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Phytochemical and Antidiabetic Activity of *Morinda citrifolia*: A Review

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Abstract: *Diabetes mellitus is a highly prevalent disease requiring continuous treatment. Long-term use of antidiabetic drugs can cause side effects. Therefore, this article was designed to provide updated information on the phytochemical and antidiabetic activity of Morindacitrifolia. This review presents the literature evidence from January 2011 to December 2021. Three bibliographic databases were used as the primary sources of information (Pubmed, Google Scholar, ScienceDirect). A total of 16 studies were used in this paper based on feasibility, including eight articles on phytochemicals and eight on antidiabetics. Phytochemical compounds in Morindacitrifolia are alkaloids, flavonoids, steroids, tannins, saponins, terpenoids, phenolics, cardiac glycosides, anthocyanins, anthraquinones, leucoantosians, coumarins, reducer compounds, and asperulosidic acid.* ***Pharmacological*** *studies reported that Morindacitrifolia was proven to have an antidiabetic activity observed from several parameters, including blood glucose levels, plasma insulin, histopathological examination, and others.*

Keywords: *antidiabetic, antihyperglycemic, hypoglycemic, Morindacitrifolia, phytochemical*

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I. Introduction

Diabetes Mellitus (DM) is a chronic disease caused by a lack of insulin production by the pancreas or impaired insulin sensitivity [1]. Diabetes mellitus is a non-communicable disease with various complications, a high mortality rate, and requires high medical costs [2]. The cases and prevalence of diabetes mellitus have continued to increase over the last few decades [1]. The Middle East and North Africa region had the highest prevalence of diabetes in adults (10.9%), while the Western Pacific region had the highest number of adults diagnosed with diabetes and had the country with the highest diabetes prevalence (37.5%) [3]. The International Diabetes Federation (IDF) estimates that 463 million adults aged 20-79 have diabetes (9.3% of all adults in this age range)[2].

There are four types of diabetes mellitus: type 1 diabetes, type 2 diabetes, gestational diabetes, and certain types of diabetes due to other causes[4]. Type 2 diabetes is a largely preventable, chronic, and progressive medical condition that results from two primary metabolic dysfunctions: insulin resistance and pancreatic β cell dysfunction leading to relative insulin deficiency. In individuals, this occurs because of modifiable lifestyle-related risk factors that interact with genetic risk factors[5].

Patients with diabetes mellitus who continue to increase in number can be reduced by various treatments that have been found. Treatment or management of diabetes mellitus has a general goal, namely improving the quality of life of people with diabetes mellitus; the long-term goal is to prevent and inhibit the progression of microangiopathy and macroangiopathy complications, and the ultimate goal of management is to reduce diabetes mellitus morbidity and mortality[6].

Treatment of type 2 diabetes includes non-pharmacological and pharmacological treatments to lower and control glucose levels. Pharmacological interventions include insulin, metformin, sulfonylureas, meglitinide, a thiazolidinedione, Dipeptidyl Peptidase-4 (DPP-4) inhibitors, Glucagon-like Peptide-1 (GLP-1) receptor agonists, and Sodium-Glucose co-Transporter 2 (SGLT2) inhibitors, while non-pharmacological interventions such as lifestyle changes and exercise [7]. Patients with diabetes mellitus require continuous treatment[8]. However, the use of these antidiabetic drugs can cause side effects in long-term use[9]. Research on various plants used as antidiabetics has been carried out to find alternatives for natural diabetes mellitus treatment and minimize side effects. Based on research, many plants can be used as antidiabetics, one of which is noni (*Morindacitrifolia* L)**.**

Morindacitrifolia L (Noni fruit) from the Rubiaceae family is a small to medium-sized tree widely distributed in the tropics. Noni fruit and leaves have been consumed as traditional food[1011]. Noni is one of the plants with broad nutraceutical and therapeutic effects, known for its medicinal value for 2000 years in Asia and

Australia. It is a plant that grows in the pacific islands and has been used to treat various diseasessuch as diabetes, high blood pressure, cancer[12], anti-inflammatory, anti-bacterial, and anti-asthma [13].

The main bioactive components of noni fruit that have been identified consist of flavonoids, iridoids, oligosaccharides, and polysaccharides [11], while in Indonesia, noni is known to have many benefits. It is due to the presence of identified secondary metabolite compounds [14].

There is much more research on phytochemicals and the development of their activities in medicine. This literature review aims to gather extensive literature on both phytochemicals and in vivo, in vitro reports reporting the antidiabetic activity of *Morindacitrifolia*.

II. Methods

The review article conducted by the researcher in this writing is a literature review study. This literature review search was conducted to find evidence of the literature on phytochemicals and in vitro, in vivo antidiabetic activity of *M.citrifolia*from January 2011 to December 2021. In this study, article searches were conducted using online media with the keywords "Phytochemical," "Antidiabetic," or "Hypoglycemic," or "Antihyperglycemic" and "*Morindacitrifolia*." The most recent information on *M.citrifolia* was collected from scientific journals accepted worldwide through PubMed, ScienceDirect, and Google scholar electronic searches. This study's original research articles were published in English and Indonesian. This review did not include articles in the form of books, review articles, systematic reviews, meta-analyses, short communications, newsletters, and expert opinions. Complete articles were collected, examined, summarized, and concluded.

III. Resultand Discussion

The literature study on the phytochemical and antidiabetic *M.citrifolia* used 16 articles, of which eight were on the phytochemical *M.citrifolia,* and eight were on antidiabetics.

3.1 Phytochemical

A phytochemical test is a method to determine the various chemical compounds that are formed and contained in plantsstarting from the chemical structure, biosynthesis, changes, metabolism, and bioactivity. The phytochemical content of *M.citrifolia*has been proven in several studies, as shown inTable 1.

Table 1. Summary of Bioactive compounds of Morindacitrifolia

Parts	*Compounds*	*Country*	*References*
Fruit	Alkaloids, glycosides, flavonoids, steroids, tannins, saponins	India	15
Flos	-Deacetyl asperuloside acid -Acid asperuloside -flavonoids, quercetin-3-O-α-L-rhamnopyranosyl-(1 → 6)-β-D-glucopyranoside - kaempferol-3-O-α-L- rhamnopyranosyl- (1 → 6)-β-D-glucopyranoside	American	16
Fruit	Steroids, cardiac glycosides, terpenoids, flavonoids	Chennai	17
Leaf	Steroids, terpenoids, glycosides, flavonoids, phenolic compounds, amino acids, reducing sugars, saponins, tannins	India	18
Fruit	Anthocyanins, anthraquinones, leucoantosians, coumarins, flavonoids	Benin	19
Leaf	organic acids	Chinese	20
Fruit	Polyphenols, alkaloids, glycosides	Benin	21
Fruit	ursolic acid	Indonesia	22

The research conducted by Ramesh et al. regarding the phytochemical analysis of *M.citrifolia used* five extracts, namely aqueous extract, ethanol extract, methanol extract, ethyl acetate extract, and chloroform extract. The aqueous extract showed the presence of carbohydrates, proteins, alkaloids, saponins, glycosides, tannins, flavonoids, and steroids. The ethanol extract shows carbohydrates, proteins, tannins, flavonoids, steroids, alkaloids, and glycosides. The methanol extract shows carbohydrates, alkaloids, saponins, glycosides, tannins, flavonoids, and steroids. The ethyl acetate extract and chloroform extract showed the presence of proteins, glycosides, tannins, flavonoids, steroids, and carbohydrates [15].

Deng et al. also conducted a study on the primary quantitative determination of *M.citrifolia*. The study was conducted using the HPLC-PDA method. This method was validated with noni blossom samples to determine LOD, LOQ, linearity, intraday and interday precision, and accuracy. There are four main compounds in M. citrifolia flowers *3* identified, namely deacetyl asperuloside acid, asperulosidic acid, flavonoids, quercetin-3-O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside (3) and kaempferol--O-α-L-rhamnopyranosyl-(1→6)-β-D-glucopyranoside [16].

Based on the study of Nagalingam et al. regarding phytochemical screening using three solvents including water extract, ethanol extract, and methanol extract from *M.citrifolia*. Phytochemical analysis of *M. citrifolia* showed the presence of all significant phytochemicals, namely steroids, cardiac glycosides, terpenoids, carbohydrates, and flavonoids, while phyllobates, anthraquinones, and resins were not found in *M. citrifolia* fruit [17].

The presence of various phytochemical compounds in the leaves of *M.citrifolia*expressed by Yee include steroids, terpenoids, glycosides, flavonoids, carbohydrates, phenolic compounds, amino acids, reducing sugars, saponins, and tannins. Several compounds have medicinal properties and health-promoting effects, namely alkaloids, phenolics, terpenoids, and cardiac glycosides, while phenolics constitute the largest phytochemical group and are said to be responsible for most of the antioxidant activity of plant extracts [18].

Adjou et al.'s investigations revealed the presence of secondary metabolites in the fruit of *M.citrifolia*,such as anthocyanins, anthraquinones, leucoanthocyanins, coumarins, and flavonoids. It was evidenced by identifying it with the first research procedure anthocyanins have been revealed by hydrochloric acid plus 5% and a few drops of ammonia to absorb, the red color changes to purplish or greenish bruises indicating the presence of anthocyanins, both leuco-anthocyanins as evidenced by hydrochloric alcohol, red cherry color or purplish indicates leucoanthocyanins. The three coumarins were identified by fluorescence at UV at 365 nm, the reaction to cyanidin revealed the four flavonoids, and finally, the reducing agent was identified by the Fehling liquor test [19].

A phytochemical test was conducted by Ly et al.using the slightly modified Cuilei method and also analyzed using TLC. The phytochemical analysis tested the leaves of *M.citrifolia*positive for flavonoids, alkaloids, tannins, triterpenoids, saponins, coumarins, anthraquinones, carotenoids, organic acids, with TLC results showing the Rf band values obtained from *M citrifolia* equivalent to common standards [20]

Next,Sina et al. tested the phytochemical activity of *M.citrifolia*,which in this study reported the presence of compounds contained in the fruit of *M.citrifolia*,such as glycosides, polyphenols, and alkaloids. Phytochemical investigations were carried out by test tube staining contained in crude water extract and *M. citrifolia*[21].

A study by Lolok et al. reported that ursolic acid had the best binding energy (-8.58 kcal/mol) and was comparable to acarbose (-8.59 kcal/mol). Ursolic acid can inhibit human pancreatic amylase, so it can be developed as a type 2 antidiabetic drug candidate as evidenced by binding, RMSD, RMSF, Rg, SASA, and MM-PBSA calculations [22].

3.2 Antidiabetic Activity *Morindacitrifolia*

M.citrifolia has many pharmacological activities and many benefits for the body. Antidiabetic activity in *M.citrifolia*has been proven in vivo, in vitro, and in clinical trials. A total of 8 research studies have been conducted, and the results of these studies as shown in Table 2.

Table2. ***Antidiabetic activity of Morindacitrifolia***

Type of extract or Formulation	*Plant part and source used for studies*	*Dose/ Concentration*	*Experimental Mode*	*Animal or disease models or Cell/specimen or object*	*Reported activity*	*Region*	*References*
			In Vivo				
Aqueous Extract *M.citrifolia*	Fruit	2 mL/kg	Streptozotocin induction (50 mg/kg BW)	Sprague Dawley male rat	The effect of *Morindacitrifolia* fruit juice is equivalent to the oral hypoglycemic drug glibenclamide, which significantly reduces hyperglycemia	India	23
Fruit Juice *M.citrifolia*	Fruit	2 mL/kg BB	Induction of Alloxan monohydrate (100 mg/kg BW)	Wistar Rat	Lowering serum glucose levels	India	24
Fruit Juice*M.citrifolia*	Fruit	2,25 gr/kg BB 4,5 gr/kg BB 9 gr/kg BB	Alloxan Induction (125 mg/kg BW)	Wistar strain male white rat	Lowers fasting blood glucose levels significantly for seven days	Indonesia	25
Fruit Juice *M.citrifolia*	Fruit	1.5 µL / g BB (p.o)	Glucose and insulin tolerance test	Male C57BL/6 mice	Improve glucose and insulin tolerance	USA	26
Fruit extract *M.citrifolia*	Fruit	211,60-252,20 mg/dL	□ Blood glucose level analysis □ Analysis of HbA1c levels □ Serum analysis (in vivo)	KKAy/ Tajcl mice	□ Decrease in serum glucose and insulin levels □ Decreased HbA1c □ Decreased HOMA-IR	Korea	27
Aqueous Extract *M.citrifolia*	Fruit	250 and 500 mg/kg BB	□ Glukosa serum □ Oral glucose tolerance test □ Enzyme-Linked Immunosorbent Assay (ELISA) □ Quantitative Real-Time PCR (qRT-PCR) (in vivo)	Swiss male rat	Aqueous extract dose that is more effective in improving glucose tolerance in the test	Brazil	28
fruit juice *M.citrifolia*	Fruit	2 mL/kg BBhari	Clinical trial (Human studies)	Patients who have been diagnosed with type 2 diabetes mellitus	Consumption of fruit juice for eight weeks experienced a significant decrease in fasting blood sugar levels and HbA1c values in type 2 diabetes	Germany	29
			In Vitro				
Fruit Ethanol Extract *M.citrifolia*	Fruit and leaves	1 mg / mL	□ Glucose absorption test □ α-amylase test □ α-glucosidase test	HepG2 cells	Ethanol extract has a mild inhibitory effect on glucosidase 57% and amylase 43.5% Scopoletin low activity on glucosidase 35.7% and amylase 23.9%	Malaysia	30
Aqueous Extract *M.citrifolia*	Fruit	250 and 500 mg/kg BB	□ Glucose uptake test □ Peroxisome Proliferator-Activated Receptor (PPAR)-γ test □ AMPK phosphorylation test	C2C12 cells	Fermentation of *M.citrifolia* ethanol extract significantly stimulated the uptake of 2-NBDG into C2C12-derived myotubes Fermentation of *M.citrifolia*ethanol extract stimulates PPAR-γ transcriptional activity Fermentation of M. citrifolia ethanol extract stimulates AMPK phosphorylation in C2C12-derived myotubes	Korea	27

3.2.1In vivo study

Based on the research results of Nayak et al., *M.citrifolia* is a medicinal plant used to treat diabetes. In this study, rats were randomly divided into four groups (control, experimental diabetes, common diabetes, and untreated diabetes), six each. The parameters tested were fasting blood glucose, body mass, the glycogen content of liver tissue, and the degree of liver degeneration. Diabetic rats were treated orally with M.citrifolia (2 mg/kg, twice daily) and common diabetes with a reference hypoglycemic drug, glibenclamide, for 20 days. In diabetic rats, there was a significant decrease in fasting glucose from an excess of 300 mg/dl (day 3) to 150 mg/dl (day 20), and this represents a reduction of 52.6%.

Meanwhile, the standard diabetes group decreased fasting blood sugar from 250 mg/dl to 125 mg/dl. A decreased fasting blood glucose level was not observed in untreated diabetic rats. In the last ten days of the treatment period, the diabetic rats and the diabetic standard group showed a significant increase in body mass of

3.0 and 8.0 percent, respectively, while the untreated diabetic rats showed a decrease in body mass (16.3 g, 8.17%) during the 20 day treatment period[23].

The study by Debi P Mishra et al. showed an experimental design by distributing different groups and the treatment given, then induction of diabetes alloxan monohydrate at a dose of 100 mg/kg BW, which had been fasted overnight. The parameters studied were blood glucose (GLU), triglycerides (TG), total cholesterol (TC), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and hemoglobin levels. The results after the induction of diabetes from several parameters showed that the serum glucose concentration decreased. Fruit juice *M.citrifolia* gave better results, but the best results were from the standard treatment of diabetes drugs, metformin[24].

Research conducted by Achmad and Jennie experimentally in vivo with a pretest and post-test control group design on diabetic male Wistar rats. White rats, as many as 30, were divided and weighed into six groups randomly consisting of group I (negative control) not being treated, group II (positive control) induced by alloxan, group III *M. citrifolia* (2.25 g/kg BW)fruit juice *M.citrifolia* fruit juice *M.citrifolia* (9 g/kg BW). The test started with acclimatization in rats for seven days, and before being induced, blood glucose levels were measured in test rats. Only groups II and IV were induced with alloxan at 125 mg/kg BW Intra peritoneally. Noni juice *M.citrifolia* from the three doses can reduce blood glucose levels in diabetic Wistar male rats for seven days [25].

Nerurkar et al. tested the antidiabetic effect of *M.citrifoliaon* mice fed a high-fat diet (HFD), using glucose and insulin tolerance test methods. C57BL/6 male mice with a dose of 1.5 g/g BW Intra peritoneally measured blood glucose levels at 0, 30, 60, and 120 minutes using a glucometer instrument. A one-way ANOVA model was used to compare the mean between four groups of animals (control HFD, control FNJ, and HFD+FNJ). In HFD-treated mice, glucose intolerance was evident at 30 and 60 minutes, normalized at 120 minutes, whereas insulin intolerance was demonstrated at 0, 30, and 60 minutes and also became normal at 120 minutes. FNJ showed improved and normalized glucose and insulin tolerance test curve and area under the curve compared to HFD-treated mice. The test results showed that FNJ supplementation increased plasma glucose levels in HFD-fed mice by modulating hepatic gene expression of gluconeogenic and glycolytic enzymes through foxO1 phosphorylation [26].

The study conducted by Lee et al. was proven by randomly dividing mice into four groups, group 1 diabetes control (DC), group 2 positive control (PC), group 3 *M.citrifolia* (MC), group 4 *M.citrifolia* (FMC) are fermented. Blood glucose levels in the FMC group were 211.60-252.20 mg/dl. The rats used were KK-Ay/Tajcl rats. The rats were fasted overnight and then anesthetized with an intraperitoneal injection of Soleil 50 (30 mg/kg). The results showed that a decrease in serum glucose levels mediated by FMC was associated with a significant reduction in insulin resistance, a decrease in HbA1c, and a decrease in HOMA-IR [27].

Inda et al.2020 regarding the therapeutic effect of two different doses (250 and 500 mg/kg) using an aqueous extract of *M.citrifolia* in Swiss male rats fed high-fat/fructose diets. Parameters tested were food intake, body weight, serum biochemistry, oral glucose tolerance test (OGTT), and enzyme-linked immunosorbent assay (ELISA), as well as histological analysis of liver, pancreas, and epididymal adipose tissue. The results of the two doses studied showed that the aqueous extract dose of 500 mg/kg was higher and more effective in improving glucose tolerance than the 250 mg/kg dose, but both doses did not affect other metabolic and histological parameters [28].

Algenstaed et al. tested the effect of *M.citrifolia* fruit juice *on* blood glucose using the noni fruit juice extract method at a dose of 2 ml/kg body weight per day, consumed by 20 patients with type 2 diabetes (DT2) who were tested for two months. Blood analysis uses parameters such as blood glucose levels, HbA1c, C-peptide, hs-CRP, triglycerides, total cholesterol, LDL, and HDL. The results showed that consumption of 2 ml/kg BW noni juice for eight weeks led to a significant decrease in fasting blood glucose levels and HbA1c values in 20 patients with type 2 diabetes, while consumption of noni juice also increased insulin excretion via C-peptide, improving the status of the immune system. Blood cholesterol and reduce hs-CRP parameters [29].

3.2.2 In vitro study

Khamis et al. aimed to determine the effect of *M. citrifolia*and biomarker scopoletin on glucose uptake in HepG2 cells (human liver hepatocellular carcinoma cells) and their inhibitory effects on amylase and glucosidase. Fruit juice extracts*M.citrifolia* 1 mg/ml, and the dose for scopoletin was 0.2 M. This study tested glucose absorption, α-amylase, and α-glucosidase. The results from several tests obtained a glucose uptake extract of 59.5%, comparable to standard metformin, while the value of scopoletin was 30.6%. The extract had mild inhibitory activity against amylase and glucosidase with inhibition percentages of 43.5% and 57%, respectively. Meanwhile, the biomarker scopoletin showed lower activity at 23.9% and 35.7% for amylase and glucosidase, respectively [30].

Lee et al. also conducted an in vitro study where an assay using C2C12 cells with glucose uptake assay resulted in FMCE significantly stimulating 2-NBDG uptake into C2Cl2-derived myotubes PPAR-γ (Peroxisome

Proliferator-Activated Receptor) assay stimulated FMCE. The transcriptional activity of PPAR-γ, whereas in the AMPK phosphorylation assay, FMC stimulated AMPK phosphorylation in C2C12-derived myotubes [27].

Morindacitrifolia L is a helpful plant for treating diabetes as an alternative to chemical drugs. There are many compounds found in *M. citrifolia,* namely flavonoids. Flavonoids, especially rutin (a glycoside of rutinose and quercetin), are known to lower blood glucose levels[23]. Flavonoids are α-glucosidase inhibitors and dipeptidyl peptidase (IV) inhibitors. -glucosidase inhibitors work by inhibiting glucose absorption in the small intestine, while dipeptidyl peptidase (IV) inhibitors work by inhibiting the enzyme dipeptidyl peptidase (IV), thereby triggering the activity of incretin hormones resulting in insulin secretion[31]. Flavonoids are protective against damage to cells that produce insulin and can restore insulin receptor sensitivity on cells and even increase sensitivity [32]. Another mechanism of flavonoids exhibiting hypoglycemic effects is reducing glucose absorption and regulating the expression activity of enzymes involved in carbohydrate metabolism [32].

IV. Conclusion

M.citrifolia has many benefits in the community as traditional medicine. Studies on the chemical components of *M.citrifolia* have been shown to contain many active substances in the fruit, leaves, and flowers, such as alkaloids, steroids, phenolics, and terpenoids. The most commonly found compounds from *M.citrifolia*that provide antidiabetic activity are phenolic compounds from the flavonoid group.

Based on in vivo and in vitro activity studies, it can be concluded that *M.citrifolia* has been shown to have antidiabetic activity. Although clinical trials need to be increased, further research needs to be done to ascertain its antidiabetic activity in the future by understanding metabolism in the body and receptor interactions associated with antidiabetic activity. Further studies of the activity of *M.citrifolia*should provide a clear source of specifications for the ingredients used, mainly when plant extracts are used

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