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A Review of Antidiabetic Potential of Indonesian Medicinal Plants on Streptozotocin (STZ)-Induced Rats

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Abstract

Diabetes mellitus represents a chronic pathological state affecting a substantial portion of the global population, characterized by elevated levels of blood glucose. The International Diabetes Federation (IDF) documented in 2022 an estimated 537 million individuals aged 20-79 afflicted with this condition. Indonesia is home to various medicinal plants used for centuries to treat various ailments, including diabetes. Some of these plants have been found to have antidiabetic properties and are currently being studied for their potential use in treating diabetes. This review integrates the potential of indigenous Indonesian medicinal plants as antidiabetic agents. Twenty-two herbal species native to Indonesia were examined in diabetic-rat models, revealing promising efficacy as alternatives to conventional antihyperglycemic therapies. These medicinal plants' bioactive constituents, including flavonoids, alkaloids, phenolics, tannins, saponins, steroids, triterpenoids, and glycosides, are hypothesized to modulate glucose metabolism. Data acquisition encompassed scholarly databases such as PubMed, Scopus, Cochrane, Google Scholar, ScienceDirect, and EBSCO, spanning literature published between 2017 and 2023. The investigation underscores the notable reduction in blood glucose levels observed in rats administered doses ranging from 100 to 800 mg/kg body weight (BW). Furthermore, the antihyperglycemic evaluation in rats involved dosing at 40-65 mg/kg BW, eliciting a sustained hyperglycemic state.

Keywords: Herbal plants, anti-hyperglycemic, blood glucose levels, streptozotocin, in vivo

Kajian Potensi Antidiabetes Tanaman Obat Indonesia pada Tikus yang Diinduksi Streptozotocin (STZ)

Abstrak

Diabetes mellitus merupakan kondisi patologis kronis yang mempengaruhi sebagian besar populasi global, yang ditandai dengan peningkatan kadar glukosa darah. International Diabetes Federation (IDF) mendokumentasikan pada tahun 2022 sekitar 537 juta orang berusia 20-79 tahun menderita kondisi ini. Indonesia merupakan rumah bagi beragam tanaman obat yang telah digunakan selama berabad-abad untuk mengobati berbagai penyakit, termasuk diabetes. Beberapa dari tanaman ini telah ditemukan memiliki sifat antidiabetes dan saat ini sedang dipelajari untuk potensi penggunaannya dalam mengobati diabetes. Ulasan ini mengintegrasikan potensi tanaman obat asli Indonesia sebagai agen antidiabetes. Dua puluh dua spesies tanaman obat asli Indonesia diteliti pada model tikus diabetes, dan menunjukkan kemanjuran yang menjanjikan sebagai alternatif terapi antihiperglikemik konvensional. Konstituen bioaktif tanaman obat ini, termasuk flavonoid, alkaloid, fenolik, tanin, saponin, steroid, triterpenoid, dan glikosida, dihipotesiskan dapat memodulasi metabolisme glukosa. Akuisisi data mencakup basis data ilmiah seperti PubMed, Scopus, Cochrane, Google Scholar, ScienceDirect, dan EBSCO, yang mencakup literatur yang diterbitkan antara tahun 2017 dan 2023. Penelitian ini menggarisbawahi penurunan kadar glukosa darah yang signifikan yang diamati pada tikus yang diberi dosis mulai dari 100 hingga 800 mg/kg berat badan (BB). Lebih lanjut, evaluasi antihiperglikemik pada tikus melibatkan pemberian dosis 40-65 mg/kg BB, yang menimbulkan keadaan hiperglikemik yang berkelanjutan.

Kata Kunci: Tanaman herbal, antihiperglikemik, kadar glukosa darah, streptozotocin, in vivo

1. Pendahuluan

Hyperglycemia is a medical condition characterized by elevated blood sugar levels beyond the normal range. This condition arises when the body is unable to produce enough insulin, a hormone that regulates blood sugar, or when the body is unable to utilize insulin effectively. Prolonged hyperglycemia significantly damaged vital organs and systems, including the cardiovascular, nervous, and renal systems, among others.[1]

Diabetes, a chronic condition affecting millions of people worldwide, is a major cause of hyperglycemia. In 2022, the International Diabetes Federation (IDF) reported that approximately 537 million adults worldwide between the ages of 20 and 79 years old have diabetes mellitus. This number is projected to increase to 643 million at a rate of 1:9 adults by 2030 and 784 at 1:8 adults by 2045.[2] There are two primary types of diabetes: Type 1 diabetes, which results from the body's autoimmune destruction of insulin-producing cells in the pancreas, and Type 2 diabetes, which arises from a combination of genetic and lifestyle factors.[3]

Effective diabetes management can be achieved through various treatment methods, including insulin therapy, oral medications, and lifestyle modifications. Insulin therapy regulates blood glucose levels, while oral medications improve insulin production or sensitivity. Healthy dietary choices and a regular exercise routine can help manage diabetes by regulating blood glucose levels and improving overall health. Depending on the severity of the condition, a combination of these treatments may be required to control diabetes effectively. Working closely with a qualified healthcare professional to develop a treatment plan that suits each individual is advisable.[4]

Antidiabetic drugs (OADs) are commonly used to manage type 2 diabetes and work by either increasing insulin production or improving insulin sensitivity. However, these medications can have potential side effects, such as gastrointestinal problems, hypoglycemia, and weight gain. In addition, OADs may not be suitable for everyone, and some people may require insulin therapy to manage their diabetes.[5] As an alternative or complementary therapy, herbal remedies have been considered to manage blood glucose levels and avoid the side effects of OADs. Herbal medicine may be a suitable option for individuals who prefer a natural approach to manage their diabetes, or for those who experience side effects from OADs. Therefore, a review of herbs that have potential as antihyperglycemic and repotedly tested in vivo so that they can be developed as phytotherapy and antihyperglycemic therapy was conducted.[6] The literature review collected from international research databases from the period of 2017 to 2023 such as PubMed, Scopus, Cochrane, Google Scholar, ScienceDirect, and EBSCO was used to identify publications that used the keywords herbal plants, anti-hyperglycemic, blood glucose levels, streptozotocin, and in vivo.

This review also considers Streptozotocin (STZ) as a diabetogenic agent used in animal studies to induce type 1 and 2 diabetes in rats. STZ selectively damages β cells in the pancreas, decreasing insulin production and increasing blood glucose levels. This makes STZ-treated rats a valuable model to study the pathophysiology of diabetes and to evaluate the efficacy of blood glucose-lowering agents. The STZ-induced diabetic rat model has been widely used to assess the blood glucose-lowering activity of various compounds, including natural products and synthetic drugs. This model is beneficial for evaluating the potential of compounds to stimulate insulin secretion or improve insulin sensitivity, as these mechanisms are impaired in STZ-treated rats, so that plants with potential as antihyperglycemic can be demonstrated preclinically in rats that have been induced with Streptozotocin (STZ.).[7]

2. Metode

A literature review was conducted using international research databases such as PubMed, Scopus, Cochrane, Google Scholar, ScienceDirect, and EBSCO. The review covered the period from 2017 to 2023 and aimed to identify publications that used the keywords

"herbal plants", "anti-hyperglycemic", "blood glucose levels", "streptozotocin", and "in vivo".

3. Result and Discussion

3.1. In Vivo Antihyperglycemic Testing Method

The in vivo antihyperglycemic testing method is a crucial and established approach commonly used to assess the effectiveness of potential antidiabetic drugs. This method involves inducing hyperglycemia in animal models, typically rats by fasting them for a period of time to ensure that they have elevated blood glucose levels before the test. Once the animals have been fasted, the test drug is administered to determine its ability to lower blood glucose levels. The drug can be administered either orally or intravenously, and blood glucose levels are measured at various intervals to evaluate its efficacy.[8]

The test drug is usually administered orally to rats in the in vivo antihyperglycemic testing method for several reasons. Firstly, oral administration is a common and convenient route of administration for drugs in animal studies. It is less invasive than other routes, such as intravenous injection, and causes less stress to the animals.[9] Secondly, rats have a well-developed gastrointestinal system that is similar to humans, making oral administration a reliable route to deliver drugs to the blood circulation. Moreover, oral administration is also an efficient way to deliver drugs to rats because they can self-administer the drug through drinking water or by gavage, which is a method of administering the drug directly to the stomach using a feeding needle. This allows for accurate dosing and makes it possible to study the effects of different drug concentrations.[10]

The in vivo antihyperglycemic testing method is a valuable tool in the development of new antidiabetic drugs because it enables researchers to study the mechanisms by which drugs lower blood glucose levels and identify potential side effects. Additionally, this method allows researchers to study the effects of combinations of drugs on blood glucose levels, providing insight into potential combination therapies.[11]

The induction of diabetes in rats is a crucial step in the in vivo antihyperglycemic testing method, as it enables researchers to evaluate the effectiveness of potential antidiabetic drugs. There are several methods for inducing diabetes in rats, including chemical induction and genetic manipulation. One of the most common methods is Streptozotocin induction.[12]

Streptozotocin (STZ) is a chemical agent that selectively destroys pancreatic β cells, which are responsible for producing insulin.[13] When administered to rats, STZ causes a decrease in insulin production, leading to hyperglycemia. This method is preferred because it is a simple and reliable way to induce diabetes in rodents. To induce diabetes in rats using STZ, the chemical is typically administered through a single or multiple intraperitoneal injections. The dose of STZ and the number of injections can vary depending on the desired severity of the diabetes induction and the experimental conditions. However, it is important to note that STZ-induced diabetes in rats may not replicate all the features of human diabetes, and the results obtained from STZ-induced diabetic rats should be interpreted with caution. Additionally, STZ can have toxic effects on non-β cells, leading to other complications and side effects.[14]

The review shows that most injection methods use the intraperitoneal route. The intraperitoneal (IP) route is a common method of injecting rats for the induction of diabetes in in vivo antihyperglycemic testing. This method involves injecting a chemical agent, such as Streptozotocin (STZ), directly into the peritoneal cavity of the rat. There are several reasons why the IP route is preferred for the induction of diabetes in rats. Firstly, the IP route is less invasive than other routes, such as intravenous injection, and causes less animal stress. This is important because stress can affect blood glucose levels and alter the outcome of the experiment. Additionally, the IP route allows for accurate dosing and can be performed quickly and easily.[15] Secondly, the IP route allows for the chemical agent to be rapidly absorbed into the bloodstream through the peritoneal membrane, leading

to a more uniform distribution of the agent throughout the rat's body. This leads to a more consistent and predictable induction of diabetes in the animal.[16]

The parameters observed in the in vivo assay to test the antihyperglycemic activity of potential drugs include fasting blood glucose levels, oral glucose tolerance tests (OGTT), area under curve (AUC), insulin levels, body weight, and histological analysis of the pancreas and liver. These parameters provide valuable information on the drug's ability to lower blood glucose levels and improve overall health in diabetic animals. The review results showed that most of the parameters used were fasting blood glucose levels. This is the blood glucose level of the animal before any drug administration. This level is elevated in diabetic animals, and the drug's ability to lower fasting blood glucose levels is a measure of its antihyperglycemic activity.[17]

3.2. Potential Plants and Bioactive Compounds Have a Role in Antihyperglycemic Activity

Based on the literature search process, 22 plant species with antihyperglycemic activity were obtained along with the test dose used, the bioactive compounds contained in the plant, the number of rats used, and the dose of Streptozotocin (STZ) used in the mouse induction test. These results are presented in Table 1.

The average test dose of 100-800 mg/kgBW has been found to be effective in reducing blood glucose levels in rats in several herbal plants. These plants include Ketimun (*Cucumis sativus* L.)[18], Ganitri (*Elaeocarpus ganitrus* Roxb.)[19], Red Gedi (*Abelmoschus manihot* (L.) Medik)[20], White Bamboo Grass (*Chromolaena odorata* (L.) R.M.King and H.Rob)[20], Matoa (*Pometia pinnata*)[21], Kemangi (*Ocimum basilicum* L.)[22], Jamblang (*Syzygium cumini* (L.) Skeels)[23], Kelor (*Moringa oleifera* Lam.)[24], Jati (*Tectona grandis* L.)[25], Binahong (*Anredera cordifolia*)[26], Insulin (*Tithonia diversifolia* (Hems.) A.Gray)[27], Purple Sweet Potato (*Ipomoea batatas* (L.) Lam)[27], Mengkudu (*Morinda citrifolia* L.)[28], Talas (*Colocasia esculenta* L. Schott)[29], Afrika (*Gymnanthemum amygdalinum* (delile) Sch. Bip. Ex Walp)[30], Pare (*Momordica charantia* L.)[31], Cincau (*Mesona palustris* BL)[32], Sereh (*Cymbopogon citratus*)[33], Salak (*Salacca edulis* Reinw)[34], Lidah Buaya (*Aloe vera*)[35], Kluwih (*Artocarpus camansi*)[36], Brotowali (*Tinospora crispa* L.)[37].

The reduction in blood glucose levels in rats after the administration of the test dose of 100-800 mg/kgBW in several herbal plants can be attributed to the presence of various bioactive compounds such as flavonoids, alkaloids, phenolic, tannin, saponin, steroid, triterpenoid, and glycosides compounds. These compounds have been extensively studied and are known to have antihyperglycemic properties. They can act by improving glucose uptake by cells, decreasing glucose absorption from the intestine, and increasing insulin secretion from the pancreas.[38] Flavonoids, alkaloids, phenolics, tannins, saponins, steroids, triterpenoids, and glycosides are all groups of plant compounds recognized for their antidiabetic properties. These compounds exhibit different mechanisms of action that contribute to their antidiabetic activity.[39]

Flavonoids are a diverse group of polyphenolic compounds that have been shown to have antidiabetic activity by improving insulin secretion and sensitivity, regulating glucose metabolism, reducing oxidative stress and inflammation, and modulating the gut microbiota. A number of flavonoids have been identified as potent insulin secretagogues, promoting insulin secretion from pancreatic β cells. Flavonoids can also enhance insulin sensitivity by increasing glucose uptake in peripheral tissues and inhibiting hepatic glucose production. Additionally, flavonoids have been found to possess antioxidant and anti-inflammatory properties, which can help reduce oxidative stress and inflammation associated with diabetes. Furthermore, flavonoids can modulate the gut microbiota, which has been implicated in the development of insulin resistance and diabetes.[40]

Alkaloids are a diverse group of nitrogen-containing compounds that have antidiabetic activity by regulating glucose metabolism, enhancing insulin sensitivity, and inhibiting carbohydrate-digesting enzymes.

Tabel 1. Plants with Antihyperglycemic Potential Along with the Test Doses Used, Bioactive Compounds, Rats Used, and STZ Dosage

No.	Plant	Plant Part	Plant Dosage	Bioactive Compounds	Rats Used (n)	Streptozotocin (STZ) Dosage	Result
1.	Ketimun (*Cucumis sativus* L.)	Fruit peel	100 mg/kgBW 200 mg/kgBW 400 mg/kgBW	Flavonoid Saponin Phenolic Steroid	Wistar male white rats (30)	40 mg/kgBW	Ethanol extract of cucumber peel had an antidiabetic effect on male white rats induced by streptozotocin at 100 mg/kgBW[18]
2.	Ganitri (*Elaeocarpus ganitrus* Roxb.)	Leaves	50 mg/kgBW 100 mg/kgBW 200 mg/kgBW	Flavonoid Tannin Saponin Triterpenoid	Wistar male white rats (25)	40 mg/kgBW	Ethanol extract of ganitri leaves significantly improved diabetic rats at 200 mg/kgBW ($p < 0.05$)[19]
3.	Red Gedi (*Abelmoschus manihot* (L.) Medik) White Bamboo Grass (*Chromolaena odorata* (L.) R.M.King and H.Rob)	Leaves	Red Gedi 100 mg/kgBW White Bamboo Grass 200 mg/kgBW Red Gedi 100 mg/kgBW & White Bamboo Grass 200 mg/kgBW Red Gedi 50 mg/kgBW & White Bamboo Grass 100 mg/kgBW	Flavonoid Alkaloid Tannin Saponin Polyphenol	Wistar male white rats (35)	30 mg/kgBW	Red Gedi (50 mg/kgBW) & White Bamboo Grass (100 mg/kgBB) effectively lower blood glucose levels in rats induced by streptozotocin[20]
4.	Matoa (*Pometia pinnata*)	Leaves	100 mg/kgBW 200 mg/kgBW 300 mg/kgBW	Alkaloid Flavonoid Saponin Tannin Steroid	Wistar male white rats (30)	40 mg/kgBW	300 mg/kgBW reduced blood glucose levels and had potential to regenerate pancreatic cells in rats at 0.6 ± 0.54[21]

5.	Kemangi (*Ocimum basilicum* L.)	Leaves	200 mg/kgBW 400 mg/kgBW 800 mg/kgBW	Flavonoid Saponin Tannin	Wistar male white rats (30)	40 mg/kgBW	800 mg/kgBW showed effective results in reducing blood glucose levels[22]
6.	Jamblang (*Syzygium cumini* (L.) Skeels)	Leaves	100 mg/kgBW 150 mg/kgBW 200 mg/kgBW	Flavonoid Tannin Alkaloid	Wistar male white rats (15)	40 mg/kgBW	200 mg/kgBW showed effective results in reducing blood glucose levels[23]
7.	Kelor (*Moringa oleifera* Lam.)	Leaves	300 mg/kgBW (n-hexane fraction, ethyl acetate fraction, ethanol-water fraction)	Alkaloid Flavonoid Saponin Tannin Steroid	Wistar male white rats (30)	30 mg/kgBW	Ethanol fraction of Moringa leaf extract (300 mg/kgBW) better lowered glucose levels (114.6 mg/dL) than n-hexane and ethyl acetate fractions[24]
8.	Jati (*Tectona grandis* L.)	Leaves	100 mg/kgBW 200 mg/kgBW 300 mg/kgBW	Quinone Steroid Glycoside Phenolic Flavonoid Alkaloid Tannin Saponin	Wistar male white rats (24)	40 mg/kgBW	Doses of 100, 200, and 300 mg/kgBW with positive control (K+) showed significant antihyperglycemic activity, increasing the average blood glucose level from 93.95 mg/dL (±17.90) to 276.35 mg/dL (±22.10) after induction[25]

9.	Binahong (*Anredera cordifolia*)	Leaves	80 mg/kgBW 100 mg/kgBW 120 mg/kgBW	Flavonoid Alkaloid Tannin Saponin	Wistar male white rats (25)	150 mg/kgBW	A concentration of 80 mg/KgBW is the most effective in reducing glucose levels compared to other concentrations and the positive group[26]
10.	Insulin (*Tithonia diversifolia* (Hems.) A.Gray) Purple Sweet Potato (*Ipomoea batatas* (L.) Lam)	Leaves	Insulin 150 mg/kgBW : Purple Sweet Potato 300 mg/kgBW Insulin 150 mg/kgBW : Purple Sweet Potato 600 mg/kgBW Insulin 300 mg/kgBW : Purple Sweet Potato 300 mg/kgBW	Flavonoid Phenolic	Wistar male white rats (25)	45 mg/kgBW	Combination group 2 (insulin leaf ethanol extract 30 mg/kgBB and purple sweet potato leaves 120 mg/kgBW) showed anti-diabetic effects, reducing blood glucose levels in rats to an average of 97.49[27]
11.	Mengkudu (*Morinda citrifolia* L.)	Leaves	200 mg/kgBW 500 mg/kgBW 750 mg/kgBW	Alkaloid Flavonoid Tannin Saponin Steroid	Wistar male white rats (30)	40 mg/kgBW	Doses of 250, 500 and 750 mg/kgBW do not have an effective reduction in blood glucose levels in streptozotocin-induced male white rats[28]
12.	Talas (*Colocasia esculenta* L. Schott)	Leaves	100 mg/kgBW 200 mg/kgBW 300 mg/kgBW	Alkaloid Flavonoid Tannin Saponin	Wistar male white rats (30)	40 mg/kgBW	The dose of 300 mg/kgBW effectively reduced blood sugar levels, with an average decrease of 102.60 mg/dL[29]

13.	Afrika (*Gymnanthemum amygdalinum* (delile) Sch. Bip. Ex Walp)	Leaves	50 mg/kgBW 100 mg/ kgBW 150 mg/kgBW	Alkaloid Flavonoid Saponin Tannin	Wistar male white rats (30)	30 mg/kgBW	Dose of 150 mg/ kgBW is an effective dose on blood glucose levels induced male rats streptozotocin[30]
14	Pare (*Momordica charantia* L.)	Fruit	400 mg/kgBW (n-hexane fraction, ethyl acetate fraction, ethanol fraction)	Flavonoid Tannin Saponin Steroid Terpenoid	Wistar male white rats (25)	40 mg/kgBW	The n-hexane fraction had the highest reduction in blood glucose levels at 70.95%, similar to the positive group's reduction of 69.65%[31]
15.	Cincau (*Mesona palustris* BL)	Leaves	54 mg/200gBW rats	Flavonoid Phenol Alkaloid Tannin	Wistar male white rats (36)	4 mg/200gBW rats	Glibenclamide & Cincau Leaf Extract had significantly lower fasting blood sugar levels than Glibenclamide & Aquades ($P < 0.001$)[32]
16.	Sereh (*Cymbopogon citratus*)	Stem	3,6 mL/200gBW	Alkaloid Saponin Flavonoid	Wistar male white rats (30)	40 mg/kgBW	Lemongrass decoction at 3.6 mL/200gBW for four weeks can reduce blood glucose levels and improve lipid profile[33]

17.	Salak (*Salacca edulis* Reinw)	Seed	4 mL/days	Flavonoid Phenolic	Wistar male white rats (24)	30 mg/kgBW	There was no significant difference between groups before treatment (p = 0.460 (p > 0.05))[34]
18.	Lidah Buaya (*Aloe vera*)	n/a	250 mg/kgBW 300 mg/ kgBW 350 mg/kgBW	Steroid	Wistar male white rats (30)	40 mg/kgBW	Dose of 250 mg/ kgBW is an effective dose on blood glucose levels induced male rats streptozotocin[35]
19.	Kluwih (*Artocarpus camansi*)	Seed	100 mg/kgBW 200 mg/ kgBW 400 mg/kgBW	Flavonoid	Wistar male white rats (24)	45 mg/kgBW	Dose of 100, 200, 400 mg/kgBW is an effective dose on blood glucose levels induced male rats streptozotocin[36]
20.	Brotowali (*Tinospora crispa* L.)	Stem	450 mg/kgBW	Alkaloid Flavonoid Glycoside	Wistar male white rats (24)	n/a	Dose of 450 mg/kgBW has antidiabetic activity comparable to glibenclamide as a synthetic oral oral synthetic antidiabetic drug[37]

Alkaloids can improve glucose metabolism by inhibiting glucose absorption in the gut, inhibition of α-amylase and α-glucosidase activities, and promoting glucose uptake and utilization in peripheral tissues. Some alkaloids have been found to enhance insulin sensitivity by increasing glucose uptake in muscle and adipose tissues. Furthermore, some alkaloids such as berberine have been shown to inhibit carbohydrate-digesting enzymes in the gut, which can help regulate blood glucose levels.[41]

Phenolic compounds are a group of plant secondary metabolites that have been found to possess antioxidant and anti-inflammatory properties. Their intake can lead to a reduction in blood glucose levels, oxidative stress, and protein glycation. Moreover, phenolic compounds can inhibit the activity of key enzymes, such as dipeptidyl peptidase-IV, which are related to carbohydrate metabolism. Furthermore, these compounds activate various biochemical pathways that improve pancreatic β-cell functions, increase insulin secretion, and improve insulin resistance. Considering the beneficial effects of phenolic compounds on diabetes management, they are a promising target for the development of new therapies for this condition.[42]

Tannins are polyphenolic compounds that have been shown to have antidiabetic activity by inhibit key enzymes responsible for the digestion of carbohydrates to glucose, namely α-glucosidase and α-amylase. These enzymes are essential for the breakdown of complex carbohydrates into simpler glucose molecules, which can then be absorbed by the body and used for energy. By inhibiting the activity of these enzymes, tannins slow down the rate of carbohydrate digestion and absorption, which can have a positive impact on blood sugar levels and insulin sensitivity.[43]

Saponins are a group of glycosides that have been found to have antidiabetic activity by activate glycogen synthesis, which is the process of converting excess glucose into glycogen for storage in the liver and muscles. This promotes the uptake and utilization of glucose from the blood, thereby reducing blood glucose levels. Saponins have been found to inhibit disaccharide activity, which is the digestion of complex sugars into simple sugars. This slows down the release of glucose into the bloodstream and helps to prevent spikes in blood sugar levels. Saponins have been found to induce insulin regeneration, which is the production of new insulin by the pancreas. This can help to increase insulin levels in the body, which is beneficial for individuals with diabetes who have impaired insulin production. Finally, saponins have been shown to inhibit the process of gluconeogenesis, which is the production of glucose from non-carbohydrate sources such as amino acids and fatty acids. By reducing the production of glucose, saponins can help to regulate blood glucose levels in individuals with diabetes.[44]

Steroids and triterpenoids are a diverse group of compounds that have been found to possess antidiabetic activity by regulating glucose metabolism and reducing oxidative stress. These compounds can enhance insulin sensitivity and promote glucose uptake and utilization in peripheral tissues, which can help regulate blood glucose levels.[45]

Glycosides are a diverse group of plant compounds which are known to possess medicinal properties, and have been found to be effective in managing diabetes. These compounds are believed to work by stimulating the secretion of insulin, enhancing insulin sensitivity, and regulating glucose metabolism. In addition, some glycosides have been found to inhibit the activity of carbohydrate-digesting enzymes in the gut, which can help regulate blood glucose levels and prevent sudden spikes in insulin secretion.[46]

3.3. Optimal Dose of Streptozotocin (STZ)

The optimal dose of streptozotocin required to induce diabetes in mice is dependent on the type of diabetes being induced due to the distinct underlying mechanisms and causes of type 1 and type 2 diabetes mellitus. Type 1 diabetes is an autoimmune disease that results from an attack by the immune system on the insulin-producing β cells in the pancreas. The damage caused by streptozotocin to the β cells leads to their destruction, thus inducing diabetes. Therefore, a higher dose of streptozotocin is required to induce type 1

diabetes in mice. In contrast, type 2 diabetes develops as a result of insulin resistance, where the body's cells become less responsive to insulin. Streptozotocin can cause damage to both the pancreatic β cells and insulin-sensitive cells, leading to the development of diabetes. Since type 2 diabetes involves both β cell damage and insulin resistance, a lower dose of streptozotocin is required to induce diabetes in mice compared to type 1 diabetes.[47]

The review results indicate that diabetes can be induced in rats by administering STZ in a dosage range of 30-150 mg/kgBW. It is noteworthy that the dose of STZ is a crucial factor in determining the extent and duration of diabetes in the rodents. Doses of 30-40 mg/kg of STZ induce transient diabetes with spontaneous recovery, whereas higher doses of 50-70 mg/kg lead to long-lasting diabetes associated with severe hyperglycemia and significant clinical signs of diabetes. Typically, low doses of STZ, given intraperitoneally are utilized to induce type 2 diabetes in rats and high doses of STZ, given intraperitoneally are utilized to induce type 1 diabetes in rats. Amongst these doses, 60 mg/kg is the most commonly used diabetogenic dose of STZ in rodents. However, as per reports, a 40 mg/kg dose of intraperitoneal STZ is optimal for creating diabetes with moderate hyperglycemia in Wistar rats.[48] When utilizing STZ doses, it is vital to take into account several factors such as the animal's age, sex, strain, and route of administration. In order to achieve a stable and permanent state of hyperglycemia, it is suggested that the STZ dose be optimized within the range of 40-65 mg/kg, while considering the aforementioned factors.[49]

4. Simpulan

A recent review of 22 herbal plants found that these plants can reduce blood glucose levels in rats induced by Streptozotocin (STZ). The reduction is due to the presence of compounds such as flavonoids, alkaloids, phenolics, tannins, saponins, steroids, triterpenoids, and glycosides. These compounds work by improving glucose uptake by cells, decreasing glucose absorption from the intestine, and increasing insulin secretion from the pancreas. The review concluded that diabetes can be induced in rats by administering STZ. The appropriate dosage depends on the diabetes targets in rats, including both type 1 and type 2 diabetes. The study found that STZ with a dose of 40-65 mg/kgBW can achieve a stable and permanent state of hyperglycemia in rats. The animal's age, sex, strain, and route of administration should be considered when determining the optimal dosage. This review highlights the potential benefits of using herbal plants to manage blood glucose levels and diabetes in rats. The information on the optimal dosage of STZ for inducing diabetes in rats can aid in conducting further research.

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