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Evaluation of Indonesian anti-obesity traditional plants: a systematic review and meta-analysis on pancreatic lipase inhibition activity

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Abstract

Research and publication discussing the performance of medicinal plants as anti-obesity have proliferated in recent years. In the view of ethnopharmacology, empiric evidence of Indonesian medicinal plants in the management of obesity is widely accepted. In an attempt to find an anti-obesity agent, it is evidenced that the disorder can be resolved through inhibition of pancreatic lipase since the mechanism allowed to retard the absorption of fat into cells. This current work aimed to screen Indonesian medicinal plants by using ethnopharmacology and meta-analysis approaches, emphasizing their ability to deal with obesity via pancreatic lipase inhibition. The study followed two stages, i.e. systematic review and meta-analysis. Firstly, articles in six scientific databases (Scopus, Science Direct, Proquest, Ebsco, Cengage Library and Emerald) were reviewed resulting in ten selected data according to inclusion and exclusion criteria. Furthermore, steps of the meta-analysis were performed on the selected data. The extraction of data in these articles collected a number of samples, average values and standard deviation of IC_{50}. The values focused on IC_{50} of samples in inhibiting lipase activities performed by plant extracts and orlistat as control. In conclusion of this study, *Moringa oleifera* is the most potent medicinal plant as anti-obesity through inhibition of pancreatic lipase, then there were top ten anti-obesity medicinal plants as follows: i.e. *kelor* (*Moringa oleifera*) leaves, *kemangi* (*Ocimum basilicum*) leaves, *asam jawa* (*Tamarindus indica*) leaves, *asam gelugur* (*Garcinia atroviridis*) fruit, *lengkuas* (*Alpinia galanga*) rhizome, and *kencur* (*Kaempferia galanga*) rhizome, *kumis kucing* (*Orthosipon aristatus*) leaves, *jambu biji* leaves (*Psidium guajava* leavaes), *serai wangi* (*Cymbopogon nardus*) and *kayu secang* (*Caesalpinia sappan*).

1. Introduction

Obesity is medically characterized as excess adiposity in tissues as a result of the disparity between energy intake and energy expenditure (Jung and Choi, 2014). Currently, the prevalence is rising at an alarming rate reaching approximately three times between 1975 – 2016 and therefore becoming a health issue worldwide (WHO, 2018). In 2016, WHO reported that more than 1.9 billion adults were overweight, while 650 million of them were obese WHO, 2018). Furthermore, obesity prevalence continues to rise, not only in adults but also in children and teenagers (Pi-Sunyer, 2009). With a rapidly growing prevalence, obesity receives a serious concern since it is associated with degenerative diseases such as diabetes, heart and liver disease, stroke, hypertension, hypercholesterolemia, kidney failure and osteoarthritis (Pi-Sunyer, 2009).

In Indonesia, obesity has become the foremost nutrition concern besides stunting (Indonesia Ministry of Health, 2018). The case in this country markedly increased from 2007-2018. The obesity proportion of Indonesian adults with a body mass index (BMI) of 27 in 2007, 2013, and 2018 reaches 10.5, 14.8, and 21.8,

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respectively, while the average proportion of obesity is 21.8. Specifically, the highest proportion is found in the Province of Sulawesi Utara (30.2); in contrast, the lowest one is attributed to the Province of Nusa Tenggara Timur (10.3) (Indonesia Ministry of Health, 2018). Besides using commercial medical drugs for reducing the incidence of obesity, treatments using traditional medicinal plants are very common in Indonesia (Gunawan *et al*., 2006; Gunawan *et al*., 2008; Saifudin *et al*., 2016).

The use of medicinal plants or commonly known as Jamu is one part of the health system in Indonesia (Elfahmi, 2014). Traditional herbal medicine has a comparative advantage due to the relatively lower cost, ease of use, and minimal side effects compared to synthetic or modern drugs. In addition, the majority believe that traditional medicinal plants can treat several diseases at once (Yabesh *et al*., 2014; Sankaranarayanan *et al*., 2010; Putri *et al*., 2016). Commercial obesity drugs to induce weight loss such as orlistat, which is commonly used and still approved by the FDA, are known to have relatively high selling prices (Finkelstein and Kruger, 2014; Daneschvar *et al*., 2016; Andre *et al*., 2017). Moreover, orlistat application was reported to give side effects such as gastrointestinal problems, headache, insomnia, constipation, and dry mouth (Gude and Ratnakumar, 2013). Thus, the exploration of medicinal plants as sources of anti-obesity agents like orlistat mechanism becomes a promising approach to overcoming obesity (Mahmoud and Elnour, 2013; Negi *et al*., 2021).

Studies on the use of herbal plants for the management of anti-obesity have been carried out, in an attempt to find safe and healthier drugs (Yun, 2010). Indonesian indigenous herbal plants vary greatly, and among them, 76 of the plants are evidenced to exert anti-obesity properties (Lahrita, 2018). Previous researches reported the performance of anti-obesity treatments using some herbal plants such as jati belanda (*Guazuma ulmifolia*), kemuning (*Murraya paniculata*) leaves, kelembak (*Rheum officinale*) roots, tempuyung (*Sonchus arvensis*) leaves (Ardiyanto *et al*., 2018; Zulkarnain *et al*., 2019) sirih merah (*Piper crocatum*) (Husnawati, 2015); asam gelugur (*Garcinia atroviridis*), kunci pepet, (*Kaempferia rotunda*), lengkuas (*Alpinia galanga*), daun asam Jawa (*Tamarindus indica* leaves), kencur (*Kaempferia galanga*) (Iswantini *et al*., 2010; Iswantini *et al*., 2015) and teh hitam (*Camelia sinensis*) (Susanto and Witjoro, 2011). The herbs for obesity treatment registered in Permenkes No. 6 Year 2016 about Indonesian indigenous herbs-based drugs included *jati belanda* and *kemuning* (Indonesia Ministry of Health, 2016).

Attempts to find the efficacy of some potential plants for anti-obesity treatment continues, emphasizing the roles of phytochemical bioactivities. Some of the bioactive compounds were reported capable of reducing obesity, including polyphenols, saponin, alkaloids, flavonoids, and saponins (Bhardwaj *et al*., 2021). How these chemicals work is intriguing since they display different mechanisms, i.e. satiety modulation, inhibition of adipogenesis and fat absorption, as well as retardation of pancreatic lipase (Seyedan *et al*., 2015). With the growing research discussing the topic, some evidence elucidated how the phytochemicals work for anti-obesity treatments, grouped into 5 basic mechanisms i.e. lowering lipid absorption by inhibition of lipase pancreatic enzyme, decreasing energy intake, rising energy expenditure, suppressing differentiation and proliferation of preadipocyte and declining lipogenesis while enhancing lipolysis (Yun, 2010).

Of all the recognized anti-obesity mechanisms, the inhibition of lipid absorption through pancreatic lipase inhibition is an interesting and relatively safe approach for the development of anti-obesity agents, because the pancreatic lipase enzyme acts in the duodenum and has the least involvement with blood circulation and the brain so that the negative effects and complications of treatment are relatively low (Mhatre *et al*., 2016). Orlistat, which is known to induce weight loss, also has an anti-obesity mechanism through the inhibition of the pancreatic lipase enzyme (Yun, 2010). The inhibition value of lipase can be expressed as IC_{50} or % inhibition (Sreerama *et al*., 2012). IC_{50} describes the concentration value of certain compounds in inhibiting 50% of pancreatic lipase enzyme activity on fat substrates, the lower the IC_{50} value, the higher its potential as an anti-obesity, while the percentage of inhibition describes the ability of certain compounds to inhibit pancreatic lipase enzyme activity under certain conditions of substrate and enzyme concentrations (Sreerama *et al*., 2012). The IC_{50} values were obtained from the least-squares regression line of the plots of the logarithm of the sample concentration (log) versus the lipase activity (%) (Shreerama *et al*., 2012). Research related to the exploration of edible medicinal plants as pancreatic lipase inhibitors is increasingly being carried out in order to find alternatives for orlistat (Rajan *et al*., 2020). However, systematic reviews and meta-analytical studies to provide information on the potential of pancreatic lipase inhibitors derived from medicinal plants commonly used by the Indonesian people have not been carried out. The purpose of this study is to evaluate Indonesian anti-obesity traditional plants on pancreatic lipase inhibition activity using a systematic review and meta-analysis. The findings of this study can provide a foundation for future research into the best group of

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medicinal plants for the development of anti-obesity products in the food industry, nutraceuticals, or pharmaceutical fields.

2. Materials and methods

2.1 Literature search

This research referred to the guidelines of a meta-analysis handbook (Borenstein *et al*., 2009). Relevant studies published in various electronic databases such as Proquest, Science Direct, Ebsco, Cengage Library, and Emerald for inhibitory lipase pancreatic were identified (up to May 2021). The five studies that we used in this research can also be found in the PubMed and Embase databases.

Keywords used in the search strategy included "anti-obesity", "medicinal plants", "lipase inhibition", "antihiperlipidemia", and "Indonesia". After reading the titles and abstracts, we excluded irrelevant studies using Collandrapp. Subsequently, the full text of all remaining articles to determine eligibility was examined (Afandi *et al*., 2021). The discrepancies were verified by discussion and consensus. We also reviewed the identified trials and review articles in reference lists to find any other potential proper articles (Afandi *et al*., 2021).

2.2 Eligibility criteria

The eligibility of the trials was determined according to criteria i.e. design for lipase inhibition experiments, the population in all researches using *in vitro* protocols for anti-obesity in the last 10 years, intervention for comparison between lipase inhibition IC_{50} properties of selected medicinal plants and orlistat; and data adequacy enabling to estimate the standardized mean difference (SMD) and the corresponding 95% confidence interval (CI). Further, all published papers we reviewed were written in English.

2.3 Data extraction

Data from each included study were extracted and integrated into the database. The following information was collected: first author, year of publication, country of origin, number of experiments, intervention, control, solvent, method, and outcomes data (IC_{50} lipase inhibition) were extracted and compiled in an Excel document.

2.4 Statistical analysis

Calculation in the meta-analysis was carried out using Hedge's method (Afandi *et al*., 2021). Data processing employed open-source software OpenMEE. Because all the observation indexes are continuous, and the measurement time of outcome is inconsistent across studies, we pooled the SMD (Standard Mean Difference) as effect size approach with a corresponding 95% CI using the random-effects model to compare the difference of mean between two treatments which were pancreatic lipase inhibition that expressed by IC_{50} of traditional plant and IC_{50} of orlistat as control. The variable used for subgroup analysis was the Indonesian name of traditional medicine. Several statistical parameters were calculated to obtain the value of SMD Hedge's d. The meta-analysis output was presented in the form of a forest plot, which included the effect size and confidence interval for each study. The highest potential of plant medicine as lipase pancreas inhibitor was determined by comparing the confidence interval to the null value.

3. Results and discussion

3.1 Systematic review diagram and characteristics of articles

A total of 326 articles (from 810 articles) were selected for full-text review, resulting in five articles that best fit the inclusion criteria. Four hundred eighty-four of them were rejected due to irrelevant content. Nine additional articles from reference lists of identified trials were included in the study because they met the inclusion criteria. Then, 331 articles were excluded because they did not meet the criteria (8 review articles, 31 articles not discussing Indonesian medicinal plants, and 291 articles with no available data for analysis). In total, the meta-analysis involved five articles that included ten data, as shown in Figure 1.

The ten studies involving thirty experiments were published from 2012 to 2021. The PICO of this research is defined as Participants, Interventions, Comparisons, Outcomes, and Study Design. Participants in *in vitro* experiment were IC_{50} lipase inhibition. Interventions were Indonesian medicinal plants, while anti-obesity medicine, i.e. orlistat was used as a comparison. The outcome of this research was the best potential lipase inhibition activity by Indonesian medicinal plants. The study design used in this research was randomized control.

There are ten data points extracted from the selected articles which can be seen in Table 1. The data point is individual unique data of IC_{50} value on pancreatic lipase, the active compound, preparation technique, and solvent used in preparation. Study ID in Table 1 indicates the numbering of data extracted from selected articles for meta-analysis which were produced from various countries. In addition, we also ensured that the anti-obesity plants summarized in Table 1 are plants that can be also found in Indonesia and are included in the plant

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Table 1. Data extracted from research article selected for meta-analysis of Indonesian herb medicine

Study ID	Author/Year	Indonesia Name	Scientific Name	Method	Solvent	Active compound	Nc	Xc	SDc	Ne	Xe	SDe
4	Adisakwattana *et al*. (2012)	Pegagan	*Centella asiatica*	IPL Sugiyama *et al*. (2007)	Aqueous	Phenolic	3	1.34	0.225167	3	120	0.017321
7	Adisakwattana *et al*. (2012)	Kumis kucing	*Orthosipon aristatus*	IPL Sugiyama *et al*. (2007)	Aqueous	Phenolic	3	1.34	0.225167	3	130	0.017321
11	Kaewpiboon *et al*. (2012)	Akar kayu kuning	*C. fenestratum*	IPL Kim *et al*. (2005)	Hexane:Dichloromethane: Ethanol (1:1:1)	Flavonoid	3	9.25	1.25	3	160	0.02
22	Buchholz and Melzig (2015)	Rosela	*Hibiscus sabdariffa*	IPL Buchholz and Melzig	Methanol	Polyphenol	3	0.0019	0.03	3	36	0.001
23	Buchholz and Melzig (2015)	Rosela	*Hibiscus sabdariffa*	IPL Buchholz and Melzig	Aqueous	Polyphenol	3	0.0019	0.03	3	41	0.006
28	Buchholz and Melzig (2015)	Asam jawa	*Tamarindus indica*	IPL Buchholz and Melzig	Methanol	N/A	3	0.0019	0.03	3	152	0.007
29	Buchholz and Melzig (2015)	Asam jawa	*Tamarindus indica*	IPL Buchholz and Melzig	Auqeous	Oleanolic acid	3	0.0019	0.03	3	212	0.002
39	Irondi *et al*. (2016)	Kemangi	*Ocimum basilicum*	IPL Eom *et al*. (2013)	Methanol then by separatory funnel with hexane, aqueous phase extracted by ethyl acetate	phenolic, flavonoid	3	3.48	0.13	3	52.14	3.96
40	Gururaja *et al*. (2016)	Kelor	*Moringa oleifera*	Masaaki *et al*. (2008)	Methanol	Niazirin	3	0.02126	0.00536	3	17.05	3.87
41	Gururaja *et al*. (2016)	Kelor	*Moringa oleifera*	Masaaki *et al*. (2008)	Methanol	Niazirin	3	0.02126	0.00536	3	42.31	16.39

IPL: Inhibition of Pancretic Lipase, Nc: Number of studies of control, Xc: Average of IC_{50} IPL of Control (Orlistat), SDc: Standard deviation of IC_{50} IPL of Control (Orlistat), Ne: Number of studies of experiment, Xe: Average of IC_{50} IPL of experiment, Sde: Standard deviation of IC_{50} of experiment.

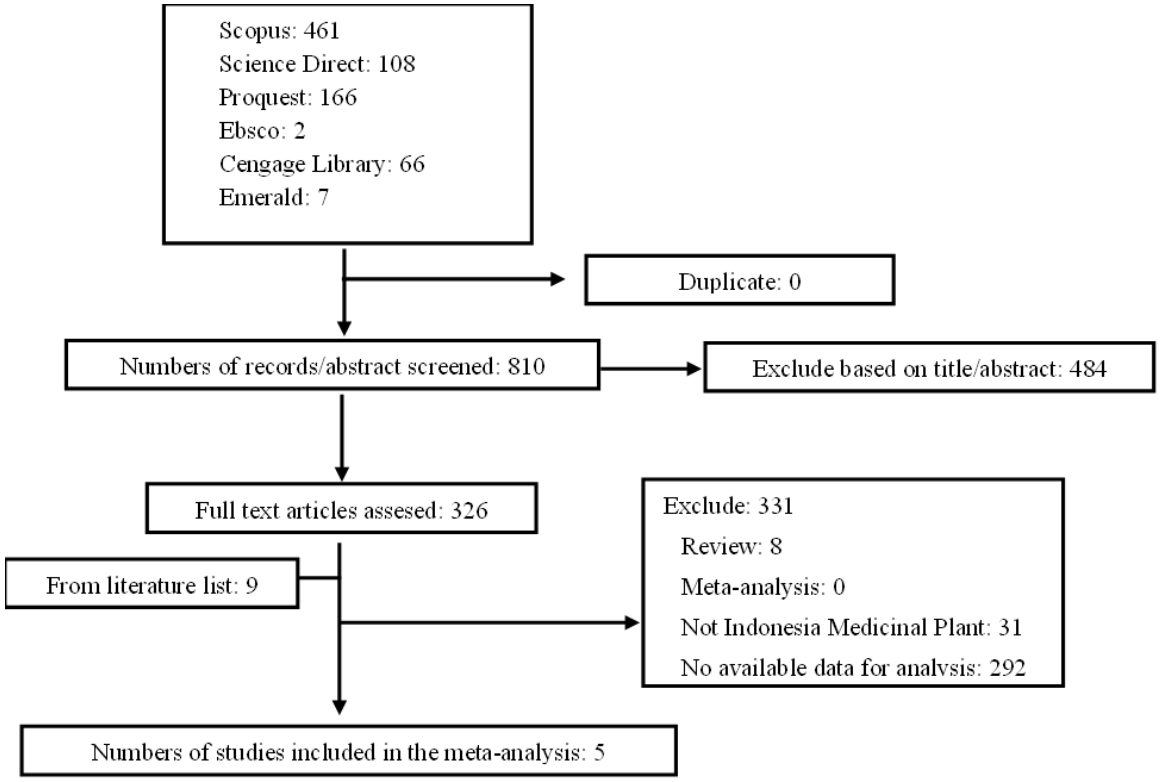

Figure 1. The PRISMA flow chart of the literature review process.

list of the herbal formulary of the Indonesian Ministry of Health. More than one data point could be extracted from one research paper as the research design allowed the IC_{50} value of pancreatic lipase, the active compound, and the solvent used in preparation as variables. Data points were then integrated statistically by inputting each effect size and standard on an openMEE application. The output of this calculation is the forest plot.

3.2 Profile of pancreatic lipase inhibition by Indonesian medicinal plants

In this work, the IC_{50} value represents the inhibitory activity against pancreatic lipase, meaning the concentration of a drug that gives a half-maximum response. The lower value of IC_{50} denotes that the drug shows more powerful inhibition. As a consequence, in this work, we searched for medicinal plants with the lowest value of IC_{50}. In this study, we filtered and selected medicinal plants that can be found in Indonesia and had the potential to anti-obesity through the pancreatic lipase enzyme inhibition mechanism, moreover, we only included medicinal plants commonly used by the Indonesian people according to the list of plants in the Indonesian Ministry of Health's herbal formulary. Additionally, the exclusion also referred to their IC_{50} being close to selected medicinal plants.

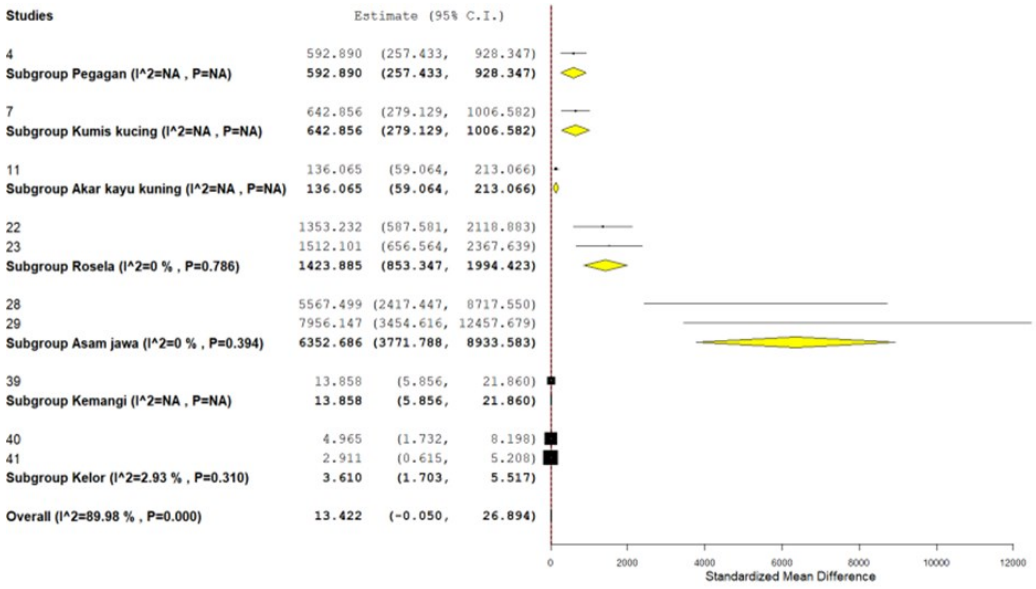

Figure 2. Subgroup analysis of the lipase pancreatic inhibition capacity in Indonesian medicinal plants. Standardized mean difference (SMD), confidence interval (CI), and point represent the estimated overall effect size (with 95% CIs) for each study.

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The forest plot (Figure 2) exhibits average and CI 98% of Indonesian medicinal plants displaying anti-obesity properties, i.e. 13.42 [-0.05, 26,89] with I2= 89.98% and P<0.001. In this regard, we found *kelor* (*Moringa oleifera*) possessing values lower than the average, i.e. 3.61 [1.70, 5.52]. *Kemangi* (*Ocimum basillicum*) also shows a relatively low IC_{50} in comparison with other studied plants. Therefore, referring to IC_{50}, two Indonesian medicinal plants showing the best inhibition against pancreatic lipase were *kelor* and *kemangi*.

Kelor leaves showed considerable inhibition of pancreatic lipase, while also significantly reducing the body mass index of obese rats (Nahar *et al*., 2016). Using *in vivo* experiments, it was evidenced able to improve lipid profiles, i.e. reducing total cholesterol, triglycerides, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL), increasing high-density lipoprotein (HDL), modulating fat deposition through down-regulating the expression of adipogenesis-associated proteins peroxisome proliferator-activated receptor gamma (PPARγ) and fatty acid synthase (FAS), up-regulating the expression of the lipolytic protein (adipose triglyceride lipase (ATGL), as well as reducing leptin concentration (Ali *et al*., 2021). The previous study using 3T3-L1 cells revealed that *kelor* leaves could diminish the expression of protein accounting for adipogenesis and lipogenesis (Kim *et al*., 2020). In the case of Indonesian medicinal plants, the studies discussing anti-obesity treatments worked with adiposity test under *in vitro* experiment (evaluation based on % lipid accumulation and % glycerol release) involving 76 plants, as the results, red ginger (*Zingiber officinale var. rubrum*) showed the most effective drug on the treatment of obesity. Meanwhile, *kelor* was also included in the top 5 plants (Lahrita, 2018). Intriguingly, *kelor* has been accepted as one of the top 50 future foods since it is rich in health-improving bioactivities (WWF, 2019).

In fact, many articles have published data related to the anti-obesity potential of medicinal plants native to Indonesia or plants commonly found in Indonesia through the pancreatic lipase inhibition mechanism, but the existing publications have not shown the IC_{50} value on pancreatic lipase, but only preliminary studies in the form of % inhibition on the pancreatic lipase, which is not applicable enough to be compared with data from other studies. In several cases, the paper only reported average values and number of samples but did not inform standard deviation. Regarding the incompletion of data, we summarized other indicators that support the analysis. A summary of data collected from various references was presented in Table 2. The extract of medicinal plants can be a potential candidate for anti-obesity when its lipase inhibition capacity ranged from 75-100%. In addition, the extract with the inhibition capacity of 50-70% and 25-50% were grouped as moderate and low, respectively, and no anti-lipase activity occurred when the capacity was <25% (Budiman *et al*., 2015). After comparing the capacity of each plant, we found some plants that show high lipase pancreas inhibition capacity, including *kemuning*, *meniran*, *daun kumis kucing*, *serai wangi*, *kayu secang, daun murbei*, *jahe*, *daun alpukat*, *jambu biji* leaves, and *jambu air* leaves (Table 2).

To enrich this study, a meta-analysis of the data which used % pancreatic lipase inhibition as an observation parameter was conducted. However, to deal with the data incompletion, the effect size was calculated according to the logarithmic natural response ratio (lnR), while the variation was determined using non-parametric variance (VlnR) (Shrestha *et al*., 2016). Considering the % inhibition used as an indicator, the best data is located on the right of the vertical line (Figure 3). Using the results of meta-analysis, Indonesian medicinal plants that showed anti-obesity properties included leaves and fruit of asam jawa (*Tamarindus indica*), asam gelugur (*Garcinia atroviridis*), asam gelugur (*Garcinia atroviridis*) fruit, lengkuas (*Alpinia galanga*) rhizome, and kencur (*Kaempferia galanga*) rhizome.

3.3 Type of active compound

In this work, phytochemicals in Indonesian medicinal plants that can serve as anti-lipase, including phenolic, flavonoid, polyphenol and niazirin was reported (Figure 4). Based on the forest plot, the overall score reached 3.6 [1.7, 5.5], while specifically, the score for phenolic and flavonoid was 13.86 [5.86, 21.86] and niazirin reached 3.610 [-0.1, 26.9]. The high inhibition level of a medicinal plant on pancreatic lipase depends on the bioactive components contained in plants and the method to optimize the extraction of bioactive components (Adisakwattana *et al*., 2012; Bucholz and Malzig, 2015). Niazirin is one of the typical phenolic glycoside compounds found in *Moringa oleifera* (Bao *et al*., 2020). Niazirin was reported to overcome the pathological condition of obesity through several mechanisms, such as inhibition of pancreatic lipase enzyme, improvement of lipid profile in db/db mice which was indicated by the decrease of low-density lipoprotein (LDL), total cholesterol (TC), and non-esterified fatty acid (NEFA) levels, as well as the increase of plasma high density lipoprotein (HDL) level after four weeks of niazirin treatment. Furthermore, niazirin was also effective in regulating energy homeostasis through AMPK pathways such as reducing fatty acid synthesis and inducing fatty acid oxidation in

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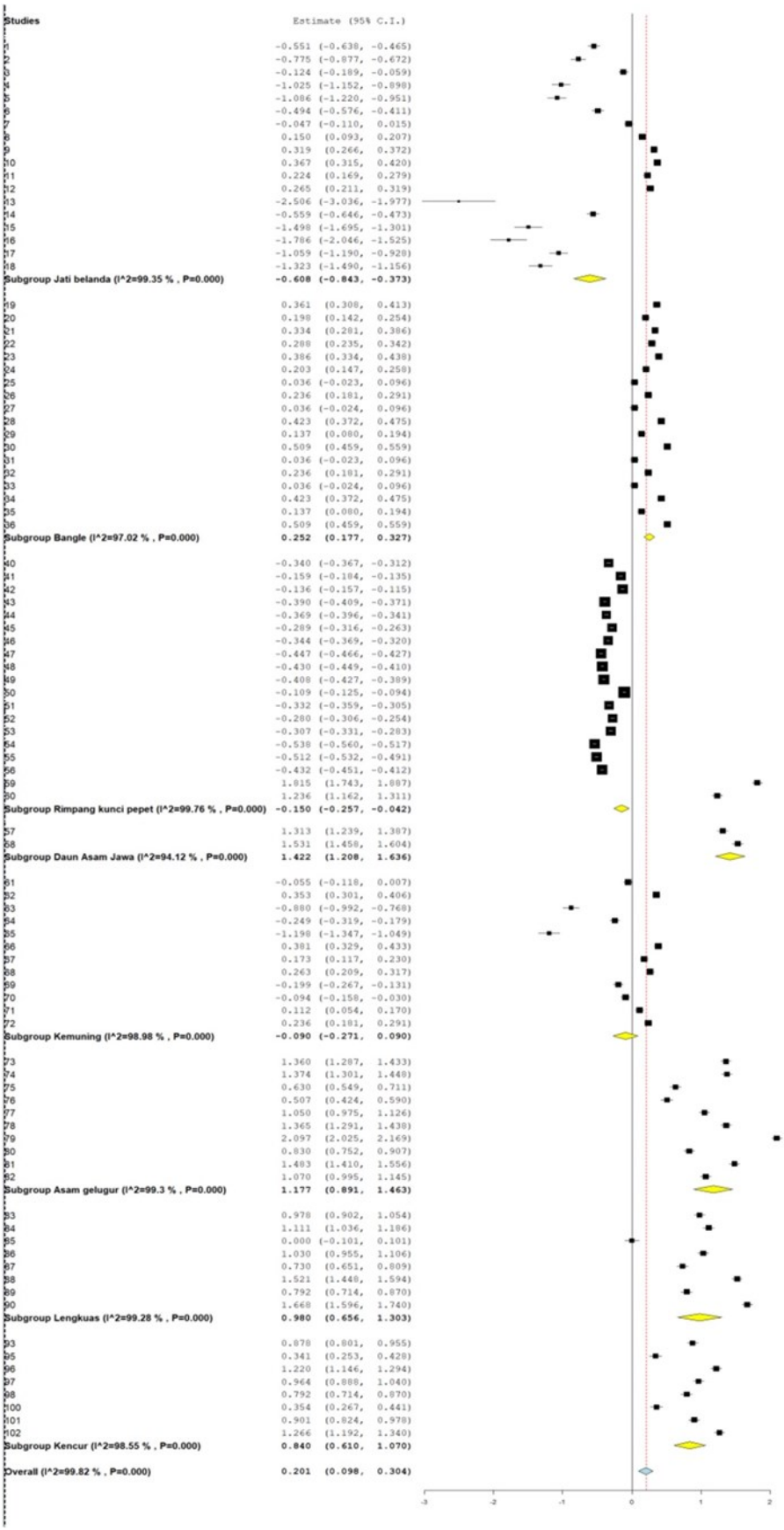

Figure 3. Meta-analysis of Indonesian medicinal plants with anti-obesity properties estimated by their inhibition of pancreatic lipase.

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Table 2. List of Indonesian medicinal plants showing anti-obesity effects.

No.	Plant source Indonesian name	Species name (latin name)	IC_{50}	Orlistat (%)	Lipase inhibition (%)	n	Concentration (mg/mL)
1.	Angkak (Kim *et al.*, 2007)	Red yeast rice	61.2±5.1	-	-	3	-
2.	Kunci Pepet (Pradono *et al.*, 2011)	*Kaempferia rotunda*	-	10.6	5.8	3	0.10
3.	Daun asam Jawa (Pradono *et al.*, 2011)	*Tamarindus indica* leaves	-	10.6	10.8	3	0.10
4.	Asam gelugur (Iswantini *et al.*, 2010)	*Garcinia atroviridis*	-	10.6	41.3	3	0.10
5.	Lengkuas (Iswantini *et al.*, 2010)	*Alpinia galanga*	-	10.6	28.2	3	0.10
6.	Kencur (Iswantini *et al.*, 2010)	*Kaempferia galanga*	-	10.6	25.5	3	0.10
7.	Bangle (Iswantini *et al.*, 2011)	*Zingiber cassumunar* Roxb.	-	17.53	21.47	3	0.10
8.	Jati Belanda (Iswantini *et al.*, 2011)	*Guazuma ulmifolia*	-	17.53	10.70	3	0.10
9.	Kemuning (Iswantini *et al.*, 2011) (IC_{50} Orlistat: 1.71 µg/mL) (Alias *et al.*, 2017)	*Murraya paniculata*	55.18µg/mL	17.53 99.6±0.3	25.66 75.6±5.4	3	0.10
10.	Pegagan (Sahib *et al.*, 2012)	*Centella asiatica*	-	21.0±0.4*	25.3±0.4*	3	0.25
11.	Mengkudu (Sahib *et al.*, 2012)	*Morinda citrifolia*	-	21.0±0.4*	25.8±0.1*	3	0.25
12.	Pare (Sahib *et al.*, 2012)	*Momordica charantia* L.	-	21.0±0.4*	21.0±1.3*	3	0.25
13.	Meniran (IC_{50} Orlistat: 1.71 µg/mL)	*Phyllanthus niruri* L.	27.65µg/mL	99.6±0.3	76.7±0.4	3	0.50
14.	Daun belimbing wuluh (Alias *et al.*, 2017)	*Averrhoa bilimbi* L. Leaves	41.45µg/mL	99.6±0.3	73.9±2.0	3	0.50
15.	Daun kumis kucing (Alias *et al.*, 2017)	*Orthosipon aristatus* leaves	34.74mg/mL	99.6±0.3	95.3±2.0	3	0.50
16.	Sambiloto (Alias *et al.*, 2017)	*Andrographis paniculata*	-	99.6±0.3	0	3	0.50
17.	Daun salam (Alias *et al.*, 2017)	*Syzygium polyanthum* leaves	-	99.6±0.3	38.2±6.5	3	0.50
18.	Temu ireng (Alias *et al.*, 2017)	*Curcuma aeruginosa* Roxb.	-	99.6±0.3	38.2±6.5	3	0.50
19.	Daun temulawak (Ado *et al.*, 2013)	*Curcuma zanthorriza* leaves	-	-	16.9	3	100
20.	Kunyit (Budiman *et al.*, 2015)	*Curcuma longa*	-	-	70.4±3.4	3	0.25
21.	Kayu secang (Ruangaram and Kato, 2020)	*Caesalpinia sappan*	-	Cetilistat:55	90	3	0.50
22.	Serai wangi (Ruangaram and	*Cymbopogon nardus*	-	Cetilistat:55	91±1.5	3	1.0

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Table 2 (Cont.). List of Indonesian medicinal plants showing anti-obesity effects.

No.	Plant source Indonesian name	Species name (latin name)	IC_{50}	Orlistat (%)	Lipase inhibition (%)	n	Concentration (mg/mL)
23.	Daun murbei (Ruangaram and Kato, 2020)	*Morus alba* leaves	-	Cetilistat:55	90±20.6	3	1.0
24.	Kayu manis (Megawati *et al*., 2020)	*Cinnamomum verum*	-	46.79	16.23	-	10
25.	Teh hijau (Megawati *et al*., 2020)	*Camellia sinensis*	-	46.79	47.82	-	10
26.	Jahe (Rahayu *et al*., 2019)	*Zingiber officinale*	-	68.90	87.30	3	0.1
27.	Daun alpukat (Ado *et al.*, 2013)	*Percea americana* leaves	-	-	92.8	3	-
28.	Sirih (Ado *et al.*, 2013)	*Piper betle*	-	-	9.9	3	-
29.	Lada putih (Ado *et al.*, 2013)	*Piper nigrum*	-	-	24.1	3	-
30.	Daun jambu biji (Ado *et al.*, 2013)	*Psidium guajava* leaves	-	-	99.0	3	-
31.	Daun jambu air) (Ado *et al.*, 2013)	*Syzygium samarangense* leaves	-	-	85.6	3	-
32.	Buah asam Jawa (Ado *et al.*, 2013)	*Tamarindus indica* fruit	-	-	68.0	3	-
33.	Daun katuk (Ado *et al.*, 2013)	*Sauropus androgynus* leaves	-	-	9.9	3	-
34.	Jeruk purut (Watanabe *et al.*, 2009)	*Citrus hystrix*	-	100	58.0	3	0.01
35.	Jintan hitam (Ado *et al.*, 2013)	*Nigella sativa*	-	-	37.1	3	-

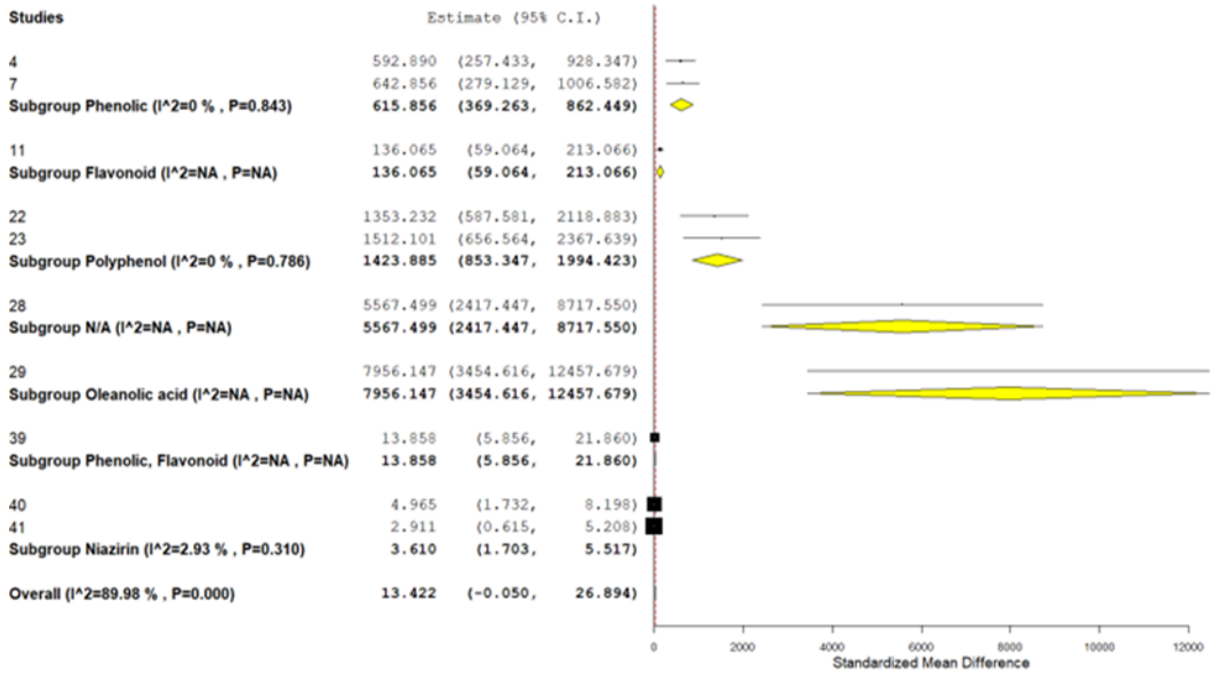

Figure 4. Forest plot of bioactive compounds from Indonesian medicinal plants. Standardized mean difference (SMD), confidence interval (CI), and point represent the estimated overall effect size (with 95% CIs) for each study.

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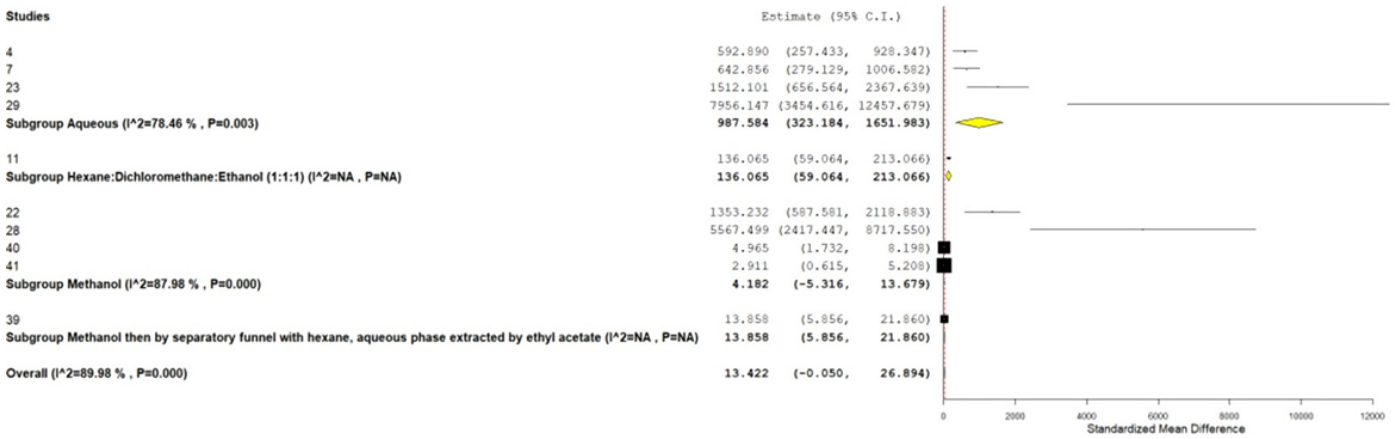

Figure 5. Forest plot of solvents applied to extract phytochemicals in Indonesian medicinal plants. Standardized mean difference (SMD), confidence interval (CI), and point represent the estimated overall effect size (with 95% CIs) for each study.

db/db mice (Gururaja *et al*., 2016; Bao *et al*., 2020).

Four main classes of phytochemicals showing anti-obesity effects are alkaloid, phytosterol, polyphenol and terpenoid (Sa'ad *et al*., 2007). Rajan *et al*. (2020) reported 5 bioactive compounds that exert lipase inhibitory effects; and they included phenolic, flavonoid, saponin, alkaloid and terpenoid. To evaluate their inhibition capacity, the IC_{50} value of lipase inhibition can be a proper indicator, resulting in flavonoids possessing a low value, meanwhile, the other groups (saponin, terpenoid and flavonoid) show a high value of IC50. Regarding their mode of action, the anti-obesity effect of flavonoids relates to their ability to reduce lipid accumulation, total cholesterol, and pancreatic lipase activity (Li *et al*., 2011; Hossain *et al*., 2016). Meanwhile, saponin acts as an anti-obesity agent through the regulation of thermogenesis, lipogenesis, and lipolysis (Chen *et al*., 2017).

3.4 Proper solvent for bioactive compound extraction

Phytochemicals responsible for anti-obesity can be extracted using various solvents. As depicted in Figure 5, the meta-analysis revealed that methanol showed the most proper solvent in the extraction of anti-obesity phytochemicals in Indonesian medicinal plants, with a score of 4.18 [-5.3, 13.7], while the overall average reached up to 13.4 [-0.05, 26.9]. Besides methanol, phytochemicals showing pancreatic lipase inhibition can be isolated by water and ethanol. However, each solvent shows dissimilar performance in how they extract anti-pancreatic lipase phytochemicals, with the following sequence: ethanol > methanol > water (Iswantini *et al*., 2011; Moon *et al*., 2018).

The bioactive compounds such as flavonoid and phenolic compounds, including niazirin, are categorized as polar to semi-polar compounds that can be effectively extracted by polar-semi polar solvents (Widyawati *et al*., 2014; Gururaja *et al*., 2016). Those facts support the results of this meta-analysis which concluded water and methanol as the best solvents to extract the anti-obesity agents in plants. Water is commonly known as the solvent used in the decoction technique for the production of jamu or other herbal products in Indonesian society (Abdillah *et al*., 2014; Putri *et al*., 2016).

3.5 Anti-obesity performed by Indonesian medicinal plants in bibliometric

Bibliometric data in the Scopus database processed by VoS Viewer indicates 4 research clusters focusing on the use of medicinal plants for the treatment of obesity. Each cluster colour occurs differently. Studies on obesity consider experimental animals, diet, body weight, review articles and medicinal plants used. Meanwhile, studies on the effect of anti-obesity are restricted to some aspects such as inhibitory activity, high-fat diet, evaluation of anti-obesity, pancreatic lipase and medicinal plants linked to their phytochemical profiles (Figure 6).

Investigation of anti-obesity treatments was carried out between 2011-2013, while numerous researches on pancreatic lipase, medicinal plants and obesity were reported between 2013-2015. Studies discussing phytochemicals were reported in 2016. It is noteworthy that studies discovering inhibition, effects of anti-obesity and pancreatic lipase are rather scarce as indicated by the dark green colour. Sweileh *et al*. (2017) reported a bibliometric analysis of obesity focusing on its relation to other topics, involved countries and authors. In this regard, the obesity-related topics covered weight reduction and physical activities, while countries dominantly contributing to the topic were USA, UK and Canada. Additionally, the foremost author of this research topic was Whittaker R.

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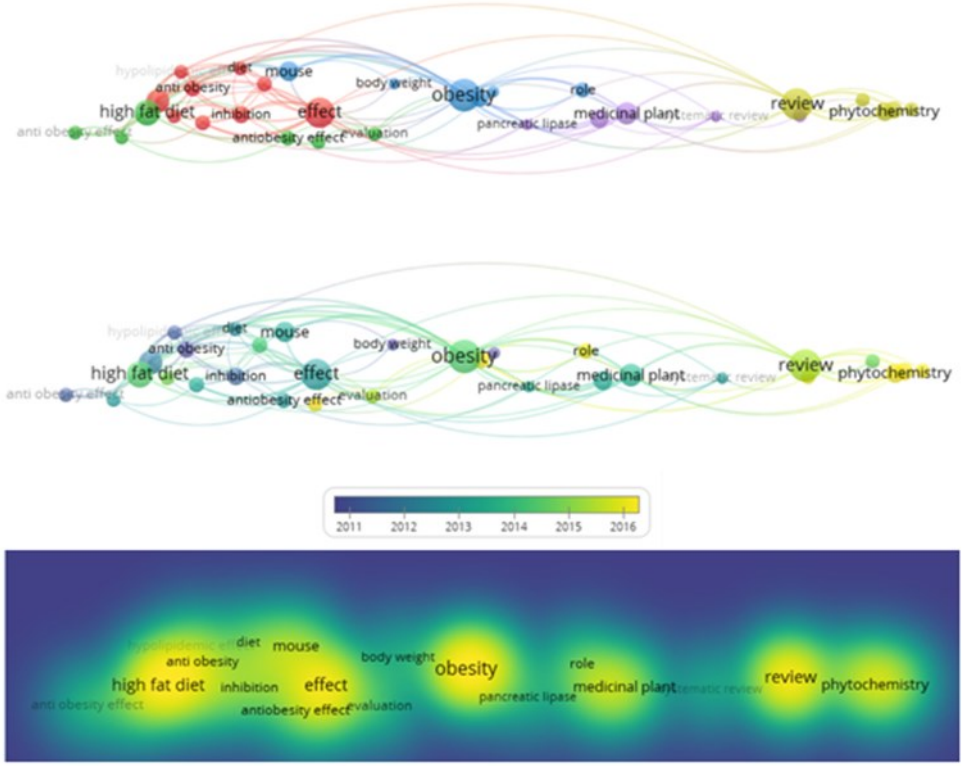

Figure 6. Distribution of medicinal plants and anti-obesity referring to Scopus database.

4. Conclusion

In general, this present work reported that *Moringa oleifera* leaves demonstrated the most potential anti-obesity in comparison with other Indonesian medicinal plants. This finding referred to the result of a meta-analysis covering 810 articles from 6 scientific databases. In addition, based on evaluation of lipase inhibition by medicinal plants, we presented 10 potential plants for management of obesity, i.e. *Moringa oleifera* leaves, *Ocimum basilicum* leaves, *Tamarindus indica* leaves, *Garcinia atroviridis* fruit, *Alpinia galanga* rhizome, and *Kaempferia galanga* rhizome, *Orthosipon aristatus* leaves, *Psidium guajava* leaves, *Cymbopogon nardus* and *Caesalpinia sappan*. The evaluation of their anti-obesity effects conformed to the inhibition of pancreatic lipase activity expressed as IC_{50}.

Conflict of interest

The authors declare no conflict of interest.

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