



Review of Mechanisms, Therapeutic Potential, And Use of Scopoletin from *Morinda Citrifolia* in the Treatment of type 2 Diabetes

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ABSTRACT:

Insulin resistance and improper glucose homeostasis are the main metabolic causes of Type 2 Diabetes Mellitus diseases (T2DM). As a result demand for new therapeutic agents with less side effects than present medicines is growing with growing prevalence of T2DM diseases. A well-known medicinal plant Noni also known as *Morinda citrifolia* has long been used in treating various diseases including metabolic diseases. A coumarin derivative scopoletin often found in Noni fruit has shown significant antidiabetic, antioxidant and anti-inflammatory properties. This Review focuses on different pathways by which scopoletin helps in controlling T2DM diseases. Various preclinical results, therapeutic potential, safety limits, and prospective clinical development are also discussed here. Scopoletin can be a promising phyto compound for management of increasing T2DM diseases and directs toward further investigation through clinical trials.

1. Introduction

A chronic metabolic disorder Type 2 Diabetes Mellitus (T2DM) is mainly caused due to insulin resistance and relative insulin deficiency. More than 500 million people are affected with T2DM. This disease can further lead to severe complications such as cardiovascular diseases, neuropathy, nephropathy, and retinopathy. Presently medicines like metformin, sulfonylureas and SGLT2 inhibitors are used to control symptoms but these are high cost medicine including side effects, and decreased efficiency with duration. (WHO)

Hence demand for phytochemical over traditional therapeutic agents is increasing. Since long centuries, Polynesian and Asian traditional medicine has been using *Morinda citrifolia*, commonly referred to as Noni. (McClatchey, W. 2002) One such bioactive compound, a coumarin derivative scopoletin known for its anti-inflammatory, antioxidant, and metabolic-modulating activities is present in this plant.

This review emphasizes on use of scopoletin for type 2 diabetes based on pharmacological activity, therapeutic activity by experimental evidence, safety and

areas of potential future research. This review emphasizes on use of scopoletin for type 2 diabetes based on pharmacological activity, therapeutic activity by experimental evidence, safety and areas of potential future research. Additionally, it highlights the need for more clinical trials to fully understand the efficacy and mechanisms of scopoletin in diabetes management. Future studies could explore its synergistic effects with other anti-diabetic agents and its long-term safety profile.

1.1 *Morinda citrifolia*: Botanical and Ethnomedicinal Background

Noni scientifically known as *Morinda citrifolia* L is a small evergreen shrub tree species belonging to the family of Rubiaceae. Even though it was originated in Asian and Australasian origins, it has been widely cultivated in tropical and subtropical regions of the world. The plant thrives in environment, such as coastal areas, lava flows and edges of forests (McClatchey, W. 2002)

M. citrifolia has long been found its place as medicine in Chinese, Polynesian, and Ayurveda to treat various ailments, including infections, inflammation, constipation, pain, and metabolic abnormalities. All the



parts of plant leaves, fruits, seeds, bark, and roots were medicinally important. (Akihisa, T *et al.*, 2007; Wang M. Y., 2002)

Noni's fruit juice is especially well-liked and has been marketed as a health supplement all over the world. It's thought to have hepatoprotective, immunomodulatory, analgesic, and antidiabetic effects. (Nerurkar PV *et al.*, 2015) A growing corpus of phytochemical and pharmacological research now supports the traditional applications, particularly when it comes to chronic conditions like Type 2 Diabetes Mellitus.

1.2 Scopoletin: Chemistry and Pharmacokinetics

A hydroxycoumarin, scopoletin has a molecular weight of 192.7 g/mol and a melting point between 204°C and 206°C. The compound's empirical formula is C₁₀H₈O₄. It dissolves a little bit in water or cold ethanol, barely soluble in benzene, soluble in hot ethanol or hot acetic acid, and readily soluble in chloroform. *Arabidopsis thaliana* produces scopoletin through the ortho-hydroxylation of feruloyl-CoA. (Kai K *et al.*, 2005)

The hepatoprotective, immunomodulatory, analgesic, and antidiabetic activity of noni juice has increased its demand in the world market as a food supplement. Various phytochemical and pharmacological studies have validated the use of traditional medicines for chronic diseases like Type 2 Diabetes Mellitus. (Wang M. Y., 2002)

M. citrifolia is known to be the major source of naturally occurring coumarin derivative scopoletin (7-hydroxy-6-methoxy-coumarin). It is also present in some medicinal plants such as *Evolvulus alsinoides*, *Artemisia capillaris*, etc. Scopoletin, has demonstrated remarkable anti-inflammatory, antioxidant, neuroprotective, and hypoglycemic activities, as mentioned in some preclinical studies. (Palu A. K. *et al.*, 2009; Yang, J., 2007)

Regarding the pharmacokinetics:

- Absorption: Scopoletin is bioavailable when taken orally but may be influenced by intestinal microbiota and pH.
- Distribution: After absorption, it is distributed throughout the liver, pancreas, and other tissues.

- Metabolism: Metabolic changes of scopoletin occur mainly in the liver through phase I and phase II. Excretion: Biliary and renal systems are responsible for excretion. (Gao X Y *et al.* 2024)

Its therapeutic efficacy and bioavailability could be enhanced by developments in formulation science and nanotechnology.

2. Scopoletin's Anti-Diabetic Mechanisms

Scopoletin has several pharmacological properties that are significant to the treatment of Type 2 Diabetes Mellitus. The key mechanisms are:

1. Antioxidant Activity: Scopoletin reduces reactive oxygen species (ROS), activates antioxidant enzymes like SOD, athione peroxidase, and protects pancreatic β -cells from oxidative damage. (Park J *et al.*, 2023)
2. Anti-inflammatory Effects: Chronic low-grade inflammation promotes insulin resistance. Scopoletin reduces pro-inflammatory cytokines such TNF- α , IL-6, and NF- κ B, improving insulin resistance. (Dey Parama *et al.*, 2022; Dussossoy E, *et al.*, 2011)
3. Insulin Sensitization: Scopoletin stimulates insulin signaling by modulating the PI3K/Akt and AMPK pathways, which improves glucose absorption and glycogen production.
4. Lipid Metabolism Regulation: It lowers triglycerides, total cholesterol, and LDL-C while boosting HDL-C, which improves lipid profiles in diabetic models. (Hui Y. *et al.*, 2000)
5. β -cell Protection: Scopoletin protects pancreatic β -cells from glucotoxicity and oxidative stress, reducing apoptosis and increasing insulin production. (Gao X Y *et al.* 2024)

2.1. Preclinical and Clinical Evidence

Scopoletin has been shown to significantly lower blood glucose levels, improve insulin sensitivity, and reduce oxidative stress, according to studies on animal models. It has helped in significant lowering of fasting blood glucose, HbA_{1c}, and lipid peroxidation indication of diabetic treated rats with scopoletin. (Hui Y. *et al.*, 2000).



Scopoletin controls diabetes and hyperglycemia. Scopoletin exhibits hypoglycemia and lipid-lowering properties in the diabetic rat model caused by streptozotocin (STZ) (Verma et al., 2013; AlZuaidy et al., 2016). Choi et al. found that via inhibiting lipid production and the TLR4–MyD88 pathways, scopoletin (0.01%) reduces hyperglycemia and hepatic steatosis in diabetic mice caused by HFD and STZ (Choi et al., 2017). Furthermore, in mice with STZ-induced diabetes, scopoletin raises postprandial blood glucose levels by suppressing the activity of enzymes that break down carbohydrates, α -glucosidase and α -amylase (Jang et al., 2018).

Extract of *Morinda citrifolia* containing scopoletin have been tested on humans for safety and other therapeutic effects such as lipid regulation and immunological boosting. These evidence are still preliminary also direct clinical trails testing of scopoletin alone in T2DM patients are yet insufficient. These findings underscore necessity to evaluate efficacy, dosage and long term safety in human populations by meticulously conducting randomized controlled trials (RCTs)

3. Safety and Toxicology Considerations

Toxicological assessments of scopoletin show a wide margin of safety at therapeutic levels. However, some instances of hepatotoxicity and neurotoxicity may occur for larger doses or continuous use. (Jamuna *et al.*, 2015)

Morinda citrifolia juice is usually considered harmless, while some reports have shown evidence of liver damage in vulnerable individuals if consumed in high quantity. To ensure safety in such cases, herbal preparations must be standardized, and quality should be controlled. (Jamuna *et al.*, 2015)

Further research on toxicity and human data is required to properly demonstrate the safety profile of scopoletin for long-term use in diabetic patients.

4. Future Directions

Future studies should focus on determining scopoletin's efficiency and safety in T2DM patients through clinical trials. The focus should also be on improving bioavailability by developing nano formulations or drug delivery systems. The synergistic

effects with existing antidiabetic medications should be investigated along with standardizing extraction and formulation techniques to ensure consistency and reproducibility. Further, the study should also focus on detailed mechanistic research to find novel molecular targets.

As interest in plant-based medicines is increasing, scopoletin shows promise as a supplementary or solo treatment in diabetes control.

5. Conclusion

A coumarin molecule, scopoletin, found in *Morinda citrifolia*, has many mechanisms that target important pathophysiological elements of type 2 diabetes mellitus, including oxidative stress, inflammation, and insulin resistance. Current preclinical research findings are directing towards the requirement of larger clinical trials to evaluate its therapeutic potential and assure safety. Scopoletin integration in diabetes therapy could provide a natural, effective alternative with fewer side effects than traditional medicines.

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6.1 Data Availability: Data are available on request basis only

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