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Naringenin: A Potential Flavonoid Phytochemical For Diabetes Management

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Diabetes mellitus is a chronic metabolic disorder characterized by persistent hyperglycemia resulting from impaired insulin secretion, insulin resistance, or both, leading to severe complications affecting multiple organs. Current antidiabetic therapies, although effective, are often associated with limitations such as side effects, high cost, and incomplete efficacy, highlighting the need for safer and more effective alternatives. Naringenin, a naturally occurring flavonoid abundant in citrus fruits, has gained significant attention for its antidiabetic potential. Its pharmacological activities include antioxidant, anti-inflammatory, insulin-sensitizing, and glucose-regulating effects, mediated through modulation of oxidative stress, inflammatory pathways, insulin signaling, and lipid metabolism. However, clinical application of naringenin is hindered by poor bioavailability, rapid metabolism, and lack of standardized formulations. Advances in delivery systems, such as nanoparticles, liposomes, and encapsulation, alongside synergistic use with conventional therapies, show promise in overcoming these limitations. This review provides a comprehensive overview of the chemical properties, mechanisms of action, pharmacokinetics, safety, therapeutic potential, and research challenges of naringenin in diabetes management. In conclusion, naringenin represents a promising supplementary therapeutic strategy for diabetes management. With further research aimed at optimizing formulation strategies, elucidating mechanisms of action, and validating its efficacy in human clinical trials, naringenin could pave the way toward innovative and safer treatment approaches for achieving improved glycemic control and long-term metabolic health.

Keywords: Anti-inflammatory; Antioxidant; Citrus fruits; Diabetes; Flavonoid; Insulin sensitization; Naringenin.

Diabetes is a chronic metabolic disorder characterized by impaired insulin production or utilization, leading to persistent hyperglycaemia and progressive damage to multiple organ systems.[1,2] Globally, the prevalence of diabetes has risen dramatically, from 200 million cases in 1990 to 830 million in 2022, with the steepest increase observed in low- and middle-income countries. In 2022, an estimated 14% of adults aged 18 years and older were living with diabetes, yet more than half were not receiving appropriate treatment. Diabetes and its complications, including cardiovascular disease, kidney failure, blindness, stroke, and lower-limb amputation, accounted for over 2 million deaths in 2021, with nearly half occurring before the age of 70. Unlike many other non-communicable diseases where mortality has declined, diabetes-related mortality continues to rise. Importantly,

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type 2 diabetes can often be prevented or delayed through lifestyle modification, and effective management strategies combining diet, physical activity, medication, and regular screening can significantly reduce complications.[3,4]

Currently available diabetic treatments include insulin therapy, oral hypoglycemic medications, and lifestyle changes.[5] However, these treatments often come with limitations such as side effects, high costs, and the inability to prevent or reverse disease progression.[6] For instance, insulin therapy can lead to weight gain and hypoglycemia, while some oral medications may cause gastrointestinal disturbances and cardiovascular issues.[7,8] Therefore, there is a pressing need for more effective and safer therapeutic alternatives. The limitations of current treatments highlight the necessity for new antidiabetic treatments that are not only effective but also have fewer side effects. Natural compounds, particularly phytochemicals, have gained attention as potential alternatives due to their diverse biological activities and lower toxicity profiles.[9]

Plant-based foods such as fruits and vegetables are an excellent source of flavonoids, a type of polyphenolic chemicals. Their anti-inflammatory, anti-oxidant, and antidiabetic properties are widely recognized.[10] Flavonoids produce their effects through several mechanisms, including the modulation of key enzymes and signaling pathways involved in glucose metabolism.[11] Phytochemicals, including flavonoids, play a significant role in diabetes management due to their ability to improve insulin sensitivity, reduce oxidative stress, and modulate glucose homeostasis.[12] These natural compounds offer a complementary approach to traditional diabetes treatments, with the potential to mitigate complications and improve overall health outcomes.[13-16] The flavonoid naringenin is commonly found in citrus fruits such as grapefruit, orange, tomato, and orange juice.[17] Its antioxidant, anti-inflammatory, and lipid-lowering properties make it a promising candidate for the management of diabetes.[18]

The primary aim of this review is to thoroughly assess the potential of naringenin as a therapeutic agent for diabetes management. This includes a comprehensive analysis of its mechanisms of action, pharmacokinetics, preclinical and clinical evidence, safety profile, and future research directions. The scope of the review encompasses an overview of current diabetes treatments and their limitations, the role of flavonoids in diabetes management, and a detailed examination of naringenin's therapeutic potential.[19]

Chemical Structure and Properties of Naringenin

Naringenin belongs to the class of flavanones, as a flavonoid. A 15-carbon structure consisting of two phenyl rings (A and B) and one heterocyclic ring (C) characterizes its chemical structure, as shown in Fig. 1. The molecular formula of naringenin is $C_{15}H_{12}O_5$. Its systematic IUPAC name is 42 ,5,7-trihydroxyflavanone.[20]

Naringenin is a crystalline compound (white to light yellow) with a melting point of 250–252 °C. It is poorly soluble in water but dissolves in ethanol, methanol, and DMSO. It shows maximum absorption at ~289 nm in methanol and has pKa values of ~7.29 and 9.05, reflecting acidic hydroxyl groups. These properties influence its solubility, reactivity, and biological interactions. Its ability to form hydrogen bonds and transfer electrons underlies its antioxidant and anti-inflammatory effects.[21,22] Citrus fruits (especially grapefruits, oranges, and peels), tomatoes, and herbs like oregano are the main dietary sources of naringenin. It is also available in supplemental forms such as capsules, tablets, powders, and functional foods. Concentrations vary depending on plant part, extraction method, and processing conditions.[23,24] The dietary and supplemental sources of naringenin are detailed in Table 1.

Pathophysiology of Diabetes Mellitus

Type 1 diabetes mellitus (T1DM) is an autoimmune disorder in which the immune system destroys pancreatic â-cells, leading to little or no insulin production. It often develops in childhood or adolescence and requires lifelong insulin therapy to regulate blood glucose and prevent complications.[25] Type 2 diabetes mellitus (T2DM), the most common form (90–95% of cases), is characterized by insulin resistance and relative insulin deficiency. Risk factors include obesity, physical inactivity, and genetic susceptibility. Once considered an adult disease, it is increasingly affecting younger populations. Management involves lifestyle changes, oral hypoglycemic agents, and sometimes insulin.[26]

Gestational diabetes mellitus (GDM) develops during pregnancy due to glucose intolerance and increases health risks for both mother and child. It raises the likelihood of complications such as preeclampsia, macrosomia, and future T2DM. Treatment typically includes dietary adjustments, physical activity, and, if necessary, insulin or oral medications.[27]

Pathophysiological Mechanisms Involved

Type 1 diabetes mellitus (T1DM) is an autoimmune disorder in which the immune system destroys pancreatic â-cells, resulting in little or no insulin production. Genetic predisposition (such as HLA gene variants) and environmental triggers like viral infections contribute to its onset, and lifelong insulin therapy is required.[25] Type 2 diabetes mellitus (T2DM), the most common form, is marked by insulin resistance and progressive â-cell dysfunction. It is influenced by obesity, poor diet, sedentary lifestyle, chronic inflammation, lipotoxicity, and genetic factors, and is increasingly seen in younger individuals. Oxidative stress, through excessive reactive oxygen species, impairs insulin signaling and â-cell function, while chronic low-grade inflammation driven by cytokines (e.g., CRP, IL-6, TNF-á) promotes insulin resistance and â-cell apoptosis. Additional contributors include lipotoxicity from excess free fatty acids, ectopic fat deposition in the liver and muscle, genetic susceptibility, and unhealthy lifestyle choices.[28] Gestational diabetes mellitus (GDM), on the other hand, develops during pregnancy due to hormonal changes and placental factors that induce insulin resistance. Risk factors include maternal obesity, advanced age, and family history of diabetes, with GDM posing risks for both mother and child and serving as a predictor of future T2DM.[29]

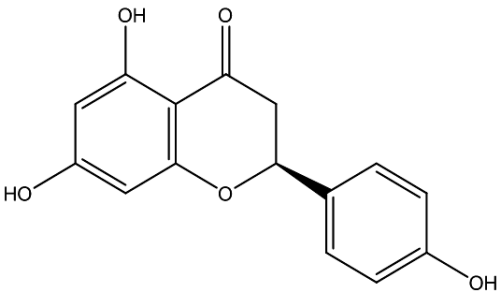

Fig. 1. Chemical structure of naringenin

Current Management Strategies and their Limitations

Diabetes management involves lifestyle modifications and pharmacological therapies, each with distinct benefits and drawbacks. These are summarized in Table 2. Healthy diet and regular physical activity form the cornerstone of diabetes care, improving glycemic control and overall health. However, sustaining these habits is often difficult due to personal preferences, physical limitations, or socioeconomic barriers. Insulin therapy is crucial for T1DM and advanced T2DM, but it is associated with hypoglycemia, weight gain, and lifelong dependence.[30] Oral antidiabetic drugs such as metformin, sulfonylureas, DPP-4 inhibitors, and SGLT2 inhibitors improve glycemic control but may cause gastrointestinal issues, hypoglycemia, or cardiovascular risks.[31] GLP-1 receptor agonists offer dual benefits of glucose regulation and

Table 1. Dietary and Supplemental Sources of Naringenin

Source Type	Examples	Form/Use	Key Notes
Dietary Sources	Grapefruit	Fruit & juice	Richest natural source of naringenin
	Orange	Fruit & peel	Peel contains higher concentrations; used in culinary & medicinal applications
	Tomato	Fruit	Lower levels compared to citrus fruits
	Oregano	Herb	Contributes to dietary intake in smaller amounts
Supplemental Sources	Capsules & Tablets	Oral supplements	Provide concentrated doses; easily accessible
	Powder Form	Nutraceutical formulations	Incorporated into health supplements for enhanced benefits
	Functional Foods & Beverages	Fortified products	Added to boost nutritional and therapeutic value

cardiovascular protection, yet their high cost and gastrointestinal side effects limit use.[32] Despite available options, long-term management remains challenging. High costs of insulin and newer agents hinder accessibility in low-resource settings. Complex regimens often lead to poor adherence, reducing treatment effectiveness. Furthermore, many patients still progress to complications such as neuropathy, retinopathy, and cardiovascular disease, underscoring the urgent need for safer, more affordable, and more effective therapies.[33]

Mechanisms of Action of Naringenin in Diabetes Management

Naringenin exerts multiple protective effects in diabetes through antioxidant, anti-inflammatory, insulin-sensitizing, and metabolic regulatory pathways. Its antioxidant activity involves scavenging reactive oxygen species (ROS) and enhancing the function of key enzymes such as superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx). This reduces oxidative stress and lipid peroxidation markers like malondialdehyde (MDA), thereby protecting tissues from diabetes-related damage.[34] Anti-inflammatory effects are mediated by inhibition of the nuclear factor-kappa B (NF-êB) pathway, which downregulates pro-inflammatory cytokines including TNF-á, IL-6, and IL-1â. Naringenin also reduces the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), further dampening inflammation and improving insulin sensitivity in diabetic models.[35] In addition, naringenin enhances insulin sensitivity by stimulating the IRS/PI3K/Akt signaling pathway and promoting translocation of glucose transporter type 4 (GLUT4) in muscle and adipose tissues, which facilitates glucose uptake and lowers blood glucose levels.[36] Naringenin also modulates lipid metabolism by regulating enzymes involved in lipid processing, lowering lipid peroxidation, and improving lipid profiles, which helps reduce cardiovascular risk associated with diabetes. Experimental studies have demonstrated significant improvements in lipid parameters following supplementation.[37] Collectively, these mechanisms contribute to improved glucose homeostasis, with naringenin supporting antioxidant defense, reducing inflammation, enhancing insulin action, and correcting dyslipidemia. This multifaceted activity highlights its therapeutic potential in managing diabetes and preventing its complications.

Pharmacokinetics and Bioavailability of Naringenin

The pharmacokinetics of naringenin are influenced by its poor water solubility, rapid metabolism, and limited systemic availability, which collectively restrict its therapeutic potential. Understanding its ADME, along with the factors affecting bioavailability and strategies to overcome these limitations, is essential for optimizing its clinical application.

ADME of Naringenin

Naringenin has poor water solubility, which limits its gastrointestinal absorption, although it is taken up mainly in the small intestine.[38] After absorption, it binds to plasma proteins and distributes to lipid-rich organs such as the liver, kidneys, and adipose tissue. In the

Table 2. Current Management Strategies for Diabetes and their Limitations

Strategy	Examples	Benefits	Limitations
Lifestyle Modifications	Healthy diet, regular physical activity	Improves blood glucose control and overall health	Difficult to maintain due to dietary preferences, physical limitations, socioeconomic constraints
Insulin Therapy	Exogenous insulin (T1DM, advanced T2DM)	Essential for T1DM, effective in controlling hyperglycemia	Risk of hypoglycemia, weight gain, lifelong administration required
Oral Hypoglycemic Agents	Metformin, Sulfonylureas, DPP-4 inhibitors, SGLT2 inhibitors	Effective in T2DM management	Side effects: gastrointestinal issues, hypoglycemia, potential cardiovascular risks
GLP-1 Receptor Agonists	Exenatide, Liraglutide, Semaglutide	Enhance insulin secretion, cardiovascular benefits	Nausea, high cost

liver, it undergoes extensive phase II metabolism, predominantly glucuronidation and sulfation, while cytochrome P450 enzymes (CYP1A2, CYP3A4) contribute to phase I reactions.[39] The resulting metabolites are eliminated largely through urine, with some biliary excretion, and the compound shows a relatively short half-life of a few hours to about a day depending on dose and route.[40]

Factors Affecting Bioavailability

Naringenin's bioavailability is influenced by multiple factors (Fig. 2). Its poor water solubility limits gastrointestinal absorption, while extensive first-pass metabolism rapidly converts it into glucuronide and sulfate metabolites, reducing systemic availability[40]. Food components also modulate absorption, with fats enhancing solubilization and uptake, whereas fibers and phytates may hinder it.[41] Formulation strategies, including liposomes, nanoparticles, and micelles, improve solubility, stability, and absorption. Moreover, individual variability, such as genetic differences in metabolic enzymes and gut microbiota composition, further impacts its pharmacokinetics and therapeutic effectiveness.

Strategies to Improve Bioavailability

Several approaches have been developed to enhance the bioavailability of naringenin. Nanoparticle- and liposome-based delivery systems improve its solubility, protect against gastric degradation, and enhance intestinal absorption, resulting in higher systemic levels.[42] Co-administration with compounds such as piperine can inhibit cytochrome P450 enzymes (CYP3A4, CYP1A2), reducing first-pass metabolism and increasing plasma concentrations.[43] Prodrug strategies have also shown promise, improving solubility and permeability, with derivatives converted back to active naringenin post-absorption.[44] Additionally, solubilizing agents like cyclodextrins and surfactants enhance dissolution in the gastrointestinal tract, further improving absorption and bioavailability.[45]

Safety and Toxicity

Naringenin, a flavonoid abundantly found in citrus fruits, possesses a favorable toxicological profile, making it generally safe for consumption. Extensive research has explored its safety aspects, revealing low acute toxicity and

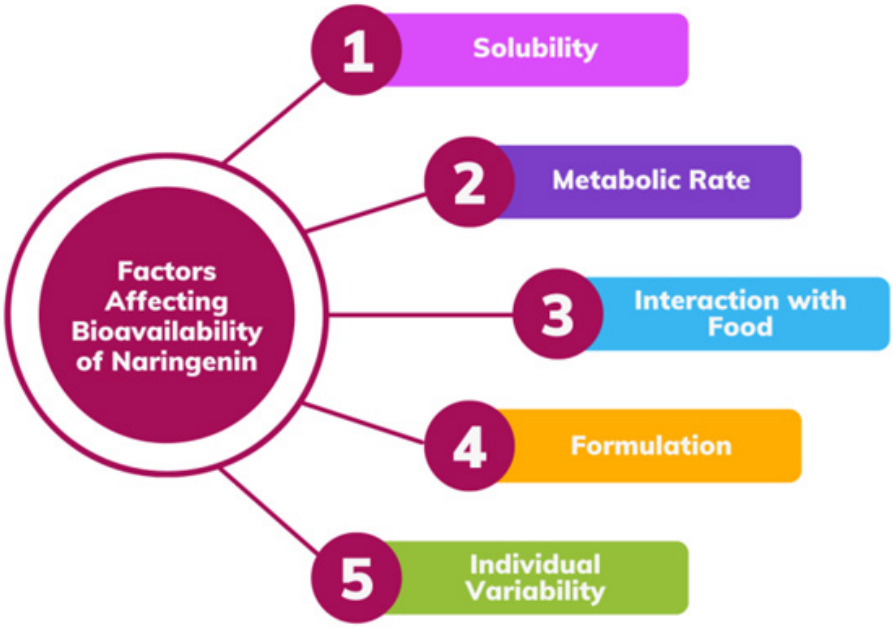

Fig. 2. Factors Affecting Bioavailability of Naringenin

Table 3. Potential Therapeutic Applications of Naringenin in Diabetes Management

Aspect	Key Features	Mechanism/Benefits
Naringenin as a Standalone Therapy	Natural flavonoid with antioxidant, anti-inflammatory, and insulin-sensitizing properties	Enhances pancreatic â-cell function, improves glucose uptake in peripheral tissues, regulates signaling pathways for glucose homeostasis, mitigates oxidative stress
Synergistic Effects with Other Antidiabetic Agents	Can be combined with metformin, sulfonylureas, insulin, or natural compounds (e.g., resveratrol, berberine)	Complements insulin signaling modulation, reduces inflammation, improves lipid metabolism; offers enhanced efficacy and better glycemic control
Formulation Considerations	Advanced drug delivery systems: nanoparticles, liposomes, encapsulation, functional foods	Improves bioavailability, stability, and targeted delivery; prolongs pharmacological effects; reduces dosing frequency; enhances absorption; enables integration into diet

minimal adverse effects in animal models and human studies. While acute toxicity studies have demonstrated high LD_{50} values, indicating low toxicity levels, chronic toxicity investigations have not reported significant adverse effects associated with prolonged naringenin exposure.[46-48] However, some studies have identified potential adverse effects, particularly at higher doses or in specific populations. These include gastrointestinal disturbances such as nausea and diarrhea, as well as potential drug interactions due to naringenin's inhibition of certain cytochrome P450 enzymes involved in drug metabolism. Additionally, rare cases of allergic reactions have been reported. For long-term use, it is crucial to follow recommended dosage guidelines and monitor for adverse effects, particularly in individuals with existing health conditions or those taking medications. Although further research is required to completely understand the safety profile of naringenin, current evidence indicates that it can be safely included in a balanced diet, provided that dosage and individual factors are carefully considered.[49,50]

Potential for Therapeutic Use of Naringenin

Naringenin has emerged as a promising candidate for diabetes management, both as a standalone therapy and in combination with existing antidiabetic agents. Furthermore, innovative formulation strategies are being explored to overcome its limited bioavailability and optimize therapeutic efficacy. These aspects are summarized in Table 3.

Naringenin as a Standalone Therapy

Naringenin holds significant potential as a standalone therapy for managing diabetes and related metabolic disorders. As a natural flavonoid with antioxidant, anti-inflammatory, and insulin-sensitizing properties, naringenin offers multifaceted benefits for improving glucose metabolism, enhancing insulin sensitivity, and mitigating oxidative stress. Studies have demonstrated its ability to enhance pancreatic beta cell function, enhance glucose uptake in peripheral tissues and regulate key signaling pathways related to glucose homeostasis. By targeting multiple pathways implicated in diabetes pathogenesis, naringenin has the potential to exert comprehensive therapeutic benefits, positioning it as a promising option for standalone treatment.[51]

Synergistic Effects with Other Antidiabetic Agents

In addition to its efficacy as a standalone therapy, naringenin may exhibit synergistic effects when combined with other antidiabetic agents. Combinatorial therapy involving naringenin and conventional antidiabetic medications, such as metformin, sulfonylureas, or insulin, could offer enhanced efficacy and improved management of diabetes. Naringenin's ability to modulate insulin signaling pathways, reduce inflammation, and improve lipid metabolism may complement the actions of existing antidiabetic drugs, leading to synergistic effects on glycemic control and metabolic parameters. Moreover, combining

naringenin with other natural compounds with complementary mechanisms of action, such as resveratrol or berberine, could further potentiate its therapeutic effects, offering novel treatment strategies for diabetes management.[52,53]

Formulation Considerations

Formulation considerations play an essential role in optimizing the therapeutic potential of naringenin. Different formulation approaches, including nanoparticles, liposomes, and encapsulation, can improve the bioavailability, stability, and targeted delivery of naringenin, enhancing its therapeutic efficacy. Nanoparticle-based delivery systems allow for controlled release and sustained delivery of naringenin, prolonging its pharmacological effects and reducing dosing frequency. Encapsulation techniques safeguard naringenin from degradation in the gastrointestinal tract, enhancing its absorption and bioavailability. Furthermore, incorporating naringenin into functional foods or nutraceutical formulations could provide convenient and palatable options for long-term supplementation, promoting adherence to therapy and facilitating integration into dietary habits. By carefully considering formulation strategies, researchers can harness the full therapeutic potential of naringenin for effective management of diabetes and metabolic disorders.[54,55]

Challenges and Future Directions in Naringenin Research

Despite its therapeutic promise, naringenin research faces challenges such as poor bioavailability, limited clinical evidence, and lack of standardization. Addressing these gaps through mechanistic studies, safety evaluation, and advanced formulations will be crucial for its clinical translation.

Current Challenges in Naringenin Research

Key challenges in naringenin research include optimizing its bioavailability, as poor solubility and extensive first-pass metabolism limit systemic exposure, making advanced delivery systems like nanoparticles and encapsulation essential.[56] Clinical translation also remains limited, with few well-designed trials and inconsistent findings slowing validation of efficacy and safety in humans. Moreover, lack of standardization in extraction, formulation, and quality control leads to variability in pharmacological outcomes, underscoring the need for standardized protocols to ensure reproducibility and reliability.[57]

Gaps in Knowledge and Research Needs

Despite growing evidence of naringenin's pharmacological benefits, important research gaps remain. A clearer mechanistic understanding is needed, particularly in vivo, to identify the molecular pathways and cellular targets involved in its therapeutic effects in diabetes and metabolic disorders. Its long-term safety profile also requires further evaluation, including studies on potential toxicity, drug interactions, and risks at higher doses. Most critically, the lack of robust clinical evidence remains a major barrier; well-designed, large-scale randomized controlled trials with extended follow-up are essential to validate its efficacy and safety in humans.[58]

Potential Future Research Directions

Future research on naringenin should prioritize well-designed clinical trials to establish its safety, efficacy, and long-term benefits in diabetes and metabolic disorders, including comparative studies with standard therapies and potential synergistic effects with other antidiabetic agents. Mechanistic investigations in animal and cellular models are needed to clarify its interactions with key pathways regulating glucose metabolism, inflammation, and oxidative stress. In parallel, optimization of formulations through advanced delivery systems, such as nanotechnology-based approaches, offers a promising strategy to overcome bioavailability challenges.[59,60] Addressing current limitations through collaborative efforts between researchers, clinicians, and industry will be essential to fully realize naringenin's therapeutic potential and translate it into clinical practice.

CONCLUSION

In this review, we explored the potential of naringenin as a therapeutic agent for diabetes management. Naringenin, a flavonoid abundantly found in citrus fruits, exhibits antioxidant, anti-inflammatory, insulin-sensitizing, and glucose-regulating properties. By modulating key cellular pathways involved in glucose metabolism, insulin signaling, inflammation, and oxidative stress, it shows promise in improving glycemic control and overall metabolic health. Naringenin therefore represents a valuable candidate for developing

innovative strategies and adjunctive therapies in diabetes, offering potential benefits in reducing complications and enhancing quality of life.

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This research did not involve human participants, animal subjects, or any material that requires ethical approval.

Informed Consent Statement

This study did not involve human participants, and therefore, informed consent was not required.

Clinical Trial Registration

This research does not involve any clinical trials.

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Author contributions

Kajal Pansare prepared the manuscript; Yogesh Ahire assisted in writing and literature support; Vinod Bairagi supervised the work and reviewed the manuscript.

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