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Review Article

## **Potential Effects of Neem Plants (*Azadirachta indica* A. Juss.) as an Antidiabetic Agent**

### **Potensi Tanaman Mimba (*Azadirachta indica* A. Juss.) sebagai Antidiabetes**

Putri Rachma Novitasari<sup>1\*</sup>, Baiq Maylinda Gemantari<sup>2</sup>, Syarifatul Mufidah<sup>3</sup>, Prita Anggraini Kartika Sari<sup>4</sup>

<sup>1</sup>Department of Pharmaceutical and Technology Pharmacy, Faculty of Pharmacy, Universitas Ahmad Dahlan, Yogyakarta, Indonesia

<sup>2</sup>Master Program of Pharmaceutical Sciences, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, 55281, Indonesia

<sup>3</sup>Department of Pharmaceutical Biology, Faculty of Pharmacy, Universitas Ahmad Dahlan, Yogyakarta, Indonesia

<sup>4</sup>Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Ahmad Dahlan, Yogyakarta, Indonesia

\*Corresponding author: Putri Rachma Novitasari | Email: putri.novitasari@pharm.uad.ac.id

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**Abstract:** Many people choose alternative medicines for Diabetes Mellitus (DM) disorders, such as herbal plants to suppress the occurrence of the disease widely. In general, DM occurs when the pancreas doesn't produce enough insulin, or when the body can't effectively use the insulin which it produces. The use of medicinal plants to treat various diseases has shown minimal side effects. Indonesia is one of the countries that has used plants as traditional medicine since ancient times. In Indonesia, thousands of species of medicinal plants have been studied to address health problems. Among the medicinal plants that have been studied is the Neem plant (*Azadirachta indica* A. Juss) which has been shown to cure various diseases. This review article describes the potential of the Neem plant as an antidiabetic. The results of this literature review, in the form of Neem herbal extracts, have quite good potential as an antidiabetic because they contain several compounds such as meliacinolin, azachdirichtin, gliserid oil, acetyl oxyturanoe acid and other compounds that can also act as antidiabetic.

**Keywords:** *Azadirachta indica* A. Juss; Neem Plants; herbal; antidiabetic.

**Abstrak:** Banyak orang yang memilih obat alternatif untuk penyakit Diabetes Melitus (DM) seperti tanaman herbal, untuk menekan terjadinya penyakit tersebut secara luas. Secara umum, DM terjadi ketika pankreas tidak memproduksi cukup insulin, maupun ketika tubuh tidak dapat secara efektif menggunakan insulin yang dihasilkannya. Penggunaan tanaman obat untuk mengatasi berbagai penyakit telah menunjukkan efek samping yang minimal. Indonesia merupakan salah satu negara yang telah menggunakan tanaman sebagai obat tradisional sejak zaman dahulu. Di Indonesia, ribuan spesies tanaman obat telah diteliti untuk mengatasi masalah kesehatan. Diantara tanaman obat yang telah diteliti adalah tanaman mimba (*Azadirachta indica* A. Juss) yang telah dibuktikan dapat menyembuhkan berbagai penyakit. Artikel review ini menjelaskan potensi tanaman mimba sebagai antidiabetes. Hasil literature review ini diperoleh informasi bahwa ekstrak herba mimba memiliki potensi yang cukup baik sebagai obat antidiabetes karena mengandung beberapa senyawa seperti meliacinolin, azachdirichtin, minyak gliserida, asam asetiloksituranoe, dan senyawa-senyawa lainnya yang juga dapat bertindak sebagai antidiabetes.

**Keywords:** *Azadirachta indica* A. Juss; Neem Plants; herbal; antidiabetic

## 1. INTRODUCTION

Diabetes mellitus (DM) is a chronic disease occurs both when the pancreas does not produce enough insulin, or when the body cannot effectively use the insulin it produces. Insulin is a hormone regulates blood sugar. According to the World Health Organization (2019), there are two types of DM, type 1 DM and type 2 DM. Type 1 DM, formerly known as juvenile diabetes or insulin-dependent diabetes, is a chronic condition in which the pancreas produces little or no insulin on its own. Meanwhile, type 2 DM is a condition of ineffective use of insulin by the body. According to the American Diabetes Association (2015), diabetes is further divided into gestational diabetes and other diabetes. The gestational diabetes refers to the initial recognition or occurrence of glucose intolerance during the period of pregnancy [1]. Other types of diabetes include genetic abnormalities in the  $\beta$ -cell of the pancreas or mutations in insulin receptor or post-receptor deformities [2].

The global prevalence of people with DM and impaired glucose tolerance has increased from year to year over the last few decades [3]. This is due to changes in lifestyle from time to time [4]. In 1980, the World Health Organization (WHO) estimated that there are 108 million people with diabetes and the number will continue to increase fourfold in 2014. According to Basic Health Research (Riskesmas) in 2013 diagnosed cases of DM in Indonesia increased from 1, 1% to 2.1% in 2017.

Treatment of DM is chronic and lifelong treatment. The treatment such as insulin and oral antihyperglycemia costs relatively expensive. It is used for a long period of time and has potentially unwanted side effects. Thus, it is necessary to find an effective drug with a low price and has relatively low side effects such herbal medicines derived from plants [5].

It was known that the use of traditional or herbal medicines in many countries are increasing. In Indonesia, Jamu as a form of herbal medicine was widely used since centuries ago both for health and to cure diseases [6]. Indonesia has around 400 ethnicities (ethnicity and sub ethnicity) where each ethnic and sub-ethnic group has its own knowledge of traditional medicine [7]. As the second largest center of biodiversity in the world after Brazil, Indonesia has about 7,000 among 30,000 plant species having medicinal properties. This wealth of biodiversity has been researched, developed and used for improving health and economic purposes, while maintaining its sustainability [8].

Various medicinal plants in Indonesia have been explored for their health benefits through research both *in vitro* and *in vivo*. In this review article, we describe the potential of medicinal plants Neem (*Azadirachta indica* A. Juss) as antidiabetic based on the effects of secondary metabolite compounds through literature studies. The Neem belongs to Meliaceae family and it has numerous bioactive components with versatile application. The leaf extract of Neem is accounted for to have different pharmacological activities like anti-inflammatory, hypolipidaemic, immunostimulant, hepatoprotective and hypoglycaemic impacts. Considering the pharmacological importance of Neem, different studies reviewed in this chapter confirming the huge possibilities of neem for prevention and treatment of diabetes. Neem is a rich source of flavonoids, terpenoids, tannins, saponins, anthraquinones, sterols and alkaloids which helps in diabetes management. Neem compounds such as rutin and quercetin have been shown to have hypoglycemic/antihyperglycemic effects whereas nimidin have the weight management ability [9].

## 2. METHODS

The method of writing this review article was the literature study of various journal articles explored from ncbi, PubMeb, and other journal sources on the internet that discuss antidiabetic from the Neem plant. Search keywords used were antidiabetic, *in vitro*, *in vivo*, mechanism of antidiabetic, Neem plats and herbs as antidiabetic, decrease oxidative stress, antihyperglycemic, Neem upregulated or downregulated GLUT-4, normalizing blood glucose, pharmacological antidiabetic action of *Azadirachta indica*. The search for scientific journals regarding medicinal plant research discussed in this review article includes research on all parts of the plant. The source of the primary data used is the national journals and international journals published over the last 16 years.

### 3. DISCUSSION

#### 3.1. Symptoms and Diagnosis Methods for DM

The symptoms of DM are approximately the same in the two major types of diabetes (DM Type 1 and DM Type 2), but their intensity are different. The initial symptoms of untreated diabetic patients are assigned to elevate blood-glucose levels. As a result, a loss of glucose in urine occurs which increases urine output, leading to dehydration accompanied by raised water consumption. Insulin deficiency results in weight loss despite of increase in appetite and food consumption. Untreated diabetic patients also suffer from nausea, vomiting, and fatigue. They are susceptible to develop skin, vaginal infections and bladder. Fluctuations in blood sugar levels can cause blurred vision. Furthermore, very high sugar-levels can result in comma and even death [10]. The most popular diagnosis methods for diabetes include the measuring of fasting plasma glucose level (FPG), which is done in the early morning. The normal patients have FPG below 100 mg/dl; those between 100 and 125 mg/dl indicate pre-diabetic while those individuals with glucose levels above 125 mg/dl are considered diabetic [11].

#### 3.2. Adverse effects of current treatment of DM

Presently, oral hypoglycemic agents and insulin are used in the treatment of DM. The main unacceptable effect of insulin is that hypoglycemia which can damage the brain. In the beginning, swelling, erythema and stinging might occur especially. Allergy to human by insulin is unusual but it still can occur. Some patients who have started insulin therapy will develop short-lived dependent edema (due to Na<sup>+</sup> retention). The most common undesirable effects of metformin are the disturbances of gastrointestinal, abdominal pain, and metallic taste. Lactic acidosis is rare but has potentially toxic effect and metformin should not be given to patients with renal or hepatic disease, hypoxic pulmonary disease, heart failure or shock. High doses of metformin can cause vitamin B<sub>12</sub> deficiency due to impaired absorption. The general adverse effects of sulfonylureas are hypoglycemia, which can be severe and prolonged. Although the allergic skin rashes and bone marrow damage can occur very rare but it can be severe. Thiazolidinediones can cause acute hepatotoxicity, weight gain, gastrointestinal disturbances [12].

In order to control these problems, it is important to know the potential of medicinal plants to cure DM. Several traditional medicines are used for the treatment of patients with DM in different ethnic societies of Asia, Africa and the South America. Even in developed countries of Europe, North America and Japan, several plant products or herbal drugs are used for the treatment of DM. Medicinal plants are the greatest importance for health of individuals and communities [13]. In this review article, we describe the potential of medicinal plants that have been studied, including Neem (*Azadirachta indica A. Juss*) as antidiabetic. **Neem is a rich source of flavonoids, terpenoids, tannins, saponins, anthraquinones, sterols and alkaloids which helps in diabetes management. Neem** compounds such as rutin and quercetin have been shown to have hypoglycemic/antihyperglycemic effects whereas nimidin have the weight management ability [1].

#### 3.3. Potential Effects of Nees Plants as Antidiabetic

Natural products are the main substances for discovering promising lead candidates, which play an important role in future drug development programs. Ease of availability, least side effects and low cost make the herbal preparations are the main role of all available therapies, especially in rural areas [14]. Since centuries, many plants are considered a basic source of potent antidiabetic drugs. The most widely used as antidiabetic herbal medicines are Neem (*Azadirachta indica A. Juss*). It belongs to the family *Meliaceae* and has been used for a long time in traditional medicine in treating several diseases, including DM. Its leaves are characterized by the presence of high fiber content that is potent in DM management and controlling of post-prandial hyperglycemia through delaying gastric emptying, increasing viscosity of GIT content thus, suppressing digestion and absorption of carbohydrate with no risk of hypoglycemia, hyperinsulinemia and undesirable weight gain [15]. The therapeutic actions to cure DM of Neem plants summarized in Table 1.

**Table 1.** Therapeutic Actions to cure DM from Neem Plants

In vitro Study

Therapeutic Action	Plant Parts	Ref.
<i>Azadirachta</i> leaves are characterized by the presence of high fiber content that is potent in diabetes management and controlling of post-prandial hyperglycemia through delaying gastric emptying, increasing viscosity of GIT content thus, suppressing digestion and absorption of carbohydrate with no risk of hypoglycemia, hyperinsulinemia and undesirable weight gain	Leaves	[15]

In vivo Study

Therapeutic Action	Plant Parts	Ref.
Increasing insulin secretion from beta cells of pancreas.	Leaves, stem barks and seeds	[16]
Normalizing blood glucose level and lipid parameters in streptozotocin induced diabetic rats.	Leaves	[17] [18]
Possesses significant antidiabetic and antihyperlipidemic activity at 400 mg/kg.	Leaves	[19]
The combined leaf extracts of <i>Vernonia amygdalina</i> and <i>Azadirachta indica</i> cause increase in insulin level and show antihyperglycemic action in diabetic rats.	Leaves	[20]
The Leaves and barks have similar glucose homeostasis as compared to standard use of insulin or control. In addition, they showed reestablishment of the SOD, NOD and GSSH function after treatment. Hence, these extracts display an enormous potential as alternative pharmacotherapy.	Leaves and barks	[21]
Decreasing basal plasma glucose, Hb1Ac. Neem extract help modulate levels of glycoxidation.	Leaves and barks	[21]
Prophylactic agent in diabetes and adjuvant to treatment (Nimbidin and Nimbin).	Root	[22]
Decreasing baseline of glucose levels by 36.91%, and decreased serum glucose by 32.18%.	Leaves	[23]
Showing gradual decrease in postprandial glucose over a period of 21 days (antihyperglycemic); controls postprandial hyperglycemia (50% reduction). Increase in G6PD activity. Increased pancreatic islet function to secrete insulin. Increased glycogen level in muscle and liver. Neem extract helps increase overall insulin levels.	Leaves	[24]

Continued table 1...		
Leaves Combined treatment with <i>vanadate</i> and aqueous extract is effective in normalizing altered antioxidant enzymes. Treatment indicates partially corrected hyperglycemia and improved enzyme levels	Leaves	[25]
Reducing glucose, cholesterol, triglyceride and free radicals in tissue. Demonstrated increase in angiogenesis.	Leaves	[26]
Alcoholic extract of root barks has antidiabetic activity by reducing blood sugar levels significantly in rats alloxan induced diabetes.	Root barks	[22]
<ul style="list-style-type: none"> <li>- Chloroform extract of <i>Azadirachta indica</i> leaves decreasing fasting glucose level and showing good oral glucose tolerance in <i>in vivo</i> studies.</li> <li>- The extract decreasing intestinal glucosidase activity while increasing liver and muscle glycogen content.</li> <li>- Chloroform extract of <i>Azadirachta indica</i> leaves exhibit pancreatic islets producing insulin.</li> <li>- Chloroform extract of <i>Azadirachta indica</i> leaves able to normalize plasma insulin secreted by <math>\beta</math>-cells and c-peptide levels</li> </ul>	Leaves	[24]
<i>Azadirachta indica</i> leaves extracts normalized blood glucose, serum insulin, lipid profile, and improved insulin signaling molecules as well as GLUT4 proteins to treat type-2 diabetes mellitus.	Leaves	[27]
Standardize aqueous extract of <i>Azadirachta indica</i> leaves significantly reduced post prandial blood sugar level, fasting blood sugar level, glycosylated hemoglobin, and insulin resistance in randomized, double blind, placebo-controlled clinical study. The extract significantly improved endothelial function and decreased systemic inflammation through oxidative stress reduction.	Leaves and twigs	[28]
Fasting blood glucose levels was significantly decreased in streptozotocin-induced diabetic rats <i>in vivo</i> .	Leaves	[29]
Single administration of ethanolic extract of <i>Azadirachta indica</i> leaves and combination with <i>Gynura procumbens</i> leaves reduced blood glucose level in alloxan-induced diabetic rats. <i>In vivo</i> treatment showed Langerhans islets and $\beta$ cells improvements.	Leaves	[30]

Continued table 1...		
<p>The pharmacological antidiabetic action of <i>Azadirachta indica</i> has examined in diabetic rats:</p> <ul style="list-style-type: none"> <li>- After treatment for 24 hours, <i>Azadirachta indica</i> 250 mg/kg (single dose study) reduced glucose (18%), cholesterol (15%), triglyceride (32%), urea (13%), creatinine (23%), and lipids (15%).</li> <li>- Multiple dose study for 15 days also reduced creatinine, urea, lipids, triglycerides and glucose.</li> <li>- In a glucose tolerance test in diabetic rats with Neem extract 250 mg/kg demonstrated glucose levels were significantly less compared to the control group. <i>Azadirachta indica</i> significantly reduce glucose levels at 15<sup>th</sup> day in diabetic rats.</li> </ul>	Leaves	[31]
<p>The meliacinolin that isolated from <i>Azadirachta indica</i> leaves acts as an antidiabetic agent in streptozotocin-nicotinamide induced diabetes mice by reducing the severity of oxidative stress and acuity of hyperglycemia induced by streptozotocin through the improvement of hyperlipidemia, insulin resistance, and antioxidant defense system. In part the antidiabetic action of meliacinolin, is attributed to the intestinal inhibition of glucose absorption. Meliacinolin can be considered a compound as an antidiabetic agent, for its hypoglycemic and insulin augmenting effect and inhibition of intestinal <math>\alpha</math>-glucosidase and pancreatic <math>\alpha</math>-amylase.</p>	Leaves	[32]

#### 4. CONCLUSION

Based on reference studies, *Neem Plants (Azadirachta indica A. Juss.)* has many effects as an antidiabetic agent with many studies proving that *Azadirachta indica* in cell culture (*in vitro*), such as improved insulin signaling molecules as well as GLUT4 protein to treat type-2 diabetes mellitus, as well as presenting the experimental animals (*in vivo*), such as increasing insulin secretion from beta cells of pancreas, normalizing blood glucose level and lipid parameters in diabetic rats, possesses significant antidiabetic and antihyperlipidemic activity, it helps modulate levels of glycooxidation, and it can decrease baseline of glucose levels and decreased serum glucose. Existing research results can be developed as a basis for *Neem (Azadirachta indica A. Juss.)* as an antidiabetic drug.

## CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest to disclose.

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