Review Article

Necessity and rationale of herb-drug interaction studies between oral hypoglycemic agents and noni (*Morinda citrifolia*): A comprehensive review

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Abstract

Diabetes mellitus, particularly type 2 diabetes mellitus (T2DM), represents a major global health challenge requiring long-term pharmacotherapy. Parallel to the widespread use of conventional oral hypoglycemic agents, there has been a marked increase in the consumption of herbal medicines and nutraceuticals for glycemic control. *Morinda citrifolia* L. (Noni) is one such widely consumed medicinal plant, traditionally used for diabetes and other metabolic disorders. Concurrent use of Noni with oral hypoglycemic drugs raises significant concerns regarding potential herb-drug interactions that may alter therapeutic efficacy or safety. This review critically examines the necessity of conducting pharmacodynamic and pharmacokinetic interaction studies between oral hypoglycemic agents and Noni. The review discusses global trends in herbal medicine use, mechanistic bases of herb-drug interactions, pharmacological properties of commonly prescribed oral hypoglycemic agents, and the phytochemical and pharmacological profile of Noni. Emphasis is placed on the scientific rationale for preclinical interaction studies, regulatory perspectives, and translational relevance to clinical practice. Understanding such interactions is essential to ensure patient safety, optimize therapeutic outcomes, and provide evidence-based guidance for the combined use of herbal products and antidiabetic drugs.

Keywords: Herb-drug interaction, *Morinda citrifolia*, Noni, oral hypoglycemic agents, pharmacodynamics, pharmacokinetics, diabetes mellitus

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic, progressive metabolic disorder characterized by insulin resistance, impaired insulin secretion, and dysregulated glucose homeostasis (Murthy and Mayuren, 2008). The global prevalence of T2DM has increased dramatically over the past few decades due to urbanization, sedentary lifestyles, obesity, and dietary changes (Nagaraju and Anilkumar, 2021). Diabetes is associated with severe microvascular and macrovascular complications, including nephropathy, neuropathy, retinopathy, cardiovascular disease, and stroke, thereby imposing a substantial economic and social burden on healthcare systems worldwide (Anusha et al., 2017).

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Pharmacological management of T2DM commonly involves the use of oral hypoglycemic agents such as sulfonylureas, biguanides, dipeptidyl peptidase-4 (DPP-4) inhibitors, thiazolidinediones, and newer drug classes (Nagaraju and Anilkumar, 2021). While these agents are effective in achieving glycemic control, long-term therapy is often limited by adverse effects such as hypoglycemia, weight gain, gastrointestinal disturbances, and declining drug efficacy over time (Murthy et al., 2013). These limitations have contributed to the growing interest in complementary and alternative medicine, particularly herbal medicines, for the management of diabetes (Nagaraju and Anilkumar, 2021).

Herbal medicines have been used for centuries in traditional medical systems such as Ayurveda, Traditional Chinese Medicine, and folk medicine (Puranik et al., 2013). In recent years, their use has expanded globally, including in developed countries, where herbal products are commonly

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consumed as dietary supplements (Puranik et al., 2013). Importantly, patients with chronic diseases like diabetes often use herbal remedies alongside prescribed medications without informing healthcare providers (Chang and Chuang, 2010). This practice significantly increases the risk of herb-drug interactions, which may lead to reduced therapeutic efficacy or increased toxicity (Pitocco et al., 2013).

Morinda citrifolia, commonly known as Noni, is one of the most popular herbal products marketed worldwide for its purported health benefits, including antidiabetic, antioxidant, anti-inflammatory, and immunomodulatory effects (West et al., 2018). Given its widespread use among diabetic patients, there is a compelling need to systematically evaluate its potential interactions with oral hypoglycemic agents (Mohammad et al., 2016). This review aims to highlight the necessity of pharmacodynamic and pharmacokinetic interaction studies between oral hypoglycemic drugs and Noni, emphasizing their clinical and regulatory relevance.

Global use of herbal medicines in diabetes management

The use of herbal medicines for diabetes management is deeply rooted in traditional practices across Asia, Africa, and Latin America (Shraddha, 2023). In countries like India and China, herbal formulations are often prescribed alongside conventional medicines, based on the belief that such combinations enhance therapeutic efficacy and reduce adverse effects (Suliman et al., 2025). Surveys indicate that a significant proportion of diabetic patients regularly consume herbal products, either as self-medication or as part of traditional treatment regimens (Sathvik, 2025).

In the modern healthcare context, herbal medicines are frequently perceived as safe due to their natural origin (Wang, 2023). However, this perception is misleading, as many herbal products contain bioactive compounds capable of interacting with drug-metabolizing enzymes, transporters, and drug targets (Ekor, 2014). Unlike conventional drugs, herbal medicines often lack rigorous standardization, quality control, and comprehensive safety evaluation. Consequently, their concurrent use with antidiabetic drugs poses potential risks that necessitate scientific investigation.

Oral hypoglycemic agents: pharmacological and pharmacokinetic considerations

Oral hypoglycemic agents remain the cornerstone of T2DM management. Sulfonylureas such as gliclazide and glimepiride exert their hypoglycemic effect by stimulating insulin release from pancreatic β-cells through inhibition of ATP-sensitive potassium channels (Nagaraju et al., 2016). While effective, these agents are associated with a high risk of hypoglycemia, particularly when their pharmacokinetics are altered (Nagaraju et al., 2016).

DPP-4 inhibitors such as sitagliptin improve glycemic control by prolonging the action of incretin hormones, thereby enhancing glucose-dependent insulin secretion and suppressing glucagon release. These agents generally have a favorable safety profile but are still susceptible to pharmacokinetic interactions affecting absorption, metabolism, or elimination (Mu et al., 2009).

Most oral hypoglycemic drugs undergo hepatic metabolism, primarily via cytochrome P450 (CYP) enzymes, and are subject to transport by efflux and uptake transporters such as P-glycoprotein (Yang et al., 2017). Any herbal product capable of modulating these pathways may significantly influence drug exposure, leading to altered therapeutic outcomes (Hyo, 2011).

Morinda citrifolia (noni): phytochemistry and pharmacological properties

Morinda citrifolia. is a tropical plant belonging to the Rubiaceae family. Different parts of the plant, including fruits, leaves, roots, and bark, have been traditionally used for medicinal purposes. Noni fruit juice is the most commonly consumed preparation and is widely marketed as a health supplement (Nascimento et al., 2025).

Phytochemical investigations of Noni have identified a diverse range of bioactive compounds, including iridoids, flavonoids, anthraquinones, scopoletin, damnacanthal, and various phenolic compounds. These constituents are believed to contribute to the plant's reported antidiabetic, antioxidant, anti-inflammatory, and hepatoprotective effects (Wang, 2002).

Experimental studies have demonstrated that Noni fruit juice can reduce blood glucose levels, improve insulin sensitivity, and modulate lipid metabolism. While these properties suggest potential therapeutic benefits, they also raise concerns regarding additive or synergistic effects when Noni is consumed alongside oral hypoglycemic agents (Dixon, 1999).

Mechanisms of herb-drug interactions

Herb-drug interactions may occur through pharmacodynamic or pharmacokinetic mechanisms. Pharmacodynamic interactions involve additive, synergistic, or antagonistic effects at the drug's site of action, potentially leading to exaggerated therapeutic responses or adverse effects (Czigle, 2023). In the context of diabetes, concurrent use of Noni and oral hypoglycemic agents may result in excessive hypoglycemia due to overlapping glucose-lowering effects (Abdulwahid et al., 2024).

Pharmacokinetic interactions involve alterations in drug

absorption, distribution, metabolism, or excretion. Herbal constituents may modulate intestinal permeability, gastric emptying, or transporter activity, thereby affecting drug absorption. More importantly, many herbal compounds can induce or inhibit CYP enzymes and drug transporters, leading to significant changes in systemic drug exposure (Nagaraju and Anilkumar, 2020).

Given the complex and multi-component nature of herbal products like Noni, predicting such interactions without experimental evidence is challenging. This underscores the importance of systematic pharmacokinetic and pharmacodynamic studies.

Necessity of pharmacodynamic interaction studies

Pharmacodynamic interaction studies are essential to evaluate the combined effects of herbal products and conventional drugs on physiological endpoints such as blood glucose and insulin levels. In diabetes management, even modest changes in pharmacodynamic response can have significant clinical implications (Gupta et al., 2017).

Animal models, including normal and diabetic rodents, provide a controlled environment to assess the safety and magnitude of combined hypoglycemic effects. Such studies help identify whether co-administration results in additive or synergistic glucose-lowering activity that may predispose patients to hypoglycemia. These findings are critical for determining the safety margins of combination therapy (King, 2012).

Necessity of pharmacokinetic interaction studies

Pharmacokinetic interaction studies are crucial for understanding how herbal products influence the disposition of oral hypoglycemic agents. Changes in pharmacokinetic parameters such as maximum plasma concentration (Cmax), area under the concentration-time curve (AUC), time to reach peak concentration (Tmax), and elimination half-life (t1/2) can directly affect drug efficacy and safety (Nagaraju and Anilkumar, 2020).

Non-rodent models such as rabbits are particularly valuable for pharmacokinetic evaluation due to their physiological similarities to humans in drug metabolism and absorption. Identifying pharmacokinetic alterations at the preclinical stage enables better risk assessment and informs the design of clinical studies (Kumar et al., 2019).

Regulatory and clinical implications

Regulatory agencies increasingly recognize the importance of evaluating herb-drug interactions, especially for widely consumed herbal supplements. However, current regulatory frameworks often lack stringent requirements for interaction studies involving herbal products (Brantley et al., 2014).

From a clinical perspective, healthcare professionals frequently encounter patients using herbal supplements alongside prescribed antidiabetic medications. Evidence from interaction studies provides a scientific basis for counseling patients, adjusting drug doses, and preventing adverse outcomes. Without such evidence, clinicians are forced to rely on anecdotal information or theoretical assumptions (Hassen et al., 2022).

Translational relevance and future directions

Preclinical interaction studies serve as an essential bridge between traditional medicine use and evidence-based clinical practice. Findings from animal studies can guide clinical monitoring strategies and inform the need for controlled human studies.

Future research should focus on standardization of Noni preparations, identification of key interacting phytoconstituents, and well-designed clinical interaction studies. Integration of pharmacogenomic approaches may further enhance understanding of interindividual variability in herb-drug interactions.

Conclusion

The concurrent use of oral hypoglycemic agents and herbal products such as Morinda citrifolia is increasingly common in diabetes management. Given the potential for significant pharmacodynamic and pharmacokinetic interactions, systematic interaction studies are not only scientifically justified but also clinically imperative. Such studies provide critical insights into safety, efficacy, and optimal use of combination therapies, ultimately contributing to improved patient outcomes and rational use of herbal medicines in modern healthcare.

Conflict of interest

The authors declare no conflict of interest.

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