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Review Article : Effect of Combination Herbal Plants Extracts on Diabetes Mellitus

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Abstract
Diabetes is a non-communicable disease with metabolic dysfunction characterized by high glucose levels due to damage to pancreatic ß cells so that insulin cannot be secreted normally by the body. Diabetes mellitus cannot be cured, but it can only be controlled with appropriate treatment. Most of the available synthetic antidiabetic treatments have serious side effects and are quite expensive. Therefore, traditional herbal medicine is an alternative which is used for some people in maintaining normal blood sugar levels. The use of herbal therapy with a combination of plant extracts has the potential to be more effective in lowering blood sugar when compared to single plant extracts. The aim of this article review is that to compile and provide a scientific overview of the various studies which have been conducted previously regarding the effectiveness of combinations of herbal plant extracts in diabetes mellitus. A comprehensive literature study was conducted by using various electronic search databases with the keyword "Combination of antidiabetic extracts" and 30 international research journals which were combined into review articles were obtained which shows that combinations of plant extracts proved to be more effective in lowering blood glucose levels compared to single herbal plant extracts.

Keywords: Antidiabetic, Combination Plant Extracts, Herbal Therapy

Review Artikel : Pengaruh Kombinasi Ekstrak Tanaman Herbal terhadap Diabetes Melitus

Abstrak
Diabetes merupakan penyakit tidak menular dengan disfungsi metabolik yang ditandai dengan tingginya kadar glukosa akibat rusaknya sel ß pankreas sehingga insulin tidak dapat disekresikan secara normal oleh tubuh. Diabetes melitus tidak dapat disembuhkan, namun hanya dapat dikendalikan dengan pengobatan yang tepat. Sebagian besar pengobatan antidiabetik sintetik yang tersedia memiliki efek samping yang serius dan harganya cukup mahal. Oleh karena itu, pengobatan herbal tradisional menjadi salah satu alternatif yang digunakan sebagian orang dalam menjaga kadar gula darah tetap normal. Penggunaan terapi herbal dengan kombinasi ekstrak tumbuhan berpotensi lebih efektif dalam menurunkan gula darah jika dibandingkan dengan ekstrak tumbuhan tunggal. Tujuan dari ulasan artikel ini adalah untuk menyusun dan memberikan gambaran ilmiah dari berbagai penelitian yang telah dilakukan sebelumnya mengenai efektivitas kombinasi ekstrak tumbuhan herbal pada diabetes melitus. Studi literatur yang komprehensif dilakukan dengan menggunakan berbagai database pencarian elektronik dengan kata kunci "Kombinasi ekstrak antidiabetik" dan 30 jurnal penelitian internasional yang digabungkan menjadi artikel review diperoleh hasil bahwa kombinasi ekstrak tumbuhan terbukti lebih efektif dalam menurunkan glukosa darah. tingkat dibandingkan dengan ekstrak tanaman herbal tunggal.

Kata Kunci: Antidiabetes, Kombinasi Ekstrak Tumbuhan, Terapi Herbal

1. Introduction

Diabetes mellitus is a chronic condition which occurs when there is an increase in a person's blood glucose levels caused by the body's inability to produce insulin normally so that the insulin produced cannot be used effectively.[1] Furthermore, insulin is an essential hormone produced by the pancreas gland which has a role in controlling levels blood sugar by playing a role in the process of glucose absorption in the body.[2] When the body lacks insulin, glucose is not used as an energy source which will result in high concentrations of glucose in the blood and cause a condition of hyperglycemia.[3] Prolonged hyperglycemia conditions will cause unwanted effects, one of which is are diabetes mellitus and various other health complications; such as, kidney and eye dysfunction and damage to the nervous system. [4]

Diabetes is divided into 3 types that are type 1 diabetes, type 2 diabetes, and gestational diabetes. Type 1 diabetes is caused by an autoimmune reaction which stops the body from making insulin. Symptom of type 1 diabetes develops quickly and it usually occurs in children, adolescents, and young adults. Meanwhile, in type 2 diabetes, the body does not use insulin properly and it is unable to maintain blood sugar levels at normal levels. Type 2 diabetes can be prevented by changing a healthy lifestyle. In addition, gestational diabetes develops in pregnant women who have never had diabetes. If a person has gestational diabetes, it is likely that their baby is at a higher risk of experiencing health problems. Gestational diabetes usually goes away after the baby is born.[5]

Based on the International Diabetes Federation (IDF) Atlas Edition 9, it is estimated that there will be 463 million people with diabetes in the world aged 20-79 years in 2019 with a prevalence of 9.3%. Diabetes is responsible for 4.2 million deaths that year. The world diabetes rate is expected to continue to increase by 578.4 million in 2030 and 700. 2 million in 2045. Indonesia is in seventh place with the highest prevalence of diabetes in the age range of 20-79 years in the world in 2019 with the highest number of cases as much as 10.7 million. With a population of Indonesia in 2019, namely 269.6 million, the prevalence of diabetes in Indonesia is 3.97%. This figure is predicted to continue to increase by 13.7 in 2030 and 16.6 million in 2045. [6]

The cost of treatment for someone with diabetes mellitus is about two times higher. Treatment of type 1 diabetes mellitus must be done with insulin therapy since the body is no longer able to produce insulin in the amount required, whereas in type 2 diabetes insulin therapy is only given when oral medication is no longer able to maintain blood sugar levels. The management and prevention of diabetes sufferers is conducted by implementing a healthy lifestyle by maintaining a healthy diet, conducting physical activities such as light exercise and maintaining a normal body weight. [7]

To date, there has not been found a drug which can completely cure diabetes. The use of insulin injections which are conducted for an undetermined period of time can cause discomfort for sufferers. Therefore, alternative treatments are needed in order to maintain the condition of diabetics stable without reducing the comfort of diabetics. Alternative medicine which is widely used by the public is the use of herbal medicine. These traditional treatments have low side effects and they are inexpensive.[8]

Herbal plants are one of sources of therapy for healing which can be relied upon. Synthetic medicine directly or indirectly also comes from secondary metabolites contained in herbal plants.[8] More than 400 medicinal plants based on the literature can reduce blood glucose levels.[9] Most of these plants contain secondary metabolites; such as, flavonoids, steroids, terpenoids, phenolics, glycosides, carotenoids, alkaloids, and phenols which have been scientifically developed as antidiabetics. [9]

Drugs which are used simultaneously at one time have the potential for chemical or pharmacological interactions to occur. The resulting interaction will have an impact on one of the genes; besides, it causes a decrease in the effectiveness of a drug and increases

the severity of side effects.[10] However, the mechanisms involved in herbal combinations are more complex since there are many compounds which are involved. Based on the literature, a combination of two herbal plants has even better anti-diabetic effectiveness when compared to a single plant.

There are various combinations of medicinal plants which are believed to be used to treat diabetes. Therefore, the purpose of writing this review article is that to compile and provide a scientific overview of the various studies which have been conducted previously regards to the effectiveness of combinations of herbal plant extracts in diabetes mellitus.

2. Methods

This article review used descriptive analysis by describing and explaining in narrative form the results of research on the literature. In addition, the data studied from each journal were plant names, plant parts used, extraction, dosage, and study type collected from various international journals about combinations of herbal plants which have anti-diabetic potential. In addition, international journal searches used the keyword "Antidiabetic extract combination" published in 2013-2023 on several sites; such as, IDF, NCBI, Pubmed, Elsevier, Google Scholar. The literature selection used as a reference source was based on inclusion and exclusion criteria by reading briefly the initial research journals which were obtained as many as 43 journals and selecting based on inclusion criteria. The inclusion criteria set were international research journals published in 2013-2023 which discussed the anti-diabetic activity of a combination of plant extracts. Research journals which were not included in the inclusion criteria were then excluded so that a total of 28 reference journals were studied and analyzed for antidiabetic activity against combinations of herbal plants as the subject matter of the articles review.

3. Result and Discussion

3.1. Combination of *Curcuma xanthorrhiza* and *Averrhoa bilimbi*

The combination of *Curcuma xanthorrhiza* and *Averrhoa bilimbi* extracts has antioxidant and anti-inflammatory activities which mutually support each other in overcoming diabetes. In male Wistar rats with streptozotocin-induced diabetes and given a combination of *Curcuma xanthorrhiza* and *Averrhoa bilimbi* extracts show effective results in lowering blood glucose levels and improving pancreatic histopathology. Giving a combination of extracts is more effective in reducing blood glucose levels compared to giving a single extract. In addition, the test results show a decrease in glucose levels after administration of a combination of extracts at a dose of 767.5 mg/kg BW which is 54.86 ± 34.61%.[11]

3.2. Combination of *Andrographis paniculata* and *Syzygium polyanthum*

The combination of *Andrographis paniculata* and *Syzygium polyanthum* extracts has several bioactive compounds which play a role in the treatment of type 2 diabetes that are Andrographolide with antidiabetic activity and protection against pancreatic beta cells, Flavonoids and tannins with antidiabetic and antioxidant activity, and eugenol with antidiabetic and anti-inflammatory effects. In rats induced by alloxan by giving a combination of *Andrographis paniculata* and *Syzygium polyanthum* extracts, it shows good effectiveness in controlling blood glucose by repairing damage to pancreatic beta cells in experimental rats. The test results show that the combination of *Andrographis paniculata* and *Syzygium polyanthum* extracts show a better percentage of blood glucose reduction than metformin and a single extract. In addition, it has an antidiabetic effect without a toxic effect with a decrease in blood glucose of 53% after being given a combination of extracts at a dose of 200 mg/kg.[12]

3.3. Combination of *Andrographis paniculata*, *Syzygium cumini*, and *Caesalpinia sappan*

The combination of *Andrographis paniculata*, *Syzygium cumini*, and *Caesalpinia sappan* extracts has potential in alternative medicine for diabetics. In this study, it shows that the combination of the three extracts can

Tabel 1. Combination of Herbal Plants with Antidiabetic Activity

No.	Plant Name	Parts Used	Type of Extract	Dose	Method	Reference
1.	*Cichorii radices* *Elymi repens rhizomata* *Helichrysi arenarii flores* *Rosae fructus* *Maydis style cum stigmatis*	Root Rhizome Flower Fruits Flower	Aqueous	12 mL/kg	Diabetic albinomice induced by standard diet and Glucose	[24]
2.	*Taraxacum officinale* L. *Momordica charantia* L.	Whole Plant	PE, chloroform, ethyl acetate, acetone, Ethanol and Aqueous	250 mg/kg and 1000 mg/kg	In vivo : STZ-induced diabetic mice In vitro : Inhibition of α-Amylase and α-Glucosidase, antioxidant DPPH assay, DPP-4 inhibitors, and Glucose Uptake Assay	[17]
3.	*Senecio biafrae* *Carica papaya* *Spondias mombin* *Xylopia aethiopica*	Leaves Seed Bark Fruits	Methanol	100 mg/kg	In vitro: Inhibition of α-Amylase and α-Glucosidase, antioxidant DPPH assay In vivo: Glucose and STZ induced diabetic mice	[26]
4.	*Urticae folia* *Taraxaci radices* *Myrtilli folia* *Rosae fructus* *Menthae folia*	Leaves Root Leaves Fruits Leaves	Aqueous	12 mL/kg	Glucose induced diabetic male albino mice (180 g and 200 g)	[27]
5.	*Inulae rhizomata* *Helichrysi arenarii flores* *Maydis style cum sigmatis* *Origani herba* *Rosae fructus* *Taraxaci radices*	Root Flower Flower Leaves Fruits Root	Distilled water	12 mL/kg	Glucose tolerance test in Male albino rats weighing between 180 g and 200 g	[28]
6.	*Equiseti arvensis herba* *Sambuci flores* *Inulae rhizomata* *Hyperici herba* *Tiliae flores* *Polygoni avicularis herba* *Myrtilli folium* *Urticae folia*	Leaves Flower Root Leaves Flower Leaves Leaves Leaves	Distilled water	9 mL/kg	Streptozotocin and nicotinamide induced diabetic Wistar rats (180 g and 200 g)	[29]
7.	*Commiphora mukul* *Commiphora myrrha* *Terminalia chebula*	Bark Bark Fruits	Ethanol and Aqueous	857 mg/kg ethanolic extract of C. *mukul*+438 mg/kg ethanolic extract of C. *myrrha*+1714 mg/kg hydro-ethanolic extract of *T. chebula*	Streptozotocin induced (60 mg/kg, bw) diabetic male Wistar rats (250±25 g)	[30]

Tabel 1. Combination of Herbal Plants with Antidiabetic Activity

No.	Plant Name	Parts Used	Type of Extract	Dose	Method	Reference
8.	*Andrographis paniculata* *Syzygium cumini* *Caesalpinia sappan*	Leaves Leaves Wood	70% Ethanol	150 mg/kg	Streptozotocin induced (35 mg/kg, bw) diabetic Sprague-Dawley rats	[13]
9.	*Andrographis paniculata* *Centella asiatica*	Leaves Leaves	95% Ethanol	30 µg/mL and 10 µg/mL	PPAR and GLUT4 gene expression by PCR, target gene expression by Quantity One software, Fibroblast cell culture 3T3-L1	[15]
10.	*Curcuma xanthorrhiza* *Averrhoa blimbi*	Rhizome Fruits	Ethanol 96%	767,5 mg/kg	STZ-induced diabetic Wistar rats (60 mg/kg, bw)	[11]
11.	*Andrographis paniculata* *Guazuma ulmifolia*	Leaves Leaves	Ethanol and Aqueous	2 g/kg and 0,5 g/kg	Alloxan induced (50 mg/kg, bw) diabetic Swiss-Webster rats (20-35 g)	[19]
12.	*Allium sativum* *Zingiber officinale* *Capsicum frutescens*	Bulbs Rhizome Fruits	Aqueous	200 mg/kg and 500 mg/kg	Alloxan induced (150 mg/kg, bw) diabetic Wistar rats (300-350 g)	[23]
13.	*Camellia sinesis* L. *Cinnamomum verum*	Leaves Wood	Methanol	200 mg/kg	Streptozotocin induced diabetic albino rats (225-250 g)	[20]
14.	*Abelmoschus Manihot* L. *Coffea arabica* L.	Leaves Seed	Ethanol 70%	Concentration of 50 ppm	Alloxan induced (140 mg/kg, bw) diabetic rats	[31]
15.	*Pterocarpus santalinus* *Stevia rebaudiana*	Bark Leaves	Distilled water	Concentration 50 µl	Alpha-Amylase Inhibitory Assay	[25]
16.	*Stevia rebaudiana* Bert *Andrographis folium*	Leaves	Aqueous	Combination of dose (*Stevia rebaudiana* : *Andrographis folium*; 30:80)	Alloxan induced (200 mg/kg, bw) diabetic male white rats (20-40 g)	[21]
17.	*Blumea balsamifera* L *Coccinia grandis* L	Leaves	Distilled water	*B. balsamifera* L to C. grandis L. (1:3, BC13) of 313.04±5.75 mg QE/g dry matter	α-amylase inhibitory, DPPH method and iodine-starch test	[18]
18.	*Physalis angulata* *Hibiscus sabdariffa*	Leaves Flower	Ethanol 70%	*Physalis angulata* with 10mg/200g BW dose and *Hibiscus sabdariffa* 30mg/200 g BW	Alloxan-induced diabetic Sprague Dawley rats (150-300g)	[32]

Tabel 1. Combination of Herbal Plants with Antidiabetic Activity

No.	Plant Name	Parts Used	Type of Extract	Dose	Method	Reference
19.	*Moringa oleifera* *Vernonia amygdalina*	Leaves	Ethanol 80%	250 mg/kg	Streptozotocin induced diabetic Wistar albino mice	[22]
20.	*Andrographis paniculata* *Syzygium polyanthum*	Leaves	Aqueous	200 mg/kg	Alloxan-induced diabetic male Wistar rats	[12]
21.	*Annona muricata* *Syzygium polyanthum* *Centella asiatica*	Leaves	Aqueous and Methanol	soursop leaves and bay leaves 1,137 ± 0,096 ; soursop leaves and pegagan leaves 0,892 ± 0,024 ; pegagan leaves and bay leaves 0,43 ± 0,019	The activity of alpha-glucosidase	[33]
22.	*Cinnamomum cassia* *Nigella sativa*	Bark Seed	Ethanol 95%	100 mg/kg and 200 mg/kg	Streptozotocin induced (45 mg/kg, bw) diabetic Wistar mice (150 and 200 g)	[14]
23.	*Picralima nitida* *Sonchus oleraceus*	Leaves Whole plant	Methanol, Alcoholic, Distilled water	150 mg/kg and 300 mg/kg	In vitro : DPPH radical-scavenging activity and Folin-Ciocalteu method In vivo : Streptozotocin induced (50 mg/kg, bw) diabetic rats	[34]
24.	*Murraya koenigii* L. *Olea europaea*	Leaves Leaves	Distilled water	200 mg/kg	Streptozotocin induced (70 mg/kg, bw) diabetic Wistar mice (300 to 345 g)	[37]
25.	*Ocimum gratissimum* *Vernonia amygdalina*	Leaves Leaves	Distilled water	250 mg/kg	Streptozotocin induced (60 mg/kg, bw) diabetic Wistar mice (150 to 250 g)	[36]
26.	*Psidium guajava* *Syzygium cumini*	Leaves Leaves	Ethanol	100µg/ml	Glucose uptake assay on cultured L6 cell lines, and alpha amylase inhibitory assay was on porcine alpha amylase	[16]
27.	*Trigonella foenum-graecum* *Cymbopogon citratus* *Triticum aestivum* *Syzgium cumini* *Bauhinia Purpurea* *Momordica charantia*	Seed Leaves Leaves Leaves Leaves Fruits	Double distilled Aqueous	500 mg/kg	Streptozotocin induced (50 mg/kg, bw) diabetic male Wistar rats weighing around 180-200 g	[38]

Tabel 1. Combination of Herbal Plants with Antidiabetic Activity

No.	Plant Name	Parts Used	Type of Extract	Dose	Method	Reference
28.	*Vernonia amygdalina* *Ocimum gratissimum* *Gongronema latifolium*	Leaves Leaves Leaves	Ethanol 95%	100 mg/kg	Alloxan-induced (150 mg/kg, bw) diabetic Wistar albino mice	[35]
29.	*Clitoria ternatea* *Punica granatum*	Flower Flower	Methanol	100 and 200 mg/kg	Alloxan monohydrate induced (150 mg/kg BW) diabetic Sprague Dawley rats weighing around 150-200 g	[39]
30.	*Cinnamomum zeylanicum* *Trigonella foenum-graecum* *Allium hirtifolium* *Syzygium aromaticum*	Bark Seed Bulbs Flower	Ethanol 80%	100-300 mg/kg	Streptozotocin induced diabetic male Wistar rats	[40]

reduce fasting blood glucose, cholesterol, and LDL levels in rats which were previously induced by injection of multiple doses of 35 mg/kg BW streptozotocin at one week intervals and it can increase the number of pancreatic ß-cells. In addition, the acute toxicity test shows that the three extracts are declared safe for consumption up to a dose of 5000 mg/kg BW. However, further research is needed to determine the mechanism of antidiabetic action and variations in the dose ratio of the three extracts.[13]

3.4. Combination of *Cinnamomum cassia* and *Nigella sativa*

In testing the combination extract of *Cinnamomum cassia* and *Nigella sativa* at a dose of 100 mg/kg and 200 mg/kg which was tested on male Wistar rats by induced streptozotocin (STZ) of 45 mg/kg after fasting overnight shows the results that the combination of the two plants can normalize glucose blood, improve glucose tolerance, lipid profile, and kidney function of rats with type 1 diabetes after induced streptozotocin (STZ). In addition, the combination of the two extracts also show a protective effect on pancreatic beta cells so that the combination of *Cinnamomum cassia* and *Nigella sativa* can be used as an additional herbal therapy in the treatment of diabetes with more significant efficacy in lowering blood glucose levels compared to a single extract.[14]

3.5. Combination of *Andrographis paniculata* and *Centella asiatica*

Based on this study, the combination of extracts from *Andrographis paniculata* and *Centella asiatica* plants can increase insulin sensitivity and glucose uptake by increasing the expression of PPAR and GLUT4 mRNA in insulin-resistant 3T3-L1 adipocytes. Furthermore, this study has provided evidence for the use of herbal medicines from these two plants in the treatment of diabetes. *Andrographis paniculata* contains an active compound, namely andrographolide, which can provide hypoglycemic and hypolipidemic effects in insulin-resistant type 2 diabetes mellitus. Meanwhile, in the *Centella asiatica* plant, glucose absorption is inhibited by destroying disaccharides and alpha-amylase.[15]

3.6. Combination of *Psidium guajava* and *Syzygium cumini*

The research result from the combination of *Psidium guajava* and *Syzygium cumini* leaves shows that the combined extracts has better activity for the treatment of diabetes compared to the individual extracts and it is comparable to the activity of acarbose. Furthermore, in this study, a glucose uptake test is conducted on myoblast cells of L6 rats

by using 3 concentrations, namely 25, 50, and 100µg/mL and it shows alpha amylase inhibitory properties. Therefore, the combined extract of the two plants can act as a better diabetes treatment. However, further studies are needed to determine the mechanism behind this synergistic or additive effect.[16]

3.7. Combination of *Taraxacum officinale* and *Momordica charantia*

In the combination of *Taraxacum officinale* and *Momordica charantia* extracts, it is obtained several bioactive compounds which play a role in anti-diabetes, that are polyphenols, chlorogenic acid, oleanolic acid, cucurbitacin A, B and E, momordicoside G and K, oleoyl ethanolamide, luteolin, hexadecanoic acid, quercetin, tannins , and hydroxycinnamic acid. These compounds have anti-diabetic effects through the mechanism of inhibiting DPP-4 enzymes, a-amylase and a-glucosidase enzymes and increasing pancreatic secretion. Moreover, the polyherbal form of the combination of the polyphenolic compounds of the two extracts is proven to have a better antidiabetic effect than the single compound. The results of in vivo testing of rats induced with STZ-NA and given a combination of extracts at doses of 250 mg/kg and 1000 mg/kg show a significant decrease in blood glucose. In addition, the results of the in vitro tests conducted show that the combination of extracts have antioxidant activity, inhibited starch digestion enzymes, inhibited DPP-4 enzymes, and increased glucose uptake by muscle cells.[17]

3.8. Combination of *Blumea balsamifera* L. and *Coccinia grandis* L

Blumea balsamifera L. contains polyphenol compounds, including xanthoxylin, eugenol, and dimethoxydurene, flavonoids, dihydroflavones, tannins, blumeatin, and quercetin. This quercetin shows antidiabetic activity. Meanwhile, the *Coccinia grandis* L plant contains metabolic compounds; such as, phenolics, alkaloids, saponins, flavonoids, glycosides, xyloglucan, taraxerol, carotenoids, and gytoxanthin. Saponin compounds are known to have high antidiabetic activity and they can inhibit alpha amylase and alpha glucosidase. Furthermore, the combination of *Blumea balsamifera* L. and *Coccinia grandis* L. leaf extracts proved to be utilized as a source of flavonoids and phenolic compounds with potential as antioxidant and antidiabetic agents. In addition, the combination of *Blumea balsamifera* L. and *Coccinia grandis* L with a ratio of 3:1 show the best formulation which could inhibit alpha amylase and increase antioxidant activity.[18]

3.9. Combination *Andrographis paniculata* dan *Guazuma ulmifolia*

The combination of *Andrographis paniculata* and *Guazuma ulmifolia* extracts has the main bioactive compounds that are andrographolide compounds with antidiabetic and anti-inflammatory activities, and tiliroside compounds with antidiabetic and antioxidant activities. Furthermore, in the Swiss-Webster rat test model, male obesity with alloxan-induced diabetes and given a combination of *Andrographis paniculata* and *Guazuma ulmifolia* extracts show a decrease in blood glucose levels and body weight and increased insulin sensitivity. The combination of the two extracts is proven to be better than a single extract so that the combination can be used as an alternative in the treatment of diabetes. In addition, the results show that the combination extract of *Andrographis paniculata* at a dose of 2 g/kg and *Guazuma ulmifolia* at a dose of 0.5 g/kg can reduce blood glucose levels by 66.01%.[19]

3.10. Combination of *Camellia sinensis* and *Cinnamomum verum*

The combination of *Camellia sinensis* and *Cinnamomum verum* extracts has bioactive compounds with antioxidant, anti-inflammatory and anti-diabetic effects, that are cinnamaldehyde, cinnamic acid, epigallocatechin gallate (EGCG), epicatechin gallate (ECG), catechins and proanthocyanidins. In testing rats induced with a dose of 40 mg/kg/day streptozotocin for 5 days shows that administration of a combination of *Camellia sinensis* and *Cinnamomum verum* extracts at 4 and 6 weeks after administration can reduce

blood glucose levels and increase body weight. The combination of extracts from the two plants has a synergistic effect which is effective in reducing blood glucose compared to the single extract. In addition, the test results show that giving a combination of extracts at a dose of 200 mg/kg has the best effectiveness in reducing blood glucose levels.[20]

3.11. Combination of *Stevia rebaudiana* Bert and *Andrographis folium*

The combination of extracts from *Stevia rebaudiana* Bert and *Andrographis folium* is known to reduce blood glucose levels in white male rats weighing 20-40 grams induced with alloxan at a dose of 200 mg/kg BB intraperitoneally until blood glucose levels reach diabetic blood sugar levels. In this study, it shows that a dose of 1.5 mg of *Stevia rebaudiana* Bert leaves and 4 mg of *Andrographis folium* leaves show fewer side effects; besides, it is safe for antidiabetic treatment. The leaves of *Stevia rebaudiana* Bert contain flavonoids and terpenoids. Meanwhile, the leaves of *Andrographis folium* contain andrographolida, both of which can lower blood glucose in male rats that were previously induced by alloxan and they have antidiabetic activity.[21]

3.12. Combination of *Moringa oleifera* and *Vernonia amygdalina*

The combination of *Moringa oleifera* and *Vernonia amygdalina* extracts contains bioactive compounds of flavonoids, sesquiterpene lactones, and saponins as anti-diabetic agents. Test conducted in streptozotocin-induced rats shows the results of testing the combination of *Moringa oleifera* and *Vernonia amygdalina* extracts at a dose of 250 mg/kg for 28 days which shows a significant decrease in blood glucose levels and it has a hepatoprotective effect. A dose of 100 mg/kg of the extract combination has nearly the same effectiveness as a dose of 1 unit of insulin in hyperglycemia in test animals and reverses oxidative stress. In addition, the combination of extracts shows an increase in total protein and albumin concentrations; besides, it is proven to give better results than a single extract so that the combination is safer in preventing liver damage in diabetics.[22]

3.13. Combination of *Allium sativum*, *Zingiber officinale*, and *Capsicum frutescens*

The combination of *Allium sativum*, *Zingiber officinale*, and *Capsicum frutescens* has potential in herbal medicine for diabetes. In this study, it shows that the combination of the three extracts can lower blood sugar levels, improve lipid profiles, increase body weight, and protect organs including the liver, kidneys and pancreas from damage in alloxan-induced rats. In addition, the three extract combinations are tested on rats and it shows a stronger effect at a dose of 500 mg/kg. However, further research is needed to understand the mechanism of action of the three extract combinations.[23]

3.14. Combination of *Cichorii radices extracts*, *Elymi repens rhizomata*, *Helichrysi arenarii flores*, *Rosae fructus*, and *Maydis style cum stigmatis*

In testing the combination of the five extracts, there are active biological compounds; such as, polysaccharides and polyphenolic compounds which have a role in the treatment of diabetes and its complications. These compounds can inhibit the formation of Reactive Oxygen Species (ROS) by inhibiting enzymes involved in the formation of free radicals. Tests on combinations of extracts of *Cichorii radices*, *Elymi repens rhizomata*, *Helichrysi arenarii flores*, *Rosae fructus*, and Maydis style cum conductes in healthy male albino rats and normoglycemic rats fed a standard diet show reduced hyperglycemia in the oral glucose tolerance test; besides, it has the highest hypoglycemic activity at a dose of 12 mL/kg/day.[24]

3.15. Combination of *Pterocarpus santalinus* and *Stevia rebaudiana*

Both of these herbal combinations have good antidiabetic and antioxidant activity. The *Stevia rebaudiana* extract has significant activity against alpha amylase and alpha glucosidase enzymes. In this case, it shows that the herb has potential as an antidiabetic

drug. In addition, the *Pterocarpus santalinus* plant has phenol and flavonoid compounds. It also has antidiabetic activity and it helps in lowering increased glucose levels and can restore insulin levels.[25]

3.16. Combination of *Clitoria ternate* and *Punica granatum*

The combination of extracts from *Clitoria ternatea* and *Punica granatum* showed significant antihyperglycemic potential in Sprague Dawley rats induced by alloxan monohydrate via the intraperitoneal route. In the combination of the two extracts, it is known that the effect is comparable to the drug metformin after 5 hours of oral administration. There are alkaloids, carbohydrates, glycosides, flavonoids, tannins and saponins in the combination of the 2 extracts which have an important role in demonstrating antidiabetic activity. This study is expected to be a new perspective for future research to develop herbal formulations for the management of diabetes at the clinical level.[39]

4. Conclusion

Based on the results of a literature studies which have been conducted on 28 international reference journals, the results showed that a combination of extracts from various antidiabetic herbal plants is proven to have a much better effectiveness in lowering blood glucose levels when compared to a single extract, because the combination of plant extracts contains more compounds with antidiabetic agents than single compounds from 1 plant. Thus, the combination of antidiabetic herbal plant extracts can be used as an alternative in the treatment of diabetes mellitus.

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