Review:

Pancreatic Lipase Inhibition Activity in Lipid Absorption Using Traditional Plants: A Systematic Review and Meta-Analysis

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Abstract: *Obesity is a complex and multifactorial disease resulting from excessive accumulation of fat. With a significant annual increase, it has become a health concern across the globe in the last decades. To tackle this problem, an exploration of traditional medicinal plants (TMP) functioning as anti-obesity drugs using an ethnopharmacology approach has been carried out. Research on the drug development of obesity treatment was directed at how to inhibit pancreatic lipase as the enzyme accounted for lipid absorption. Using a systematic review and meta-analysis, this current study investigated TMP anti-obesity from the articles published in 6 scientific databases, i.e., Scopus, Science Direct, Proquest, Cengage Library, Ebsco, and Emerald, using particular keywords. The review resulted in 19 articles containing 91 eligible data based on inclusive and exclusive criteria. Meta-analysis extracted data as follows: IC_{50}, number of replications, and standard error, regarding the anti-obesity effects of medicinal plants and orlistat as a positive control. The results showed 8 medicinal plants showing anti-obesity via inhibition of pancreatic lipase, including* Solenostemma argel, Garcinia vilersiana, Phyllanthus chamaepeuce, Cassia auriculata, Moringa oleifera, Ficus carica, Ocimum gratissimum, *and* Adiantum capillus-veneris.

Keywords: *anti-obesity; ethnopharmacology; medicinal plants; meta-analysis; lipase inhibition*

■ INTRODUCTION

The obesity problem has been on the rise worldwide, with a dramatic increase [1]. Obesity refers to a multifactorial state that harms health due to excessive fat accumulation in adipose. The disparity results from a chronic imbalance between food intake and energy expenditure. Energy excess is restored as triglycerides in adipose, and it continues to expand, which can lead to an increment of fat storage and then impair health [2-3]. Obesity is often defined using a body mass index (BMI) of ≥ 30 kg/m^2 [1].

Obesity as a complex disease relies on the combination of several factors, including genetics, environment, behavior, social, and economic [4-5]. Besides genetic factors, the current human lifestyle, which is characterized by limited physical activities and dysregulation of the meal, is deemed able to stimulate the pathogenicity of obesity [6-7]. In addition, obesity is

the cause of comorbidities, including the development of type 2 diabetes mellitus, coronary disease, cardiovascular disease, various cancers and other health problems which can lead to further morbidity and mortality [8-9]. Specifically, some diseases, including hypertension, diabetes, insulin resistance, atherosclerosis, and sleep apnea, are associated with obesity [10]. With the increase of obesity-related diseases and becoming a global health concern, there is a crucial demand for how to develop attempts in the prevention, treatment, and management of obesity [11].

Orlistat, an anti-obesity drug, inhibits the activity of pancreatic lipase, thus reducing fat absorption into cells [12]. European Medicines Agency (EMEA) and the US still recommend orlistat as an anti-obesity drug which is considered a safe alternative compared with other drugs [12]. Therefore, research discussing obesity management without producing side effects have been increased incredibly. In this regard, ethnopharmacology becomes the foremost approach for future drug development [13-14].

The most common active compounds exhibiting anti-obesity effects, involved in weight loss, fat mass, and plasma triglycerides/cholesterol both *in vitro* and *in vivo* are flavonoids [15-17]. Sub-class of flavonoid compounds commonly found in plants (fruits, stems, roots) that have anti-obesity effects are tiliroside (kaempferol 3-*O*-glucoside-6"-*E*-coumaroyl or [(2R,3S, 4S,5R,6S)-6-[5,7-dihydroxy-2-(4-hydroxyphenyl)-4-oxo-chromen-3-yl]oxy-3,4,5-trihydroxyoxan-2-yl]methyl(*E*)-3-(4-hydroxyphenyl) -prop-2-enoate) [15]. Trans-tiliroside in doses of 0.1, 1, and 10 mg/kg bw strongly inhibited weight gain, especially visceral fat weight, and increased plasma glucose levels after glucose loading in rats [15]. It was also found that tiliroside can inhibit triglyceride accumulation and glycerol-3-phosphate dehydrogenase activity in 3T3-L1 cells [18]. Tiliroside shows the ability to be an anti-obesity which is better than orlistat [19].

Next, flavonoid compounds commonly found in plants with great bioactivity potential are quercetin [20-21]. In addition to flavonoids, pancreatic lipase inhibitory phytochemicals contained in plants or isolated from plants have been reported to be saponins, polyphenols, alkaloids, carotenoids, and terpenes [22-23]. Phenolic derivatives such as chlorogenic acid, catechin, and caffeic acid have a positive correlation with pancreatic lipase inhibition [24].

Some countries have their own empiric evidence on how diseases, primarily obesity, are treated by using herbs and medicinal plants [25]. There are 5 groups of herbal-based treatments for obesity, i.e., reduction of energy intake, increment of energy expenditure, reduction of lipogenesis and enhancement of lipolysis, attenuation of differentiation and proliferation of pre-adipose, as well as reduction of fat absorption [14]. The mechanism of fat absorption reduction via inhibition of pancreatic lipase can be noted as an important base in the exploration of herb-based treatment, with the mode of similar action to orlistat [14].

Although sample evidence on pancreatic lipase inhibition by traditional medicinal plants (TMP) has been reported, there is no systematic review and meta-analysis focusing on the topic, especially aiming to compare the efficacy of such plants compared with orlistat as standard. This present work aimed to screen medicinal plants able to function as anti-obesity agents recognized globally via inhibition of pancreatic lipase. The main data used in the meta-analysis referred to the ability of lipase inhibition based on inhibition of pancreatic lipase at 50% (expressed as IC_{50}) while also compared with orlistat.

■ MATERIALS AND METHODS

Literature Search

The present systematic review and meta-analysis complied with Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) according to the guideline handbook [26-27]. During the study, we did a checklist based on the PRISMA statement table. Numerous kinds of literature discussing anti-obesity were collected through various article databases such as Science Direct, Proquest, Ebsco, Emerald and Cengage Library (up to May 2021). A total of 19 research articles selected were able to be accessed through PubMed and Embase databases. The search of articles employed the following keywords: "anti-obesity", "medicinal plants",

and "lipase inhibition". We screened the titles and abstract, then excluded irrelevant research articles by using Collandrapp. Subsequently, we examined the full text of all remaining articles to determine eligibility. The discrepancies were verified by discussion and consensus. We also reviewed the identified trials and reviewed articles in reference lists to find any other potential proper articles.

Eligibility Criteria

Studies were eligible for the present systematic review and meta-analysis according to the following criteria: (1) design: lipase inhibition experiment; (2) population: all research articles carried out using *in vitro* protocols for anti-obesity treatment published in the last 10 years; (3) intervention: comparison between lipase inhibition IC_{50} properties selected medicinal plants and orlistat; and (4) data: adequate information (data) for calculating the standardized mean difference (SMD) and the corresponding 95% confidence interval (CI). Further, all published papers were written in English.

Data Extraction

Extraction and integration of data collected from the selected articles were performed by using Collandrapp. The following information was extracted using a predefined form, i.e., first author name, year of publication, country of origin, number of experiments, intervention, control, solvent, method, and outcomes data (IC_{50} lipase inhibition). The discrepancies were verified by discussion and consensus.

Statistical Analysis

Meta-analysis was conducted in qualified research papers according to certain criteria. The papers shall contain the following information: averaged concentration of compounds in traditional medicinal plants and orlistat for IC_{50}, number of replications, and standard deviation. Since all the observation indexes are continuous and the measurement time of outcome is inconsistent across studies, we pooled the SMD with a corresponding 95% CI using the random-effects model.

■ RESULT

Trial Selection and Risk of Bias Assessment

The initial search from 6 scientific databases successfully collected and identified 810 articles, of which 326 articles were chosen for full-text review, resulting in 19 articles [28-46] that met the inclusion criteria. Meanwhile, the rest (484 articles) was rejected due to incompatible substance from the title and abstract. Nine additional articles from reference lists of the identified trials were included in the study because they met the inclusion criteria. Following a full review, a total of 331 articles were excluded (8 review articles, 291 not having data compatible with analysis). Totally the meta-analysis involved 19 articles. The stage of article selection is exhibited in Fig. 1.

Characteristics of Articles

Nineteen selected articles contained 91 experimental data published between 2011 and 2021. The PICO of this research is defined as Participants, Interventions, Comparisons, Outcomes, and Study Design. Participants in the *in vitro* experiment were IC_{50} pancreatic lipase inhibition. Interventions used were medicinal plants. Comparisons were orlistat as an anti-obesity drug. The outcome of this research was the best potential lipase inhibition activity by medicinal plants. The study design used in this research was randomized control.

The Most Promising Anti-Obesity Plants

Inhibition of pancreatic lipase

In this work, our systematic review and meta-analysis used IC_{50} of pancreatic lipase inhibition as the criteria for screening studies. Summary table of meta-analysis (Table 1) and additional table about data collection for meta-analysis (Table S1), meta-analysis modeling indicated an overall standardized mean difference (SMD) of 12.75 (95% CI 10.144-15.362) with $I2 = 89.83\%$ and $P < 0.001$. There were 8 medicinal plants from all studied countries that showed smaller effect size than the average, i.e., *Solenostemma argel* (Hargel)

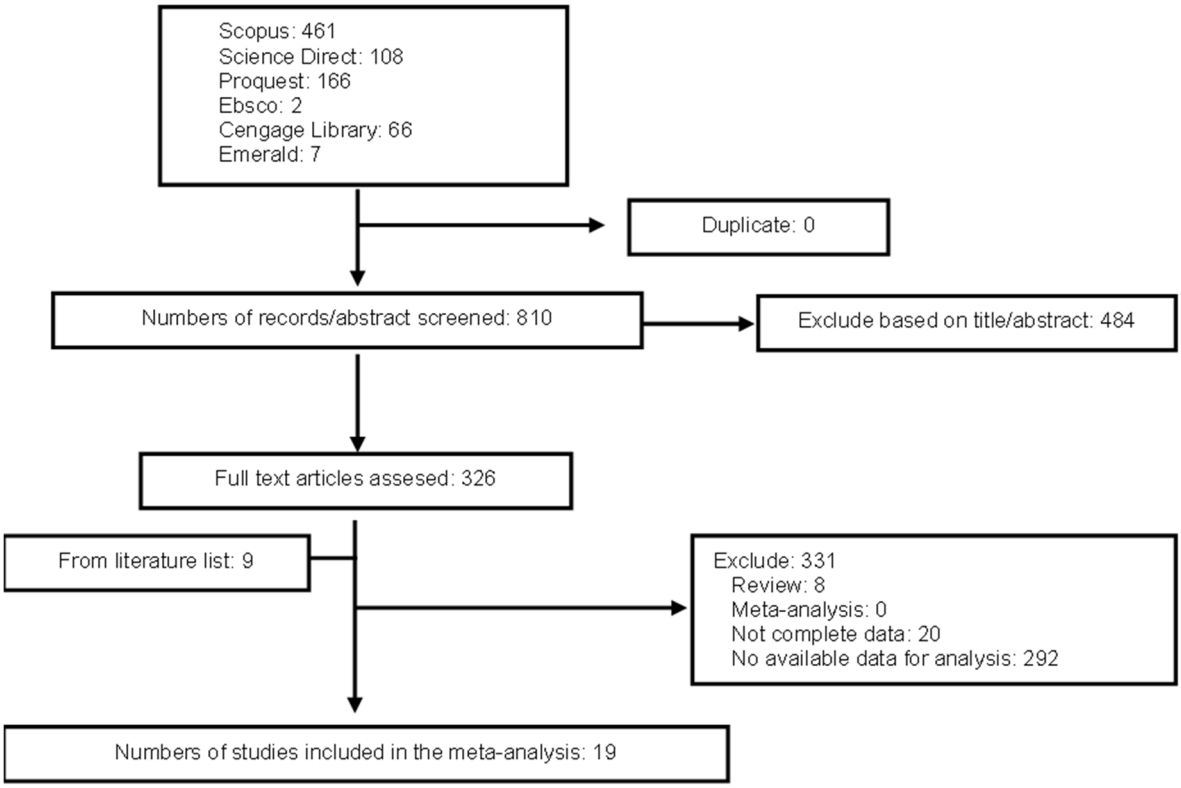

Fig 1. The Prisma flow diagram of the systematic review process

-2.166 (95% CI -12.211-7.875), *Garcinia vilersiana* 0.030 (95% CI -1.570-1.777), *Phyllanthus chamaepeuce* 0.173 95% CI -1.430-1.777), *Cassia auriculat* (Tanner's Cassia) 3.235 (95% CI -12.211-7.875), *Moringa oleifera* (Drumstick tree) 3.610 (95% CI 3.689-14.467), *Ficus carica* 6.178 (95% CI 1.703-5.517), *Ocimum gratissium* (African basil) 9.058 (95% CI 3.689-14.467), and *Adiantum capillus-veneris* (southern maidenhair fern) 10.422 (95% CI 4.312-16.533).

Bioactive compounds contributing to anti-obesity

Medicinal plants with anti-obesity effects were screened in the previous stage according to their inhibitory activity against pancreatic lipase (expressed as IC_{50}). The further stage focused on the selection of bioactive compounds most contributing to anti-obesity via inhibition of pancreatic lipase. The results indicated different scores of SMD between compounds, i.e., flavonoid-alkaloid 0.102 (95% CI -1.031-1.234], niazirin 3.610 (95% CI 1.703-5.517), mallic acid 6.178 (95% CI 2.645-9.711), flavonoid 6.316 (95% CI 0.507-12.126], 5-Methoxy-7-hidroxy-9,10-dihydro-1,4-phenanthrenequinone 7.727 (95% CI 3.071-12.382), combination of tannin, phenolic and flavonoid 7.977 (95% CI -2.379-18.333), and ferulic acid 10.422 (95% CI 4.312-16.533); those compounds are lower than the average 12.753 (95% CI 10.144-15.362). Niazirin belongs to a group of phenolic glycosides [47]. Based on the forest plot, herbal plants with flavonoids and alkaloids exerted a powerful inhibitory activity towards pancreatic lipase compared with those with flavonoids or phenolics alone. The inhibition rate of plants containing flavonoids and alkaloids reached 60, higher than those containing flavonoids.

Solvents used to isolate the bioactive compounds

The most proper solvent to extract bioactive compounds for anti-obesity was ordered as follows: ethanol 70% with a homogenizer, ultrasonication, ethanol 90% with ultrasonication, methanol with ultrasonication, ethanol 50% with ultrasonication, methanol, water, and ethyl acetate. From Table 1 comparison of solvent to IC_{50} indicated that ultrasonication-assisted extraction would improve the inhibition of pancreatic lipase in comparison with maceration. Ethanol 70% is the best solvent. Compared to methanol, extraction of the anti-obesity

Table 1. Summary table of the Metaanalysis

Subgroup*	Country	Solvent	Bioactive molecule	N	Effect size (random effect model)			SE	p-value	Heterogeneity		Egger's test
					SMD	C.L (Lower to Upper)				I^2	Q	
Cassia Siamea	India	Ethanol	Cassiamin A	3	22.69	9.75	35.62	43.55	NA	NA	NA	NA
Miurdannia ioriformis	Thailand	Aqueous	Phenolic	3	543.38	235.93	860.83	24564.61	NA	NA	NA	NA
Stevia rebaudiana	Thailand	Aqueous	Phenolic	3	2619.73	1137.50	4101.96	571366.70	NA	NA	NA	NA
Centella asiatica	Thailand	Aqueous	Phenolic	3	593.39	257.65	929.13	29293.91	NA	NA	NA	NA
Carthamus tinctorius	Thailand	Aqueous	Phenolic	3	2678.56	1163.05	4194.08	596666.30	NA	NA	NA	NA
Ginkgo biloba	Thailand	Aqueous	Phenolic	3	2390.89	1038.14	3743.63	475385.10	NA	NA	NA	NA
Orthosipon aristatus	Thailand	Aqueous	Phenolic	3	643.39	279.36	1007.43	34439.29	NA	NA	NA	NA
Cassia angustifolia	Thailand	Aqueous	Phenolic	3	3951.29	1715.67	6186.91	1299331	NA	NA	NA	NA
Gynostemma penthaphyllum	Thailand	Aqueous	Phenolic	3	2706.69	1175.26	4238.12	610454.50	NA	NA	NA	NA
Morus alba	Thailand	Aqueous	Phenolic	3	493.38	214.22	772.53	20251.41	NA	NA	NA	NA
C. fenestratum	Thailand	Hexane:Dichloromethane:Ethanol (1:1:1)	Flavonoid	3	136.06	59.06	213.06	1543.48	NA	NA	NA	NA
Cassia auriculata	UK	Methanol	Flavonoid	4	3.24	1.13	5.34	1154	NA	NA	NA	NA
Achillea santolina	Algeria				575508.82	-118268.27	1269285.91	693777.09	<0.01	90.84	NA	0.410
		Ethyl acetate fraction	Phenolic	3	4172746.16	1011836.15	6533656.17	1.45×10^{12}	-	-	-	-
		Butanol fraction	Phenolic	3	561932.83	243995.27	879870.41	2.63×10^{10}	-	-	-	-
		Butanol fraction	Saponin	3	44751.52	19431.43	70071.61	1.67×10^{8}	-	-	-	-
Zizyphus lotus	Algeria				689657.39	-179526.11	1556640.91		<0.01	91.63%	NA	0.412
		Ethyl acetate fraction	Phenolic	3	5075449.49	220379.37	7947102.61	2.15×10^{12}	-	-	-	-
		Butanol fraction	Phenolic	3	674770.742	292990.27	1056551.215	3.79×10^{10}	-	-	-	-
		Butanol fraction	Saponin	3	1556640.91	-179526.12	4427.78	666379.40	-	-	-	-
Passiflora nitida	Japan	20% Ethanol + 80% water	Flavonoid	3	14.49	7.02	25.94	23.31	NA	NA	NA	NA
Garcinia vilersiana	Thailand	Ethanol	Flavonoid, Alkaloid	3	0.03	-1.57	1.63	0.67	NA	NA	NA	NA
P. chamaepeuce	Thailand	Ethanol	Flavonoid, Alkaloid	3	0.17	-1.43	1.78	0.67	NA	NA	NA	NA
Hibiscus sabdariffa	Germany				1423.98	853.34	1994.42		0.78	0%	NA	NA
		Methanol	Polyphenol	3	1353.23	567.58	2116.80	152603.70	-	-	-	-
		Aqueous	Polyphenol	3	1512.10	656.56	2367.63	190538.20	-	-	-	-
Mentha aquatica	Germany				60821.94	-63161.18	184805.07		<0.01	91.28%	NA	NA
		Methanol	NA	3	2852.16	1239.42	4465.99	677901.10	-	-	-	-
		Aqueous	NA	3	129859.26	56381.91	203310.62	1.41×10^{9}	-	-	-	-
Punica granatum	Germany				5312.83	3668.78	6957.48		0.34	9.74	NA	<0.001
		Methanol	NA	3	3806.40	1652.80	5960.16	1207443	-	-	-	-
		Aqueous	NA	3	4836.04	2969.25	10703.92	3894288	-	-	-	-
		Methanol:aqueous (1:1)	NA	3	6700.83	2909.55	10492.12	3741769	-	-	-	-
		Methanol:aqueous (2:1)	NA	3	6407.71	2792.27	10033.15	3421569	-	-	-	-
Tamarindus Indica	Germany			3	6352.69	3771.78	8933.58		0.39	0%	NA	NA
		Methanol	NA	3	5567.49	2417.44	8717.62	2583087	-	-	-	-
		Aqueous	NA	3	7956.14	3454.61	12457.67	5275024	-	-	-	-

Olea europaea	Germany				10274.50	1220.34	19328.65		0.06	72.27%	NA	NA
		Methanol	NA	3	4495.51	2820.39	10170.62	3515973	-	-	-	-
		Aqueous	NA	3	15921.58	6913.26	24929.90	21124736	-	-	-	-
Rosmarinus officianalis	Germany				7044.81	4208.66	9880.96		0.59	0%	NA	NA
		Methanol	NA	3	6413.81	2784.92	1604.69	3428079	-	-	-	-
		Aqueous	NA	3	8035.16	3409.93	12591.40	5380326	-	-	-	-
Peumus boldus Molina	Germany				10102.09	3036.16	17168.01		0.12	59.27%	NA	NA
		Methanol	NA	3	7300.20	3169.79	11430.60	4441077	-	-	-	-
		Aqueous	NA	3	1474.73	6400.53	2300.93	18107421	-	-	-	-
Ocimum gratissimum	Nigeria	Methanol then by separatory funnel with hexane, aqueous phase extracted by ethyl acetate	Phenolic, Flavonoid	3	9.06	3.69	14.43	7.50	NA	NA	NA	NA
Ocimum basilicum	Nigeria	Methanol then by separatory funnel with hexane, aqueous phase extracted by ethyl acetate	Phenolic, Flavonoid	3	13.85	5.85	21.86	16.67	NA	NA	NA	NA
Moringa oleifera	India				3.61	1.70	5.51		0.31	2.93%	NA	NA
		Methanol	Niazirin	3	4.97	1.73	8.19	2.72	-	-	-	-
		Methanol	Niazirin	3	2.91	0.61	5.21	1.37	-	-	-	-
Dendrobium formasum Roxb	Thailand				12.86	0.72	24.99		0.05	74.35	NA	NA
		Methanol (FII2 of Fraction Ethyl acetate, hexane gradient chromatography column)	Confusarin	3	20.33	8.71	31.94	35.11	-	-	-	-
		Methanol (GIII2 of fraction CH2-Cl2-Hexane gradient chromatography column)	5-Methoxy-7-hydroxy-9,10-dihydro-1,4-phenanthren equinone	3	7.73	3.07	5.21	5.64	-	-	-	-
Adiantum capillus-veneris	Jordan	water	Ferulic acid	3	10.42	4.31	16.53	9.72	NA	NA	NA	NA
Ficus carica	South Africa			3	55.06	23.87	86.26		<0.01	87.56%	NA	0.03
		Hexane	Malic acid	3	11.97	5.01	18.93	253.34	-	-	-	-
		Ethyl acetate	Malic acid	3	2.69	0.46	4.90	12.61	-	-	-	-
		Ethanol	Malic acid	3	0.03	-1.57	1.63	1.27	-	-	-	-
		Aqueous	Malic acid	3	0.02	-1.57	1.63	0.67	-	-	-	-
		Hexane	Malic acid	3	401.91	174.50	629.31	13461.78	-	-	-	-
		Ethyl acetate	Malic acid	3	15.02	6.37	23.67	19.48	-	-	-	-
		Ethanol	Malic acid	3	0.188	-1.41	1.79	0.67	-	-	-	-
		Aqueous	Malic acid	3	3.85	1.15	6.56	1.90	-	-	-	-
		Hexane	Malic acid	3	221.98	96.37	347.58	4106.92	-	-	-	-
		Ethyl acetate	Malic acid	3	2316.53	1005.85	3627.20	447192.90	-	-	-	-
		Ethanol	Malic acid	3	11.01	4.61	17.55	10.91	-	-	-	-
		Aqueous	Malic acid	3	6.27	2.38	10.16	3.94	-	-	-	-
Grapefruit	China	70% Ethanol	Phenolic, Flavonoid	3	63.15	27.38	98.92	333.03	NA	NA	NA	NA
Pomelo	China	70% Ethanol	Phenolic, Flavonoid	3	24.74	10.65	38.82	51.65	NA	NA	NA	NA
Kumquat	China	70% Ethanol	Phenolic, Flavonoid	3	205.93	89.40	322.46	3534.72	NA	NA	NA	NA

Citrus Mandarin, Owari unshu	China	70% Ethanol	Phenolic, Flavonoid	3	10.33	7.83	38.82	28.66	NA	NA	NA	NA
Ponkan	China	70% Ethanol	Phenolic, Flavonoid	3	19.14	0.19	30.08	31.18	NA	NA	NA	NA
Tingerine	China	70% Ethanol	Phenolic, Flavonoid	3	22.40	9.66	35.16	42.45	NA	NA	NA	NA
Lemon	China	70% Ethanol	Phenolic, Flavonoid	3	131.82	57.22	206.41	1448.65	NA	NA	NA	NA
Sweet orange	China	70% Ethanol	Phenolic, Flavonoid	3	13.75	5.81	21.70	16.43	NA	NA	NA	NA
Solenostemma argel	Egypt				-2.17	-12.21	7.87		<0.01	91.06%	NA	0.74
		Methanol (ultrasonic)	Flavonoid	3	0.66	-0.98	2.31	0.70	-	-	-	-
		Aqueous (ultrasonic)	Flavonoid	3	25.63	11.04	40.22	55.41	-	-	-	-
		50% Ethanol (ultrasonic)	Flavonoid	3	7.83	3.12	12.54	5.78	-	-	-	-
		70% Ethanol (ultrasonic)	Flavonoid	3	-31.63	-49.60	-13.66	84.06	-	-	-	-
		90% Ethanol (ultrasonic)	Flavonoid	3	-22.13	-34.76	-9.50	41.49	-	-	-	-
Rumex maderensis	Portugal				22.01	14.75	29.27		0.96	0%	NA	0.08
		Methanol	Flavonol, Catechin	3	21.54	9.25	33.83	39.33	-	-	-	-
		Methanol	Flavononol, Catechin	3	21.14	9.07	33.22	37.93	-	-	-	-
		Methanol	Flavonol, Catechin	3	23.67	10.11	37.16	47.38	-	-	-	-
J. communis	India				20.13	7.45	32.81		<0.01	90.93%	NA	0.23
		Toluene	Tanin, Phenolic	3	46.19	20.01	72.38	582.08	-	-	-	-
		Chloroform	Tanin, Phenolic	3	46.19	20.01	72.38	178.53	-	-	-	-
		Methanol	Tanin, Phenolic, Flavonoid	3	0.001	-1.59	1.60	0.67	-	-	-	-
		Ethyl acetate	Tanin, Phenoluc, Flavonoid	3	7.59	3.00	12.18	5.472	-	-	-	-
		Aqueous	Tanin, Phenolic, Flavonoid	3	61.43	7.90	29.06	315.20	-	-	-	-
Echium angustifolium	Palestine				27.94	17.13	38.74		0.17	40.34%	NA	0.01
		Hexane	Saponin	3	26.62	11.47	41.77	59.75	-	-	-	-
		Acetone	Saponin	3	37.72	16.31	59.12	119.23	-	-	-	-
		Methanol	Flavonoid	3	43.67	18.91	69.43	159.59	-	-	-	-
		Aqueous	Flavonoid	3	16.40	7.90	29.06	29.15	-	-	-	-
Anchusa ovata	Palestine				200.59	69.81	331.37		<0.01	87.35%	NA	0.08
		Hexane fraction	Saponin	3	747.23	324.45	1170.02	46531.08	-	-	-	-
		Acetone fraction	Tannin, Phenolic	3	613.86	266.54	961.19	31403.24	-	-	-	-
		Methanol fraction	Phenolic, Tannin, Terpenoid	3	96.65	37.60	135.71	626.46	-	-	-	-
		Aqueous fraction	Phenolic, Tannin, Alkaloid	3	109.72	43.71	157.73	846.02	-	-	-	-

P. mildbraedii	Nigeria				25.66	-12.72	64.06		0.01	87.35%	NA	NA
		Ethanol	Flavonoid, Saponin	3	47.72	20.67	74.78	190.50	-	-	-	-
		Hexane fraction	Flavonoid, Saponin	3	9.27	3.32	13.22	6.37	-	-	-	-
M. flagellipes	Nigeria				16.54	10.96	22.11		0.56	0%	NA	0.01
		Ethanol	Flavonoid, Saponin	3	14.90	6.32	23.49	19.19	-	-	-	-
		Hexane Fraction	Flavonoid, Saponin	3	15.31	6.50	24.13	20.22	-	-	-	-
		Butanol fraction	Flavonoid, Saponin	3	23.11	9.93	36.29	45.19	-	-	-	-
Eletaria cardamomium	Saudi Arabia	Aqueous	Phenolic, flavonoid	3	156.48	67.93	245.04	156.49	NA	NA	NA	NA
Overall					12.75	10.14	15.36		<0.01	89.93%	NA	<0.01

*References of Subgroup 1-91 = [28-46]. Abbreviation: N = Sample size of study; SMD = Standardized Mean Difference; SE = Standard Error; Q = homogeneity test; I^2 = Index 95%; CI = Confidence Interval around I2; NA = Not available

compound by ethanol produced a much higher amount of yield, reaching up to 2.5 times higher than methanol.

Countries with the most appreciable anti-obesity effect

From the screening of articles published in 6 databases, there was no research paper from Indonesia that meets the criteria of meta-analysis. The absence of Indonesian research articles could relate to a scarcity of research publications on herbal plants promoting anti-obesity activities. In addition, the published articles did not fit the criteria. Meta-analysis indicated some potential countries that are associated with plants containing an inhibitor of pancreatic lipase, i.e., Egypt, the UK, South Africa, India, Thailand, and Jordan, respectively. The effect size of these countries was better than the overall score.

Research mapping related to anti-obesity

In this work, we portrayed research focusing on anti-obesity. Analysis of bibliometric data accessed from 6 databases suggested 4 research clusters of obesity, each displayed in different colors. Green cluster represented *in vivo* anti-obesity experiments using experimental animals such as a rat. The experiment applied various methods and evaluated the lipid profile of the animals. Meanwhile, the yellow cluster delineated studies on the mode of action of anti-obesity drugs, covering the investigation of PPARγ gene expression, adipose alteration, lipogenesis, and lipid accumulation. However, this group of research was scarcely conducted, as presented in pale-yellow color. In addition, the red cluster displayed studies on other bioactivities, such as anti-diabetic activity via α-glucosidase and α-amylase test, and their relationship with bioactive compounds in drugs such as flavonoids. The blue cluster depicted pharmacotherapy experiments, disease diagnosing, and evaluation of potential plants for medicines. However, the pale blue color indicated that the studies on this cluster were scant (Supplementary File).

Based on bibliometric data from 6 databases within the last 10 years analyzed using VoS viewer, we noted current anti-obesity research discussing phytochemical profiles and obesity management directly on obese individuals. From this bibliometric, a considerable rise in anti-obesity studies started in 2015. As illustrated in the graph, research topics on light colors indicated that they were intensively carried out; on the contrary, topics on dark color were rarely studied. We also found that TCM became massively published topics, while research on the mechanism of anti-obesity effect by lipase inhibition and phytochemicals was rarely investigated (Fig. S1 and S2).

■ DISCUSSION

In this meta-analysis, we present 91 experimental data regarding the use of medicinal plants from numerous countries, in which these plants provide anti-obesity effects via inhibition of pancreatic lipase under *in vitro* experiments. The data used are eligible, following verification based on inclusion criteria, including the presence of IC_{50} value, number of replications, and standard deviation. As one of the key

criteria, we define IC_{50} as a minimum concentration required to inhibit the activity of pancreatic lipase by 50%. It is well-known that pancreatic lipase constitutes a pivotal enzyme that dictates fat absorption [14]. Hence, a drug or a compound showing lower IC_{50} is more powerful as an inhibitor. Actually, the mechanism of anti-obesity through pancreatic lipase inhibition is applied by a conventional drug, i.e., orlistat [48]. Furthermore, the inhibition of such enzymes has been massively studied. This condition provokes exploration of medicinal plants highlighting their ability to retard pancreatic lipase as an attempt in search of anti-obesity drugs.

Among 91 plants studied, we show 8 TMP exhibiting the most appreciable source of anti-obesity according to effect size compared with orlistat. These plants include *Solenostemma argel*, *Garcinia vilersiana*, *P. chamapeuce*, *Cassia auriculata*, *Moringa oleifera*, *Ficus carica*, *Ocimum gratissium* and *Adiantum capillus-veneris*. These plants are applied in different parts of the plant, such as the leaf, fruit, and root. Meanwhile, there are 5 bioactive compounds functioning as a pancreatic lipase inhibitor, i.e., phenolic, flavonoid, saponin, alkaloid, and terpenoid [36,48]. Other studies reported some potential bioactive compounds for inhibiting pancreatic lipase, i.e., flavonoid, phenol, and alkaloid [48-50]. Consistent with former studies, this meta-analysis also demonstrates that secondary metabolites suitable for anti-obesity include a combination of flavonoid-alkaloid, niazirin, malic acid, flavonoid, 5-methoxy-7-hidroxy-9,10-dihydro-1,4-phenanthrenequinone, a combination of tannin, phenolic, and flavonoid, as well as ferulic acid.

Regarding the relationship between solvent and pancreatic lipase inhibition, extraction of bioactive compounds using ethanol and methanol with an ultrasonication system is associated with higher inhibitory activity. Ultrasonication-assisted extraction enables the enhancement of efficiency, selectivity of the process, high reproducibility, less amount of solvent used, shorter time, and higher production content yield [51]. Hence, these advantages are reasons for the popularity of ultrasonic in plant-source extraction for drug development [52]. Solvents are often selected for their polarity. A polar solvent is highly effective in isolating and dissolving polar and semi-polar compounds, and vice versa [53]. Solvent classification according to a degree of polarity can be sequenced (non-polar to polar) as follows: hexane < chloroform < ethyl acetate < acetone < ethanol < methanol < water [53]. Ethanol is the ideal solvent for the extraction of polyphenols, including flavonoids. In addition, concerning safety, ethanolic extract appears to be safer for humans. Meanwhile, methanol is proper for the extraction of flavonols with a higher molecular weight and alkaloid is best extracted by ethanol rather than methanol and water [54-55].

Solenostemma argel is a traditional perennial herb widely distributed in some regions such as Egypt, Africa, and Arabian Peninsula [56]. Besides providing inhibition towards pancreatic lipase, the anti-obesity mechanism by the argel is based on its stimulatory effect on the expression of β-oxidation, modulation of adipokine activity, regulation of satiation hormone, control of body weight, and improvement of lipid profile [57]. The flavonoid in the argel is reported as a main contributor to anti-obesity [31]. Another potential plant for anti-obesity management is *Garcinia vilersiana*, popular as yellow mangosteen. Several species of Garcinia can be found in tropical regions of Asia, Africa, and Polynesia, and they are included in ayurvedic medicine [58]. In this meta-analysis, *Garcinia vilersiana* originates from Thailand. Flavonoids and alkaloids in yellow mangosteen are two bioactive compounds responsible for anti-obesity activity [29]. *Phyllanthus chamapeuce*, a member of Phyllanthus, mostly occurs in tropical and sub-tropical areas in Asia, Africa, America, and Oceania, and for *Phyllanthus chamaepeucea*, it is distributed in Asia countries such as Malaysia and Thailand [59-60]. In addition, we also observed *P. chamaepeuce* from Thailand as one of the anti-obesity agents, in which flavonoids and alkaloids are also key bioactive compounds for curing obesity [29].

Moreover, *Cassia auriculata*, widely recognized as avartaki in India, is an annual or biennial shrub found throughout the country and in this work, Indian avartaki is one of the ayurvedic plants [61]. Avartaki exerts anti-obesity properties regarding its ability to reduce the action of pancreatic lipase as well as diminishing

adiposity differentiation which leads to body weight loss [62]. Flavonoid is a bioactive compound responsible for the anti-obesity effect of avartaki [34]. *Moringa oleifera*, also known as the drumstick tree, is a popular plant throughout the world and spread in most parts of the globe, including India, Asia, and Africa [63]. With its stunning bioactivity, moringa leaf is listed in the top 50 future plants [64]. Anti-obesity activity by moringa leaf relates to its action on inhibition of pancreatic lipase as well as regulation of fat storage through the down-regulating expression of adipogenesis-associated proteins peroxisome proliferator-activated receptor gamma (PPARγ) and fatty acid synthase (FAS), up-regulating the expression of the lipolysis-related protein, i.e. adipose triglyceride lipase (ATGL), suppressing content of leptin, retarding expression of lipogenesis, and adipogenesis-related proteins [65-66]. In addition, moringa leaf is reported to be able to improve lipid profile by reducing the content of total cholesterol, triglyceride, low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL), but at the same time, increasing high-density lipoprotein (HDL) [65]. The experiment in animal subjects indicates that moringa enables to decline in body weight of obese rats significantly [67]. The incredible activity of moringa as an anti-obesity agent is associated with the presence of niazirin [46], which belongs to a member of phenolic glycoside [68].

Ficus carica, also known as fig, originates from Southwest Asia and East Mediterranean; and the plant is believed as one the first cultivated plants in human history [69]. In this meta-analysis*, Ficus carica* is from South Africa. *Ficus carica* often relates to management of diabetes; hence its activity as an anti-obesity agent is linked to the ability of the plant to regulation of glucose, lipid metabolism, and oxidative stress [70]. The malic acid in *Ficus carica* is the main actor in its anti-obesity effect [30]. In addition, *Ocimum gratissium* can be found in tropical regions of Asia and Africa, such as Nigeria, which is widely applied in folkloric medicine [71-72]. In this work, *Ocimum gratisimum* studied originates from Nigeria, emphasizing the performance of anti-obesity by phenolic and flavonoids in the plant [73]. Some fern species, *Adiantum capillus-veneris* is popularly applied in traditional medicine in many parts of the world, including China, India, and the United States Pharmacopoeia [74]. Ferulic acid isolated from the plant is revealed to provide an anti-obesity effect [45]. Regarding the mode of action, the anti-obesity effect of bioactive compounds in fern species depends on how they regulate the activity of gastrointestinal enzymes, especially those that account for the digestion and absorption of carbohydrates and lipids. This suggests that bioactive compounds in fern plants can perform dual targets in the regulation of glycemia, which is associated with obesity and diabetes [73].

Brief Description of the Mechanism of Pancreatic Lipase Inhibition by Bioactive Compounds

Pancreatic lipase is an important enzyme of pancreatic juice responsible for the digestion of dietary triglycerides in the small intestine into free fatty acids and diacylglycerol [49]. The way of inhibiting pancreatic lipase enzymes by orlistat or tetrahydrolipstatin itself is to form a covalent bond with the active serine moiety site of lipases and then inactivate them to hydrolyze dietary fat [75]. The bioactive molecules that have potential as pancreatic lipase inhibitors are also the same, which will bind to the active site of the lipase enzyme located in the stomach and small intestine, changing the conformation of the enzyme, thereby inhibiting catalytic activity, thereby reducing digestion and absorption of fat and accumulation in tissues. Adipose tissue to achieve obesity control [76-77]. The advantage of lipase inhibitors acting on peripheral elements in the development of new drugs is that they do not enter the human blood vessels and nervous system and do not affect the balance between the body's minerals and bone circulation lipase inhibition [77-78]. The lipase inhibitor has proven to be relatively safe [49].

Limitations and Strengths of This Study

This present systematic review and meta-analysis possess several limitations that are worth nothing. First, although the search strategy of this study was comprehensive, it is possible that pertinent unpublished reports or studies published in languages other than English are not included in this study. Future studies

should consider gray literature apart from easily accessible international databases and include publications with no language limitation, unpublished resources, including books, dissertations, and non-English publications. Second, the trials involved in this work include studies published in the last 10 years (2010–2021) considered as recent research reporting pancreatic lipase inhibition by anti-obesity plants. Future works covering previous years' research should be envisaged. Third, there are several articles in which the procedure fits our criteria for pancreatic lipase inhibition. However, the description of the intervention is inadequate to explain the number of repetitions of samples and orlistat, and the value of the standard deviation or standard error is not shown. Therefore, some articles are excluded after full-text reading because they only show % inhibition without providing the IC_{50} value of pancreatic lipase inhibition.

The strength of the current meta-analysis is the coverage of traditional plant medicines from many parts of the world as anti-obesity with specific mechanisms as an inhibitor of pancreatic lipase. Moreover, we perform subgroup analysis to identify the main sources of heterogeneity and introduce the influence of secondary metabolites in each intervention, as well as specific solvents used in the extraction procedure. Ultimately, using VoS viewer, this study is enriched with a review of how far studies pertaining to obesity are carried out.

■ CONCLUSION

The electronic search collected 810 research articles from 6 scientific databases, and 91 of them contained eligible data reporting the use of TMP for treating anti-obesity via inhibition of pancreatic lipase. Among these plants, we found some plants showing the best anti-obesity activity, i.e., *Solenostemma argel*, *Garcinia vilersiana*, *P. chamaepeuce*, *Cassia auriculata*, *Moringa oleifera*, *Ficus carica*, *Ocimum gratissimum*, and *Adiantum capillus-veneris*, respectively. Their anti-obesity effects were evaluated according to the inhibition of pancreatic lipase expressed as IC_{50}. One explanation of their bioactivity is related to the content of bioactive compounds such as flavonoid, alkaloid, phenolic, malic acid, and ferulic acid. To isolate specific compounds acting as pancreatic lipase inhibitors, the use of solvents, i.e., 70% ethanol, 90% ethanol, and methanol, combined with ultrasonication, were reported to show the best outcome.

■ AUTHOR CONTRIBUTIONS

Designed the subject and revised the article: Hasim and Didah Nur Faridah. Developed inclusion and exclusion criteria, developed and performed the search strategy, conducted the statistical analysis, and wrote the article: Frendy Ahmad Afandi, Eka Nurul Qomaliyah, Hasim, and Didah Nur Faridah. Screened relevant literature, and made decisions according to inclusion and exclusion criteria: Frendy Ahmad Afandi and Eka Nurul Qomaliyah.

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