INTRODUCTION

Diabetes mellitus (DM) is a medically abnormal state characterized by chronically elevated blood glucose levels. DM is a complex metabolic illness. The long-lasting and diverse signs of hyperglycemia include improper protein, fat, and carbohydrate metabolism. Abnormalities in insulin secretion or action bring on hyperglycemia. Diabetes has a complicated etiology, develops over time, and manifests in several ways. 

Hyperglycemia and the associated protein, lipid, and carbohydrate metabolic dysfunctions impact many physiological organs and impair their ability to operate normally. The primary cause of these disruptions, which occur gradually over time, is the detrimental effects of hyperglycemia and its associated metabolic anomalies on the typical structure and function of the microvasculature and macro vasculature, which form the basis of organ structure and function throughout the body.

The relationship between oxidative stress and type 2 Diabetes (T2DM) and metabolic syndrome (MS) has been studied. In fact, oxidative stress has been related to several diseases, including the emergence of insulin resistance (IR), cellular dysfunction, mitochondrial dysfunction, and diabetic consequences. Oxidative stress is characterized by an imbalance in the ability of the enzymatic and nonenzymatic antioxidant systems to protect against the production of oxidant species, such as reactive oxygen species (ROS) and reactive nitrogen species. Oxidative stress harms tissues and cells by altering the molecular structure of cell components.

Numerous plants have been used for therapeutic purposes since dawn. Most plant components have been employed as extracts, and they may have antioxidant and anti-inflammatory qualities connected to conditions like diabetes, atherosclerosis, neurodegenerative illness, or cancer. Through this review, it is hoped that we will gain a better understanding of how antioxidants in plants are a promising alternative in reducing blood glucose in a patient with diabetes mellitus.

METHODS

Online journals and publications inspired this literature review’s methodology. Google, Google Scholar, Pubmed, NCBI with keywords “Antidiabetic (Anti hyperglycemic) extract”, “Polyphenol”, dan “Pholyphenol and diabetic”. The inclusion criterion is the journal 2013-2023.

RESULTS

Natural chemicals, especially those with a plant origin, are the primary source for discovering promising lead candidates in creating novel medications. Due to their widespread availability, low cost, and few side effects, plant-based treatments are the most popular accessible medication, particularly in rural regions. Many plants have been used for years as a primary source of effective anti-diabetic drugs. Particularly in resource-limited nations, medicinal plants cure diabetes to relieve the population’s financial burden from the price of traditional medicines. Today, it is encouraged to utilize medicinal plants to treat conditions like diabetes since they include a variety of phytoconstituents.
Table 1. Analysis of experimental study of plants’ effect on DM

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Design</th>
<th>Intervention</th>
<th>Result</th>
</tr>
</thead>
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<tr>
<td>Astini et al.14</td>
<td>Randomized post-test only control group design.</td>
<td>Soursop leaf extract with different concentrations (50 mg/kgBW, 100 mg/kgBW, 150 mg/kgBW) in hyperglycemic-induced mice</td>
<td>The soursop leaf extract group with a dose of 150 mg/kgBW gave better results in reducing fasting blood glucose after treatment and increasing the number of beta cells and blood at doses below 200 mg (toxic dose). Greater glucose levels reduction in a group with bay leaf extracts 5 mg/kgBW compared to other groups.</td>
</tr>
<tr>
<td>Wahjuni et al.15</td>
<td>A true experimental study with pre-and post-test control group design.</td>
<td>Bay leaf extract with different concentrations (0.5 mg/kgBW, 2.0 mg/kgBW, 5.0 mg/kgBW) compared to the group that given glibenclamide (control) in hyperglycemic-induced mice</td>
<td>There was a decrease in blood glucose levels in the positive control and treatment groups. The most significant results in reducing glucose were obtained in the group with Ambon banana peel extract with a dose of 400mg/kgBW</td>
</tr>
<tr>
<td>Inayati et al.16</td>
<td>An experimental study with pre and post-control group design</td>
<td>Ambon banana peel extract was given at different doses (400 mg/kgBW and 800 mg/kgBW) compared to the group that was given metformin (control) in hyperglycemic-induced mice</td>
<td>Bitter melon fruit extract can reduce glucose levels, but dosage variation had no impact on glucose reduction in diabetic rats.</td>
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<tr>
<td>Erdawati and Syahruddin.17</td>
<td>Pre and Post-test only control group design</td>
<td>Bitter melon fruit extract with different concentrations (0.4 mL/200gBW, 0.6 mL/200gBW, 0.8 mL/200 g BW, 1 mL/200gBW) compared to the group that given glibenclamide (control) in hyperglycemic induced mice</td>
<td>The most significant reduction in blood glucose by giving SE was seen in SE 200 mg/kgBW but not higher than the control group. GLUT 4 expression was increased significantly in SE 200 mg/kgBW but still lower than in the control group</td>
</tr>
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</table>
| Hidayat and Lusia.18 | Post-test only control group design | Sambiloto extract (SE) with different dosage concentrations (50mg/kgBW, 100mg/kgBW, and 200 mg/kgBW) compared to the group that was given metformin (control) in hyperglycemic induced mice | Such flavonoids, terpenoids, saponins, carotenoids, alkaloids, and glycosides, that may have anti-diabetic characteristics. By raising insulin production or decreasing intestinal glucose uptake, the antihyperglycemic action brought on by treatment with plants typically helps enhance pancreatic tissue function. By increasing mitochondrial oxygen consumption, impairing mitochondrial function, or activating nitric oxide (NOX), an evolutionarily conserved ROS-producing enzyme, sustained hyperglycemia causes ROS overproduction. Oxidative stress, which arises from either increased ROS production, decreased endogenous antioxidant activity, or both, is a significant contributor to diabetes mellitus by causing insulin resistance and cell dysfunction. Additionally, diabetic complications, which cause long-term disability and death in patients with diabetes, are directly linked to oxidative stress. In fact, under normal physiological conditions, there are numerous potential antioxidant defenses against widely produced ROS, including non-enzymatic antioxidants like vitamins, metal ion chelators, and glutathione, as well as enzymatic antioxidants like superoxide dismutase (SOD), glutathione peroxidases (GPx), and catalases (CAT). However, oxidative stress will occur once the balance between ROS and antioxidants is disturbed. As we progress in this review, recent studies in the literature demonstrate that polyphenols can have meaningful therapeutic effects in managing diabetes and its complications. A class of phytochemicals known as polyphenols may positively impact health. They are divided into molecules that are non-flavonoid (phenolic acids, hydroxycinnamic acids, lignans, stilbenes, and tannins) and flavonoid (flavonols, flavonals, flavones, flavanones, and anthocyanins). Indeed, it has been proposed that polyphenols can reduce significant T2D symptoms (such as fasting and postprandial hyperglycemia) by preventing the activity of disaccharidas (such as a-amylase and a-glucosidase) in the intestinal lumen. The absorption of simple sugars may be decreased due to this restriction on the breakdown of dietary polysaccharides. The same is also true, albeit to a smaller amount, for glucose uptake by adipose tissue. Skeletal muscle constitutes a sizable mass of tissue, and an increase in this tissue’s glucose uptake contributes significantly to keeping blood sugar levels low. Polyphenols may also have significant anti-diabetic effects by enhancing muscle and adipocyte glucose absorption. Polyphenols are the most abundant antioxidants in the diet of humans. Even though other phytochemicals besides polyphenols are crucial for the benefits that fruits and vegetables have on our health, this review will concentrate on the significance of polyphenols as effective molecules against T2D. Plants’ secondary metabolism produces polyphenols in response to biotic and abiotic stress. Examples of simple phenolic acids include hydroxybenzoic and hydroxycinnamic acids, or flavonoids, which are C6-C3-C6 molecules with two aromatic rings (rings A and B) linked by three carbons and often arranged as an oxygenated heterocycle (ring C). Indeed, it has been proposed that polyphenols can reduce significant

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T2D symptoms (such as fasting and postprandial hyperglycemia) by preventing the activity of disaccharidases (such as a-amylase and a-glucosidase) in the intestinal lumen. The absorption of simple sugars may be decreased due to this restriction on the breakdown of dietary polysaccharides. The same is also true, albeit to a smaller amount, for glucose uptake by adipose tissue. Skeletal muscle constitutes a sizable mass of tissue, and an increase in this tissue's glucose uptake contributes significantly to keeping blood sugar levels low. Polyphenols may also have significant anti-diabetic effects by enhancing muscle and adipocyte glucose absorption. Polyphenols are the most abundant antioxidants in the diet of humans. There is mounting evidence that certain polyphenols in the diet help stave against diabetes. This post discusses certain foods high in polyphenols and their potential effects on blood sugar. We included five studies that related to plants' antioxidant effect in DM. There were sour sops (Annona muricata), bay leave (Laurus nobilis), banana (Musa paradisiaca L.), bitter melon (Momordica charantia) and sambiloto (Andrographis paniculata). Analysis of all of the studies that were reviewed showed in Table 1.

**SOUR SOP**
A study discovered that the extract from sour sops leaves possesses enzymatic and non-enzymatic antioxidant properties. Reactive oxygen species (ROS) can harm tissue, although enzymatic antioxidant activity such as catalase, superoxide dismutase, and glutathione reductase protects against this damage. Flavonoids, ascorbic acid, and reduced glutathione are examples of non-enzymatic antioxidants that have both a scavenging and a protective effect on ROS. These extracts can also prevent ROS from forming.

This sour sops fruit, seeds, leaves, bark, and roots are used in stew, powders, and extract form (extracted with hot water). It is known that an extract of the sour sops leaves can repair the dysfunction and injury of the pancreatic beta cells, which decreases oxidative stress in pancreatic beta cells, thus improving the integrity of the beta cells and causing the regeneration of beta cells in the pancreatic islets of Langerhans. According to earlier studies, pancreatic beta cells regenerate after receiving sour sops leaf extract. It may be linked to an increase in insulin synthesis by the pancreatic beta cells, which would lower fasting blood glucose levels. The sour sops leaf extract has been shown to have an antihyperglycemic effect in additional pharmacological studies.

**BAY LEAVE**
To lower blood glucose and Advanced Glycation End Products (AGES) levels, Indonesian bay leaf extracts are antihyperglycemic; phyto components predominantly play a role through insulin secretion by pancreatic cells or change glucose metabolism. Through processes for maintaining functional beta cells and enhancing pancreatic action, which leads to insulin secretion by islets of Langerhans, phyto boosts insulin secretion by -pancreatic cells. Diabetes is treated using two strategies that increase insulin production and decrease alpha-glucosidase activity, an enzyme involved in the breakdown of carbohydrates that enter the body and are converted to glucose. The process of turning carbs into glucose can be suppressed when the alpha-glucosidase enzyme is active, which has the effect of reducing blood sugar.

**BITTER MELON**
Bitter melon contains flavonoids, saponins, and polyphenols. The content of that bitter melon is. Helpful in lowering blood sugar is charantin, insulin polypeptide-P, and lectins content saponins, flavonoids, polyphenols, and vitamin C from bitter melon serves as an antioxidant that aims to protect free radicals can interfere with the existence of Leydig cells due to diabetes. Bitter melon has a hypoglycemic effect by lowering blood sugar by inhibiting gluconeogenesis in the liver, protecting pancreatic cells, increasing insulin sensitivity, and reducing oxidative stress. Hypoglycemic protein polypeptide-p, often known as p-insulin, resembles insulin. Insulin P can be used as a substitute for plant insulin in people with type 1 diabetes since it mimics the effect of human insulin in the body. Recently,
the gene sequence encoding 498 bp for the polypeptide p gene in bitter melon was cloned and produced. Additionally, it was shown that a recombinant polypeptide had a hypoglycemic impact in rats with alloxan-induced diabetes. Consuming bitter melon seed extract lowers blood sugar levels in type 1 diabetes (STZ) brought on by streptozotocin. This demonstrates that substances found in bitter melon that aren’t insulin are also useful for treating diabetes.

**SAMBILOTO**
One of Indonesia’s most widely distributed plants is the sambiloto (*Andrographis paniculata*). This plant can be found across Indonesia, usually in bushes or untamed vegetation that grows in yards or plantations. Sambiloto is a plant with flavonoids, alkaloids, terpenes, and glycosides. It also includes a variety of secondary metabolites. These secondary metabolite molecules are thought to have a high antioxidant content, which suppresses different oxidative stress conditions that result in organ damage due to blood sugar dysregulation.

**CONCLUSION**
Several promising herbal remedies contain useful antioxidants to reduce blood glucose in diabetes mellitus. Further research is needed to know the best administration method and dosage so it can be administered safely to diabetes patients.

**CONFLICT OF INTEREST**
We declare that there were no conflicts of interest in this study.

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**AUTHOR CONTRIBUTION**
All of the authors equally contributed to the study.

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