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The Impact of Sambiloto Extract (*Andrographis paniculata*) as a Potential Antidiabetic Treatment

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ABSTRACT

Diabetes mellitus (DM) is a metabolic disease caused by an inappropriate increase in blood glucose levels. The development of traditional medicines, including extracts, fractions, and isolates from plants, remains highly intriguing and challenging. Andrographis paniculata is a one of medicinal plants with a long history of use in Asia for the treatment of various ailments. Andrographolide, a bioactive compound found in A. paniculata, has been extensively studied for its medicinal benefits, specifically its antidiabetic effects. This study employs a literature review approach to investigate the effect of Sambiloto extract (Andrographis paniculata) as an antidiabetic medication using Google Scholar, Science Direct, and PubMed databases. The publication year range for the literature data sources is from 2020 to 2024. Based on the conducted searches, three reference journals are included in this study. Andrographolide, the active compound contained in Sambiloto, may act as an antidiabetic medication through various mechanisms, thus representing a potential treatment for diabetes mellitus.

1. Introduction

Non-communicable diseases (NCDs) present a substantial challenge to global health, affecting both developed and developing nations. They account for a substantial proportion of deaths worldwide, with the leading cause of cancer, cardiovascular diseases, chronic respiratory diseases, and diabetes. NCDs are also responsible for a large percentage of premature deaths occurring between the ages of 30 and 69. In Indonesia, NCDs are the primary cause of mortality, accounting for 73% of deaths in 2016. The prevalence of NCDs in Indonesia, including diabetes mellitus, heart disease, dyslipidemia, obesity, lung disease, cancer, and kidney disease, is largely attributed to environmental changes, technological advancements, and lifestyle factors.[1]

Diabetes mellitus (DM) is a metabolic disease characterized by elevated levels of glucose in the bloodstream. There are several types of DM, namely Type 1, Type 2, Gestational Diabetes, Neonatal Diabetes, Maturity-Onset Diabetes of the Young (MODY), and secondary diabetes linked with endocrine problems or steroid usage. The primary subtypes namely 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM). T1DM generally affects younger individuals and is caused by insulin secretion disorders, while T2DM, commonly affecting middle-aged and elderly adults, arises from insulin action disorders. Lifestyle factors, dietary habits, and persistent hyperglycemia contribute to the development of T2DM.[2] In 2017, approximately 462 million people received a diagnosis of T2DM, which accounted for 6.28% of the total population. The International Diabetes Federation (IDF) reported that in 2017, as many as 425 million persons between the ages of 20 and 79 had diabetes. Out of these cases, 7 million remained undiagnosed. Projections indicate a potential increase of 200 million people affected by

2040 due to aging, lifestyle changes, and rising obesity rates. Approximately 25% of individuals over the age of 65 are estimated to have diabetes mellitus (DM).[3] In 2019, the IDF reported 6.2% national prevalence of diabetes mellitus (DM) in Indonesia and subsequently raised to 10.8% in 2021. This alarming trend places Indonesia among the top 10 countries with the highest prevalence of DM, while also indicating the most substantial increase. Furthermore, the 2018 Indonesian Basic Health Survey (RISKESDAS) revealed that 10.9% of the population aged 15 and above are affected by type 2 DM. Notably, a substantial proportion of DM patients experience acute or chronic complications, specifically microvascular and macrovascular issues linked to high blood sugar levels, resulting in life-threatening conditions including cardiac failure, coronary artery disease and chronic kidney disease. Considering its substantial effect on quality of life and the associated financial burden, diabetes stands as a critical chronic disease that demands effective management and treatment.[4]

Type 2 diabetes mellitus (T2DM), or non-insulin dependent diabetes mellitus (NIDDM), accounts for around 90-95% of all occurrences of diabetes. This type of diabetes is characterized by two primary abnormalities associated with insulin: insulin resistance and β-cell malfunction. Insulin resistance occurs when there is a failure in several cellular pathways, resulting in a reduced response or sensitivity of cells in peripheral tissues. For instance, the sensitivity of cells such as those in liver, muscle, and adipose tissue to insulin decreases. In the beginning, the body compensate the reduced insulin sensitivity through requiring hyperactivity of the β-cells function in order to maintain normal blood sugar levels. Nevertheless, the increased production of insulin by these β-cells eventually becomes inadequate to counterbalance the reduced insulin levels, and accompanied by β-cell dysfunction, ultimately resulting in insulin deficiency and progression into diabetes mellitus.[5]

In managing type 2 diabetes mellitus (T2DM), lifestyle interventions (nutrition and physical activity), oral antidiabetic medications (biguanides, sulfonylureas, and α-glucosidase inhibitors), injectable medications (such as "insulin and glucagon-like peptide-1 agonists [GLP-1])", surgical treatment, complementary and alternative therapies are generally employed.[6] The exploration and development of traditional medicines, including extracts, fractions, and isolates from plants, remain of great interest and pose significant challenges. *Andrographis paniculata*, a medicinal plant with an extensive cultural history in Asia, has been utilized to address various health conditions.[7]

Andrographis paniculata (Burm.f.) Nees, belonging to the Acanthaceae family, holds a prominent position in traditional Asian medicine. Originated from India and Sri Lanka, it is now extensively farmed across Southeast Asia. This medicinal plant has been utilized for centuries in various traditional systems to combat infectious diseases, fevers, and liver and stomach ailments. Its reputation extends to its detoxifying, carminative, and tonic properties. Numerous scientific studies have shed light on the diverse pharmacological activities of *Andrographis paniculata*. These include anticancer, anti-HIV, anti-inflammatory, immuno-modulatory, antibacterial, anti-spasmodic, antipyretic anticarcinogenic, antidiabetic, anti-infective, antioxidant and hepatoprotective effect.[8]

Andrographis paniculata contains lactones, flavonoids, aldehydes, diterpenes, alkenes, ketones, and other bioactive chemicals. Andrographolide, which is also referred to as kalmegh, neo-andrographolide, dioxyandrographolide as well as dihydroandrographolide, is mostly present in plant's leaves and is responsible for its bitter flavor. The plant's leaves and stems include gums, flavonoids, tannin and mucilage. The therapeutic efficacy of these chemical compounds depends on their presence and function in the human body. High-pressure chromatography is a suitable method for identifying and establishing the standard composition of the primary active components found in *A. paniculata*. The leaves have the maximum concentration (2.39% w/w) of andrographolide, whereas the seeds have the lowest concentration.[9]

Andrographolide, a bioactive compound present in *A. paniculata*, has been extensively researched for its medicinal benefits. It has been found to have antiviral, antimicrobial, antitumor, anti-inflammatory, antioxidant, cardioprotective, neuroprotective and hepatoprotective activities. Other bioactive compounds found in Kalmegh are neo-andrographolide, deoxyandrographolide, andrographin andrograpanin and andrographiside. Moreover, the medicinal benefits of this substance are enhanced by the presence of flavonoids such as quercetin, kaempferol, and apigenin.[9] Andrographolide is the main diterpenoid found in the leaves of the species. Additionally, other related diterpenoids such as 14-deoxy-11,12-didehydroandrographolide, deoxy andrographolide, isoandrographolide and neoandrographolide and have been isolated from the leaves in various amounts. Several andrographolide analogs have been chemically produced and discovered to exhibit strong anticancer characteristics, as well as the ability to block glucosidase.[10]

A study by Nugroho et al. (2013) found that an extract of *A. paniculata* containing andrographolide was able to reduce blood glucose levels and increase the number of pancreatic beta cells in diabetic rats induced by streptozocin. Andrographolide was found

to be effective in improving insulin sensitivity through increasing the absorption of glucose, activating the insulin signaling pathway, and preventing the activation of nuclear factor kappa-B (NF-KB) signaling caused by. tumor.necrosis factor-alpha (TNF-a) in.3T3-L1 cells. Moreover, it has been discovered that andrographolide inhibits the expression of PPARy in the early stages of differentiation, thereby impeding the differentiation of 3T3-L1 cells into mature adipocytes. Consequently, it holds promise as a potential therapeutic agent for the management of obesity and diabetes. Additionally, a recent study found that a combination of *A. paniculata* and *Centella asiatica* herbal extracts successfully enhanced the expression of PPARy and GLUT-4 genes in insulin-resistant 3T3-L1 adipocytes. [11]

2. Methods

The methodology utilized in this study involves conducting a thorough literature review to evaluate the effectiveness of sambiloto extract (*Andrographis paniculata*) as an antidiabetic agent. Reference article searches were conducted utilizing reputable databases such as Google Scholar, ScienceDirect, and PubMed, with a publication date range restricted from 2020 to 2024. The inclusion criteria encompassed Indonesian-language journals published within the past five years (2020-2024) and encompassing quantitative research studies, meta-analyses, experiments, and journals explicitly discussing the effects of sambiloto extract as an antidiabetic agent. Exclusion criteria included journals that merely discussed sambiloto's effects but also involved diseases other than diabetes, systematic reviews, and journals lacking full text availability. Articles were retrieved using the keywords SAMBILOTO" AND/OR "*Andrographis paniculata*" AND/OR "Andrographolide" AND/OR "DIABETES". Data analysis was conducted descriptively based on the effects of sambiloto extract as an antidiabetic agent. Consequently, three reference journals were deemed relevant and included in this study.

3. Results

This study aimed to examine the efficacy of sambiloto extract (Andrographis paniculata) as a potential antidiabetic agent. After a thorough literature review, three pertinent journals were identified and their findings are summarized in Table 1.

Table 1. Articles on the effects of sambiloto extract (*Andrographis paniculata*) as an antidiabetic agent

Article Code	Author, Year of The Article	Article Tittle	Research Findings
A-1[12]	"R. Hidayat, P. Wulandari, 2022	"Effect of *Andrographis paniculata* on Blood Sugar Levels Through Regulation of Alpha-Glucosidase Enzyme Expression: An In Vivo Study."	• Table 1 illustrates the efficacy of AP extract in reducing blood glucose levels. Groups P1, P2, and P3 exhibited a superior ability to lower blood sugar levels compared to group K1, which served as the untreated control. Treatment groups P1 and P2 demonstrated a less optimal reduction in blood sugar levels compared to K2, which received acarbose treatment. Notably, group P3 achieved a more optimal reduction in blood sugar levels compared to group K2, which received acarbose treatment. The data suggests a positive correlation between the dosage of AP extract and its effectiveness in lowering blood sugar levels. • Table 2 illustrates the potential of AP extract in diminishing alpha-glucosidase enzyme activity. Groups P1, P2, and P3 exhibit a greater capacity to reduce alpha-glucosidase enzyme activity compared to the untreated group K1. Treatment groups P1 and P2 demonstrated a less optimal reduction in alpha-glucosidase enzyme activity compared to K2, which received acarbose treatment. Notably, group P3 exhibited a more optimal reduction in alpha-glucosidase enzyme activity compared to K2, which received acarbose treatment. It is evident that a higher dosage of AP extract corresponds to an enhanced ability to reduce alpha-glucosidase enzyme activity. • Our research findings suggest that the extract derived from *Andrographis paniculata* possesses the ability to effectively reduce blood sugar levels. This effect is achieved through the inhibition of alpha-glucosidase enzyme activity within

			the intestinal tract of rats.
A-2[13]	"N. Azizah, N. Syamsi, C.R. Nayoan, A.A Muthmainnah Tanra, 2022"	"*Uji Efektivitas Ekstrak Herbal Daun Sambiloto (Andrographis panicula) Terhadap Kadar Gula Darah pada Tikus Putih (Rattus Norvegicus) Jantan yang di Induksi Aloksan*."	• Administration of sambiloto leaf extract (*Andrographis paniculata*) at doses of 100 mg/kgBW, 200 mg/kgBW, and 400 mg/kgBW has been demonstrated to possess anti-diabetic properties in male white rats (Rattus norvegicus) induced with alloxan. Notably, the 400 mg/kgBW dosage of sambiloto leaf extract (*Andrographis paniculata*) exhibited the most significant efficacy in reducing blood glucose levels in male rats (Rattus norvegicus) induced with alloxan.
A-3[14]	"N.T. Astuti, P.R. Novitasari, R. Tjandrawinata, A.E. Nugroho, S. Pramono, 2022"	"Anti-diabetic effect of andrographolide from Sambiloto herbs (*Andrographis paniculata* (Burm.f.) Nees) through the expression of PPARγ and GLUT-4 in adipocytes."	• The antidiabetic effect of andrographolide, a compound derived from the Sambiloto herb (*Andrographis paniculata* (Burm.f.) Nees), is achieved by expressing "PPARγ and GLUT-4 in adipocytes". This study assessed the capacity of glucose absorption of the samples using mature adipocytes. Figure 3b illustrates the glucose absorption capacity of andrographolide (at concentrations of 1.4, 2.8, and 5.6 μM) and pioglitazone (at a concentration of 0.02 μM) on mature adipocytes. All groups demonstrated absorption in 2 hours following treatment, and the duration of treatment directly correlated with the extent of absorption (2–8 hours). All group had an increased glucose absorption capacity as compared to the negative control group treated with 0.03% DMSO). After 2 hours of treatment, however, both the andrographolide group and the positive control (pioglitazone) demonstrated nonsignificant absorption potential. The positive control (pioglitazone 0.02 μM) had a maximum absorption capacity of 92.71% at 8 hours. In comparison, the andrographolide treatment groups of 1.4, 2.8, and 5.6 μM had absorption capacities of 83.97%, 93.85%, and 98.89%, respectively ($p < 0.05$). The findings of this research suggest that andrographolide, when used in isolation, exhibits similar glucose absorption activity to pioglitazone.

Andrographis paniculata, also known as *Sambiloto*, is a commonly used medicinal plant in alternative medicine. It is valued for its various pharmacological qualities, such as its ability to treat diabetes, reduce inflammation, combat obesity, act as an antioxidant, and alleviate symptoms of dengue fever. It is important to emphasize that *A. paniculata* has the potential to interact with several types of conventional drugs. The secondary metabolites of *A. paniculata*, namely 14-deoxy-11,12-didehydroandrographolide, andrographidine A and andrographolide (AND), demonstrate elevated affinities and bind to receptors that regulate CYP450 metabolism enzymes, specifically the constitutive androstane receptor and pregnane X receptor (PXR). *A. paniculata* and its main secondary metabolite, andrographolide, have been found to hinder the function of various enzymes, such as CYP2E1, and decrease the production of CYP2C9 and CYP3A proteins in human liver cytochrome and Caco-2 cell lines.[15]

The ethanol extract of *Andrographis paniculata* (APE) and andrographolide (AND) have been found to alter the pharmacokinetic profile of certain drugs. APE and AND have the ability to enhance the clearance (CL) value and substantially decrease the area under the curve (AUC) of theophylline, etoricoxib, nabumetone, and naproxen. On the other hand, APE has the ability to increase the area under the concentration-time curve (AUC) and decrease the clearance (CL) of gliclazide and midazolam. Moreover, the main constituent of APE has the ability to modify the pharmacokinetic characteristics of aminophylline, doxofylline, meloxicam, glyburide, glimepiride, metformin, and warfarin by augmenting their AUC and Tmax values while dramatically diminishing their CL values.[15]

In individuals with type II diabetes, there is a significant reduction in the ability of skeletal muscles to take up glucose, leading to higher levels of glucose in the bloodstream. In a study conducted by Jaiyesimi (2020), it was noticed that treatment with phenolic-rich A. paniculata extract led to a gradual decrease in serum glucose concentrations. This suggests that the

extract has the ability to enhance glucose homeostasis. This discovery is consistent with prior studies conducted by Ajiboye et al. Insulin is essential for regulating glucose levels in the body by helping glucose enter muscle and fat cells and decreasing the production of hepatic glucose, therefore maintaining normal blood sugar levels. Nevertheless, continued exposure of beta cells to high blood sugar levels might result in gradual beta-cell depletion, reduced efficiency, and possible beta-cell dysfunction, ultimately leading to insufficient insulin production. This deficit has consequences for the activation of hepatic gluconeogenic enzymes in individuals with diabetes mellitus. Significantly, the use of *A. paniculata* extract, which is rich in phenolic compounds, has been linked to a rise in insulin levels in the bloodstream. This indicates that it has the ability to stimulate the regeneration of beta cells in the pancreatic islets, leading to improved secretion and effectiveness of insulin.[16]

The investigation was conducted on the effect of 21 days of administration of free and bound phenolic extracts of A. paniculata on fasting blood glucose levels (mg/dL) in alloxan-induced diabetic rats. Significant elevations ($p < 0.05$) in fasting blood glucose levels were detected in experimental groups following 72 hours of exposure to 150 mg/kg body weight of alloxan monohydrate. After 21 days of treatment, however, a significant increase in fasting blood glucose levels ($p < 0.05$) was noted in untreated diabetic controls (255.08 ± 0.24) in comparison to normal controls (79.68 ± 0.38) only. Conversely, a significant decrease ($p < 0.05$) was evident in diabetic groups given free and bound phenolic extract of *A. paniculata* at 50 and 100 mg/kg body weight in comparison to untreated diabetic controls. However, there was no significant decrease ($p > 0.05$) compared to normal controls and controls given 5 mg/kg body weight of glibenclamide.[16]

Another parameter measuring the effect of free and bound phenolic extract administration of *A. paniculata* for 21 days on serum insulin levels (µmol/L) in alloxan-induced diabetic rats. The results indicate a statistically significant reduction ($p < 0.05$) in insulin levels in the untreated diabetes control groups compared to the normal control groups exclusively. Nevertheless, when the free and bound phenolic extract of A. paniculata was given at doses of 50 and 100 mg/kg body weight, there was a significant increase in insulin levels ($p < 0.05$) in the groups treated with the extract, as compared to the diabetic control group that did not receive any treatment. However, the observations in the groups treated with the extract did not show any significant differences ($p > 0.05$) when compared to both the normal control group and the group that received a dose of 5 mg/kg body weight of glibenclamide.[16]

Thiazolidinediones (TZDs), a class of oral medications, are used for treating diabetes mellitus (DM), particularly type 2 DM with insulin resistance. These medications act as PPARγ agonists, enhancing insulin sensitivity. PPARγ, a molecular target for type 2 diabetes treatment, is downregulated during tissue insulin resistance. By activating PPARγ, TZDs influence the transcription of genes involved in lipid and glucose metabolism, such as fatty acid transport, adipocyte fatty acid-binding protein, acyl-CoA fatty acid synthase, glucokinase, lipoprotein lipase, and GLUT-4. However, it's important to note that these medications are linked to certain side effect such as weight gain, congestive heart failure, fluid retention as well as edema.[14]

A recent study by Astuti (2022) has demonstrated the time-dependent enhancement of glucose uptake ability by andrographolide, with the effect being concentration-dependent. This suggests that increased PPARγ in mature adipocytes may enhance GLUT-4 expression, leading to improved glucose uptake. The study's findings indicate that andrographolide increases "PPARγ and GLUT-4 expression at the mRNA level in mature adipocytes", with comparable or even superior efficacy to pioglitazone. Consequently, andrographolide may exhibit similar effects to pioglitazone in enhancing cellular glucose uptake and insulin sensitivity, suggesting its potential as an alternative therapeutic option for type 2 diabetes.[14]

4. Conclusion

Sambiloto extract (*Andrographis paniculata*) exhibits the potential to reduce blood glucose levels and elevate serum insulin concentrations in experimentally induced diabetic animal models. Andrographolide, the primary compound within *Andrographis paniculata*, has demonstrated anti-diabetic properties through the inhibition of alpha-glucosidase enzymes and the enhancement of PPARγ and GLUT-4 expression. These actions facilitate improved cellular glucose uptake and insulin sensitivity, suggesting the potential of sambiloto extract as an alternative therapeutic approach for the management of type 2 diabetes.

5. Acknowledgements

None

6. References

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