected to reduce 0.5-1 kg body weight (BW) per week⁵. For example, a low-energy diet that consisted of 50-60%

carbohydrate, 20-30% fat, and 12-30% protein could reduce 5.25 cm waist circumference in obese people after eight weeks of intervention⁶. Buckland's study reported that a low-energy diet with a 20% energy deficit (about 600 kcal per day) and distributed for 20% breakfast, 30% lunch, 30% evening meal 30%, and 20% snacks were given in obese women for two weeks could reduce 1 kg BW and 0.35 kg/m²BMI⁷. However, most obese people have low complaints to undergo their recommended diet although they had been assisted by a peer group⁸. They also consumed more than 100% of their daily energy intake since they were unable to control their appetite. Therefore, it is needed to make innovations for the reduction of BW and waist circumference.

Functional foods have been developed for obesity treatments either in animal models or in human subjects. Administration of 5 ml/day virgin coconut oil containing medium chain triglyceride for four weeks in Wistar male rats with obesity reduced appetite but did not reduce BW and visceral fat mass⁹. Another study reported that Wistar female rats with obesity treated with 70 mg/kg BW root extract of white turmeric (*Curcuma zedoaria*) containing curcumin for 30 days had reductions of BW from 192.99±4.103 g to 188.08±4.66 g, total cholesterol, triglyceride (TG), and low-density lipoprotein (LDL-C) levels, and increases of high-density lipoprotein (HDL-C) level¹⁰. Meanwhile, the Harahap study reported that the administration of 200 g per day of green coffee containing chlorogenic acid for eight weeks in women with obesity could reduce by 4.1±1 kg BW¹¹. Anthocyanin is the other bioactive compound in the flavonoid family group and has also been reported to have an anti-obesity effect on the reduction of triglyceride levels and adipogenesis. Butterfly pea flowers, for instance, have high anthocyanins levels, especially delphinidin, which reported to prevent weight gain by reducing adipogenic gene expression and activating lipase hormones in preadipocyte cells incubated with 500-1,000 µg of butterfly pea flower

extract for 24 hours¹². In addition, delphinidin activated adenosine monophosphate-activated protein kinase (AMPK) and reduced peroxisome proliferator-activated receptor gamma PPAR-γ expression, which result in inhibitions of adipogenesis and lipogenesis¹³. Consequently, anthocyanin administration becomes a potential compound to reduce body weight and improve lipid profiles in vivo and in human studies. From several in vivo studies, the administration of butterfly pea flower extracts and kombucha has different effects in terms of BW and lipid profiles. Therefore, this study aimed to analyze systematically the effects of butterfly pea flowers on BW or BMI, and lipid profile (total cholesterol, LDL-C, HDL-C, and triglyceride) in rodents with obesity.

METHODS

Data Sources and Collection

This research study adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) eScR-checklist¹⁴. We identified original articles which matched the inclusion criteria such as experimental studies using the RCT method, rodents with obesity and or dyslipidemia, butterfly pea flowers treatment, free-full text, publication from 2019 to 2023, and English or Indonesian version. Relevant and selected articles were downloaded from several journal databases such as Google Scholar, PubMed, ResearchGate, and Science Direct using some keywords: butterfly pea flowers or *Clitoria ternatea* and obesity or dyslipidemia, for those databases. The main outcomes of the research study were BW, BMI, and lipid profiles (total cholesterol, LDL-C, HDL-C, and or TG).

Study Criteria

We selected full-text articles using the Population, Intervention, Comparator, Outcome, and Study Design (PICOS) protocol to exclude full-text articles, which did not match the inclusion criteria (Table 1)¹⁵.

Table 1. Population, Intervention, Comparator, Outcome, and Study design (PICOS)'s Criteria for Selecting Full-Text Article

Variable	Inclusion criteria	Exclusion criteria
Population	Rodent	-
Intervention	Butterfly pea flowers	Mixed with other plants
Comparator	Treatment and control groups	-
Outcome	BW or BMI, total cholesterol, LDL-C, HDL-C, or TG levels	-
Study Design	RCT	Published before 2018, and incomplete articles

*PICOS (Population, Intervention, Comparator, Outcome, and Study design (PICOS) Model for Clinical Question

Search Strategy

Two authors (FU and AAR) independently evaluated all four journal databases, which were initially searched, screened, and downloaded all selected full-text articles. We recorded all those articles, which were then screened and selected according to titles, abstracts, and eligible criteria. We discussed any disagreement of several evaluated articles to achieve consensus on whether or not those articles were eliminated from this study.

Data Extraction and Synthesis

We evaluated the quality of selected full-text articles and assessed bias risks using the SYRCLEs tool, which consisted of 10-item assessments (D1-10)¹⁶. The selected articles were further analyzed by comparing authors, publication year, country, research subject, control, intervention, and research findings.

RESULTS AND DISCUSSION

Figure 1. The selection process of eligible full-text articles, which matched the inclusion and exclusion criteria, used the PRISMA approach. We obtained 1,745 full-text articles from the Research Gate, Pubmed,

Science Direct, and Google Scholar databases. There were 14 among 1,745 articles, which were further evaluated for relevant topics by screening title and abstract. However, 10 articles were excluded from this study because of *in vitro* studies.

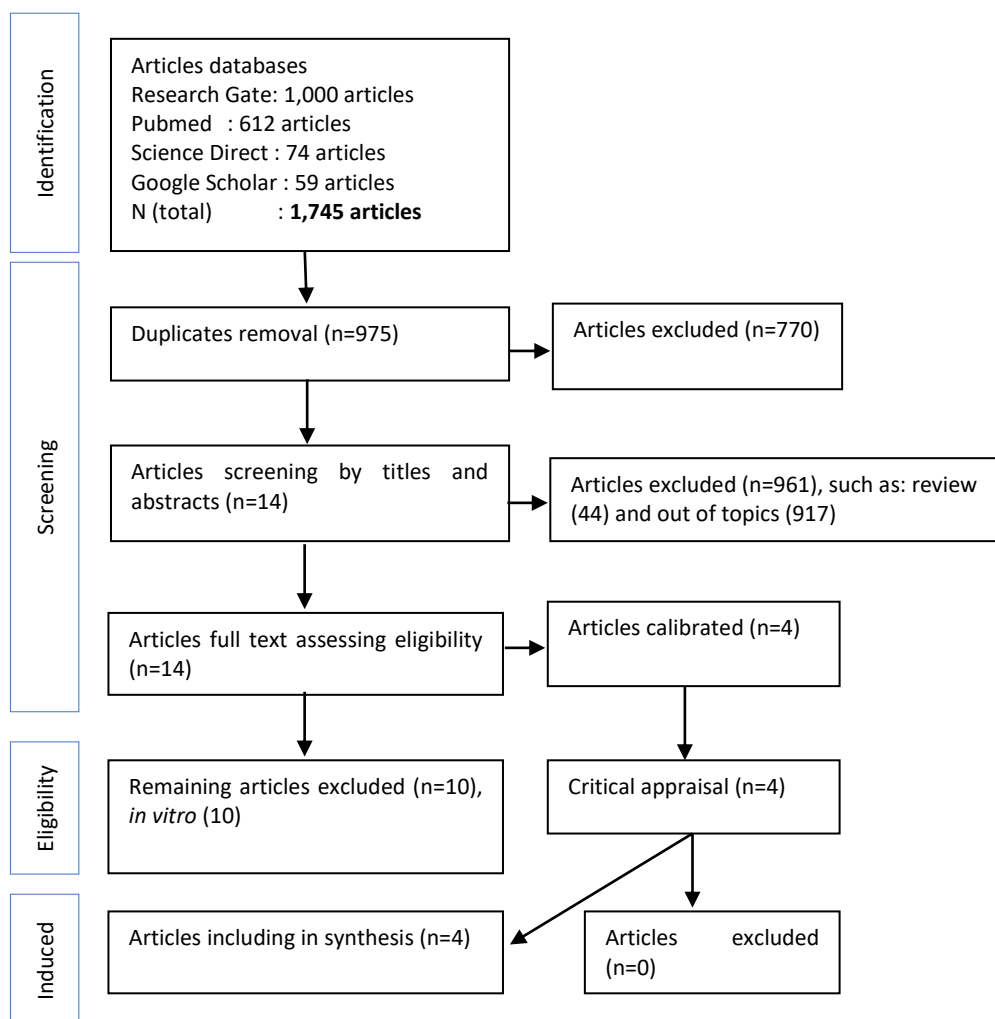


Figure 1. Selection Process of Eligible Research Articles Based on The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Flow Chart

In this study, we used the SYRCLEs tool for assessing the quality and bias risk of four full-text articles (Table 2). Overall, all studies had low bias risk except Arifah and her coworker’s study, which did not provide animal handling during their experiment. Meanwhile, a highly bias risk was found in Tunna’s study

because they gave a standard diet and diazepam in the positive control group of mice, which was compared to the mice treatment groups with a standard diet and theaqueous extracts of *Bambusa polymorpha*, *Mentha piperita*, or *C.ternatea*.

Table 2. Quality assessment and bias risk of four selected articles using the Systematic Review Centre for Laboratory Animal Experimentation (SYRCLEs) tool

Authors	D1	D2	D3	D4	D5	D6	D7	D8	D9	D10
Wang et al., 2022 ¹⁷	+	+	+	+	+	+	+	+	+	+
Arifah et al., 2022 ¹⁸	+	+	+	?	+	+	+	+	+	+
Permatasari et al., 2022 ¹⁹	+	+	+	+	+	+	+	+	+	+
Tunna et al., 2020 ²⁰	+	+	+	+	+	+	+	+	+	-

* SYRCLEs (Systematic Review Centre for Laboratory Animal Experimentation) Tool For Assessing Risk of Bias ¹⁶

(+) low risk, (?) unclear, (-) high risk.

Characteristics of Selected Studies

Based four eligible articles, they had some different characteristics regarding research country, animal model, diet type, extraction method, research design, and research findings (Table 3). The animal studies were performed by researchers in China, Indonesia, and Thailand. The three animal studies used at least 30 mice for their experiments while one research study used 30 rats¹⁸. They used four different types of diet: High Fat High Fructose Diet (HFFD), High Fat Diet (HFD), Cholesterol Fat Enriched Diet (CFED), and standard diet. In terms of the extraction method of butterfly pea flowers, Wang and Tunna's studies used aqueous extracts while Arifah and Permatasari's studies used ethanol extract and a fermented kombucha of butterfly pea flowers respectively. The RCT experiment was applied to all research studies but the Tunna's study used a positive control group and did not allocate

anegative control group. The complete research findings were found in Wang and Permatasari studies while Arifah and Tunna Studies only reported lipid profiles and BW reduction respectively¹⁷⁻²⁰.

Administration of 1,000 mg/kg BW of the aqueous extract of butterfly pea flower for seven days reduced by 16.39% BW in mice with normal diet²⁰. Meanwhile, another study reported that the administration of 130 mg/kg BW butterfly pea flowers kombucha inhibited weight gain from 0.83 ± 0.13 g/day to 0.59 ± 0.10 g/day in mice with CFED¹⁹. In contrast, Wang's study reported that administration of 0.25 and 0.50% of the aqueous extract of butterfly pea flower petals for 15 weeks did not affect BW in mice with HFFD. However, the highest dose of the aqueous extract of butterfly pea flowers (2%) prevented weight gain (about 39 mg) in mice with HFFD, but it did not reach significantly compared to the negative control¹⁷.

Table 3. The effects of Butterfly pea flowers (*C. ternatea* L.) on Body Weight, Body Mass Index, and Lipid Profiles in Rodents

No.	Author/Year	Countries	Sample	Control	Intervention	Research Design	Findings
1.	Wang et al., 2022 ¹⁷	China	40 Male C57BL/6J mice	Normal Standard diet Negative Control: HFFD	Control: HFFD + 0.25 %, 0.5 %, and 2 % (w/w) of the aqueous extract butterfly pea flowers in drinking water in 15 weeks	RCT, pre-post with the control group	The LDL-C level was lower in the mice treated with the aqueous extract of <i>Butterfly pea flowers</i> than in the mice control group. The aqueous extract significantly reduced total cholesterol compared to the control group.
2.	Arifah et al., 2022 ¹⁸	Indonesia	30 Male Wistar rats	Normal Standard diet Negative Control: HFD Positive Control: HFD + simvastatin 0,18 mg/kg BW	Control: HFD+100 mg, 200 mg, and 400 mg/kg BW the ethanol extract of butterfly pea flowers in 14 days	RCT, pre-post with the control group	400 mg/kg BW the ethanol extract of butterfly pea flowers significantly reduced total cholesterol, LDL-C, and HDL-C in Male rats.
3.	Permatasari et al., 2022 ¹⁹	Indonesia	40 Male Swiss Albino mice	Normal standard diet Negative Control: CFED	control: CFED+65 and 130 mg/kg BW butterfly pea flowers kombucha 21 days	RCT, pre-post with the control group	The weight gain in CFED+ 65 and 130 mg/kg BW butterfly pea flowers kombucha BW rat groups was significantly lower than the CFED rat group ($p < 0.001$). The administration of 130 mg/kg BW butterfly pea flowers kombucha had better effects on reducing total cholesterol, LDL-C, triglyceride level, and increasing HDL-C, compared to the lower dose and control (-) group.
4.	Tunnaet al., 2020 ²⁰	Thailand	30 Male Swiss Albino mice Anxiety models	Positive Standard diet+Diazepam 0.25 g/kg BW	control: Standard diet+1.000 mg/kg BW the aqueous extract of Bambusa polymorpha, Mentha piperita, and <i>C. ternatea</i> for 7 days	RCT, pre-post with the control group	In the mice treated with 1.000 mg/kg BW, the aqueous extract of Butterfly pea flower extract had the highest BW reduction (16.39%) compared to the other mice groups.

From 1.745 original research articles, we have four articles that investigated the effects of butterfly pea flowers on BW, BMI, and lipid profiles although it has some variations in terms of animal model, diet type, extraction method, research design, and research findings. The BW reduction was found in three original articles while the changes in lipid profiles were only found in one original article. In general, the research findings indicated that the administration of butterfly pea flowers reduces BW, BMI, total cholesterol, LDL-C, and triglyceride levels and increases HDL-C levels in mice or rats with HFFD, HFD, CFED, and anxiety models.

There are several reasons why administration of butterfly pea flowers has different effects in reducing BW. At first, mice naturally have neophobic properties and are sensitive to new objects and feed. Meanwhile, the rats have a higher appetite so they have a tendency to consume more foods, which affects weight loss during administration of the butterfly pea flowers²¹. Moreover, all experiments among rat models treated with butterfly pea flowers did not use the BW parameters. Therefore, we cannot speculate that butterfly pea flowers have anti-obesity activity. Secondly, CFED or HFFD might provide a higher calorie intake to the mice so that the anti-obesity effect of the butterfly pea flowers is lower than mice with a normal diet. In addition, the BW reduction in mice with HFFD (12±6.00 g) is lower than the BW reduction in mice with CFED (23.4 ±0.53 g). This diet discrepancy is perhaps caused by the presence of carbohydrates in CFED, compared with fructose in the HFFD.

The differences in BW reduction in mice after treatment with giving butterfly pea flowers are also contributed to the extraction methods and their phytochemicals. Wang's study reported that the aqueous extract of Chinese butterfly pea flower powder had 3.336±71 ppm total flavonoids and 815.93±30 ppm anthocyanin level¹⁷. In comparison to Wang's study, Tunna and coworkers did not report the total flavonoids and anthocyanin levels in the aqueous extract of butterfly pea flowers. Meanwhile, Arifah's study only presented the qualitative data of total flavonoids and anthocyanin in the ethanol extract of butterfly pea flowers. Permatasari's study also did not present total flavonoids and anthocyanin data in the butterfly pea flowers kombucha¹⁸⁻²⁰. Therefore, the BW reduction is not fully attributed to the phytochemical content in butterfly pea flower extracts.

Based on the research design among four research studies, only Tunna's study did not have a negative control group²⁰. In addition, all articles did not calculate the sample size and present the sampling technique. In the Permatasari's study, they used 40 mice

but there is no further information on whether or not mice were randomly divided into four groups¹⁹. The sample size of mice and rats in all articles met the minimal requirement of the RCT experiments. Wang and Permatasari's

All studies administered butterfly pea flower extracts at the beginning of their experiment and did not make the obese mice and rats^{17,18}. Arifah's study made a rat model with hyperlipidemia and Tunna's study made a mice model with anxiety. In terms of duration, all four articles have different time interventions^{18,20}. The longest time of intervention was found in Wang's study while the shortest intervention was in Tunna's study^{17,20}. So we think that research design also influences the BW reduction after butterfly pea flower treatment.

The second effect of butterfly pea flowers is to improve lipid profile in mice or rats with CFED, HFFD, HFD, and a normal diet. The higher dose of butterfly pea flower extracts is more effective to reduce total cholesterol, LDL-C, and TG levels, and to increase HDL-C levels, compared to the lower dose of butterfly pea flower extracts. Administrations of 400 mg/kg BW of the ethanol extract of butterfly pea flowers for 14 days and 2% of the aqueous extract of butterfly pea flowers for 15 weeks reduced total cholesterol, LDL-C, and TG levels and increased HDL-C levels^{18,19}. In Permatasari's study, administration of 65 mg/kg BW butterfly pea flowers kombucha for 21 days reduced total cholesterol, LDL-C, and TG levels, and increased HDL-C levels¹⁹. Unfortunately, Tunna's study did not report the effect of aqueous extract of butterfly pea flower on lipid profiles in their article²⁰. Therefore, administration of butterfly pea flower extracts indicates a different effect on lipid profile depending on animal model, extraction method, intervention time, and duration.

One study has reported that butterfly pea flowers contain anthocyanin, alkaloids, tannins, flavonoids, terpenoids, and phenol²². Delphinidin is a family member of anthocyanins that is mainly found in butterfly pea flowers, which can reduce body fat by downregulation of the expression of adipogenesis and lipogenesis biomarkers such as peroxisome proliferator-activated receptors-gamma (PPAR-γ). Delphinidin also activates AMPK, increasing adipose triglyceride lipase. This enzyme plays an important role in lipolysis and the catabolism of fatty acid into energy^{13,23}. In addition, delphinidin can inhibit body fat accumulation (adipogenesis) by reduction of PPAR-γ expression to prevent weight gain during intervention²⁴. Secondly, cyanidin-3-O-glucoside is another member of anthocyanins that is also found in butterfly pea flowers (Figure 2)²⁵.

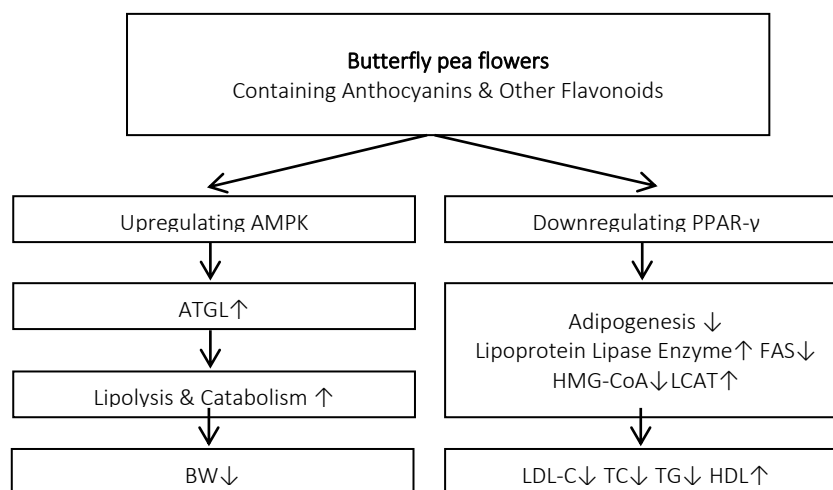


Figure 2. Action Mechanism of Anthocyanins & Other Flavonoids-derived from Butterfly Pea Flowers to Reduce Body Weight and to Improve Lipid Profile

The other phytochemical such as flavonoids can improve lipid profile by increasing the lipoprotein lipase enzyme, which catalyzes the formation of very low-density lipoprotein for transporting TGs which hydrolyze their fatty acids and glycerol. Circulated fatty acids are then absorbed by skeletal muscles and other tissues to be stored and used as an important energy source. Flavonoids have another effect to inhibit Fatty Acid Synthase (FAS), which directly inhibits the formation of fatty acids and TGs.^{23,26} Flavonoids also help lower LDL levels by inhibiting LDL oxidation and 3-Hydroxy-3-Methyl-Glutaryl-Coenzyme A (HMG-CoA) reductase for cholesterol synthesis and increasing LDL receptors on liver cell membranes for transporting lipids in the blood²³. Furthermore, flavonoids play a vital role in the increase of HDL-C levels through the enhancement of Lecithin Cholesterol Acyl Transferase (LCAT) activity, converting free cholesterol into cholesterol esters to become more water soluble to interact with the lipoprotein as core particles of new HDL-C (Figure 2).

CONCLUSIONS

Administration of butterfly pea flowers has beneficial effects on the reduction of BW, total cholesterol, LDL-C, and TG levels, and the increase of HDL-C levels in mice and rats with CFED, HFFD, HFD, and normal diet. However, the research findings vary in terms of animal model, diet type, extraction method, and research design. This systematic review provides important evidence to further investigate the therapeutic effects of butterfly pea flower extracts on BW, BMI, body fat content, leptin level, and lipid profiles in mice or rats with obesity and/or dyslipidemia.

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Conflict of Interest and Funding Disclosure

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