Effects of *Imperata cylindrica* on Anti-hyperlipidemia: A Review

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Abstract: *Imperata cylindrica* is a well-known species of perennial rhizomatous grass native to tropical South East Asia, which possesses extensive medicinal value. It has major constituents such as saponin, flavonoid, phenols, and glycosides, efficacious as an anti-hyperlipidemia. Studies of pharmacological activities of *I. cylindrica*, a nutritious, medicinal herb, showed that it could cause blood lipid levels to be reduced. This systematic review article was designed to determine the existing studies related to the efficacy of *I. cylindrica* to lower blood lipid levels. PubMed and Scopus databases were used to search for suitable keywords such as *Imperata cylindrica*, cogongrass, hypolipidemic, triglyceride, cholesterol, low-density lipoprotein (LDL), and very-low-density lipoprotein (VLDL). Based on provided protocol, in this systematic review, we extracted the data and evaluated the quality of articles by two reviewers. (4) Results 73 articles were the search results and based on the inclusions and exclusions criteria, 8 articles were included in the final review. These studies demonstrated that two active compounds of *I. cylindrica*: flavonoids and saponins, were beneficial to reduce blood lipid levels. However, further clinical studies are urgently required to provide adequate evidence on the use application of *I. cylindrica* in medicinal properties.

Keywords: *Imperata cylindrica*; hyperlipidemia; cholesterol; triglyceride; LDL.

1. Introduction

The prevalence of hyperlipidemia and subsequent coronary artery disease is high among developed countries as well as in regions with lower income levels [1,2]. As the World Health Organization (WHO) reported, cardiovascular diseases are the most common cause of death in the world. However, changing the lifestyle and medication in these diseases could attenuate it [3,4]. Hyperlipidemia is a lipid metabolic disorder characterized by elevated lipid levels in the blood, including total cholesterol, triglycerides, and LDL, commonly called hypercholesterolemia or hypertriglyceridemia [5,6].

Hyperlipidemia is a chronic disease that requires treatment in the long term [7,8]. The clinical benefits provided from pharmacological treatment in hyperlipidemia should not lessen our attention to reduce the side effects caused by long-time treatment of anti hyperlipidemia in patients [1,9]. Currently, herb-based traditional medicine has been widely used, and WHO initiated to development of herbal-based medicine as a potential therapeutic strategy [10], including treatment for hyperlipidemia [11]. Cogon grass (*Imperata cylindrica*), a member of the *Gramineae* family, is found all over the place but is often considered useless and treated as a weed. However, this plant is extensively utilized in traditional medicine, particularly Asia

[12]. *Imperata cylidrica* is known to have functions to reduce plasma lipid concentrations [12-14].

There vast amount of kinds of literature that depicts that *Imperata cylindrica* possess major phytochemical constituents such as saponins, flavonoids, glycosides, phenols, and coumarins [15]. The rhizomes of *I. cylindrica* had been identified as containing many compounds with biological properties such as arundoin, cylindrin, cylindol, graminones, cylindrene, imperanene, and fernenol [16]. Scientific pharmacology research on *I. cylindrica* have shown that several substances from it exhibit an extensive range of biological activities, for instance: hemostasis, improvement of urination [17], analgesic, anti-inflammatory and anti-pyretic [18], enhancement of the immune system [15,16], antibacterial [19], anticancer [20], etc.

In this review, we designed to systematically demonstrate the advances achieved in anti-hyperlipidemia of *Imperata cylindrica* related studies in recent decades, along with the mechanisms. Furthermore, we provided a systematic overview of the available information of *I. cylindrica,* including *in vivo studies* and *clinical trials*.

2. Materials and Methods

The databases used for data search were PubMed and Google scholar to examine the proper keywords such as *Imperata cylindrica* OR cogongrass AND hypolipidemic; *Imperata cylindrica* OR cogongrass AND triglyceride; *Imperata cylindrica* OR cogongrass AND cholesterol; *Imperata cylindrica* OR cogongrass AND LDL OR VLDL.
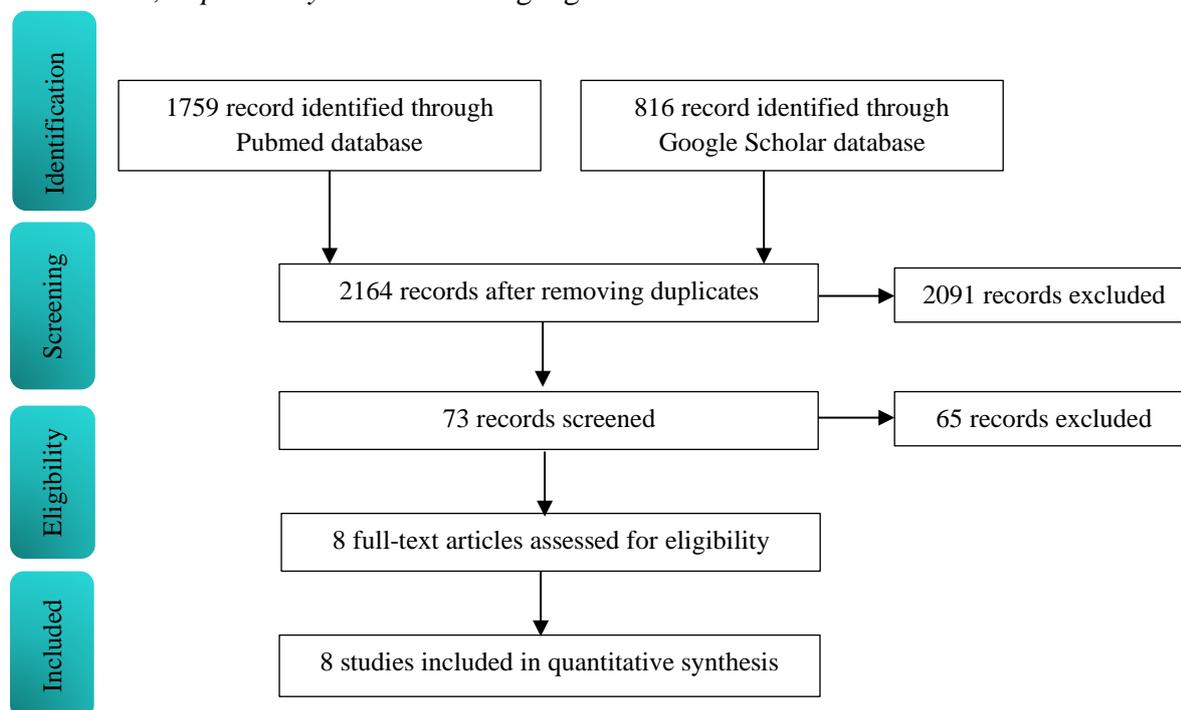

Figure 1. Flow diagram showing the number of records identified, screened, extracted, and included in the final analysis.

All inclusion criteria were defined in the studies we reviewed in this article. The categories of research were included clinical trials and *in vivo* studies that evaluated the potential of anti hyperlipidemia of *I. cylindrica*. However, the requirements criteria for articles were the international journal articles with the United Nations (UN) language, journal articles with Bahasa (Indonesian language), publication period from 2011 to 2021, and original

research articles. The articles with only provided abstract sections were excluded from the review. Some articles were omitted because they were about the non-medicinal term of use. Two reviewers independently extracted the data from articles to fill in table items. Subsequently, the bias assessment was carried out for clinical trials and *in vivo* studies. According to Ma (2020), for clinical trials, we provided three bias assessment scales: Jadad scale [21], Newcast Ottawa Scale (NOS) [22], and Cochrane Risk of Bias Tool [23,24]. The determination of journal validity was using recommended viewed through the parameters of the Jadad scale (a score of ≥ 3 were categorized as high-quality studies), NOS scale (a score of ≥ 7), and Cochrane Risk of Bias Tool by checking at the provisions of low bias risk (a score of ≥ 3), high bias risk (a score of ≤ 2), and unclear (a score of ≤ 4). The appropriate requirement for validity was when two different scales showed high scores. However, bias assessment for the *in vivo* studies was using recommended Cochrane Risk of Bias Tool [23,25]. The journal article was extracted and considered valid when it provided author's name, year of publication, type of research, the sample, hyperlipidemia stimulation type, *I. cylindrica* derivative products used, a certain dosage of *I. cylindrica*, parameters measured, and the outcomes.

3. Results and Discussion

3.1. Study selection.

We initially retrieved a total of 2575 potentially eligible articles in the database search; 1759 were found in Pubmed, and 816 were taken from Google scholar. 411 articles were excluded because of being duplicates. 2164 articles met the exclusion criteria. 2091 articles were also excluded because they were review articles or part of the book, and some did not match the topic based on the abstract and title. 73 articles were then screened for the inclusion criteria, and 65 articles were removed because of their study about the effect of *I. cylindrica* on other diseases. Therefore, 8 articles were included in the final analysis after assessing bias (see Figure 1).

Tabel 1. The article bias analysis results using Cochrane risk of bias tool.

No	Author	Year	Random sequence generation	Allocation concealment	Blinding of the participant and personal	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Conclusion
1.	Anggraeni *et al.* [26]	2017	×	√	?	?	√	√	√	Good
2.	Robianto *et al.* [27]	2019	√	√	?	√	√	√	√	Good
3.	Khaerunnisa *et al.* [12]	2020	√	?	?	√	√	√	√	Good
4.	Khaerunnisa *et al.* [28]	2014	√	×	?	√	×	√	√	Good
5.	Hsieh *et al.* [29]	2014	√	×	?	√	√	√	√	Good
6.	Ihsan *et al.* [30]	2018	√	√	?	√	√	?	?	Good
7.	Jue *et al.* [13]	2012	×	√	?	√	×	√	√	Good
8.	Cho *et al.* [31]	2017	√	√	√	√	√	√	√	Good

Note: √: Low-Risk Bias,; ×: High-Risk Bias,; ?: Unclear

3.2. Article bias analysis.

According to the bias analysis, as shown in Table 1, we evaluated the Jadad scale, NOS, and Cochrane risk of bias tool, which were applied for clinical trials. However, the *in vivo*

studies were using only the Cochrane Risk of Bias Tool. Based on the Cochrane Risk of Bias Tool, the study was determined for risk parameters including blinding of outcome assessment (detection bias), the highest risk of bias was detected in allocation concealment (selection bias), and incomplete outcome data (attrition bias). The incomplete parameters were found in the participants and personnel blinding (performance bias) because some articles provided inadequate information about the investigators who conducted the research (see Figure 2). Despite this, the *in vivo* studies provided higher scores than clinical trials as it was aforementioned that these meant fewer systematic errors found in the research process. Clinical trials were categorized as valid when according to the Jadad scale, 5 (maximum of 5), NOS scale was 8 (maximum of 13). As presented in Table 2, we retrieved only one clinical trial that was considered to have no systematic errors in the research process.
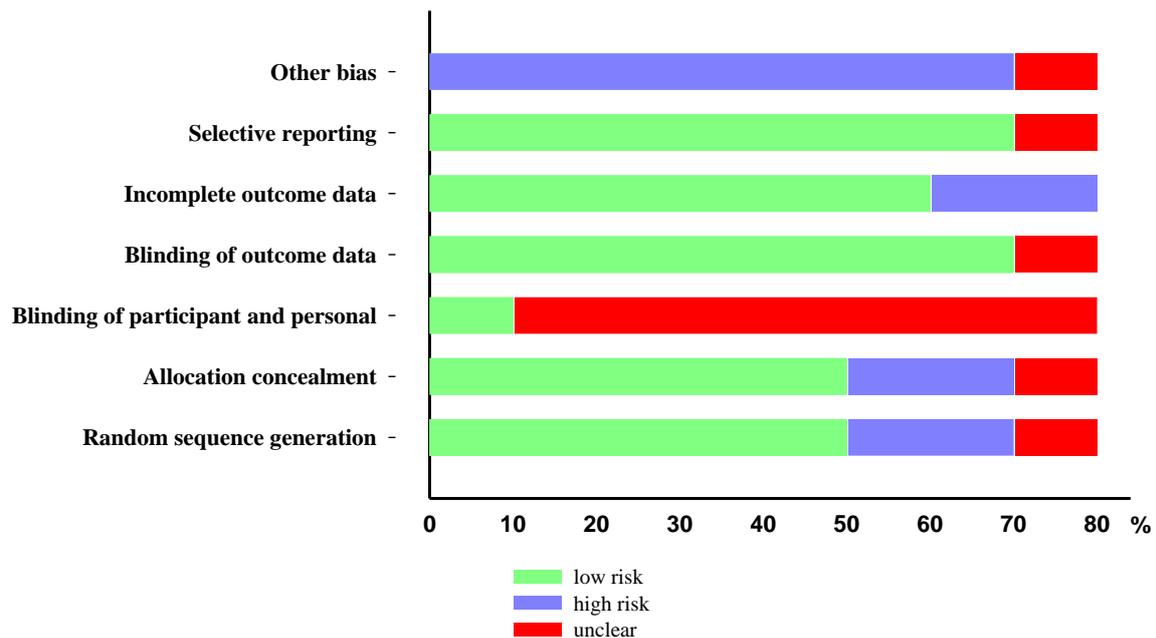

Figure 2. Graph of bias analysis assessment results using Cochrane parameters.

Table 2. The validity results of the clinical trial.

No	Author	Year	NOS Scale	Jadad scale	Cochrane	Conclusion
1.	Cho., *et al* [31]	2017	8 (Good)	5 (Good)	Good	Valid

Note: Journal validity results using three bias assessment scales

3.3. Potential anti-hyperlipidemia Imperata cylindrica.

Table 3 shows the summary results of a systematic literature review analysis about the potential efficacy of *Imperata cylindrica* as an anti-hyperlipidemia through *in vivo* studies. However, Table 4 demonstrated the result of a systematic literature review analysis in the clinical trial. Several studies indicated that the root part (rhizome) [12,26,27]. The other segment was leaves [29] and the whole piece of the plant [30]. Moreover, several studies used certain preparations of plants such as root's polysaccharides [13] and powder [28,31].

The outcome of studies was identified that three *in vivo* studies showed a decrease in serum levels, including total cholesterol, triglycerides, and LDL. Most *in vivo* studies demonstrated a reduction in total cholesterol levels [13,26,27,29,31]. Two studies showed the decrease in TG level [29, 31], and three studies provided the reduced level of LDL [12,30,31]

The experimental dose of *I. cylindrica* administered in the *in vivo* studies varied from a range of 75 mg/kg BW to 500 mg/kg BW. While in a clinical trial, the dose was administered

at 2400 mg/day. Of 8 articles retrieved, 6 articles showed that their *in vivo* studies led to lower lipid levels in the blood and one clinical trial we reviewed [12,13,26,28-30]. Aside from that, an *in vivo* study showed a less significant effect [27].

Table 3. The validity results of the *in vivo* studies.

No.	Author	Year	Type research	Sample	inducer	Derivative products *I. cylindrica*	Dosing	Measured parameters	Outcome		
									TC	TG	LDL
1.	Anggraeni *et al.* [26]	2017	*in vivo*	Male rat age 8-10 mnggu (*Mus muscularis*)	Administration of intragastric olive oil	Root extract	90 mg/kg BW and 115/kg BW	Total Serum Cholesterol	↓	ND	ND
2.	Robianto *et al.* [27]	2019	*in vivo*	21 Female rats aged 8- 12 weeks	Administration of *water ad libitum*	Root extract	90 and 115 mg/kg BW per day	Total serum cholesterol	↑	ND	ND
3.	Siti Khaerunnis *et al.* [12]	2020	*in vivo*	Male Wistar rats aged 2-3 months, weight 180-200 mg	Giving ad libitum access to food and beverages	Root extract	75 mg/kg BW	Total Cholesterol, LDL	ND	ND	↓
4.	St. Khaerunnis *et al.* [28]	2018	*in vivo*	28 male Wistar rats aged 3 months, weighing 180−200 grams.	High-fat diet	Dry powder	75 mg/kg bb ethanol extract and acetate fraction	Enzyme activity of SOD	↓	ND	ND
5.	Hsieh *et al.* [29]	2014	*in vivo*	Male Golden Syrian hamster, weight 260-270 g	PME diet	Leaf extract	ND	Total cholesterol, TG	↓	↓	ND
6.	Ihsan *et al.* [30]	2018	*in vivo*	24 Male mice (*Mus musculus* L.) with an average weight of 30.6 grams and an average age of 35 days	High-fat diet and administration of propylthiouracil drugs (PTU)	Whole plant parts	250 ml/kg BB and dose 500 ml/kg BB	LDL levels	ND	ND	↓
7.	Jue *et al.* [13]	2012	*in vivo*	Male rat	Administration of streptozotocin (STZ): a mouse model of diabetes	Polysaccharides Roots reeds	Low doses and high doses	TC, TG, LDL-C	↓	↓	ND

Note: ND: No Data; ↓ Significant Decreased; ↑ Significantly Increased

Tabel 4. The valid results of clinical trials.

No.	Author	Year	Types of research	Research design	Sample	Derivative products of I.cylindrica	Dose	Length of use	Research group		Outcome		
									Control group	Treatment group	TC	TG	LDL
1	Cho *et al.* [31]	2017	Clinical trial	Case control	60 participants	Tablets YY-312 (herbal extract powder, *I. cylindrica* Beauvois, Citrus Markovich, and *Evodia officinalis* comparison 5:2:3)	2400 mg/day	12 weeks	*Placebo group control*	Patients with a BMI of 25.0–29.9 kg/m2 with YY-312	↓	↓	↓

Note: ↓: Significant decreased,; Total Cholesterol (TC), Triglyceride (TG), Low-Density Lipoprotein (LDL)

3.4. Effects of Imperata cylindrica in intestinal lipid absorption.

To date, 72 compounds from *I. cylindrica* were identified; among them, flavonoids and saponins are the main compositions. The potential bioactive saponins may contribute either directly or indirectly to inhibit lipid absorption in the intestinal tissue. Saponins exhibit binding formation between lipids and bile acids to generate a strong field complex that prevents the process of lipid emulsification. Saponins may block the formation of micelles with lipids during digestion in the small intestine; thus, lipids absorption availability into enterocytes was reduced. Saponins are also inhibited by bile acid and lipid reabsorption due to the formation of

large mixed micelles. This formation is water-insoluble, so it can not be absorbed by the intestines and then excretes in the feces [32]. Inhibition of reabsorption of bile acids from the intestine stimulates the metabolism of cholesterol in the liver then converts it into bile acids [33].

In addition, saponins inhibit the activity of pancreatic lipase enzymes, thus suppressing the lipid degradation process [34,35]. It leads to a reduced lipid absorption process in the intestinal. Ali *et al.* (2019) demonstrated this pathway through *in vivo* study using an albino Wistar rat administered with a high-fat diet and saponins taken from the combination of *Trigonella foenum-graecum* seeds, *Asparagus officinalis* shoots, *Glycyrrhiza glabra,* and *Saponaria officinalis* rhizomes. They found that the administration of saponins from this combination significantly caused in lowering of serum triglyceride levels compared to the control [34,36].

3.5. Effects of Imperata cylindrica in the induction of lipoprotein lipase activity.

Imperata cylindrica contains flavonoids that possess biological activities, mainly causing the increase of lipoprotein lipase enzyme activity [37]. Lipoprotein lipase is abundant in adipose tissue and skeletal muscle's capillaries and plays a role in the triglycerides hydrolysis process into free fatty acids and glycerol [38,39]. In muscles, free fatty acids are provided for energy formation and an energy reservoir in adipose tissue. It leads to lower blood triglyceride levels. Hil *et al.* (2012) demonstrated a similar pathway through *in vitro* study with the administration of flavonoids quercetin, catechin, naringenin, luteolin, kaempferol, and genistein. Their research found that administering quercetin, kaempferol, and catechins to culture media can significantly reduce the free fatty acid (FFA) level. Flavonoids luteolin also caused significantly reduced triglycerides to level through *in vitro* study [40]. Furthermore, Mazumder *et al.* (2021) demonstrated a similar pathway through *in vivo* study with the administration of flavonoids from the combination of *Azadirachta indica* A. Juss., *Trigonella foenum-graecum* L., *Allium sativum* L., and *Zingiber officinale*. Their research found that the administration of this combination significantly caused a reduction in triglycerides level through *in vivo* study [41].

3.6. Effect of Imperata cylindrica in the SREBP-1c and PPAR-α gene induction pathways.

The anti-hyperlipidemic activity of *Imperata cylindrica* is due to the presence of flavonoids *I. cylindrica* which can affect the coding genes SREBP-1 and PPAR-α. At the physiological state, SREBP-1c and SREBP-2 genes are synthesized in the liver tissue. SREBP-1c supports the fatty acid biosynthetic pathway, and SREBP-2 maintains cholesterol synthesis [42]. SREBP-2-gen responsive in cholesterol biosynthetic pathways include the enzyme HMG-CoA synthase, HMG-CoA reductase, farnesyl diphosphate synthase, and squalene synthase which play a role in the process of cholesterol synthesis [42]. Other SREBP-1c target genes encode enzymes in the liver's synthesis of triglycerides and phospholipids [42]. Induction in the SREBP-1c gene can increase the formation of triglycerides and then be stored in the liver tissue. Thus, the activity of SREBP-2 leads to a decrease in cholesterol synthesis [42].

The transcription activity of the SREBP-1 gene may also be enhanced by the activation of the target protein PPAR-α. PPAR-α is known to function as a target protein that regulates lipoprotein metabolism and controls directly or indirectly lipogenic pathways in the liver tissue. Lipogenesis is a metabolic pathway that allows the synthesis of fatty acids when dietary lipids are abundant. PPAR-α agonists can increase the transcription activity of the SREBP-1c gene

by interacting with the promoter elements of SREBP-1c [43]. Similarly, Mulvihil *et al.* (2009) demonstrated the effects of flavonoid naringenin administration through *in vivo* study. Their findings showed that administering flavonoid naringenin increased the expression of the SREBP-1 liver gene by 3.9 times compared to the controls [44]. In addition, they found that flavonoids significantly increased PPAR-α regulation by 30% compared to controls [44].

3.7. Effects of Imperata cylindrica on 3-hydroxy-3-methyl-glutaryl-CoA Reductase inhibition.

The activity of *I. cylindrica* as anti hyperlipidemia is partly due to a decrease in the activity of 3-hydroxy-3-methyl-glutaryl-Coenzyme A (HMG-CoA) reductase, which is likely due to the presence of flavonoid content in *I. cylindrica* [45]. Flavonoids content has hydrophobic characteristics that allow it to bind HMG-CoA reductase and cause decreasing its activity [46]. HMG-CoA reductase is one of the enzymes that play a role in the process of cholesterol synthesis [46]. The formation of cholesterol begins from the alteration of Acetyl - CoA to HMG-CoA, which provides HMG-CoA synthase. HMG-CoA then converts into mevalonate acid with the role of HMG-CoA reductase to form cholesterol [46]. Kwon *et al.* (2010) showed similar effects on the administration of flavonoid bud *R. damascena* through *in vivo* study. They found that giving flavonoid *R.damascena* significantly inhibited the activity of the HMG-CoA reductase enzyme [47]. Decreased activity of HMG-CoA reductase can suppress the process of cholesterol formation, thus causing a decrease in cholesterol synthesis [46]. Bao *et al.* (2016) demonstrated a related pathway using *in vivo* study with flavonoid *Lomagonium rotatum* administration. Their results demonstrated that administering the flavonoid *Lomagonium rotatum* significantly lowered the total cholesterol level compared to the controls [48]. Further, Halim *et al.* (2021) demonstrated a related pathway using *in vivo* study with flavonoid *Carica papaya Linn* administration. Their results demonstrated that administering the flavonoid of *Carica papaya Linn* significantly lowered total cholesterol levels compared to the controls [49].

Simultaneously, cholesterol and other lipid components are formed in the liver and then released into the blood circulation in VLDL form [2]. Afterward, VLDL activates lipoprotein lipase located in the capillaries causing VLDL triglyceride hydrolysis and reducing free fatty acids and glycerol. The remaining VLDL molecules will then be removed from circulation or undergo further transformation will become lipoprotein lipase forming LDL [2]. When cholesterol synthesis in the liver decrease, it leads to cause suppression in the cholesterol synthesis process. When VLDL formation is reduced, the LDL formation is also dropped. These processes lead to serum LDL levels decreased. Babandi *et al.* (2018) demonstrated a similar pathway using *in vivo* study with the administration of flavonoids taken from *Combretum micranthum*. They found a significant decrease in serum LDL level in all treatment groups after giving flavonoid *Combretum micranthum* for two weeks [50]. Further, Sun *et al.* (2021) demonstrated a related pathway using *in vivo* study with the administration of flavonoids taken from *Chrysanthemum*. They found a significant decrease in serum LDL level in all treatment groups after six weeks of flavonoid administration of *Chrysanthemum* [51].

In contrast, Robianto et al. (2019) research demonstrated that *Imperata cylindrica* significantly caused inadequate effects to lower total cholesterol. Their study was focused on the effects of *Imperata cylidrica* as a contraceptive and its effectiveness in lowering total cholesterol. They employed female mice aged 8-12 weeks in the estrus phase to evaluate the vaginal swab cytology [27]. In the estrus phase, the vaginal mucosa undergoes structural changes that are affected by an increase in sex hormones such as FSH (Follicular Stimulating

Hormone), LH (Lutheal hormone), progesterone, and estradiol [52,53]. These hormones cause effects by bonding with their respective receptors. The molecular mediators of estrogenic activity are alpha and beta estrogen receptors (ERα and ERβ) [54,55]. In addition, some non-steroidal plant bioactive such as polyphenols in particular flavonoids can recognize Erα and Erβ hormone receptors and have been considered as food phytoestrogens or endocrine disruptors [54]. At the same time, flavonoids can bind directly to Erα and Erβ [54,56]. The administration of flavonoids concomitantly with an increase in hormone sex such as estrogens lead to cause crosstalk between hormones and flavonoids. Subsequently, the flavonoid activity is inadequate.

However, some limitations still need to be noted in the current study. Future endeavors are valuable to evaluate each active compound of *I. cylindrica* and its role in reducing lipid levels. In addition, clinical trials are supposed to be established as requirements for using *I. cylindrica* in anti-hyperlipidemia treatment.

4. Conclusions

The eight studies of *Imperata cylindrica* we included in this paper reported beneficial effects on hyperlipidemia. However, the extent to which we can conclude the valuable effects of *I. cylindrica* as an anti-hyperlipidemic treatment is still restricted. The present study demonstrated that *I. cylindrica* caused the decrease in total levels of cholesterol, triglycerides, and LDL through *in vivo* studies and clinical trials. Further clinical studies are urgently required to provide adequate evidence on the application of *I. cylindrica* in medicine. Due to the limitations of current evidence, the need for better quality, either *in vivo* and randomized control trials (RCTs), to evaluate the efficacy of *I. cylindrica* is warranted.

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Conflicts of Interest

The authors declare no conflict of interest.

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