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Diabetes Mellitus And The Therapeutic Potential Of Phaleria Macrocarpa Extract: A Review

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Abstract: *Background: The rising prevalence of diabetes mellitus globally necessitates the exploration of alternative treatment options. Phaleria macrocarpa, known for its traditional use in the treatment of various ailments, has garnered interest as a potential adjunctive therapy for diabetes. Objective: This review synthesizes current research on the efficacy and safety of Phaleria macrocarpa in the management of diabetes, outlining its therapeutic potential, pharmacological mechanisms, and future research directions. Methods: A comprehensive literature search was conducted, encompassing studies that investigated the effects of Phaleria macrocarpa on diabetes-related parameters in preclinical and clinical settings. Results: The collected data suggest that Phaleria macrocarpa may improve blood glucose control and insulin sensitivity. Several studies indicate a positive effect on metabolic parameters in diabetes. However, the safety profile warrants further investigation, as does the standardization of dosages. Conclusions: While preliminary findings show promise for the integration of Phaleria macrocarpa into diabetes care, extensive clinical trials are required to confirm efficacy and establish safety. Moreover, a better understanding of the plant's bioactive compounds, their mechanisms of action, and potential interactions with standard diabetes treatments is essential. The cultural importance of Phaleria macrocarpa supports its continued investigation, recognizing the need to respect and integrate traditional knowledge with contemporary medical practices.*

Keywords: *Phaleria macrocarpa, diabetes management, herbal medicine, traditional use, efficacy, safety.*

INTRODUCTION

Diabetes mellitus is a chronic metabolic disorder characterized by high levels of glucose in the blood. It can arise due to insufficient insulin production or the body's cells becoming less responsive to insulin, leading to three main types: Type 1 diabetes, Type 2 diabetes, and Gestational diabetes. (Symptoms & Causes of Diabetes, 2022) Diagnosis involves various blood tests measuring blood sugar levels, with ongoing management essential for preventing long-term complications such as cardiovascular disease, kidney damage, nerve damage, and eye problems (Tran et al., 2020). Diabetes mellitus is a widespread chronic condition with significant public health and socioeconomic consequences. Its prevalence is rapidly increasing due to factors such as economic progress, aging populations, urbanization, dietary shifts, decreased physical activity, and changes in lifestyle and cultural norms. (Prevalence of chronic conditions, 2023)

The World Health Organization has reported that the number of people suffering from diabetes worldwide is considerable, with estimates reaching into the hundreds of millions. In

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specific numbers, there are reports of 347 million people globally affected by diabetes, and it has been associated with millions of deaths annually (Saleem et al., 2021). Additionally, forecasts have suggested that by 2035, the diabetic population could surge to around 592 million people (Gunathilaka et al., 2022). The World Health Organization has stated that a significant number of people are affected by diabetes worldwide, with estimates reaching into the hundreds of millions. Reports indicate that 347 million individuals globally suffer from diabetes, and it is linked to millions of annual deaths. Projections also indicate an increase in the diabetic population to approximately 592 million people by 2035.

The significance of the disease is multi-faceted: **Health Implications:** Uncontrolled diabetes can lead to a variety of severe complications, such as cardiovascular disease, kidney damage, nerve damage, and eye problems, which can significantly decrease quality of life and increase mortality (Pontarolo et al., 2015). **Economic Impact:** The financial burden associated with diabetes care is massive, encompassing both direct costs such as medical care and medications, as well as indirect costs like loss of workforce productivity. The global cost of diabetes was estimated at US$673 billion in 2015, and these expenses are expected to increase along with the disease prevalence (Lorenzoni et al., 2017). **Social Consequences:** Individuals with diabetes often require life-long treatment and daily self-management, which can pose challenges in their personal and social lives. Given these implications, prevention and effective management of diabetes are crucial to reduce its impact on individuals and societies. This includes promoting healthier lifestyles, increasing access to healthcare services, and ensuring that those with diabetes receive adequate treatment and regular monitoring to prevent complications (Pontarolo et al., 2015) (Saleem et al., 2021) (Lorenzoni et al., 2017) (Gunathilaka et al., 2022).

Conventional treatments for diabetes mellitus aim to manage blood glucose levels, alleviate symptoms, and prevent complications. Management options depend on the type of diabetes and may involve lifestyle modifications such as diet, exercise, weight management, and smoking cessation. Medications for Type 1 Diabetes include lifelong insulin therapy through injections or an insulin pump. Type 2 Diabetes often starts with lifestyle changes, and medications may be added to improve insulin use or production. medications include:Metformin:(Dennedy et al., n. d)

Decreases glucose production in the liver and improves insulin sensitivity. Sulfonylureas: Stimulate the pancreas to produce more insulin. DPP-4 inhibitors: Help increase insulin release and decrease the liver's glucose production. GLP-1 receptor agonists: Mimic a natural hormone to increase insulin release and decrease glucagon levels. SGLT2

inhibitors: Cause the body to excrete excess glucose in the urine. Insulin therapy may also be used in Type 2 diabetes if other medications are not sufficient. **Blood Sugar Monitoring:** Regular monitoring of blood sugar levels is essential to managing diabetes effectively. Patients may need to check their blood sugar several times per day and adjust their insulin doses, diet, and activities based on the readings. **Education and Support:** Diabetes self-management education and support are critical to teach patients how to manage their condition and live healthy lives. **Preventing and Managing Complications:** Regular health check-ups are recommended to screen for complications such as kidney disease, eye damage, and nerve damage. Managing blood pressure and cholesterol levels, taking aspirin for certain patients, and not smoking also help prevent complications. (Fernando et al., 2022)

The goal of treatment is to keep blood glucose levels as close to normal as safely possible, which often involves a combination of therapies and requires ongoing adjustments by healthcare providers (Standards of Medical Care in Diabetes—2013, 2012) (Standards of Medical Care in Diabetes, 2004). Herbal medicine, also known as phytotherapy or botanical medicine, involves using plant-derived materials or preparations with therapeutic properties to treat various health conditions. In the context of diabetes management, herbal medicine can be considered as an alternative or complementary therapy to conventional treatments (Tran et al., 2020).

Here are some key points regarding herbal medicine in the context of diabetes: **Historical Usage:** For centuries, different cultures have used herbal medicines to manage diabetes. Medicinal plants are a part of traditional knowledge passed down through generations. 2. **Modern Relevance:** Despite advances in conventional medicine, interest in herbal remedies continues to grow, as they are perceived to be natural and potentially less prone to side effects (Neamsuvan et al., 2015). **Therapeutic Potential:** Many plants have been investigated for their antidiabetic properties, with some showing promise in lowering blood glucose levels, improving insulin sensitivity, or enhancing pancreatic function (Spunde et al., 2014). **Examples:** Over 350 traditional plants have been recorded for the treatment of diabetes, although relatively few have been scientifically evaluated for efficacy and safety. Examples include bitter melon, cinnamon, fenugreek, and ginseng (Spunde et al., 2014). **Research and Development:** The potential for developing new oral hypoglycemic agents from traditional medicinal plants is an area of interest, with research ongoing into the bioactive compounds these plants contain (Tran et al., 2020). **Integration with Conventional Care:** Herbal medicines may complement standard diabetes treatments.

However, it is crucial for patients to consult healthcare professionals before using them to avoid adverse interactions with prescribed medications and ensure safe and appropriate use (Tran et al., 2020). **Cultural and Local Practices:** The use of medicinal plants varies significantly across cultures and regions, with local flora often dictating which plants are used. For example, the Dayak Ngaju ethnic group in Central Kalimantan uses specific plant species indigenous to their region to treat diabetes (Fujianti et al., 2021). Blood Sugar Monitoring: Regular monitoring of blood sugar levels is essential for effective diabetes management. Patients may need to check their blood sugar several times per day and adjust their insulin doses, diet, and activities based on the readings. Education and Support: Diabetes self-management education and support are critical in teaching patients how to manage their condition effectively for a healthy life.

Preventing and Managing Complications: Regular health check-ups help screen for complications such as kidney disease, eye damage, and nerve damage. Managing blood pressure and cholesterol levels, taking aspirin for certain patients, and not smoking also help prevent complications. In summary, herbal medicines offer potential alternatives or complements to standard diabetes treatments, but their use should be approached cautiously, with professional guidance to ensure that they are safe, appropriate, and effective in managing diabetes (Tran et al., 2020) (Neamsuvan et al., 2015) (Spunde et al., 2014). Phaleria macrocarpa, also known as Mahkota Dewa or God's Crown, is a tropical fruit tree native to Papua, Indonesia. It has been widely used in traditional medicine across Asia for its potential medicinal properties. (Type 1 diabetes research paper jrhmc, 2020) (Medical Advisor Journals : Alfalfa, The Functional Herb Which Protects Our Body Against Type 2 Diabetes, Researchers Reveal, 2019) Phaleria macrocarpa is believed to have healing properties for numerous ailments due to its phytochemical content. (Hendra et al., 2011)

Phaleria macrocarpa is heralded for its potential medicinal benefits in traditional use. Scientific studies are still ongoing to fully understand its efficacy and safety profile. Professional medical guidance is crucial when considering it for therapeutic use, especially for conditions like diabetes, to ensure safety and monitor for any possible adverse interactions with conventional medications. (CBD, 2018) (Brown & Winterstein, 2019) Phaleria macrocarpa, also known as Mahkota Dewa or God's Crown, is a tropical fruit tree native to Papua, Indonesia. It has been widely used in traditional medicine in Asia due to its potential healing properties. Ongoing scientific research aims to understand its effectiveness and safety profile across various conditions. Seeking professional medical advice is crucial before considering it for therapy, especially for conditions like diabetes, to ensure caution and

monitor possible adverse interactions with conventional medications. (Iffland & Grotenhermen, 2017)

METHODS

This comprehensive review is based on the latest scientific databases on the families Phaleria macrocarpa,. The database was scanned from March 2001 to March 2024 for animal, in vitro, and studies. clinical. A systematic database search using the keywords " Phaleria AND macrocarpa ", was carried out. Only published data were included in this study; meanwhile, untitled references in English are not included. An extensive literature search was conducted to collect data, involving the use of scientific reports published in Frontiers, Science Direct, Scopus, Google Scholar, Pub Med, Wiley Online Library, Elsevier, and other references over the past two decades. Data collected regarding Botany, Phytochemistry, Traditional Uses, Pharmacology of the Apocynaceae Family and critically analyzed, and future strategies as well as appropriate perspectives of the plant as a new natural resource are discussed

RESULTS AND DISCUSSION

1. Phaleria macrocarpa: Botanical Overview

Taxonomy is the scientific method used to arrange all living organisms into a hierarchical structure, with different levels such as Domain, Kingdom, Phylum, Class, Order, Family,,Genus and Species. When discussing a plant in terms of taxonomy its placement within these levels would be detailed. For Phaleria macrocarpa,the taxonomic classification would be: Kingdom: Plantae Division:Magnoliophyta (flowering plants) Class:Magnoliopsida (dicotyledons) Order:Myrtales (a group of flowering plants including myrtle familyand others) Family:Thymelaeaceae(a family of flowering plants known asthyme or mezereumfamily) Genus :Phaleria Species:P. macrocarpa (Plant taxonomy, 2006) (Merckx et al., 2012)

Phaleria macrocarpa is a tropical evergreen tree that can reach a height of approximately 5 meters (16 feet). It features glossy, dark green leaves and produces fruit that changes to a vibrant red color when ripe. The fruits are generally round with seeds contained in a fleshy body. All parts of the plant, such as the fruits, seeds, leaves, and bark, are utilized in traditional medicinal practices across Southeast Asia. However, caution should be exercised and professional guidance sought due to potential toxicity and side effects associated with its medicinal use. The efficacy of Phaleria macrocarpa in

traditional medicine lies in its alleged healing properties including anti-inflammatory, anticancer, antidiabetes effects; however scientific research supporting these claims varies. (Or & Olalere, 2016)

The distribution and cultivation of a plant pertain to its geographic presence and how it is grown. **Distribution:** Refers to the areas where the plant is naturally found. This can range from very localized (endemic to a certain area) to widespread across continents. Climate, altitude, soil type, and other ecological factors affect where plants can thrive. For example, Phaleria macrocarpa, also known as Mahkota Dewa or God's Crown, is native to Papua, Indonesia, where it grows in its natural tropical habitat. **Cultivation:** Involves the human act of growing plants in specific conditions for various uses, such as for food, medicine, or ornamentation. Cultivation can be done on different scales from home gardens to large farms or in controlled environments like greenhouses.

As regards the cultivation of Phaleria macrocarpa, given its usage in traditional medicine, there's interest in farming the species for harvesting its medicinal components. Cultivation practices would consider the natural conditions the plant thrives in, such as temperature, humidity, and soil fertility, to ensure healthy growth and potentcy of its phytochemicals. This transition to cultivated status may help mitigate over-harvesting from the wild, as is the case with the African cherry, which is also used medicinally and is now being cultivated to prevent its exploitation (Stewart, 2003). In the context of conservation and sustainability, understanding the proper cultivation methods is essential, particularly for species that have significant medicinal value and are at risk of over-harvesting from their natural habitats.

Ethnobotany studies the relationship between plants and people, focusing on how different cultures use plants for various purposes, including medicine, nutrition, and rituals. Traditional uses of plants are often based on indigenous knowledge passed down through generations. In traditional medicine, plants are utilized for their therapeutic properties to treat various ailments. For instance, Phaleria macrocarpa, known as Mahkota Dewa or God's Crown, is native to Indonesia and has been used across Asia for its purported medicinal properties. Different parts of the plant, such as the fruits, seeds, leaves, and bark, are used to treat a wide range of health issues, including inflammatory conditions, cancers, and diabetes. It's important to note that scientif ic evidence for these traditional uses varies, and use of such plants should always be informed by contemporary medical advice to prevent toxicity and side effects (Lall & Kishore, 2014) (Ali & Chaudhary, 2011) (Rizk, 1987).

The ethnobotanical context gives insight into how local knowledge and cultural traditions guide the use of plants and underscores the importance of preserving this knowledge for future generations as well as for potential drug discovery and development (Khan et al., 2021) (Łuczaj et al., 2012) Diabetes Mellitus is a metabolic disorder characterized by high levels of glucose (sugar) in the blood resulting from problems with insulin production, insulin action, or both. The pathophysiology and complications of diabetes vary according to the type of diabetes—Type 1, Type 2, and Gestational Diabetes. (Diabetes mellitus, 2006)

2. Diabetes Mellitus: Pathophysiology and Complications

Pathophysiology: Type 1 Diabetes: This is caused by an autoimmune attack on the insulin-producing beta cells in the pancreas, leading to little or no insulin being produced. Without insulin, glucose cannot enter cells and remains in the bloodstream. **Type 2 Diabetes:** This form of diabetes is characterized by insulin resistance, where the body's cells do not respond properly to insulin, and eventually, insulin deficiency, when the pancreas cannot produce enough insulin to overcome this resistance. **Gestational Diabetes:** Occurs when hormonal changes during pregnancy cause insulin resistance. Although this usually resolves after pregnancy, it can increase the risk of developing Type 2 diabetes later in life.

Complications:(Mitanchez et al., 2015) Complications of diabetes arise primarily from prolonged periods of high blood sugar levels and can affect various organ systems. They are generally categorized as either acute or chronic. **Acute Complications: Diabetic Ketoacidosis:** Typically seen in Type 1 diabetes when the absence of insulin in the bloodstream leads to the breakdown of fats for energy, producing ketones, which cause the blood to become acidic. **Hyperosmolar Hyperglycemic State:** Seen in Type 2 diabetes characterized by extremely high blood sugar levels without significant ketones, leading to severe dehydration and altered consciousness. **Chronic Complications: Microvascular Damage:** Affecting small blood vessels, leading to diseases such as retinopathy (eyes) , nephropathy (kidneys) , and neuropathy (nerves). **Macrovascular Damage:** Affecting larger blood vessels, which increases the risk of cardiovascular diseases such as heart attack and stroke. **Diabetic Foot:** Resulting from a combination of neuropathy and poor circulation, leading to foot ulcers and infections that can be severe enough to require amputation.

3. Medicinal Potential of Phaleria macrocarpa

Managing diabetes through lifestyle changes, medication, and regular monitoring of blood glucose levels can help prevent or delay these complications (Continuing Professional Development: An outline of acute and chronic complications of diabetes, 2014) (Rivera et al., 2015). Phaleria macrocarpa, also known as Mahkota Dewa or God's Crown, is traditionally used in Southeast Asian folk medicine for its purported therapeutic properties. It is believed to have anti-inflammatory, anticancer, antidiabetic, and other medicinal effects. Different parts of the plant, such as the fruits, seeds, leaves, and bark, are used to treat a variety of health conditions. Despite its traditional uses, the scientific research supporting these medicinal claims for Phaleria macrocarpa is not conclusive, and the efficacy of these treatments can vary. Additionally, there should be caution regarding its use due to potential toxicity and side effects. It is essential to consult healthcare professionals before using Phaleria macrocarpa for medicinal purposes (Lall & Kishore, 2014).

4. Mechanisms of Action

The mechanisms of action refer to how a substance, such as a drug or a phytochemical from a plant, produces its effects on the body. While my sources don't specifically detail the mechanisms of action for Phaleria macrocarpa, I can provide a general explanation relevant to medicinal plants. Plants like Phaleria macrocarpa contain various phytochemicals with potential medicinal properties that can act through different mechanisms:**Anti-inflammatory:** Compounds may inhibit enzymes or signaling pathways involved in inflammation, reducing swelling and pain. **Anticancer:** Certain phytochemicals might induce apoptosis (programmed cell death) in cancer cells, inhibit their growth, or prevent the formation of new blood vessels that tumors require to grow. **Antidiabetic:** Some substances can increase insulin secretion, improve insulin sensitivity, or slow down carbohydrate digestion and glucose absorption, resulting in better blood sugar control. **Antioxidant:** Many plant compounds can neutralize free radicals, preventing oxidative stress and cellular damage. **Immune Modulation:** Components might enhance or suppress the immune response, which can be beneficial in various diseases and disorders.

The bioactive compounds in traditional medicinal plants interact with the body's own biochemical pathways to exert their effects. However, it's important to note that the precise mechanisms of action for the compounds within Phaleria macrocarpa and their

clinical relevance require further scientific study to fully understand and confirm their efficacy and safety (Lall & Kishore, 2014) (Ali & Chaudhary, 2011)

5. Efficacy and Safety

The efficacy and safety of medicinal plants, including Phaleria macrocarpa, depend on the presence of various bioactive compounds and their interactions with the body. While traditionally used for a range of medicinal purposes, the scientific evidence supporting the efficacy of Phaleria macrocarpa is limited and requires more rigorous clinical studies to substantiate the health claims associated with its use. As with many medicinal plants, there are also safety considerations.

Phaleria macrocarpa might have potential side effects or toxicities, especially if consumed inappropriately. Without extensive research and clinical trials, the full safety profile of Phaleria macrocarpa remains unclear. Therefore, it's essential to exercise caution and seek professional healthcare advice before using Phaleria macrocarpa or any traditional medicinal plant for therapeutic purposes (Lall & Kishore, 2014).

6. Clinical Studies and Evidence

Clinical studies refer to research conducted with human participants to evaluate the effectiveness, safety, and mechanisms of action of medical strategies, treatments, or devices. These studies can range from small-scale preliminary trials to large, randomized controlled trials that provide high-quality evidence. Evidence from clinical studies is essential to scientifically validate the efficacy and safety of treatments, including those derived from medicinal plants like Phaleria macrocarpa. Well-designed clinical studies can help determine whether the traditional uses of the plant are supported by empirical data, may identify side effects, and can assess the plant's potential role in modern medicine.

However, for many traditional medicinal plants, there may be a lack of rigorous clinical trials due to various reasons, such as limited funding, logistical challenges, and the complexity of testing plant extracts with multiple compounds. As a result, while there are many anecdotal and traditional reports supporting the use of plants like Phaleria macrocarpa, such claims require thorough investigation through clinical research to establish their validity in the context of evidence-based medicine. Without such studies, the clinical evidence for the medicinal use of Phaleria macrocarpa remains inconclusive (Lall & Kishore, 2014).

7. Limitations and Future Research

The limitations in the study of medicinal plants like Phaleria macrocarpa often involve a lack of comprehensive clinical trials to substantiate traditional medicinal claims.

Inadequate funding, complexity of isolating and testing specific compounds, as well as potential variability in plant preparations add to these challenges.

Future research should focus on conducting methodologically sound clinical trials to better understand the efficacy and safety profile of these plants. Investigating their pharmacological mechanisms and therapeutic potential could bridge the gap between traditional uses and evidence-based medicine. This could lead to the development of new treatments and a better understanding of the risks associated with their use (Lall & Kishore, 2014).

CONCLUSION

In conclusion, Diabetes Mellitus is a chronic condition with significant global impact, characterized by high blood glucose levels and associated with various complications. While modern medicine offers several treatments for managing diabetes, there is growing interest in the therapeutic potential of traditional medicinal plants such as Phaleria macrocarpa. Traditionally used in Southeast Asian folk medicine, Phaleria macrocarpa is reputed to have antidiabetic, anticancer, and anti-inflammatory properties, among others. Despite these traditional claims, scientific evidence supporting the medicinal effectiveness of Phaleria macrocarpa specifically for diabetes treatment is limited and not well-established in clinical studies.

Future research should aim to conduct comprehensive clinical trials to verify its safety and efficacy. Additionally, it is crucial to elucidate the mechanisms of action of its bioactive compounds and to understand its full pharmacological potential. The exploration of Phaleria macrocarpa, alongside other medicinal plants, can contribute to the development of new diabetes treatments. However, until more robust evidence is available, it is imperative for patients and healthcare providers to rely on proven therapies and to approach the use of Phaleria macrocarpa extract with caution, always in consultation with a medical professional (Neamsuvan et al., 2015) (Kargıoğlu & Arı, 2017) (Odeyemi & Bradley, 2018) (Tran et al., 2020) (Spunde et al., 2014).

Supplementary Materials:-

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