The effectivities of anti-diabetic of *Chromolaena odorata* L. in lowering blood sugar level: A systematic review

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Abstract. Diabetes has become a significant problem that has reached an alarming level. Nowadays, almost one billion people around the world live with diabetes. In 2019, Indonesia occupied the seventh position in the world with 10.7 million people live with diabetes. Although various antihyperglycemic agents are available, diabetes is still a significant problem in the world. Asiam weed (*Chromolaena odorata* L.) is widely used in Indonesia and traditional medicine to treat diabetes. This study aimed to determine the phytochemical content of *C. odorata* extract and analyze the effectiveness of the anti-diabetic of *C. odorata* extract in lowering blood sugar levels. The method used in this study is a systematic review with journals derived from the online databases of PubMed and Google Scholar. The journals used are journals that discuss *C. odorata*, extract, anti-diabetic, and blood sugar. Journal search results show, eight studies explain the potential anti-diabetic activity of *C. odorata* extract in lowering blood sugar levels. Data synthesis from several studies shows that *C. odorata* extract has potential anti-diabetic activity because it contains phytochemicals in the form of alkaloids, flavonoids, phenols, saponins, and tannins which are potent antioxidants and cytoprotectants that can lower blood sugar levels.

1. Introduction

Diabetes is a condition in which insulin cannot be produced in sufficient quantities, or the use of endogenous insulin is not good, resulting in high blood glucose levels [1]. Diabetes itself has become a significant problem that has reached an alarming level. Indonesia in 2019 was in the 7th position in the world, with 10.7 million people suffering from diabetes [2]. The report on the Basic Health Research (2018) shows that based on doctors' diagnoses, there was an increase in the prevalence of 2% from 2013 to 2018 in individuals aged 15 years [3]. Although various antihyperglycemic agents are available, diabetes is still a significant problem globally, so many medicinal plants or bioactive constituents are used as diabetes drugs [4]. Medicinal plants were chosen considering their advantages are easy to obtain, low toxicity, fewer side effects, and low price [5,6]. One of the medicinal plants that act as an antihyperglycemic, namely the kirinyuh plant, many studies has been carried out on the anti-diabetic potential contained in kirinyuh leaf extract [7].

Kirinyuh (*Chromolaena odorata* L.) is a weed that is widely used in Indonesia [8]. Several regions in Indonesia recognize kirinyuh leaf as a traditional medicine to treat diabetes [7]. The results of identifying the phytochemical components of kirinyuh leaves indicate the presence of flavonoids and phenolic acids known as potent antioxidants that can prevent oxidative damage [9]. Antioxidant activity can prevent free radicals, which are the etiology of various degenerative diseases such as diabetes [10]. Many studies on the anti-diabetic activity of kirinyuh plant extracts have been carried out and have shown potential in lowering blood sugar levels [11, 12]. Although many studies have been carried out, it is still necessary to conduct a literature review to make it easier to obtain more systematic information about the kirinyuh plant extract (*C. odorata* L.) in lowering blood sugar levels in people with diabetes. Writing this systematic review can improve understanding and provide conclusions on existing research results so that it becomes more comprehensive to be applied [13].

2. Methodology

The research design used in this study is the systematic review method. A systematic review is a detailed and comprehensive search strategy and plans to reduce bias by identifying, assessing, and
synthesizing all relevant studies [14]. PRISMA-P 2015 was used to determine the journal to be used [15]. Literature searches were carried out from the PubMed and Google Scholar search engines. Search journals using the PICO (Population, Intervention, Comparison, Outcome) method through the PubMed search engine. Meanwhile, from Google Scholar, researchers used the keywords "diabetes OR diabetes mellitus OR hyperglycemia AND Chromolaena OR Chromolaena odorata OR siam weed AND low blood sugar" and "diabetes OR diabetes mellitus OR hyperglycemia AND Chromolaena odorata AND decreased blood sugar levels."

3. Results

Journal results obtained from Google Scholar were 238 journals, and through PubMed, four journals were obtained. After being assessed by PRISMA, eight journals met the inclusion criteria (Table 1), and then data extraction and synthesis were carried out. Assessment of the quality of the literature using the JBI Critical Appraisal Checklist for Quasi-Experimental Studies (Non-Randomized Experimental Studies) criteria resulted in eight kinds of literature in the excellent category, and then data extraction was carried out. The journals used in this study are: Onkaramurthy et al. (2012), Wunu, Beama dan Rame (2019), Yudistira, Lidia dan Manafe (2018), Omonije, Saidu dan Muhammad (2020), Abdullahi, A. et al. (2020), Adedapo et al. (2016), Yusuf, et al.(2020), and Idoko et al. (2018).

4. Discussion

4.1 Phytochemical content of C. odorata extract

Research on kirinyuh (C. odorata) plant extracts is increasing due to many studies on the role of natural ingredients in the treatment and clinical planning of diseases related to oxidative stress and tropical diseases [16]. Omonije, Saidu, and Muhammad reported identifying that the tannins, saponins, alkaloids, flavonoids, phenols, glycosides, and steroids are the content of the phytochemical composition of the root extract. Tannins in the roots of C. odorata contained 54.76±4.08 mg/100g, 322.78±17.35 mg/100 g saponins, 74.34±6.08 mg/100 g alkaloids, 79.63±4.55 mg/100 g flavonoids, and phenols 154.32±11.21 mg/100g [16]. Based on Agaba, Fawole, and Claudius-Cole identification, C. odorata leaves contain 41 mg/g tannins, 331.7 mg/g saponins, 12.2 mg/g alkaloids, and 7.7 mg/g flavonoids, and 38.6 mg/g phenol. The Phytochemical saponins have the highest concentration in both leaves and roots [17]. Bamisaye et al. identified C. odorata plants containing high phenol content with 0.076% in leaves and 0.091% in roots [18]. The quantitative analysis of phytochemical components conducted by Melinda et al. showed that C. odorata had a high total phenol component of 455.55±4.59 g/mg GAE [19]. In addition, the antioxidant capacity of C. odorata also showed a flavonoid content of 62.83±0.30 mg/mL CE [21]. The number of flavonoids in plant extracts can show a direct correlation to antioxidant activity [20]. This was confirmed by the presence of FRAP activity of 1.297 ± 0.06 [19]. This test is an essential indicator in seeing the potential for antioxidant activity by looking at the ability of a component to convert Fe3+ into Fe2+ [21]. In addition, Omokhua reported that based on the results of qualitative analysis of phytochemical components in C. odorata plants contained phenols, flavonoids, saponins, and tannins in both biotypes, namely Asian/West African Biotype and Southern African Biotype [22].

There are variations in the phytochemical composition of the kirinyuh plant extract depending on the sampling season, where the plant grows, and the polarity of the solvent used [23]. Extraction is the process of withdrawing the dissolved chemical content to separate it from the insoluble material using a liquid solvent [24]. Extraction is generally carried out using a solvent based on its solubility with other components in the mixture, such as water and other organic solvents [25]. Solvents can affect the extraction because chemical compounds will easily dissolve with solvents with the same polarity [26]. Compounds such as flavonoids have different polarities depending on the hydroxyl group [27]. Septiana and Asnani reported that ethanol solvent has a polarity similar to flavonoids, so that it is effective in dissolving and producing higher flavonoid compounds than water, methanol, and acetone at the same concentration.

4.2 Role of compounds in C. odorata extract

The previous studies reported that C. odorata leaf extract has active components that act as antioxidants and cytoprotective [29]. The antioxidant activity in the leaf extract of C. odorata can fight
free radicals induced by alloxan to prevent damage to pancreatic cells. In addition, the extract of *C. odorata* can encourage the repair of pancreatic cells so that there is an increase in insulin secretion and a decrease in blood sugar levels [7]. The antioxidant activity of the *C. odorata* extract was determined by two in vitro methods, [30]. The resulting extract showed DPPH radical activity with an IC50 value of 191.68±1.68 g/mL (IC50 of ascorbic acid 45.89±0.78 g/mL) [16].

Flavonoids have been identified as excellent aldose reductase inhibitors [30]. The flavonol class in the flavonoid content of *C. odorata* is quercetin which has anti-diabetic activity [31]. Increased insulin secretion is carried out by reducing apoptosis, pancreatic cell proliferation, decreasing insulin resistance, supporting GLUT4 translocation through the PI3K/AKT and AMPK pathways, and preventing inflammation and oxidative stress in muscles [16]. In type 2 diabetes, GLUT4 expression is severely impaired and contributes significantly to the pathophysiology of insulin resistance due to defects in GLUT4 translocation intracellular signaling due to disturbances in peripheral cells [32]. The ability of flavonoids to lower blood glucose levels is also associated with upregulation of hepatic superoxide dismutase activity, downregulation of hepatic malondialdehyde, decreased expression of CYP2E1, and increased glucose transporter 4 (GLUT4) in skeletal muscle [33]. In addition, flavonoids also increase adipocyte GLUT4 activity, reduce GLUT2 expression and increase hepatic/adiposity peroxisome proliferator-activated receptor gamma (PPARγ) expression [34]. Flavonoids in inhibiting inflammation and tissue damage bind free radicals using their phenolic OH groups so that they can neutralize free radicals (such as ROS) [35]. Flavonoids are also known to reduce lipid peroxidation by inhibiting cell necrosis and increasing vascularity [36]. Increased vascularity can prevent cell damage and increase cell regeneration [7].

Alkaloids in *C. odorata* can lower blood sugar by inhibiting glucose absorption from the intestine, increasing glucose transport into the bloodstream, stimulating glycolysis, and preventing the synthesis of glucose 6-phosphate dehydrogenase plays a role in gluconeogenesis [37]. This can prevent the formation of glucose from sources other than carbohydrates [37]. Jung et al. reported that the alkaloids could inhibit glucosidase activity [34]. Alkaloids also work by stimulating the hypothalamus to secrete growth hormone-releasing hormone (GnRH), increasing pituitary growth hormone secretion [38]. High growth hormone levels can encourage the liver to secrete insulin-like growth factors (IGF-1) [38]. IGF-1 plays a role in reducing gluconeogenesis so that insulin requirements and blood glucose levels decrease [38]. In addition, alkaloids also inhibit the protein tyrosine phosphatase PTP-1B, which causes downregulation in insulin signaling pathways [39]. Alkaloids can also increase glucose uptake in -TC6 and C2C12 cells, acting as insulin sensitizers in in managing type 2 diabetes and suggesting antioxidant potential by reducing H2O2-induced oxidative damage in -TC6 cells [18]. In addition, the alkaloids were also able to stimulate basal glucose uptake in adipocytes and inhibit glycogen phosphorylase [18].

Saponins are the phytochemical components detected in the root extract of *C. odorata* in large quantities, which have a hypoglycemic effect that can help regulate plasma glucose levels and prevent diabetic complications [40]. Saponin bioactivity in treating diabetes is associated with increased adipisin, GLUT4, and PPARγ genes and reduced expression of G6Pase and FABP4, and also inhibit the action of the -glucosidase enzyme so that carbohydrates are not immediately converted into glucose and inhibited the absorption of sugar in the small intestine, and can affect the composition of cell membranes by reducing the absorption of molecules disrupting glucose transporters [41]. Saponins also increase insulin secretion in pancreatic cells and reduce blood sugar levels [42].

Tannins can lower blood glucose levels by increasing glycogenesis [38]. The astringent effect of tannins works by forming a protein coat on the mucous membrane surrounding the intestine and inhibiting glucose absorption [41]. Tannins have a cytoprotective mechanism by the ability of these molecules to complex in the walls of the digestive tract because of cannot be absorbed [43]. However, other derived constituents can be absorbed by degrading monomers by microflora [44]. In addition, tannins also have a substantial proliferative effect on cells that supports cytoprotective activity [45]. Cell protection is also provided by inhibiting the cell cycle, increasing cell viability, and apoptosis- reducing ROS levels [46].

Furthermore, phenol supports physiological benefits such as antioxidant, anti-tumor, and anti-diabetic effects [47]. The anti-diabetic effect of polyphenols works by regulating insulin secretion, inhibiting glucosidase and increasing antioxidant activity [48]. Steroids can stimulate insulin secretion in pancreatic cells, so help lower blood sugar levels [49].
4.3 The Effect of C. odorata extract in anti-diabetic

The study of Onkaramurthy et al. showed in lowering blood sugar levels in Wistar rats after 6 hours of administration of ACO 200 mg/kg BW [4]. Yusuf et al. also reported a significant decrease in blood sugar levels in Wistar rats on the 3rd and sixth days after being given 400 mg/kg BW of C. odorata extract daily [50]. In animals being tested, it is necessary to standardize and validate the diabetic state. It is essential to know that the tested animal has type I or type II diabetes or both [51]. Streptozotocin is well known for causing functional defects in pancreatic cells [52]. Streptozotocin also causes an increase in blood sugar because it can damage the cells in the islets of Langerhans [53]. The decrease in blood sugar levels is believed because previous studies have shown that C. odorata extract has a hypoglycemic effect [54]. The content of phenols, alkaloids, tannins, flavonoids, and saponins in the leaf extract of C. odorata was reported to lower blood sugar levels by stimulating insulin production in the islets' cells Langerhans [55]. C. odorata is also reported to have 11 flavonoid components with antioxidant and anti-inflammatory activities [56]. In addition, C. odorata has hypoglycemic activities such as promoting insulin secretion, reducing glucose production from within, decreasing glucose absorption in the intestine, and regenerating pancreatic cells [57]. So that one of the mechanisms is to increase insulin secretion and increase the regeneration of pancreatic cells [50].

Abdullahi et al. showed that female white rats were given 300 mg/kg BW of C. odorata powder orally per day experienced a significant decrease in blood sugar levels on days 7, 14, and 21, where the activity was dose-dependent [58]. In pre-clinical and clinical studies, phytochemical components such as alkaloids, flavonoids, terpenoids, and glycosides were found to be effective as anti-diabetic drugs [59].

The study by Adedapo et al. showed a significant decrease in blood sugar levels in male albino rats treated by C. odorata leaf extract during pre-treatment and post-treatment, which was dose-dependent [54]. This study also showed that C. odorata leaf preparations contain tannins, saponins, flavonoids, and anthraquinones that have medicinal effects [54]. The hypoglycemic effect achieved can be caused by glucose uptake in the periphery, an increase in insulin secretion, inhibition of glucose absorption in the intestine, inhibition of endogenous glucose production, and regeneration of cells Langerhans [54]. Tannins have anti-diabetic effects by inhibiting the activity of amylase and glucosidase [60]. Flavonoids are also reported to be potent glucosidase inhibitors [61].

Saponins are also reported to lower serum insulin levels in diabetic patients and fasting blood sugar levels [62]. Saponins can be classified as hypoglycemic agents because they have activity in lowering serum cholesterol [63]. The use of C. odorata leaves in the study conducted by Adedapo et al. showed the content of substances capable of providing a hypoglycemic effect and, in low doses, capable of being a potential agent in treating diabetes mellitus [54]. Idoko et al. [64] reported that white Wistar rats were given C. odorata leaf extract showed a significant decrease in blood sugar levels. Yusuf et al. study [50] showed the number of doses taken on the anti-diabetic effect produced. In addition, the decrease in blood glucose that occurs may also be due to the content of magnesium (Mg) and manganese (Mn), which function as cofactors for the enzymes glucokinase, glyceral kinase, and glucose 6-phosphate [65]. Magnesium (Mg2+) is a cofactor required in the glycolysis of glucose [66]. Diabetic states also occur when alloxan injected in mice produces ROS that causes pancreatic cell damage [67]. ROS are formed because glucose is oxidized after binding to glycated proteins. The combination of protein and oxidized glucose can form AGEs (advanced glycogen end-products) can cause tissue damage [67]. Anti-diabetic potential in plants with astringent abilities can reduce blood sugar levels by forming a protective layer in the intestines, inhibiting glucose absorption [68]. C. odorata has phytochemical components such as flavonoids, saponins, alkaloids, steroids, and tannins [69]. However, the anti-diabetic mechanism of C. odorata plant extract is still unknown, with antioxidant activity on C. odorata being a hypothesis that supports its anti-diabetic ability [12]. Studies by Vaisakh and Pandey reported that C. odorata has active components that act as antioxidants and cytoprotective [29]. The root extract of C. odorata contains flavonoid constituents, saponins, and tannins, which may have hypoglycemic activity. The role of antioxidants is known to control blood sugar levels and prevent diabetes complications [40].

It was found that the phenol content (154±11.21 mg/100 g) in the extract of C. odorata was higher than the results of the study reported by Agaba et al. [17] but lower than the level (397.48±3.07 mg/100 g) as previously reported for the leaf extract of Vernonia amygdalina (Asteraceae) [70]. The anti-
diabetic effect of polyphenols is carried out by regulating insulin secretion by increasing antioxidants and inhibiting glucoamylase [70]. Flavonoids are reported to have anti-diabetic properties by modulating blood glucose transport, namely by increasing insulin secretion, inhibiting apoptosis, promoting pancreatic cell proliferation, and reducing insulin resistance [70]. Flavonoids also promote GLUT4 translocation by P3K/AKT and AMPK pathways inhibits inflammation and oxidative stress in muscle [16]. The IC50 value is related to the oxidant activity of plant extracts so that in this study, it can be concluded that C. odorata extract can reduce free radicals [16].

5. Conclusion
The plant extract of C. odorata has five main phytochemical components in the form of saponins, flavonoids, phenols, tannins, and alkaloids, which can be anti-diabetic by lowering blood sugar levels in experimental animals by influencing various mechanisms. Although saponins are the most common secondary metabolites found in this plant, flavonoids are thought to be the most influential bioactive components as anti-diabetics. The potential of this antidiabetic activity is not only due to its antioxidant effect that can increase insulin sensitivity and secretion, it also inhibits the formation of ROS in C. odorata plant extracts, but also as an anti-inflammatory. There are also other components, such as astringents, that play a cytoprotective role. Further research is needed on the extract fraction of the kirinyuh plant (C. odorata) to find out more about the main constituents/metabolites that have anti-diabetic activity.

Conflict of Interest
There are no conflicts of interest in this article

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