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Meta-Analysis

Effectiveness of *Hibiscus sabdariffa Linn* for Obesity Treatment: A Systematic Review of Randomized Controlled Trials

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ABSTRACT

Background: *Hibiscus sabdariffa* Linn. (*H. sabdariffa*), commonly known as Rosella plants in Indonesia, has had various uses in the food and beverage industry and traditional medicines for hundreds of years. The main compounds of *H. sabdariffa* have been stated to have anti-obesity effects through its biologically active compounds. This review systematically evaluates the evidence from human randomized clinical trials on the effects of *H. sabdariffa* extract in obesity, including decreased bodyweight, normalizing the blood lipid profile, and modulating appetite-related biomarkers.
Subjects and Method: This review is based on the patient, intervention, comparison, and outcome (PICO) procedure**,** with the patient is people with obesity, the intervention is the administration of *H. sabdariffa* extract compared to control that given placebo, and the outcomes are reduced body weight and fat accumulation, normalize blood lipid profiles, and regulate biomarkers related to appetite. Articles used are limited to the publication year between 2013 and 2021. Search is done through PubMed, ScienceDirect, Wiley Online Library, Scopus, and Google Scholar with the keywords "*hibiscus sabdariffa* and obesity", "*hibiscus sabdariffa* and lipogenesis", "*hibiscus sabdariffa* and energy metabolism", and "*hibiscus sabdariffa* and appetite".
Results: The search resulted in 10 studies involving 453 subjects. We proved several significant effects of *H. sabdariffa* extract on obese subjects. Administration of *H. sabdariffa* extract for several doses and several days can improve anthropometry measurement, fat accumulation, increased satiety sensation, while the appetite sensation mainly for fatty, sweet, and salty foods was decreased.
Conclusion: This review suggests that the benefit of H. sabdariffa to people with obesity are associated with body weight and blood lipid profile-lowering effect; however, more high-quality clinical trials are needed.

Keywords: *Hibiscus sabdariffa*, obesity, appetite

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BACKGROUND

The increasing worldwide prevalence of obesity has become the fifth worldwide cause of death and the primary factor that leads to various high mortality prevalence diseases, including hypertension, type 2 diabetes, cardiovascular disease, and various types of cancer (Liu et al., 2017). In Indonesia, according to the latest study by Indonesia's Ministry of Health in 2019 showed an increase in the incidence of obesity by seven percent (Riset Kesehatan Dasar (RISKESDAS),

2019). Because various treatment methods of obesity have been used, neither clinically nor not, have short-term effects, there is an urgent need to find another kind of treatment that might have long-term effects and mild side-effects (Annamalai et al., 2016). Therefore, many studies concerned with this issue are being developed, utilizing medical plants.

Medical plants are common in society because they are classified as safe, easy to obtain, and relatively cheap (Bule et al., 2020). *Hibiscus sabdariffa* Linn. (*H. sabdariffa*), commonly known as Rosella plant in Indonesia, is one of the plants stated to have anti-obesity effects through its biologically active compounds (Ojulari, Lee and Nam, 2019). The calyx of this plant has been used in the food and beverage industry and traditional medicines for hundreds of years (Borrás-Linares et al., 2015; American Diabetes Association, 2018). The main compounds of *H. sabdariffa* that have been proven to have pharmacological effects are organic acids, anthocyanins, polysaccharides, and flavonoids. Studies on obese mice revealed several mechanisms and active compounds related to these anti-obesity effects, such as polyphenols that can regulate glucose metabolism in obese patients. In addition, *H. sabdariffa* is also rich in minerals, amino acids, and vitamin C. This makes *H. sabdariffa* has anti-oxidant, anti-inflammatory, and anti-cholesterol effects (Jabeur et al., 2017).

Several studies have shown that *H. sabdariffa* can significantly reduce the levels of total lipids, cholesterol, and triglycerides (Alarcon-Aguilar et al., 2007). Human studies have shown that oral administration of *H. sabdariffa* liquid extract can significantly reduce body weight and abdominal fat accumulation in obese patients. *H. sabdariffa* was taken orally daily for 42 days and showed a reduction in body weight and normal LDL, HDL, and cholesterol levels (Diez-Echave et al., 2020). The previous has shown that *H. sabdariffa* can handle FGF21 resistance that plays a role in energy homeostasis in adipose tissue and reduces weight through the browning of white adipose tissue (Kartinah et al., 2021). The browning of white adipose tissue has been known to increase energy expenditure through non-shivering thermogenesis. In addition, some bioactive phytochemicals derived plants may also act to suppress appetite. The possible target is the appetite hormone (Stuby et al., 2019). However, the exact mechanism is unclear.

This whole potency makes *H. sabdariffa* a great candidate for the treatment of obesity. In recent years, the number of human randomized controlled trials studies targeting *H. sabdariffa* potency as an anti-obesity drug has increased, making us feel the need for a systematic review of this topic. Therefore, this review aims to explore the effects of *H. sabdariffa* extract in obese subjects, including decreased bodyweight, normalized blood lipid profile, and modulate appetite-related biomarkers.

SUBJECT AND METHOD

1. Study Design

This study was a systematic review focused on human randomized controlled trials (RCTs). The published article was systematically reviewed to assess the anti-obesity effect of *H. sabdariffa*. This study is based on the Patient, Intervention, Comparison, and Outcome (PICO) procedure, with the patient are people with obesity, the intervention is the administration of *H. sabdariffa* extract compared to control that given placebo, and the outcomes are reduced body weight and fat accumulation, normalize blood lipid profiles, and regulate biomarkers related to appetite. Article search is done through electronic databases (i.e., PubMed,

ScienceDirect, Wiley Online Library, Scopus, and Google Scholar). The search terms based on MESH are "*hibiscus sabdariffa* and obesity", "*hibiscus sabdariffa* and lipogenesis", "*hibiscus sabdariffa* and energy metabolism", and "*hibiscus sabdariffa* and appetite". The articles used in this study are limited to the publication years between 2013 and 2021.

2. Inclusion Criteria

The included studies must follow these inclusion criteria: (a) the type of study was RCTs; (b) the research population must be included at least 10 participants in each group; (c) the research subjects must be overweight and/or obese (BMI≥25 kg/m2), (d) the interventions were *H. sabdariffa* extract; and (d) trials with an appropriate control group (i.e., placebo).

3. Exclusion Criteria

Exclusion criteria were as follows: (a) the research is in vitro, in vivo, article review, abstract meeting, and abstract without a full script; (b) interventions were phytochemicals derived from *H. sabdariffa*; and (c) subjects were consuming any drugs that might affect the results.

4. Data Analysis

First, the authors screened the articles by title and abstract and retrieved relevant full-article text. Furthermore, the reevaluation of the full text article against the eligibilty was performed based on the inclusion and exclusion criteria. In this study identified 443 potentially qualified articles. Of these, 238 were excluded after manual deduplication filtering. After screening titles and abstracts, and based on inclusion and exclusion criteria, 195 articles were deleted. Finally, ten articles met the inclusion criteria. Data from the eligible studies were extracted independently which included (a) general information (author, title, publication year, and randomization), (b) subjects (sample size, BMI range, and age), (c) intervention, (d) control, and (c) outcomes.

RESULTS

A systematic article searches in this study identified 443 potentially qualified articles. Of these, 238 were excluded after manual deduplication filtering. After screening titles and abstracts, and based on inclusion and exclusion criteria, 195 articles were deleted. Finally, ten articles met the inclusion criteria. The systematic flowchart is displayed in Figure 1. The baseline characteristic of all the participants and study characteristics are summarized in Table 1 and Table 2. Among all the studies, 453 participants were included, with two studies including men only, two studies including women only, and the rest included both men and women. The nutritional regiments guide for all the selected studies is summarized in Table 3.

The main results of this study are the reduction of body weight and fat accumulation, the normalization of blood lipid profile, and the regulation of biomarkers related to appetite compared to the control group. The outcome are summarized in Table 4, denoted with "-" and "+".

1. Weight loss and change in fat accumulation

Out of ten selected studies, four reported body weight and fat accumulation (Table 4). The study by Marhuenda et al. (2020) showed that the administration of *H sabdariffa* extract for 84 days could reduce body weight, body mass index, and fat mass, especially fat of the trunk (chest and torso). A study by Herrans-Lopez et al. (2019) showed an overall improvement in the anthropometric parameters determined in the groups taking *H sabdariffa* compared to control after two months in bodyweight, abdominal circumference, and percentage of *body fat*. Another study by Boix-Castejon et al. (2018) showed similar results. Taking

H sabdariffa extract for 56 days showed a better anthropometric improvement, especially on body weight, triceps skinfold thickness, body fat, and hip circumference. However, a study from Chang et al. (2014) showed no significant difference between the treatment and the control groups.

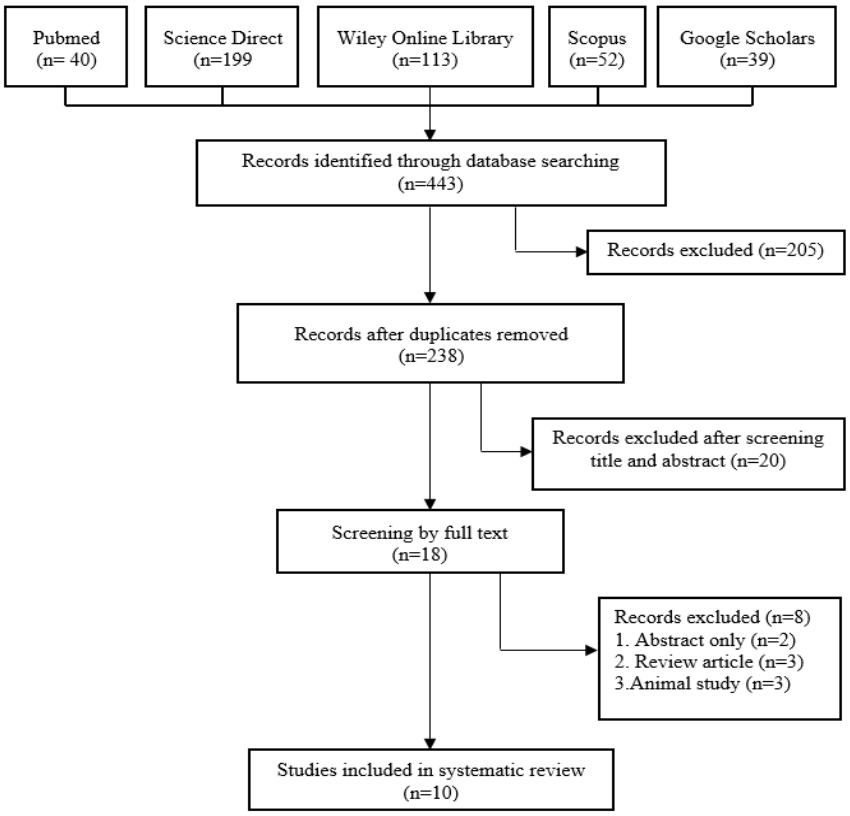

Figure 1. Systematic review flowchart

Table 1. Baseline characteristics

Study (Year)	Type of study	Participants (n)	Age (years)	Sex	BMI (kg/m²)	Follow up (days)
(Marhuenda et al., 2020)	RCT	84	18-65	Both	25-35	84
(Serna et al., 2021)	RCT	33	18-65	Both	25–34.9	120
(Aguirre-García et al., 2019)	RCT	20	45-64	Both	n.r	60
(Abubakar et al., 2019)	RCT	25	n.a	Male	n.r	14
(Herranz-López et al., 2019)	RCT	46	36-69	Female	24-34	92
(Boix-Castejón et al., 2018)	RCT	54	30-75	Female	25–34,9	56
(Hajifaraji et al., 2018)	RCT	43	30-60	Both	n.r	84
(Asgary et al., 2016)	RCT	40	≥ 18	Both	n.r	28
(Chang et al., 2014)	RCT	36	18-65	Both	≥27	84
(Sabzghabaee et al., 2013)	RCT	72	12-18	Male	n.r	30

Table 2. Study characteristics

Study	Type of study	Plant Formula	Inclusion criteria	Exclusion criteria
(Marhuenda et al., 2020)	RCT	*Hibiscus sabdariffa* + *Lippia citriodora*	1. Age between 18 and 65 years 2. Both sexes 3. Body mass index (BMI) between 25 and 35 kg/m²	Had illness, pharmacological treatment, toxicological habits, and allergies
(Serna et al., 2021)	Co-RCT	*Hibiscus sabdariffa* + *Lippia citriodora*	1. Age between 18–65 years old 2. Both sexes 3. Body mass index (BMI) between 25–34.9 kg/m² 4. Weight maintained in the last three months 5. Do not modify nicotinic habits 6. Absence of disease	1. Had chronic diseases, illness, thyroid dysfunction, and allergies 2. Carrying out or intend to carry out any type of diet during the study 3. Pregnant woman
(Aguirre-García et al., 2019)	RCT	*Hibiscus sabdariffa*	1. Patients with a lipidic profile, with higher lipid levels than those established as high limits, no matter the base disease 2. Ages were within the range of 45 - 65years old	1. Patients who were receiving a lipid level lowering treatment 2. Lack of commitment to the treatment 3. Voluntarily giving up. 4. Usual diet modification during treatment 5. The beginning of some lipid levels lowering treatment during the study.
(Abubakar et al., 2019)	Co-RCT	*Hibiscus sabdariffa*	1. Male 2. Have 1 to 10% CVD risk in 10 years 3. Not taking BP medication 4. Not having kidney, liver or chronic diseases 5. Smoking or not smoking 6. Signed informed consent	n.r
(Herranz-López et al., 2019)	RCT	*Hibiscus sabdariffa* + *Lippia citriodora*	1. 36-69 years old 2. Both sexes 3. 24-34 kg/m² of body mass index (BMI)	1. Total cholesterol <200 mg/dl 2. Presence any obesity-related pathology 3. Use prescription medication for cholesterol / hypertension 4. Hormone replacement therapy 5.Consumption of antioxidant supplements/drugs 6. Alcohol addiction 7. Pregnant/lactating woman
(Boix-Castejón et al., 2018)	RCT	*Hibiscus sabdariffa* + *Lippia citriodora*	1. Females 2. BMI 25–34.9 kg/m²	1. Presence of any obesity related Pathology 2. Use of prescribed medication for hyper-cholesterolemia or hypertension

Study	Type of study	Plant Formula	Inclusion criteria	Exclusion criteria
				3. Consumption of antioxidant supplements/Drugs 4. Frequent alcohol consumption 5. Pregnant/lactating.
(Hajifaraji et al., 2018)	RCT	*Hibiscus sabdariffa*	1. Patients with polygenic dyslipidemia and had the following criteria: a) total cholesterol > 200 mg/dl, b) LDL-C >180 mg/dl, c) HDL-C <45 mg/dl for men and <55 mg/dl for women 2. Having no history of diseases like diabetes, cardiovascular diseases, nephritic syndrome, liver diseases, and thyroid gland dysfunction 3. Not taking lipid-lowering drugs 4. Not smoking 5. Not having special diets such as being vegetarian	1. Had allergy to sour tea 2. Preferred not to drink sour tea 3. Took a trip during the course of study
(Asgary et al., 2016)	RCT	*Hibiscus sabdariffa*	1. Being diagnosed with MetS and had the following five components: (a) abdominal obesity, defined as waist circumference >102 cm for men or >88 cm for women, (b) elevated serum TG (≥150mg/dL), (c) low serum HDL-C (<40mg/dL for men and <50 mg/dL for women), (d) hypertension (blood pressure (BP) ≥ 130/85 mmHg) or current treatment for hypertension, and (e) impaired fasting glucose (FPG ≥ 110 mg/dL) 2. Age > 18 years 3. Free of diseases affecting serum lipids (e.g., thyroid disorders and pancreatitis) 4. Not using drugs or supplements affecting serum lipids (e.g., statins, fibrate derivatives, estrogens, progestins, β-blockers, thiazide diuretics, and fish oil) within the last 3 months and at present 5. Not using any antidiabetic drug including insulin within the last 3 months and at present 6. Free of liver or kidney disease 7. Not being substance abuser (including alcohol) or smoker	1. Had allergic reaction to roselle 2. Irregular use of the capsules (consumption of less than 80% of total capsules during the study

Study	Type of study	Plant Formula	Inclusion criteria	Exclusion criteria
			8. Not being pregnant or lactating (for women).	
(Chang et al., 2014)	RCT	*Hibiscus sabdariffa*	1. 18-65 years old 2. Both sexes 3. Body mass index (BMI) ≥27 4. Had fatty liver 5. Not under a course of treatment	1. Had a drinking habit (≥20 g alcohol daily) 2. Hal ALT 3-fold higher or bilirubin above 2 mg/dl^{-1} 3. Had kidney disfunction 4. Had cardiovascular diseases 5. Had endocrine or severe systemic disturbance 6. Had mental disorders
(Sabzghabaee et al., 2013)	RCT	*Hibiscus sabdariffa*	1. At least had one of these criteria; serum triglyceride >90 percentile, serum total cholesterol >90 percentile, LDL >90 percentile, HDL <10 percentile 2. Not using tobacco 3. No history of alcohol consumption or drug abuse 4. No history of metabolic diseases like diabetes, thyroid gland function, nephrotic syndrome, chronic pancreatitis, and liver and glad bladder diseases 5. Had no drug consuming which affect lipid profiles	1. Lack of patient's compliance with drug regimens at least for 1 week 2. Pregnancy and lactating women 3. Had drug sensitivity

Table 3. Nutritional regimens

Study (Year)	Type of study	Form of Extraction	Daily intake	Time of intake
(Marhuenda et al., 2020)	RCT	Capsule	1 x 1	n.r
(Serna et al., 2021)	Co-RCT	Capsule	2 x 1	Before breakfast
(Aguirre-García et al., 2019)	RCT	Capsule	2 x 3	n.r
(Abubakar et al., 2019)	Co-RCT	Beverage	2 x 1	With breakfast and lunch
(Herranz-López et al., 2019)	RCT	Capsule	2 x 1	Before breakfast
(Boix-Castejón et al., 2018)	RCT	Capsule	1 x 1	Before breakfast
(Hajifaraji et al., 2018)	RCT	Beverage	2 x 1	Between meals
(Asgary et al., 2016)	RCT	Capsule	1 x 1	n.r
(Chang et al., 2014)	RCT	Capsule	2 x 3	After meals
(Sabzghabaee et al., 2013)	RCT	Capsule	1 x 1	n.r

Table 4. Primary outcome

Study (Year)	Type of study	Primary outcome			
		Body weight	Fat accumulation	Blood lipid profile	Appetite-related biomarkers
(Marhuenda et al., 2020)	RCT	+	+	-	-
(Serna *et al.*, 2021)	Co-RCT	-	-	-	+
(Aguirre-García et al., 2019)	RCT	-	-	+	-
(Abubakar et al., 2019)	Co-RCT	-	-	-	-
(Herranz-López et al., 2019)	RCT	+	+	+	-
(Boix-Castejón et al., 2018)	RCT	+	+	-	+
(Hajifaraji et al., 2018)	RCT	-	-	+	-
(Asgary et al., 2016)	RCT	-	-	+	-
(Chang et al., 2014)	RCT	+	+	+	-
(Sabzghabaee et al., 2013)	RCT	-	-	+	-

2. Change in blood lipid profile

Out of ten selected studies, six significant reported changes in blood lipid profile, including LDL, HDL, cholesterol, and triglyceride, the rest three study did not take the blood lipid profile measurement as a parameter, and the other one showed no significant effect. Among all these studies, low-density lipoprotein cholesterol and serum triglyceride showed a significant decrease in the cases group, but changes in high-density lipoprotein cholesterol levels were not significant.

3. Change in biomarkers of appetite

Out of ten selected studies, there are only two studies that reported significant changes in biomarkers-related appetite. The prominent biomarkers in these studies are anorexigenic hormone leptin (Serna et al., 2021) and glucagon-like peptide 1 (GLP1), and orexigenic hormone ghrelin (Boix-Castejón et al., 2018). In addition, appetite sensation and satiety sensation also showed exciting results. It was observed that compared to the control group, administration of *H sabdariffa* extract increased satiety and decreased appetite sensation, mainly for fatty, sweet, and salty foods.

DISCUSSION

The findings from ten RCTs revealed mostly conclusive evidence that *H. sabdariffa*, either alone or in combination with other plants, can effectively reduce body weight and fat accumulation, normalize blood lipid profile, and modulate biomarkers related to appetite in obesity. No severe side effects have been reported. *H. sabdariffa* has several biologically active compounds responsible for the anti-obesity activity, including polyphenols, organic acids, and anthocyanins. A study has shown that lipid accumulation in high fat-fed obese mice reduces hepatic lipid accumulation, and these effects have been associated with their high content of anthocyanins (Hirunpanich et al., 2006). Additionally, the high organic acid content is the anti-obesogenic potential because of its ability to decrease fatty acid synthesis in obese rats and reduce body weight in overweight adults (Hayamizu et al., 2003). Nevertheless, anti-obesogenic flavonoids and phenolic acid reported are inhibitory effects on adipogenesis and leptin expression responsible for reducing food intake and increasing energy expenditure (Hsu and Yen, 2007). Interestingly, this study reveals that anti-obesity effects from *H. sabdariffa* in humans also show tremendous results, including a reduction in weight loss, fat accumulation, blood lipid profile, and an increase in anorexigenic hormones increase appetite.

The high content of polyphenol and antioxidants can also prevent dyslipidemia (Serban et al., 2015). Several previous studies have shown that using *H. sabdariffa* extract has been studied in various clinical studies to help induce weight loss in a controlled diet program (Marhuenda et al., 2020). The promising effects of polyphenols generate weight loss, mass fat, and body mass index. Polyphenols can reduce fat tissue volume through lipogenesis, increase fatty acid oxidation, and activate the AMP-activated protein kinase (AMPK) pathway through adiponectin activation. This hormone modulates several metabolic processes, including the oxidation of fatty acids (Herranz-López et al., 2015).

On the other hand, satiety is essential for consistent weight loss. Limiting food or calorie intake in obese patients as a therapy to reduce body weight will generally cause anxiety or discomfort in the sufferer so that in the end, it often does not last long and the patient returns to compulsive behavior, and the weight returns even up to many times (Ural et al., 2017). Interestingly, another study suggests that the effect of other polyphenols is that they can modulate several biomarkers related to appetite. These biomarkers include the anorexigenic hormones GLP-1 and leptin. The anorexigenic hormone is a hormone that can suppress the appetite or stimulate satiety.

GLP-1 is an anorexigenic hormone produced by L cells in the intestine. L cells play a role in stimulating insulin secretion and simultaneously promoting satiety (Lutz, 2016). Leptin, which is secreted by adipose tissue, is an anorexigenic hormone, is also referred to as lipostatic hormone (Wansink and Sobal, 2007). Leptin decreases appetite by stimulating the secretion of anorexigenic peptides by the hypothalamus, increasing basal metabolism, decreasing lipogenesis, and increasing lipolysis to produce energy (Timper and Brüning, 2017). Thus, although calorie deficit is paramount for weight loss, the development of *H. sabdariffa* extract as a dietary supplement to modulate appetite-related biomarkers appears to be one of the reasons methods that are expected to be good candidates for use in weight management by maintaining long-term weight loss and preventing weight gain or the yo-yo effect (Boix-Castejón et al., 2018).

Our systemic review also showed that *H. sabdariffa* extract has significant effects on the blood lipid profile, which includes cholesterol, HDL, LDL, and triglycerides. Abnormal levels in the body fat profile are closely related to obesity and are often found in obese people. This effect is attributed to the high anthocyanin content of *H. sabdariffa* (Hajifaraji et al., 2018). Anthocyanins have been shown to increase PPAR-γ gene expression (Aboonabi et al., 2020). PPAR-γ is a nuclear transcription factor and plays a significant role in fat and glucose homeostasis through regulation of storage and catabolism of intake of fat and glucose and differentiation of adipocytes (Janani and Ranjitha Kumari, 2015).

There were some limitations in this study; the heterogeneity of the included studies which might affect the evidence quality, and the limited number of articles used in this review due to human RCTs studies that focused on the effect of *H. sabdariffa* in obesity is limited. However, focusing on human RCTs and having some database and keywords to search the article should be the strength of this study. To summarize, this systemic review adds the growing body of evidence corroborating the potential effect of *H. sabdariffa* extract as a candidate for people with obesity. *H. sabdariffa* shows promise as a safe and beneficial herbal medicine to prevent and manage obesity. To better evaluate the potency of *H. sabdariffa* for obesity treatment, increasing the number and size of human RTCs, expanding the diversity of ethnicities, and estimating the correct dose are needed.

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None.

AUTHOR CONTRIBUTION

Neng Tine Kartinah gave the idea and reviewed the article. Suci Anggraini designed the study, did the search, reviewed the data, drafted and edited the article. All authors have read and approved content of the article.

CONFLICT OF INTEREST

The authors declare that there is no competing financial interest or personal relationship that could have appeared to influence the work reported in this study.

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