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Review Article

Critical Review of 1-Deoxynojirimycin (DNJ) in Mulberry in Curing Diabetes Mellitus

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Abstract

Diabetes mellitus, a chronic condition marked by elevated blood glucose levels, has become a global health concern, requiring effective and sustainable treatments. 1-Deoxynojirimycin (DNJ), an iminosugar primarily found in the root extract and also in other parts of mulberry (*Morus alba* L.), has emerged as a promising natural compound for diabetes management due to its potent α-glucosidase inhibitory effects. This article explores the mechanisms, efficacy, and future prospects of DNJ in mulberry root and leaf extracts for diabetes therapy, positioning it as a compelling candidate for integrative diabetic care. DNJ works by inhibiting diabetic-related enzymes (α-glucosidase) in the small intestine, which slows carbohydrate digestion and reduces postprandial glucose spikes, a critical factor in managing diabetes. In addition to its impact on glucose metabolism, DNJ has been observed to enhance insulin sensitivity, potentially improving glucose uptake and reducing insulin resistance in peripheral tissues. Research into the bioavailability and pharmacokinetics of DNJ indicates that although it has moderate oral absorption, advancements in formulation techniques are enhancing its therapeutic potential. Preclinical and clinical studies confirm that mulberry root and leaf extracts containing DNJ effectively modulate blood sugar levels, supporting their role as an anti-diabetic agent. DNJ offers significant promise as a natural, less invasive alternative to synthetic anti-diabetic drugs, with a favorable safety profile and potential for broad application in diabetes management.

Keywords

α-Glucosidase inhibition, blood glucose regulation, diabetes management, 1-deoxynojirimycin, mulberry extract, natural remedies

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Introduction

Diabetes mellitus, a chronic metabolic disorder marked by elevated blood sugar levels, has become one of the most pressing global health challenges, affecting millions worldwide (Dadhwal & Banerjee, 2023). Effective management of diabetes is critical to prevent complications like cardiovascular disease, neuropathy, and kidney failure (Tang et al., 2023; Yadav et al., 2022). Conventional diabetes treatments, including insulin therapy and oral hypoglycemic drugs, can be effective but often come with side effects such as gastrointestinal discomfort, weight gain, and the risk of hypoglycemia (Feng et al., 2022; Parida et al., 2020). These drawbacks have spurred interest in plant-based and natural remedies that offer fewer adverse effects, one of the most promising being 1-deoxynojirimycin (DNJ) found in mulberry (*Morus alba* L.) root and leaf extracts (Bai et al., 2023; Bharathi, Susikaran, Parthiban, et al., 2024; Bharathi, Susikaran, Vijay, et al., 2024).

Mulberry trees are known for their rapid growth and can range in size from small shrubs to larger trees, typically reaching heights of 10–15 m (33–50 feet) (Bharathi, Susikaran, Parthiban, et al., 2024; Bharathi, Susikaran, Vijay, et al., 2024; Thaipitakwong, 2020). The leaves of mulberry trees vary depending on the species, but are generally broad and simple with a serrated edge. The leaves of the white mulberry are especially significant as the primary food source for silkworms (*Bombyx mori*), making this plant essential for the silk industry (Bharathi et al., 2020; Yu et al., 2024).

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DNJ, an iminosugar, is known for its potent α-glucosidase inhibitory effects, which are central to controlling blood glucose levels. α-Glucosidase is an enzyme in the small intestine responsible for breaking down carbohydrates into glucose (Jan, Parveen, et al., 2021; Jan, Zahiruddin, et al., 2021; Vidyashree et al., 2020). By inhibiting this enzyme, DNJ slows down carbohydrate digestion, thus reducing the post-meal spikes in blood sugar, which is essential in diabetes management. This mechanism is especially valuable for individuals with diabetes, as it provides a natural way to stabilize blood glucose levels after meals, reducing the risk of hyperglycemia (Khanpara & Sojitra, 2022). DNJ's glucose-mimicking structure also allows it to interact with other enzymes involved in glucose metabolism, further enhancing its antidiabetic potential (Ramos et al., 2021; Zhang et al., 2022).

Research on DNJ has shown promising results in both animal and human studies, with findings that mulberry root and leaf extracts were rich in DNJ and can lower blood glucose levels, improve insulin sensitivity, and reduce markers of long-term blood sugar control, such as glycated hemoglobin (HbA1c) levels (Acharya et al., 2022; Jan, Parveen, et al., 2021; Jan, Zahiruddin, et al., 2021). In individuals with type 2 diabetes, insulin resistance is a key problem, where cells fail to respond adequately to insulin, leading to elevated blood sugar levels (Alugoju & Tencomnao, 2023). DNJ's potential to improve insulin sensitivity could help alleviate this aspect of diabetes, supporting better overall glucose management and possibly reducing the strain on pancreatic β-cells responsible for insulin production (Ahn et al., 2023).

Beyond its blood glucose-lowering properties, DNJ has shown potential as an antioxidant and anti-inflammatory agent (Ma et al., 2024). Chronic inflammation and oxidative stress are closely associated with diabetes and its complications, and DNJ's ability to mitigate these factors further enhances its value as a comprehensive natural therapy for diabetes (Walkowiak-Bródka et al., 2022). This multifunctional approach makes DNJ a compelling alternative to synthetic drugs, which often target only one aspect of diabetes management (Sarkhel et al., 2020).

Furthermore, DNJ faces certain challenges, particularly regarding its bioavailability and stability when taken orally. Advances in formulation methods, such as encapsulation and sustained-release delivery systems, are currently being explored to improve its absorption and effectiveness (Liu et al., 2023; Yu et al., 2024). Standardizing extraction methods for DNJ is also crucial for ensuring consistent therapeutic quality (Thaipitakwong, 2020). In conclusion, DNJ in mulberry root and leaf extracts represents a promising natural compound in the fight against diabetes. With its ability to inhibit carbohydrate digestion, improve insulin sensitivity, and reduce oxidative stress, DNJ offers a holistic approach to diabetes care (Foong et al., 2024). This article will delve into DNJ's role in diabetes management, examining its mechanisms, benefits, research findings, and future potential as a natural therapeutic agent for diabetes.

Biochemical Profile of 1-DNJ in Mulberry Root Extract

The extraction of DNJ from mulberry root is a critical step in obtaining its concentrated form for medicinal use. Various methods are used to isolate DNJ, including water-based, ethanol, and enzymatic extraction techniques (Abbas et al., 2024). Extraction by water is one of the simplest and safest method involving boiling the root in hot water, but it may yield lower concentrations of DNJ. Ethanol extraction, while more complex, tends to provide higher yields but requires careful handling and additional purification steps. Enzymatic extraction is a newer method that utilizes enzymes to break down cell walls, maximizing DNJ yield without compromising its stability (Afzal et al., 2021; Bai et al., 2023). Advanced methods like ultrasound-assisted extraction and supercritical fluid extraction are also being explored to optimize the extraction process, ensuring that DNJ is efficiently isolated and maintained in its most bioactive form (Maqsood et al., 2022; Yang et al., 2023).

DNJ's biochemical effectiveness is largely due to its unique structure. As an iminosugar, DNJ resembles glucose molecules, but has a nitrogen atom replacing the oxygen atom within its ring structure (Bashir & Dar, 2022). This glucose-like configuration allows DNJ to interact with enzymes involved in carbohydrate metabolism, particularly α-glucosidase, the enzyme responsible for breaking down carbohydrates into glucose (Mehrotra, 2021). By binding to α-glucosidase, DNJ inhibits its action, thus slowing carbohydrate digestion and reducing post-meal blood glucose spikes. This structural mimicry also enables DNJ to potentially modulate other enzymes related to glucose metabolism, making it a versatile agent in blood sugar regulation (Afzal et al., 2021; Yadav et al., 2022).

Despite its therapeutic potential, DNJ's bioavailability, or the extent to which it is absorbed into the bloodstream, presents certain challenges. DNJ has moderate oral bioavailability, meaning only a portion of the ingested dose is absorbed, limiting its effectiveness (Mai et al., 2024). Researchers are working to improve DNJ's bioavailability through encapsulation methods, which protect DNJ from degradation in the digestive tract, and sustained-release formulations that prolong its presence in the bloodstream (Choi et al., 2022). Once absorbed, DNJ distributes to tissues, where it inhibits α-glucosidase and supports insulin sensitivity. DNJ is primarily metabolized in the liver and excreted *via* the kidneys, with a relatively short half-life, which may necessitate repeated dosing to achieve sustained therapeutic effects (Wang et al., 2022).

Mechanism of Action of 1-DNJ in Diabetes Management

The mechanism of action of DNJ in diabetes management primarily revolves around its ability to inhibit α-glucosidase, an enzyme involved in carbohydrate digestion. Found in

mulberry root extract, DNJ's structure mimics glucose, allowing it to bind competitively to α-glucosidase (Feng et al., 2022; Priya, 2023). This binding inhibits the enzyme's activity, slowing the breakdown of complex carbohydrates into glucose within the small intestine. As a result, DNJ minimizes the rapid glucose absorption that typically follows meals, helping to prevent postprandial blood glucose spikes, a significant factor in managing diabetes (Figure 1). Additionally, DNJ's effect on insulin sensitivity contributes to its anti-diabetic properties, especially in type 2 diabetes (Chen et al., 2020). By improving the cellular response to insulin, DNJ supports glucose uptake in peripheral tissues, reducing overall blood glucose levels and alleviating the strain on pancreatic β-cells. Beyond these direct effects, DNJ may also exhibit antioxidant properties, mitigating the oxidative stress and inflammation associated with chronic hyperglycemia (Fatima et al., 2023). Together, these actions make DNJ an effective natural agent for glucose regulation, offering a multipronged approach to diabetes management. As interest grows in plant-based treatments for diabetes, DNJ stands out for its targeted biochemical actions and potential to complement existing therapies (Abudurexiti et al., 2023).

Research Studies on DNJ's Efficacy in Diabetes Management

Research on the efficacy of DNJ in diabetes management has yielded promising results in both animal models and human trials (Chen et al., 2023; Ma et al., 2022). Preclinical studies on diabetic rodents have demonstrated that DNJ, primarily derived from mulberry root extract, can significantly reduce blood glucose levels, lower HbA1c (a long-term marker of blood sugar control), and improve insulin sensitivity (Dhananjaya et al., 2022). These animal studies also indicate that DNJ's inhibition of α-glucosidase effectively delays carbohydrate digestion, reducing postprandial blood sugar spikes, a crucial factor in preventing the progression of diabetes (Yu et al., 2024). In human clinical trials, DNJ-containing mulberry extracts have shown similarly beneficial effects. For instance, trials with patients with type 2 diabetes and prediabetes have found that DNJ supplementation led to moderate reductions in post-meal glucose levels and improved markers of insulin sensitivity (Maqsood et al., 2022; Truzzi et al., 2024). These studies suggest that DNJ can complement traditional diabetes treatments, particularly in managing blood glucose fluctuations. However, further research is necessary to determine the optimal dosing, long-term effects, and DNJ's effectiveness across diverse patient populations (Afzal et al., 2021). Additionally, ongoing studies are investigating DNJ's potential role as an adjunct therapy, exploring its synergistic effects with existing anti-diabetic medications. Collectively, these findings underscore DNJ's promise as a natural, plant-based option for diabetes management, with the potential to reduce reliance on synthetic drugs and mitigate related side effects (Qiao et al., 2022; Verma et al., 2022).

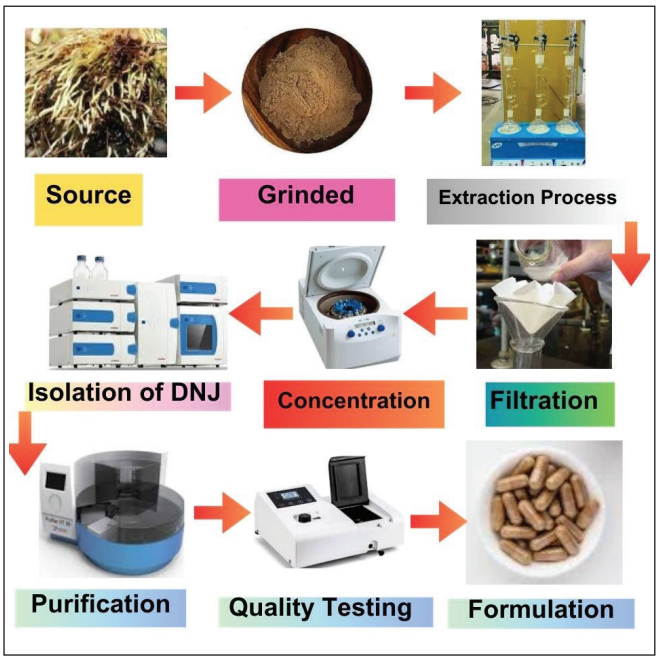


Figure 1. Flowchart for "Mechanism of Extraction of 1-Deoxynojirimycin (DNJ) from Mulberry Root Extract in Diabetic Management."

Animal Models and Preclinical Studies on DNJ's Efficacy in Diabetes

DNJ, a naturally occurring iminosugar found in mulberry root extract, has garnered significant attention in diabetes research, particularly due to its promising effects observed in animal models and preclinical studies (Ramappa et al., 2020). These models serve as crucial platforms for evaluating DNJ's anti-diabetic efficacy before advancing to human clinical trials. Numerous studies have demonstrated DNJ's ability to lower blood glucose levels in diabetic animal models, such as streptozotocin-induced diabetic rats, and genetically modified mice (Dimitrijević et al., 2021). In these studies, the administration of DNJ has resulted in significant reductions in fasting blood glucose and postprandial glucose levels. For instance, one study reported that DNJ supplementation led to a marked decrease in HbA1c levels, a key indicator of long-term glycemic control, suggesting its potential to improve overall metabolic health (Al Masum et al., 2024).

Moreover, DNJ's mechanism of action has been explored in these models, primarily focusing on its inhibitory effect on α-glucosidase, an enzyme that facilitates carbohydrate digestion in the intestines (Wang et al., 2024). By inhibiting this enzyme, DNJ slows the breakdown of complex carbohydrates, leading to a more gradual release of glucose into the bloodstream (Bai et al., 2023). This mechanism not only helps in regulating blood sugar spikes after meals but also

supports improved insulin sensitivity (Hao et al., 2024). In addition to its glucose-lowering effects, preclinical studies have also suggested that DNJ may possess antioxidant properties, further mitigating oxidative stress associated with diabetes (Marchetti et al., 2021; Parida et al., 2023). As a result, these animal studies underline DNJ's multifaceted role in diabetes management, showcasing its potential as a natural therapeutic agent. Continued research is essential to validate these findings further and to explore the full range of DNJ's benefits in diabetes therapy (Ma et al., 2022).

Clinical Trials on DNJ and Mulberry Extracts

Clinical trials investigating the efficacy of DNJ and mulberry extracts in diabetes management have provided valuable insights into their potential benefits for individuals with diabetes (Verma et al., 2022). Several randomized, double-blind, placebo-controlled trials have been conducted to assess the effects of DNJ supplementation on glycemic control in patients with type 2 diabetes and prediabetes. In one notable study, participants who received DNJ-enriched mulberry extract exhibited significant reductions in postprandial blood glucose levels compared with the placebo group. These findings were corroborated by improvements in HbA1c levels, suggesting that DNJ not only aids in immediate glucose regulation but also contributes to long-term glycemic control. The trials have also focused on safety profiles, revealing that DNJ and mulberry extracts are generally well tolerated, with few adverse effects reported (Chen et al., 2023; Park et al., 2021). This favorable safety profile is particularly appealing for individuals seeking natural alternatives to traditional antidiabetic medications, which often come with a range of side effects. Additionally, some studies have explored the potential of DNJ to enhance insulin sensitivity, further supporting its role in improving metabolic health (Zhang et al., 2024). However, while the results are promising, the trials have highlighted the need for larger-scale studies to confirm the findings and to determine optimal dosing strategies (Foong et al., 2024; Lim et al., 2024). Furthermore, variations in the formulation of mulberry extracts and extraction methods could influence the bioavailability and efficacy of DNJ, emphasizing the importance of standardization in future research (Parida et al., 2023). Overall, the clinical trials provide a foundation for understanding the role of DNJ and mulberry extracts in diabetes therapy, paving the way for their potential integration into comprehensive diabetes management strategies (Table 1).

Table 1. Notable Clinical Trials are Investigating the Role of 1-Deoxynojirimycin (DNJ) in Mulberry Root Extract in Managing Diabetes.

Clinical Trail	Participants	Dosage	Duration	Findings	References
1. Effects of mulberry root extract on blood glucose levels in patients with type 2 diabetes.	Adults with type 2 diabetes.	1,000 mg mulberry leaf extract (MLE).	12 weeks	Significant reduction in fasting blood glucose and HbA1c levels compared to placebo. Improved insulin sensitivity.	Riche et al. (2017)
2. Hydro-alcoholic extract of *Morus nigra* reduces fasting blood glucose and HbA1c% in diabetic patients.	Men with impaired glucose tolerance and T2DM.	4% hydro-alcoholic extract (3 mL extract @ three times a day).	12 weeks	After 3 months, both FBS and HbA1c% were significantly reduced in patients under mulberry leaves extract-treatment.	Momeni et al. (2021)
3. Effect of low-dose mulberry fruit extract on postprandial glucose and insulin responses.	Patients with type 2 diabetes.	0.75 g of MFE added to ~50 g of available carbohydrates from rice.	Mean 2 h PPG and PPI	MFE appears to dose-dependently reduce acute PPG and PPI in individuals with type 2 diabetes and may be a feasible dietary approach to help attenuate glycemic exposures.	Mela et al. (2024)
4. MLE affects metabolic profiles and oxidative stress in patients with type 2 diabetes mellitus.	Sixty patients with T2DM.	300 mg DNJ @ two times/day.	12 weeks	Mulberry extract among subjects with T2DM had beneficial effects on HDL-cholesterol, insulin and MDA levels but did not affect other metabolic profiles.	Taghizadeh et al. (2022)

(Table 1 continued)

(Table 1 continued)

Clinical Trail	Participants	Dosage	Duration	Findings	References
5. MLE improves glycemic response and insulinemic response to sucrose in healthy subjects.	Glycemic and insulinemic response to 75 g sucrose in healthy individuals.	75 g sucrose + white MLE or 75 g sucrose alone.	Capillary blood samples were collected at 15-min intervals in the first hour and at 30-min intervals over the second hour to determine glucose and plasma insulin levels.	The addition of MLE to sucrose resulted in a significantly lower glycemic response and insulinemic response compared to a matched placebo (sucrose alone).	Thondre et al. (2021)
6. The aim of this exploratory study was to investigate the effects of MLE on the glycemic indexes (GI) of common dietary carbohydrates.	The participants were randomized to receive glucose (three occasions), glucose + MLE, sucrose + MLE, maltose + MLE, and maltodextrin + MLE.	Orally consumed during seven visits (every 3 days).	Blood glucose level was tested at 15 min before and at 15, 30, 45, 60, 90, and 120 min after carbohydrate intake.	MLE reduced the GIs for maltose, sucrose, maltodextrin, and glucose by 53.11%, 33.51%, 31.00%, and 8.12%, respectively. The co-consumption of MLE with sucrose, maltose, or maltodextrin can reduce the GI values of these carbohydrates.	Wang et al. (2018)

Note: FBS: Fasting blood sugar; HbA1c: Glycated hemoglobin; HDL: High density lipoprotein; MDA: Malondialdehyde; PPG: Photoplethysmography; PPI: Proton pump inhibitors; T2DM: Type 2 diabetes mellitus.

Potential Benefits and Limitations of 1-DNJ in Diabetes Therapy

The potential benefits of DNJ in diabetes therapy are noteworthy, primarily due to its natural origin and multifaceted mechanisms of action. DNJ, derived from mulberry root and leaf extracts, exhibits strong α-glucosidase inhibitory activity that effectively slows carbohydrate digestion and reduces postprandial blood glucose spikes. This can lead to improved glycemic control, making it a valuable adjunct to traditional diabetes treatments (Ignat et al., 2021). Additionally, DNJ may enhance insulin sensitivity, further supporting blood glucose regulation and potentially alleviating the strain on pancreatic β-cells (Lv et al., 2022). Unlike many synthetic anti-diabetic medications, DNJ has a favorable safety profile, with fewer side effects reported, which makes it appealing for long-term use in managing diabetes (Jan et al., 2022; Yang et al., 2023). However, there are limitations to consider. The bioavailability of DNJ is moderate, which can restrict its therapeutic efficacy; therefore, the optimization of its formulation for better absorption is essential (Mehrotra, 2021). Moreover, while preclinical and preliminary clinical studies show promise, larger, well-designed clinical trials are needed to establish definitive efficacy, optimal dosing, and long-term safety (Liu et al., 2022; Ramappa et al., 2020). Another challenge is the standardization of DNJ extraction methods, as variations can affect the concentration and activity of the active compound in commercial products. Despite these limitations, ongoing research into DNJ's role in diabetes therapy offers hope for integrating natural remedies into comprehensive diabetes management strategies (Bai et al., 2023; Vyry et al., 2024).

Conclusion

DNJ extracted from different parts of the mulberry plant represents a promising natural approach to diabetes management. Its unique biochemical properties, particularly their ability to inhibit α-glucosidase, make it an effective agent for controlling postprandial blood glucose levels, which is crucial for preventing the complications associated with diabetes. The potential benefits of DNJ, such as improved insulin sensitivity and a favorable safety profile, position it as a valuable complement to conventional anti-diabetic therapies. While research has demonstrated its efficacy in both preclinical and clinical studies, further investigation is essential to fully understand its mechanisms, optimize its formulations, and establish standardized dosages for clinical use. Additionally, exploring DNJ's role in combination with other anti-diabetic agents may enhance its therapeutic effectiveness and provide a holistic strategy for diabetes management. As the demand for natural remedies continues to rise, DNJ's application in dietary supplements and functional foods could offer a practical and accessible means for individuals who are at risk of or are managing diabetes. Overall, the integration of DNJ into diabetes treatment protocols holds significant promise for improving glycemic control, minimizing side effects, and enhancing patient outcomes, paving the way for a future where natural compounds like DNJ play a pivotal role in holistic diabetes care. Continued research and development in this area will be

crucial to unlocking the full potential of DNJ in combating this chronic disease.

Abbreviations

DNJ: 1-Deoxynojirimycin; FBS: Fasting blood sugar; HDL: High density lipoprotein; MLE: Mulberry leaf extract; PPG: Photoplethysmography; PPI: Proton pump inhibitors.

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