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Review Paper

Future Directions in research on Betel Leaf and Diabetes Management

Patil Pranjali*, Pituk Swapnanjali, Patil Sanika, Mokashi Ojas, Prashant Kumbhar

Ashokrao Mane College of Pharmacy, Peth-Vadgaon Maharashtra, India

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ABSTRACT

When insulin production or action is impaired, a metabolic condition known as diabetes mellitus (DM) sets up, causing persistently high blood sugar levels. By 2025, diabetes will have impacted an estimated 300 million people worldwide, according to the World Health Organisation. Insulin and oral hypoglycemic medications are examples of current treatments that can cause unwanted side effects. Traditional betel leaf, or Piper betle L., has antidiabetic effects, and this research investigates such effects. This study compares the effects of betel leaf juice to those of metformin, a popular antidiabetic drug, on lipid profiles, liver enzymes & blood glucose.

INTRODUCTION

Metabolic ailment recognised as diabetes mellitus (DM) is characterized by a long-term disruption in the metabolism of carbohydrates and elevated blood sugar levels brought on by the death or damage of β cells & target. [1] The metabolic condition known as diabetes mellitus (DM) affects

people of all ages, but it is most common in middle-aged adults. Long-term diabetes causes problems in many physiological systems, including the kidneys. Using data from 40 nations, the World Health Organization (WHO) extended predictions to the 191 WHO member states for the years 2000 and 2030. [2] The International Diabetes Federation (IDF) has generated other

***Corresponding Author:** Patil Pranjali

Address: Ashokrao Mane College of Pharmacy, Peth-Vadgaon Maharashtra, India

Email ✉: pranjaliipatil2003@gmail.com

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estimations which incorporate all 216 United Nations countries, were created to update the previous IDF estimates. It is projected that 300 million people worldwide would suffer from diabetes in 2025. [3] Diabetes management is a global health concern, with no effective medication having been found to date. Modern diabetes treatment options include insulin & drugs such as troglitazone, glucosidase inhibitors, metformin & sulfonylureas. The risk of serious adverse effects, including lactic acidosis, liver problems, and diarrhoea, has been recognised, though. [4] Approximately 143 million people are already impacted, and the number is growing daily; by 2030, it is expected to affect 366 million people globally. [5] One of the most well-known medicinal plants in Asia is betel leaf (*Piper betle*-Piperaceae). Traditional medicine is prepared from plant leaves to cure a variety of illnesses. [6] Because of its great abundance and low cost, it could encourage more research in the food and pharmaceutical industries. [7] Betel vine is another name for betel leaf. Most nations, including India, use it extensively for chewing habits in order to prevent bad breath, strengthen gums, and increase digestive fire [8]. Because of their astringent flavour, betel leaves are also cooked and used as cough medication. [9] The leaves are applied to purulent ulcers and used to treat lung and stomach problems in youngsters. [10] Their potassium nitrate level is high (0.26-0.42%). Glucose, fructose, maltose, and sucrose are the sugars found in betel leaves. Since ancient times, *P. betle* L. [11] extracts have been utilized to extravagance a variability of illnesses because of their vital antibacterial, antioxidant, anticancer, and antiallergic qualities. [12] Alloxan-induced diabetic rats were used to assessment aqueous and alcoholic extracts of *Epipremnum aureum* for antidiabetic properties. It's possible that flavonoids are causing the hypoglycemic impact through a mechanism unrelated to insulin

production. instance, [13] by blocking intestinal glucose absorption or endogenous glucose synthesis. Thus, goal was to examine *P. betle* L.'s antidiabetic and antioxidant qualities in fish that have been administered diabetes. The antidiabetic properties of *P. betle* L. extract in an induced fish model have never been documented before. [14]

OBJECTIVES

1. Investigate the potential antidiabetic properties of betel leaf extracts or compounds. [15]
2. Isolate and identify the specific bioactive compounds responsible for the antidiabetic effects. [16-17]

Characteristics:

Morphology Characters

Simple, alternating, petiolate, stipulate, reticular venation, oval bladder (8.0–18.0 cm by 6.0–12.0 cm), with a glossy upper surface, yellowish green petiole (2.0–6.0 cm) that is somewhat canaliculate, cordate at the base, and acuminate at the apex. [18] The petiole, which connects the leaf blade to the stem, is cylindrical in shape and has a little swell at the base. It is rather short. The climbing vine stem type, which frequently has a green or brownish stem and Where leaves appear, nodes and internodes are prominent; internodes are lengthy. [19]

Microscopic Characters

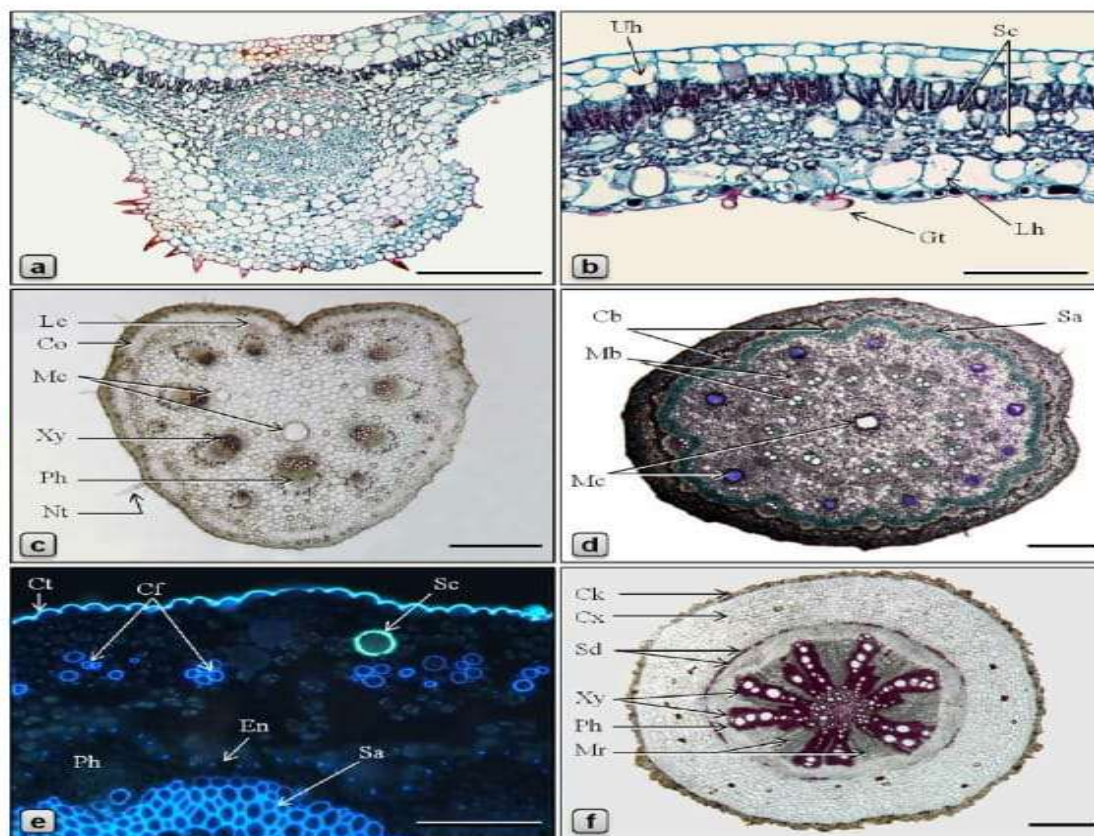
Leaf powder: This powder has a slick feel and is grayish green in hue. Stomata: Three to five subsidiary cells surround the guard cells in the cyclocytic stomata. [20]

Secretory Cells: The leaf contains calcium oxalate crystals, mucus canals, and secretory cells. The leaf contains both spiral and annular xylem vessels. [21]



Trichomes: Simple unicell and multicell trichomes are present in the leaf.

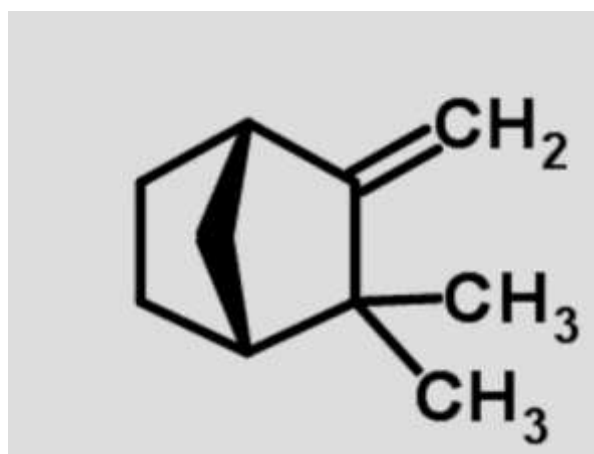
Epidermis Cell: There are pieces of epidermis cells in the leaf. Tracheary elements: Pieces of the secondary wall of the tracheary elements are present in the leaf. [22]



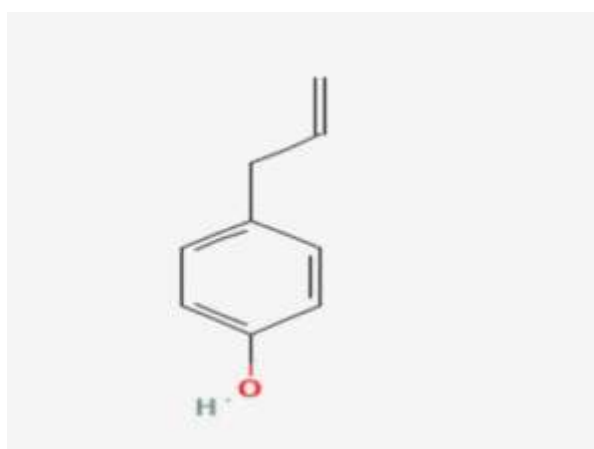
Phytochemical constituents

All extracts except water extract are produced when betel leaf is extracted using various solvents, including chloroform, ether, ethanol, and water extract, which yield phytosterol. [23] Petroleum ether extracts did not include alkaloids, but ethanol and water extracts did contain water, tannins, phenols, and carbohydrates. Only the water

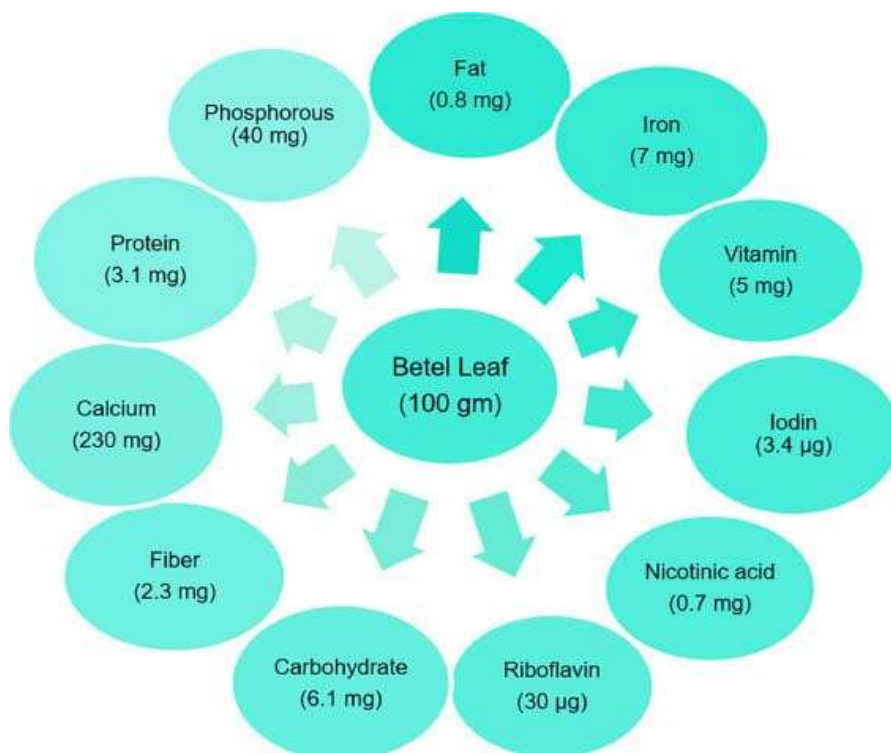
extract included flavonoids, while the ethanol extract contained essential oil. [24-25] The two most significant chemical components are chavicol (53.1%) and chavibetol acetate (15.5%). Additional ingredients were a-pinene (0.21%), 1,8-cineole (0.04%), safrole (0.11%), ally pyrocatechol diacetate (0.71%), eugenol (0.32%), camphene (0.48%), and chavibetol methyl ester (methyl eugenol 0.48%). [26]



Chavicol



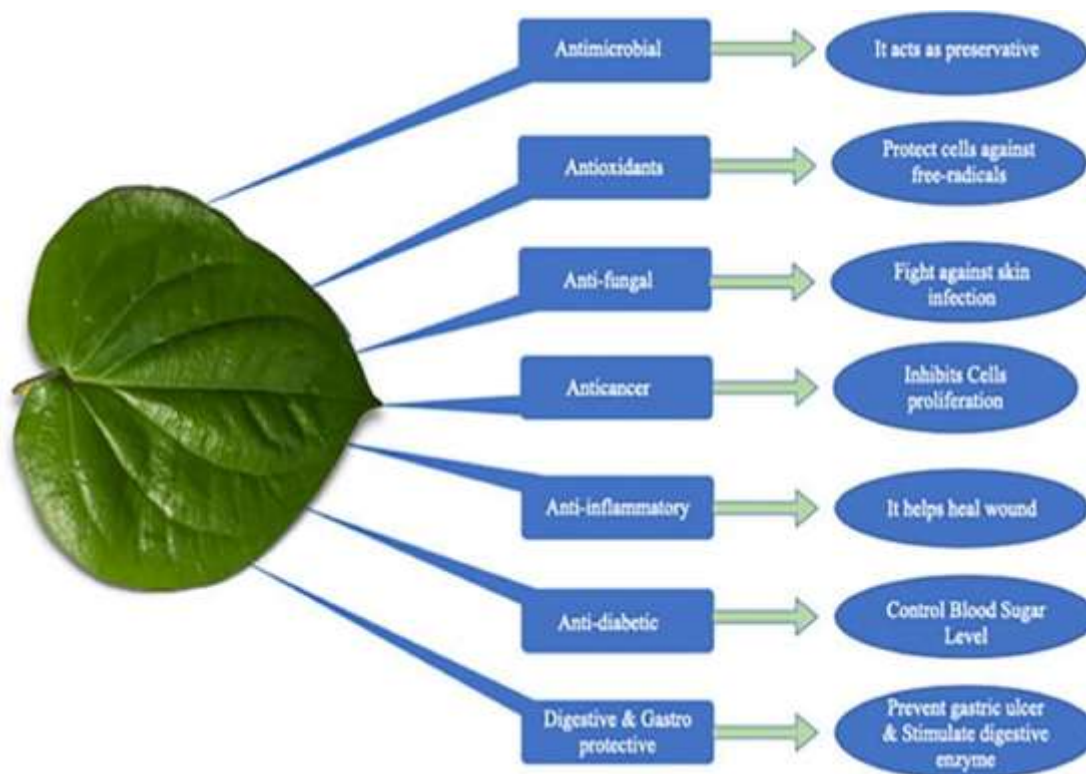
Camphene



Medicinal Uses

- 1) Respiratory health: Betel leaves can help treat respiratory infection, such as asthma, colds, coughs and bronchitis.
- 2) Digestion: Betel leaves increase metabolism, which triggers circulation and stimulates the intestines to absorb vitamins and nutrients.

- 3) Antiseptics and anti-fungal: Betel leaves have antimicrobial agent that combat bacteria that cause bad breath, cavities, plaque, and tooth decay.
- 4) Depression: Betel leaves assist create feelings of lightheartedness, wellbeing, and even happiness by promoting activity in the central nervous system.



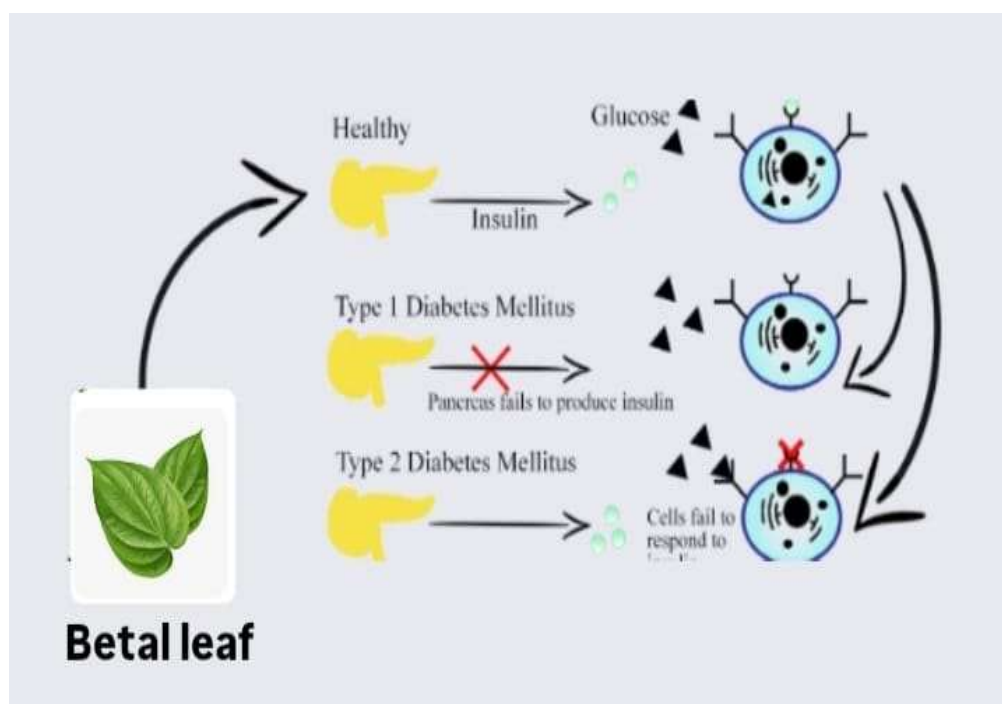
MECHANISM

Betel leaf, specifically Piper betel, has shown potential antidiabetic properties through various mechanisms: Potential antidiabetic effects of betel leaf, and more especially Piper betel, have been demonstrated via a number of mechanisms: Insulin sensitivity may be improved by betel leaf extract, which would make it easier for glucose to enter cells and lower blood sugar levels.[27] In order to help prevent oxidative stress and damage to pancreatic cells, the leaf extract has been shown to raise antioxidant levels, including pancreatic enzymatic antioxidants and plasma non-enzymatic antioxidants.[28] A diminution in quantity of

glucose taken into bloodstream may result from betel leaf's inhibition of intestinal glucose uptake.

Regenerating pancreatic cells: According to certain research, betel leaf extract may aid in the regeneration of pancreatic cells, which could enhance the production of insulin. [29] It has been demonstrated that betel leaf improves lipid profiles by lowering triglyceride and cholesterol levels.

Anti-inflammatory effects: By lowering oxidative stress and inflammation, the leaf's anti-inflammatory qualities may also help to achieve its antidiabetic goals. [30]



In Vivo Antidiabetic activity of glucose-induced fish

Effects of glucose administration on fish in vivo; samples of blood, liver, tissues, and epaxial musculature had glucose levels ranging from 1.3 ± 0.15 , 0.5 ± 0.1 , 0.02 ± 0.02 , and 0.01 ± 0.00 mg/dl, respectively. These results demonstrated the antidiabetic action in fish in good health. [31] After three hours, the levels of fish with glucose-induced hyperglycemia were 3.7 ± 0.2 , 0.5 ± 0.20 , 0.2 ± 0.20 , and 3.6 ± 0.2 mg/dl, respectively. When *P. betle* L. was treated with glucose-induced fish, the ethanolic extract showed values of 1.9 ± 0.35 , 0.5 ± 0.25 , 0.2 ± 0.25 , and 0.8 ± 0.2 mg/dl. [32]. In comparison, the values of a conventional drug were 1.0 ± 0.40 , 0.2 ± 0.1 , 0.2 ± 0.26 , and 0.2 ± 0.1 , respectively. Fish level range injections caused by glucose were seen twenty-four hours later. Fish given glucose show an in vivo antidiabetic benefit, according to the ortho-toluidine technique. A slightly modified approach was used to perform the in vivo investigation on *Clarias gariepinus* (catfish), which were acquired from Kunnavakkam, Kanchipuram, Tamil Nadu. The

specimen of fish was housed in a laboratory. The concentrations of metformin hydrochloride, glucose, and *P. betle* L. ethanolic extract ranged from 200 mg/ml. [33]. Preparing the test specimen. The blood samples were centrifuged right away at 3000 rpm for 10 minutes.

In vitro Antidiabetic Activity

The α -amylase activity of PBE was assessed using a modified version of [34]. A phosphate-buffer saline solution (0.02 mol/l, pH 6.8) was used to dissolve 0.1 mg/ml α -amylase. Mix α -amylase solution (0.25 ml) with sample solutions (3.125, 6.25, 12.5, 25, 50, and 100 μ g/ml) and incubate at 37°C for 5 minutes. Before commencing the reaction, 0.5 ml of 1.0% (w/v) starch substrate solution was added to the incubation medium. The reaction was stopped after three minutes at 37°C by adding 0.5 ml of a reagent solution containing 1% dinitrosalicylic acid, 0.05% Na₂SO₃, and 1% NaOH. The mixture was heated to 100°C for 5 minutes. [35] After three minutes at 37°C, boiling the liquid at 100°C for five minutes terminated the process. Next, 0.5 ml of

1% dinitrosalicylic acid, 0.05% Na₂ SO₃, and 1% NaOH was added. A spectrophotometer measured absorbance (Abs) at 540 nm after the sample cooled to room temperature.

Toxicological study

When examining the toxicology of betel leaf (Piper betle) for its potential antidiabetic benefits, it's important to assess both its safety and the implications of long-term use. Habitually used in several cultures for its medicinal properties, betel leaf raises safety concerns, especially when consumed in large amounts or over extended periods. [37]

1. Active Compounds: Betel leaves contain beneficial bioactive compounds such as polyphenols, flavonoids, and alkaloids (like arecoline). However, some of these compounds may pose risks at high doses. [38]

2. Potential Toxicity:

- Association with Areca Nut: Betel leaf is commonly chewed with areca nut, which carries health risks, including cancer and oral health problems. This combination may heighten health risks. [39]
- Long-term Use Risks: Chronic consumption of betel quid (betel leaf with areca nut) has been linked to oral cancers and other health issues, though studies on isolated betel leaf are limited. [40]
- Liver and Kidney Concerns: Some research suggests that excessive consumption of betel leaf extracts may lead to liver and kidney toxicity. [41]

3. Animal Studies: Research involving animals has looked at the safety and effectiveness of betel leaf extracts for lowering blood sugar levels. [42] These studies often monitor blood glucose, liver and kidney function, and examine tissue for

damage from prolonged exposure to high doses. [43]

4. Dose-Response Relationship: The effects of betel leaf depend significantly on the dosage; lower to moderate doses may be beneficial without major toxicity, while higher doses could lead to adverse effects. [44]

5. Clinical Research: There is limited clinical evidence on the safety and efficacy of betel leaf in humans. More extensive studies are needed to determine safe dosage ranges and potential side effects. [45]

6. Regulatory Status: Betel leaf is recognized as traditional medicine in some regions, while in others, it may face regulation due to its association with areca nut and related health risks. [46] In summary, while betel leaf shows promise for antidiabetic activity, careful consideration of its safety profile is crucial, particularly regarding long-term use and potential interactions with other substances. Consulting healthcare professionals before using it for health purposes is advisable.

CONCLUSION

Piper betle leaf demonstrates significant antidiabetic properties in diabetic rats by improving insulin sensitivity, lowering blood glucose levels & enhancing lipid profiles. Its bioactive compounds, such as chavicol and eugenol, may contribute through antioxidant activity, glucose absorption inhibition, and hepatic enzyme modulation. However, as excessive ingestion may result in hepatotoxicity and nephrotoxicity, more research is required to assess long-term safety & efficacy of betel leaf consumption in people. While it shows promise as an adjunctive diabetes treatment, careful consideration of dosage and duration is essential.

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