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Antihyperglycemic Effects of Gynura Procumbens: A Review of *In Vivo* Studies

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ABSTRACT

Background: Indonesia is the seventh country with the most diabetes mellitus (DM) patients worldwide. DM can increase the risk of other diseases, even death. Generally, people with diabetes need to take at least two antidiabetic drugs to control blood glucose. However, antidiabetic drugs cause many side effects for Type 2 DM (T2DM) patients. Herbal medicines are proposed to be an alternative because they are more natural, might have milder side effects, are easier to obtain, and are more affordable than conventional medicines. One of herbal plants with a potential for use as an antidiabetic drug is Gynura procumbens (Lour) Merr. (Compositae).

Aims: This study aims to summarize preclinical *in vivo* studies on the antihyperglycemic effects of G. procumbens and its possible underlying mechanisms.

Methods: Literature search was conducted from four electronic databases (PubMed, Scopus, ProQuest, Portal Garuda) up to 17 August 2023. We included *in vivo* experimental studies using hyperglycemic animal models to study the antihyperglycemic effects of G. procumbens. Methodological qualities were evaluated using the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES).

Results: A total of 11 studies were included in this review. Primary outcomes obtained from these studies showed that G. procumbens produced significant antihyperglycemic effects in diabetic animal models.

Discussion and Conclusion: G. procumbens controls blood glucose levels in T2DM animal models by increasing hepatic and peripheral glucose regulation. However, G. procumbens did not significantly increase insulin secretion. Further studies are needed to determine the best extraction method and the optimal dose of G. procumbens as an antihyperglycemic agent.

Keywords: Gynura Procumbens; Hyperglycemia; Type 2 Diabetes Mellitus

Abbreviations: DM: Diabetes Mellitus, WHO: World Health Organization, GP: Glutathione Peroxidase, SD: Superoxide Dismutase, STZ: Streptozotocin

Introduction

Diabetes mellitus (DM) prevalence is increasing all over the world. Based on data from the World Health Organization (WHO), 8.5% of the world's population aged 18 years and older were diagnosed with DM in 2014 [1]. Indonesia is ranked as the seventh country with the highest DM prevalence, with a total of 10.7 million cases in 2019 [2]. Uncontrolled DM could lead to various complications, even death. In 2019, DM was attributed to 1.5 million deaths [2]. Pharmacological therapy is often needed to prevent DM complications. While pharmacological therapy remains the primary choice, some medications can cause unwanted adverse effects [3]. Herbal treatments have been recently proposed as an alternative option for DM patients [4]. One of the herbal plants with a potential antidiabetic effect is Gynura

procumbens (Lour.) Merr. a herbal plant that grows in tropical Asian countries [5,6]. G. Procumbens has thick leaves and hardened stems with purple tint. G. Procumbens has been used to treat fever, skin rashes, infections from virus and ringworm [7]. G. procumbens has also been studied for its antihypertensive, anticancer, anti-inflammatory properties [8-10]. These properties are attributable by G. procumbens phenolic compounds such as quercetin, kaempferol, astragalin, chlorogenic acid, and rutin [11,12]. Present studies focused on G. Procumbens hypoglycemic effects using *in vivo* and in silico approaches [13-15]. Despite those promising results, its efficacy and mechanism of action need to be further elucidated to be evaluated in human. A comprehensive and systematic review of the existing literature is still lacking. It is important to evaluate available evidence to establish its efficacy, safety, and potential mechanism of G. procumbens for diabetic therapy. Therefore, this study aims to systematically summarize *in vivo* studies on the antihyperglycemic effect of G. procumbens and the potential mechanisms involved.

Methods

Search Strategy

Literature search was conducted on 17 August 2023 from four electronic databases (PubMed, Scopus, ProQuest, and Portal Garuda) with the following terms: (Gynura procumbens) AND ((hyperglycemic) OR (glucose) OR (Type 2 Diabetes Mellitus) OR (T2DM) OR (Diabetes Mellitus) OR (DM)).

Eligibility Criteria

We included *in vivo* experimental studies using hyperglycemic animal models. There were no restrictions in animal models, method of induction, administration method, dosage, and duration of treatment. We also included full-text studies written in English and Indonesian. Studies without appropriate control or primary outcomes were excluded.

Data Extraction

The following information was extracted: authors, publication year, animal species, types of hyperglycemic-inducing agents, diabetic condition criteria, dosages of G. procumbens, duration of treatment, and measurement outcomes. The primary outcomes were blood glucose levels. Secondary outcomes were HbA1c levels, plasma insulin levels, insulin sensitivity, and glucose tolerance.

Quality Assessment of Studies

The quality of included studies was evaluated using the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies (CAMARADES). Three potential judgments for risk of bias were determined for each trial, low risk, unclear risk, and high risk.

Results

Characteristics of the Included Studies

A total of 485 studies were identified from four electronic databases. An additional study was identified through a citation search. Duplicate records and studies that did not meet the inclusion criteria were excluded. The full texts of 30 articles were retrieved and assessed for eligibility. Eight articles were excluded due to different study design. four studies were excluded due to inappropriate control and outcome measures. Three article was retracted by its publisher. As a result, 15 *in vivo* studies were included in this review. Table summarizes the characteristics of the included studies [12-26] (Table 1). Animal models used in these studies were all rodents. Rats and mice were commonly used in animal studies for the safety and effectiveness of novel compounds [27]. Most studies used male Sprague-Dawley or Wistar rats, while one used C57BL/KsJ-db/db mice [18], two used Swiss albino mice [17,19] and one used Swiss-Webster strained Mus musculus [26]. The Indonesian Food and Drug Authority (BPOM/Indonesian FDA) guidelines for preclinical pharmacodynamic studies required a minimum of five samples in each group [28]. One study did not report the sample size in each group [18]. Except for four studies [14,16,23,25], five or more samples were included in each group. Animal models were either chemically induced or genetically diabetic. One study used C57BL/KsJ-db/db mice as db/db mice is a monogenic model of obesity-induced type 2 DM with mutations in the gene encoding hypothalamic leptin receptors, which causes leptin resistance [18].

Table 1: Characteristics of the included studies.

Author (year)	Part of plant	Animal model, diabetic induction	Diabetic state criteria	Extract type, Intervention doses (mg/kgBW)	Control (mg/kgBW)	Evaluation Duration	Results	Possible Mechanism	Class of compound	Compound
Jobaer [16]	Leaf	Wistar albino rats (n= 4-5 per group), Alloxan (150 mg/kg BW)	FBG ≥162 mg/dL	Methanolic (250 mg/kg BW)	Glibenclamid (5 mg/kg BW)	24 days	Methanolic extract and its various fractions exhibited statistically significant ($p < 0.001$) blood-glucose-lowering activity. Various fractions caused significant reductions in the blood glucose levels, of 52.82%-70.37% vs 63.24% (Control), with petroleum ether (PESF) being the highest.	NA	Phytols	Lupeol, stigmasterol, friedelanol acetate, β-amyrin, and a mixture of stigmasterol and β-sitosterol
Nath [17]	Leaf	Female Swiss albino mice (n=9 per group), Alloxan (150 mg/kg BW)	BG increase 3-4-fold	Ethanolic (0.5%, 1.0%)	Basal diet	21 days	Significantly ($P<0.05$) increased body weight during the second and the third week whereas decreased, feed intake and water intake of alloxan-induced diabetic mice. A significant reduction of cholesterol, triglycerides (TG), low density lipoproteins (LDL) while increased high density lipoproteins (HDL)	NA	NA	NA
Tahsin [13]	Leaf	Male Wistar rats (n = 10 per group), Alloxan (150 mg/kg BW)	BG ≥445 mg/dL	Ethanolic	Metformin (1.6-8 mg/kg BW)	42 days	In OGTT and anti-hyperglycemic tests, G.procumbens extract exert significant ($P < 0.05$) and highly significant ($P < 0.01$) hypoglycemic activity in a dose-dependent manner and its comparable to metformin. Safety: 50 times greater than that of the medium dose (750 mg/kg) of G. procumbens did not cause lethality in rodents whereas 100% rodents dies from 50-fold dose of metformin.	Increase insulin release	Flavonoids and phenols	NA
Guo [18]	NA	C57BL/KsJ-db/db mice	N/A	Ethanolic (3 g/kg BW)	Metformin (200 mg/kg BW)	5 weeks	Ameliorated insulin utilization rate of DM mice; reduced FBG; inhibited hepatic injury and steatosis.	Activating PI3K/Akt signalling pathway	Flavanoids, phenols	Quercetin, caffeic acid, kaempferol, sinapic acid and vanillic acid
Amin [19]	Leaf	Swiss albino mice (n= 8 per group), Alloxan (100 mg/kg BW)	BG ≥252 mg/dL	Ethanolic (100, 200 mg/kg BW)	Metformin (15 mg/kg BW) & Glibenclamide (15 mg/kg BW)	28 days	Aqueous extract significant lowers cholesterol, triglycerides (TG), HDL, LDL level, SGPT, SGOT, ALP and creatinine level. Ethanolic extract lowers LDL, SGOT, and creatinine level.	NA	Phenols	NA

Kamaruzaman [20]	Leaf	Male rats (n = 7 per group), STZ (50 mg/kg BW)	FBG ≥ 270 mg/dl	Aqueous (150, 300, 450 mg/kg BW)	Metformin (500 mg/kg BW)	14 days	Administration of 450 mg/kg GP showed a significant reduction of fasting blood glucose	NA	Flavonoids and phenols	Quercetin, rutin
Choi [21]	NA	Male ICR mice (n = 7 per group), STZ (60 mg/kg BW)	FBG ≥ 250 mg/dL	Aqueous (300 mg/kg BW)	Acarbose (100 mg/kg BW)	120 minutes	Lowered postprandial blood glucose.	Inhibiting α-glucosidase and α-amylase	Flavonoids	Catechin, kaempferol, myricetin, quercetin
Algariri [22]	Leaf	Sprague Dawley rats (n = 6 per group), STZ (55 mg/kg BW)	FBG ≥ 270 mg/dL	Ethanolic extract fractionated into ethyl acetate, n-butanol, and aqueous (500, 1000, 2000 mg/kg BW)	Metformin (500 mg/kg BW)	14 days	Reduced blood glucose and body weight in treatment groups with the highest effectivity in n-butanol fraction extract. No observed acute toxicity effects at a dose of 2000mg/kg BW	NA	Flavonoids, phenols	NA
Sunarwidhi [23]	Leaf	Male Wistar rats (n = 4 per group), Alloxan (150 mg/kg BW)	FBG ≥150 mg/dL	Ethanolic (150 mg/kg BW)	Glibenclamide (0.45 mg/kg BW)	15 days	Reduced preprandial and postprandial blood glucose. Mechanisms: morphology improvement of Langerhans islets and b cells	NA	Flavonoids	Quercetin
Algariri [24]	Leaf	Sprague Dawley rats (n = 6 per group), STZ (55 mg/kg BW)	FBG ≥270 mg/dL	Ethanolic (100 mg/kg BW of concentration 95%, 75%, 50%, 25%, 0%)	Metformin (500 mg/kg BW)	7 hours and 14 days	Reduced blood glucose with the most potent effect in 25% ethanolic extract.	Similar to metformin (inhibition of increased rates of hepatic gluconeogenesis and improvement of insulin sensitivity)	Flavonoids, phenols	Chlorogenic acid, rutin, astragalin and kaempferol-3-O rutinoside
Lee [25]	Leaf	Male Sprague Dawley rats (n= 4-5 per group), STZ (55 mg/kg BW)	FBG ≥234 mg/dL	Ethanolic and aqueous (50, 100, 150 mg/kg BW)	Glibenclamide (5 mg/kg BW), Metformin (500 mg/kg BW)	42 days	Significantly reduced FBG in diabetic rats treated with all doses of ethanolic extract and 50, 100 mg/kg BW of aqueous extract; reduced HbA1c; no significant changes in plasma insulin level.	Promoting glucose metabolism via glycolytic pathway and inhibiting hepatic endogenous glucose production via the gluconeogenic pathway	Flavonoids	NA

Sofia [26]	Leaf	Male *Swiss-Webster* strained *Mus musculus* (n=5 per group), Alloxan (130 mg/kg BW)	FBG ≥200 mg/dL	Ethanolic (100, 150, 200 mg/kg BW)	Glibenclamide (10 mg/kg BW)	7 days	Significant reduction in blood glucose in the intervention group of 150 and 200 mg/kg BW doses	Inhibiting α-glucosidase and α-amylase	Flavonoids	NA
Hassan [12]	Leaf	Male Sprague Dawley rats (n=5 per group), STZ (55 mg/kg BW)	FBG ≥270 mg/dL	Aqueous (500 and 1000 mg/kg BW)	Metformin (500 mg/kg BW)	14 days	Reduced FBG in the group receiving 1000 mg/kg BW extract and metformin; no changes in insulin level and glucose absorption; minimal effects on the viability of b-cells	Improved glucose tolerance in the treated group; increased glucose uptake by muscle tissues	Flavonoids	Rutin, quercetin, kaempferol, and kaempferol-3-O-rutinoside
Akowuah [15]	Leaf	Male Sprague Dawley rats (n=6 per group), STZ (55 mg/kg BW)	FBG ≥250 mg/dL	Methanolic extract fractionated in n-butanol (1 g/10 ml per kg BW)	Glibenclamide (0.025 mg/kg BW)	7 hours	N-butanol fraction shows a significant hypoglycemic effect in diabetic rats at hour 5 and hour 7 after the administration of the extracts	NA	Flavonoids	Quersetin, kaempferol
Zhang [14]	Leaf	Male Sprague Dawley rats (n=4-5 per group), STZ (60 mg/kg BW)	FBG ≥300 mg/dL	Ethanolic (50, 150, 300 mg/kg BW)	Metformin (500 mg/kg BW), Glibenclamide (5 mg/kg BW)	7 days	Decreased serum glucose in diabetic rats treated with 150 mg/kg BW of extract. No acute toxicity at dose 5g/kg BW	Biguanide-like activity	NA	NA

In most studies, Streptozotocin (STZ) [12,14,15,20–22,24,25] (50-60 mg/kg BW) was used, while newer studies tend to use Alloxan [13,16,17,19,23,26] (100-150 mg/kg BW) as chemical induction for diabetes, as these two agents induced damage to pancreatic islets' beta cells, resulting in insulin deficiency [29]. The Indonesian Food and Drug Authority (BPOM/Indonesian FDA) mentioned that normal blood glucose levels of rats and mice ranged from 62-175 mg/dL and 50-135 mg/dL, respectively, while blood glucose levels of 200-350 mg/dL were considered diabetic [28]. Except for two study [16,23], the diabetic state criteria used in these studies ranged from ≥200-300 mg/dL. Nath et al, define diabetic criteria as blood glucose increase of 3-4-fold [17]. One study diabetic state criterion is not stated. Almost all of the studies used G. procumbens leaf, except two studies did not mentioned what part of plant that they use. Ethanolic and aqueous extracts of G. procumbens were mostly used with ranging dosages (50-3000 mg/kg BW). Two studies used methanolic extract [15,17]. Nath et al, measure doses using basal diet percentage [17]. Some studies used multiple dosage regimens to assess the dose-dependent effect of extracts [12,14,15,19,20,22,24-26], and the remaining studies used single dosage regimens of extracts. Animal models were treated with G. procumbens extract for a duration ranging from seven hours to six weeks. Two articles studied the acute effects of G. procumbens on blood glucose levels [15, 24].

Glibenclamide (0.025-15 mg/kg BW) and metformin (1.6-500 mg/kg BW) were two antidiabetic medications mostly used as the reference standard to compare the effect of the extract, except for one study that used acarbose [21] and one other used basal diet [17]. Compounds examined in included studies are mostly flavonoids and phenols, while only one study investigating phytol's [16]. Despite that, only half of the studies mentioned its specific compound. Most compounds in G. procumbens are quercetin, kaempferol, rutin, kaempferol-3-O, stigmasterol, and β-sitosterol [12,15,16,18,20,21,23,24].

Quality of Studies

Figures 1 & 2 show the quality assessment of the included studies using the modified CAMARADES tool. Overall, risk of bias of all 15 studies was low. Only 1 study states their sample calculation method. Quality of assessment of included studies are presented in Figures 1 & 2. Only 1 study states their sample calculation method. One third of included studied displays randomization methods. All of the studies use appropriate animal model. Only four studies were not conducted in controlled environment. Most of studies are done according to an-

imal welfare regulation. All of the included studies were published in peer-reviewed publication. However, none of those studies reported blinded induction of hyperglycemia, and blinded outcomes assessment. Additionally, about half of the included studies did not state their conflict of interest.

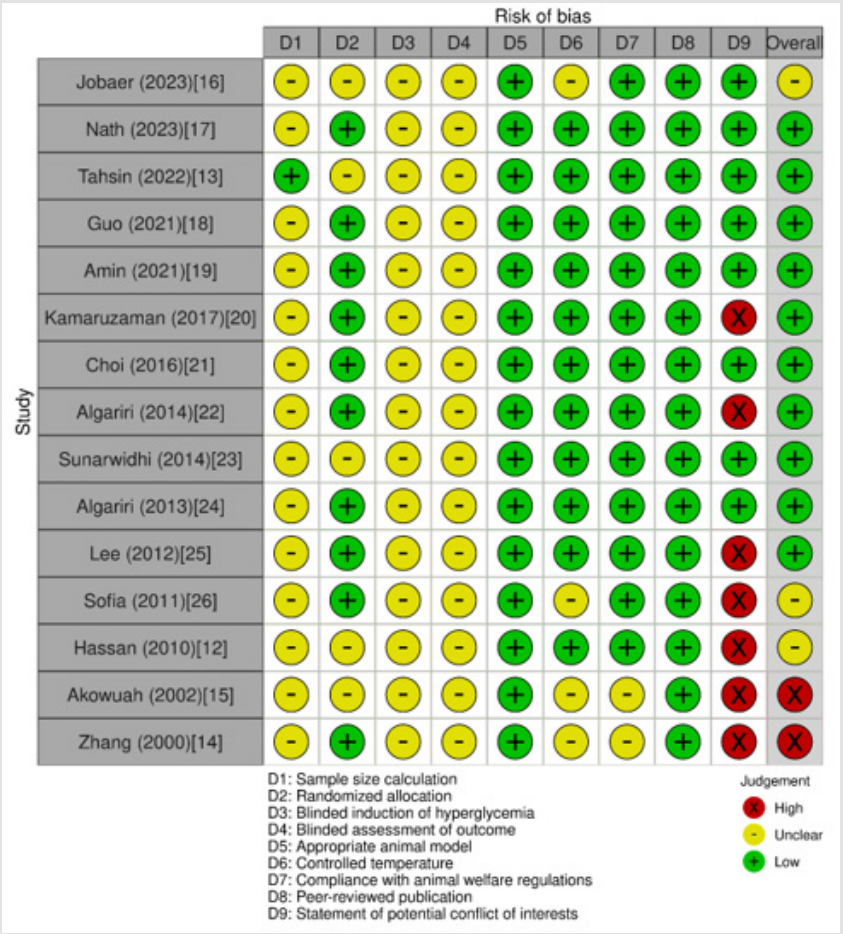

Figure 1: Risk of Bias Graph.

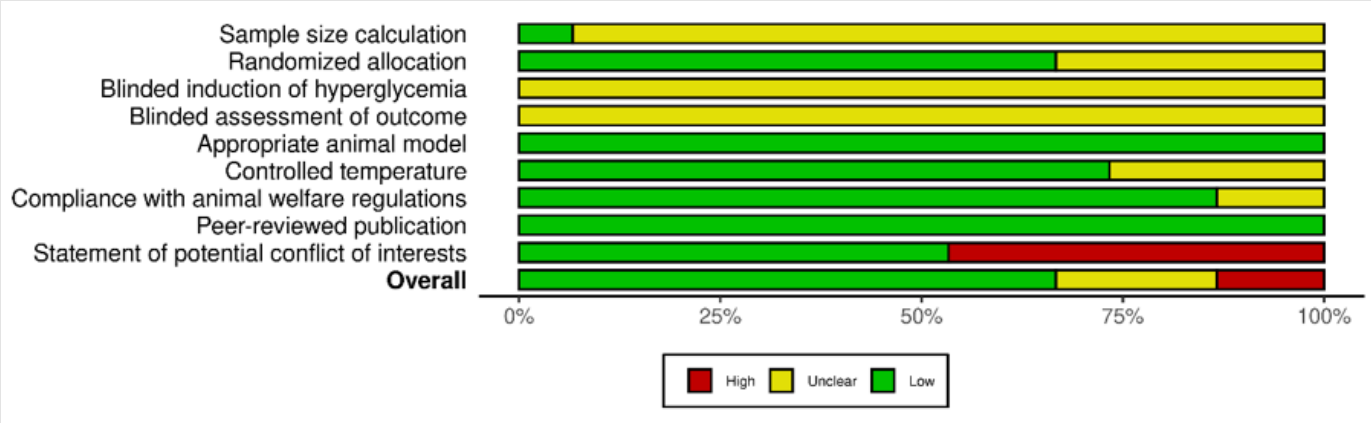

Figure 2: Summary of Risk of Bias.

Discussion

Of the 15 studies involved, all showed significant results from G. procumbens as an antidiabetic. These studies reported that administration of the leaf extract could reduce blood glucose levels in rats. In addition, reduction in cholesterol, TG, LDL, increased HDL were also reported by some studies. Quercetin is one of the most flavonoids found in G. procumbens. Quercetin works as an antioxidant that protects pancreatic beta cells from oxidative damage by inducing the activity of antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPX), and catalase. In addition, quercetin also works as an antidiabetic by inhibiting the activation of phosphoinositol-3-kinase (PI-3K/Akt), inhibiting the glucose transporter GLUT 2 in the intestine, and reducing lipid peroxidase [29]. Guo et al. also reported the involvement of G. procumbens in the PI3K/Akt signalling pathway in T2DM [18]. Quercetin, other flavonoids, and glycosides of flavonoids also potentially increased glucose uptake in muscle tissue in STZ-induced mice [25]. The study of Algariri et al. stated that flavonoids and phenol are bioactive components that commonly cause pharmacological effects in a herbal plant, especially with their antioxidant properties[24]. The flavonoid content in G. procumbens can also control postprandial glucose levels by influencing the hydrophobic and hydrophilic properties of the alpha-amylase and alpha-glucosidase enzymes [21]. Whereas, phenol can postpone diabetes complication which is glycation [30]. Both carbohydrate metabolism enzymes work to increase the absorption of glucose in the small intestine.

As a result of alpha-amylase and alpha-glucosidase inhibition, carbohydrate absorption is reduced, resulting in decreased postprandial glucose levels. [21,26,31-33] Phytols which is contained in in G. procumbens may also ameliorate insulin resistance and reduced insulin signal transduction caused by TNF-α [16]. Other antidiabetic mechanisms of G. procumbens include increasing the activity of glucokinase, pyruvate dehydrogenase, and phosphorylation of ATP-citrate, which play a role in glucose regulation. Research also found the role of G. procumbens in increasing the activity of fructose-1,6-bisphosphatase, phosphofructokinase, and hepatic hexokinase [34]. Increase of insulin secretion has also been proposed by Tahsin et al as a significant elevation in serum insulin level of rats were seen in treatment group [13]. However, research by Hassan et al. reported that the aqueous extract of G. procumbens did not stimulate insulin secretion [12]. The study concluded that the hypoglycemic effect of G. procumbens stems from increased hepatic or peripheral glucose utilization but not as an insulinotropic [12]. The solvents used for extracting G. procumbens leaves in this study were water, ethanol, and methanol, which are polar solvents. Research conducted by Lee et al. used ethanol and water to extract G. procumbens. This study found that ethanol has a more significant effect than aqueous extract on diabetes parameters, one of which is fasting blood glucose. This study also concluded that the ethanolic extract of the leaves had an antidiabetic effect equivalent to that of metformin [25].

This finding probably occurs due to the low solubility of flavonoids in water [24]. From these findings, the different solvents used in the studies could affect the antidiabetic properties of G. procumbens. Three studies by Zhang et al., Algariri et al., and Tahsin et al., observed the toxicity evaluation of the G. procumbens leaf extract were reported to be safe. In the study by Zhang et al., acute toxicity was evaluated in two groups of BALB/c mice, where one group was given the extract at a dose of 1 g/kg, and the other group was given 5 g/kg. Both groups showed no signs of toxicity, such as restlessness, respiratory distress, seizures, or coma, and remained alive for seven days. There was also no alteration of P450 enzymes; hence it is unlikely to have pharmacokinetic interaction with other medicines [14]. The study of Algariri et al. assessed the acute and sub-chronic toxicity of the ethanolic extract of the leaves of G. procumbens in female rats. At a maximum dose of 2,000 mg/kg, no signs of toxicity were found after 14 days of observation. Extracts can be declared safe based on these tests because the LD50 exceeds 2000 mg/kg. There were also no signs of illness in the mice involved in the subacute test for 28 days, and all mice lived until the end of the observation period. The assessments were animal growth rate, liver function examination, kidney profile, and hematological analysis [22]. Tahsin et al. reported, 50 times greater than that of the medium dose (750 mg/kg) of G. procumbens did not cause lethality whereas all of rodents dies from 50-fold dose of metformin [13].

This systematic review reinforces the initiation of clinical trials. The included studies used a similar animal model, and almost all studies conform to the DM criteria set by BPOM. Moreover, this paper only involves studies with defined control which ensures the validity and reliability. However, this systematic review has several limitations. First, different range of doses, solvents, and duration of the study, which could affect the significance of the results. In addition, more results could be obtained from other Asian countries as our search strategy only included articles with English and Indonesian language.

Conclusion

In conclusion, based on our systematic review, G. procumbens leaf extract has sufficient evidence of efficacy and safety as an antihyperglycemic agent in animal research by increasing hepatic and peripheral glucose regulation and promoting insulin release. Further clinical trials on human subjects are needed to determine its efficacy, safety, and dosage of G. procumbens extract as an antidiabetic.

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Conflict of Interest

The authors declare no conflict of interest.

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