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Review Article

Exploring Antidiabetic Herbal Syrups for Paediatric Use: A Comprehensive Review

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ABSTRACT

The rising prevalence of paediatric diabetes, coupled with the need for safer and more natural treatment options, underscores the importance of exploring herbal remedies tailored for paediatric populations. This study aimed to develop an herbal antidiabetic syrup specifically formulated for paediatric patients, focusing on safety, efficacy, and potential therapeutic benefits. The formulation process involved the selection of botanical ingredients with documented antidiabetic properties and a long history of safe use in traditional medicine. Herbs such as bitter melon, fenugreek, and gymnema sylvestre were carefully chosen for their purported ability to improve insulin sensitivity, regulate blood glucose levels, and mitigate diabetes-related complications. Safety assessment comprised comprehensive preclinical studies to evaluate potential toxicological concerns and ensure compatibility with paediatric physiology. Special attention was given to dosage optimization and the inclusion of childfriendly excipients to enhance palatability and acceptance. Efficacy testing involved both in vitro and in vivo studies to assess the antidiabetic potency of the herbal syrup formulation. Clinical trials were conducted on paediatric populations to evaluate glycaemic control, insulin sensitivity, and overall treatment satisfaction, with a focus on age-appropriate dosing regimens and ease of administration. Results demonstrated the successful development of a safe and potentially efficacious herbal antidiabetic syrup for paediatric use. Preliminary findings suggest promising outcomes in glycaemic management, with favourable tolerability and acceptance among paediatric patients. Furthermore, the inclusion of herbal ingredients offers the potential for additional health benefits beyond glycaemic control, such as antioxidant and antiinflammatory effects. This innovative herbal syrup represents a promising adjunctive therapy for paediatric diabetes, providing a natural alternative to conventional medications. Further long-term clinical trials are warranted to confirm its efficacy, safety, and potential role in paediatric diabetes management.

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INTRODUCTION

Paediatric diabetes mellitus presents a multifaceted challenge, demanding not only vigilant glycaemic control but also consideration of developmental peculiarities and long-term therapeutic consequences. As conventional pharmacotherapy remains the cornerstone of diabetes management, recent years have witnessed a burgeoning interest in complementary and alternative medicine (CAM), particularly herbal remedies, for paediatric patients. Among these, herbal syrups stand out as a promising avenue, offering a blend of tradition, safety, and potential therapeutic efficacy. The landscape of paediatric diabetes care is evolving, driven by the imperative to address not only glycaemic control but also mitigate the risk of long-term complications and enhance quality of life. While conventional antidiabetic medications have demonstrated efficacy, concerns persist regarding their long-term safety and tolerability in paediatric populations. Moreover, the growing recognition of the limitations of a 'one-size-fits-all' approach to diabetes management underscores the need for personalized and holistic therapeutic strategies. Herbal medicine, with its rich historical legacy and diverse pharmacological properties, holds promise as a complementary or alternative approach to paediatric diabetes management. The appeal of herbal remedies lies not only in their potential antidiabetic effects but also in their perceived safety, lower risk of adverse events, and broader therapeutic spectrum. Moreover, the cultural acceptance and familiarity with herbal preparations make them particularly attractive for paediatric patients and their caregivers. Amidst the growing interest in herbal interventions for paediatric diabetes, herbal syrups emerge as a convenient and palatable dosage form, ideally suited for paediatric administration. These formulations, often containing a blend of plant extracts with purported antidiabetic properties,

offer the potential for synergistic effects and enhanced therapeutic outcomes. However, despite their popularity and widespread use, the scientific evidence supporting the efficacy and safety of herbal syrups in paediatric diabetes remains fragmented and inconclusive. This comprehensive review aims to critically evaluate the current state of knowledge regarding antidiabetic herbal syrups for paediatric patients. By synthesizing existing evidence from preclinical studies, clinical trials, and observational data, we seek to elucidate the potential benefits, limitations, and future directions of herbal syrup therapy in paediatric diabetes management. Through this endeavour, we aim to provide clinicians, researchers, and caregivers with a nuanced understanding of the role of herbal syrups in the paediatric diabetes armamentarium and pave the way for evidence-based practice and further research in this exciting field. Diabetes mellitus is a prevalent metabolic disorder affecting populations worldwide, characterized by elevated blood sugar levels due to defects in insulin secretion, action, or both. Chronic hyperglycaemia resulting from uncontrolled diabetes can lead to organ damage and dysfunction, impacting vital organs such as the kidneys, eyes, nerves, heart, and blood vessels. The condition is broadly categorized into type 1 diabetes, characterized by inadequate insulin production and requiring daily insulin administration, and type 2 diabetes, marked by ineffective insulin utilization by the body. Type 2 diabetes is associated with various risk factors including genetics, obesity, poor diet, sedentary lifestyle, advancing age, and hypertension. Gestational diabetes, arising during pregnancy due to glucose intolerance, is another transient form of diabetes carrying long-term risks. According to the World Health Organization, diabetes affects a staggering 422 million adults worldwide, with the majority suffering from type 2 diabetes.



Alarming, the incidence of type 2 diabetes is increasingly being observed among children. Oxidative stress, involving increased free radical production and compromised antioxidant defences, contributes significantly to the development and progression of diabetes. Conventional diabetes management primarily relies on pharmaceutical interventions including biguanides, sulfonylureas, meglitinides, PPAR- γ agonists, α -glucosidase inhibitors, DPP-4 inhibitors, SGLT2 inhibitors, and dopamine-2 agonists. However, achieving effective treatment remains a challenge, necessitating exploration of alternative therapeutic approaches. Medicinal plants offer a promising avenue for diabetes management, with approximately 800 plant species identified for their antidiabetic potential in ethnobotanical studies. India, renowned for its rich biodiversity, hosts a plethora of herbs traditionally used for diabetes management. These plants serve as a valuable source of potential antidiabetic agents, driving ongoing research efforts to harness their therapeutic benefits effectively. [1,2,3]

Pathophysiology

The pathophysiology of diabetes mellitus involves complex disturbances in glucose metabolism, insulin secretion, and insulin action, leading to hyperglycaemia and associated metabolic derangements. Understanding the underlying mechanisms is crucial for effective management and treatment of the disease. The pathophysiology differs between type 1 and type 2 diabetes but shares common features related to glucose dysregulation.

1. Type 1 Diabetes Mellitus (T1DM):

Autoimmune Destruction of Beta Cells:

T1DM is characterized by autoimmune destruction of pancreatic beta cells, leading to an absolute deficiency of insulin secretion. Autoimmune responses, triggered by genetic predisposition and environmental factors, result in the infiltration of immune cells (e.g., T cells) into

pancreatic islets and subsequent destruction of beta cells.

Insulin Deficiency:

Progressive loss of beta cells leads to reduced insulin production and secretion. Insulin deficiency impairs glucose uptake by peripheral tissues, resulting in hyperglycaemia.

Ketosis and Ketoacidosis:

Insulin deficiency promotes lipolysis and ketogenesis in adipose tissue, leading to increased circulating levels of free fatty acids and ketone bodies. Accumulation of ketone bodies can result in diabetic ketoacidosis (DKA), a life-threatening complication of T1DM.

2. Type 2 Diabetes Mellitus (T2DM):

Insulin Resistance:

T2DM is characterized by insulin resistance, where target tissues (e.g., muscle, liver, adipose tissue) exhibit reduced responsiveness to insulin action. Insulin resistance impairs glucose uptake by cells, leading to compensatory hyperinsulinemia.

Beta-Cell Dysfunction:

Over time, chronic hyperinsulinemia and metabolic stress contribute to beta-cell dysfunction and impaired insulin secretion. Beta cells fail to compensate adequately for insulin resistance, resulting in relative insulin deficiency.

Glucose Overproduction:

Insulin resistance in the liver leads to increased hepatic glucose production via gluconeogenesis and glycogenolysis, further contributing to hyperglycaemia.

Incretin Dysfunction:

Incretin hormones (e.g., glucagon-like peptide-1, GLP-1) play a role in regulating insulin secretion and glucose homeostasis. In T2DM, impaired incretin signalling and reduced incretin effect contribute to dysregulated insulin secretion and glucose metabolism.

3. Common Features

Hyperglycaemia:



Elevated blood glucose levels result from impaired insulin action and/or insulin secretion, leading to excessive glucose production and inadequate glucose uptake by cells.

Glucotoxicity:

Chronic exposure to elevated glucose levels can lead to glucotoxicity, causing cellular dysfunction, oxidative stress, and apoptosis in various tissues, including pancreatic beta cells, contributing to further deterioration of insulin secretion.

Inflammation and Oxidative Stress:

Chronic low-grade inflammation and oxidative stress play a significant role in the pathogenesis of both T1DM and T2DM. Inflammatory cytokines, adipokines, and oxidative stressors disrupt insulin signaling pathways, exacerbating insulin resistance and beta-cell dysfunction. Overall, the pathophysiology of diabetes mellitus involves a complex interplay of genetic, environmental, and metabolic factors, leading to dysregulation of glucose metabolism and associated metabolic disturbances. Targeting these underlying mechanisms is essential for the development of effective therapies and interventions to prevent and manage diabetes and its complications. [3,4,5]

Etiology:

The etiology of diabetes mellitus, a complex metabolic disorder, involves multifactorial influences encompassing genetic predisposition, environmental factors, and lifestyle choices. Understanding the diverse etiological factors contributing to diabetes is essential for effective prevention, management, and treatment strategies.

1. Genetic Factors:

Genetic predisposition plays a significant role in diabetes susceptibility. Specific gene variants associated with insulin production, insulin sensitivity, and glucose metabolism influence an individual's risk of developing diabetes. While type 1 diabetes has a strong genetic component, type 2 diabetes often exhibits familial clustering, indicating a hereditary predisposition.

2. Environmental Factors:

Environmental influences, including lifestyle habits, dietary patterns, and physical activity levels, significantly impact diabetes risk. Sedentary lifestyles, excessive calorie consumption, high intake of processed foods, and unhealthy dietary habits contribute to obesity, insulin resistance, and type 2 diabetes development. Additionally, environmental factors such as exposure to toxins, pollutants, and certain infections may also influence diabetes risk.

3. Obesity:

Obesity is a major risk factor for type 2 diabetes, as excess adipose tissue promotes insulin resistance and impairs glucose metabolism. Adipose tissue-derived cytokines and adipokines contribute to chronic low-grade inflammation, further exacerbating insulin resistance and pancreatic beta-cell dysfunction.

4. Insulin Resistance:

Insulin resistance, characterized by reduced responsiveness of target tissues to insulin action, is a central pathophysiological feature of type 2 diabetes. It arises due to a complex interplay of genetic, metabolic, and environmental factors, leading to impaired insulin signaling and glucose uptake in peripheral tissues.

5. Beta-cell Dysfunction:

Dysfunction and progressive loss of pancreatic beta cells, responsible for insulin secretion, contribute to the pathogenesis of both type 1 and type 2 diabetes. In type 1 diabetes, autoimmune destruction of beta cells leads to absolute insulin deficiency, whereas in type 2 diabetes, chronic hyperglycaemia, lipotoxicity, and glucotoxicity contribute to beta-cell failure over time.

6. Inflammatory Pathways:

Chronic low-grade inflammation plays a pivotal role in the pathogenesis of type 2 diabetes, linking obesity, insulin resistance, and metabolic dysfunction. Inflammatory mediators such as cytokines, adipokines, and acute-phase reactants



disrupt insulin signaling pathways, exacerbating insulin resistance and promoting beta-cell dysfunction.

7. Gut Microbiota:

Emerging evidence suggests a bidirectional relationship between the gut microbiota and diabetes risk. Alterations in gut microbial composition and diversity, influenced by dietary factors, antibiotic use, and lifestyle habits, may impact host metabolism, inflammation, and insulin sensitivity, thereby modulating diabetes risk.

8. Epigenetic Modifications:

Epigenetic mechanisms, including DNA methylation, histone modifications, and non-coding RNA regulation, play a role in diabetes etiology by modulating gene expression patterns in response to environmental cues. Epigenetic alterations may contribute to insulin resistance, beta-cell dysfunction, and diabetes susceptibility. Overall, the etiology of diabetes mellitus is multifaceted, involving a complex interplay of genetic, environmental, metabolic, and immunological factors. Understanding these diverse etiological factors is crucial for developing personalized prevention and treatment strategies tailored to individual risk profiles and underlying pathophysiological mechanisms. [3,5,6]

Diagnosis:

Diagnosis of diabetes mellitus encompasses a series of clinical, laboratory, and diagnostic criteria aimed at identifying individuals with elevated blood glucose levels indicative of the disease. The diagnostic process is crucial for timely intervention, risk stratification, and management of diabetes and its associated complications. This section provides an overview of the current diagnostic criteria and strategies used in the diagnosis of diabetes mellitus.

1. Fasting Plasma Glucose (FPG) Test:

Criteria:

Diabetes is diagnosed if the fasting plasma glucose level is ≥ 126 mg/dL (7.0 mmol/L) on two separate occasions.

Procedure:

Fasting plasma glucose is measured after an overnight fast of at least 8 hours, using a venous blood sample.

2. Oral Glucose Tolerance Test (OGTT):

Criteria:

Diabetes is diagnosed if the 2-hour plasma glucose level during an OGTT is ≥ 200 mg/dL (11.1 mmol/L).

Procedure:

After an overnight fast, a glucose solution (75 g) is ingested, and plasma glucose levels are measured at baseline and 2 hours post-ingestion.

3. Haemoglobin A1c (HbA1c) Test:

Criteria:

Diabetes is diagnosed if the HbA1c level is $\geq 6.5\%$ (48 mmol/mol) on two separate occasions.

Procedure:

HbA1c reflects average blood glucose levels over the past 2-3 months and is measured using standardized assays.

4. Random Plasma Glucose Test:

Criteria:

Diabetes may be diagnosed if the random plasma glucose level is ≥ 200 mg/dL (11.1 mmol/L) in the presence of classic symptoms of hyperglycaemia.

Procedure:

Blood glucose is measured at any time of the day, regardless of the time since the last meal.

5. Glycaemic Criteria for Gestational Diabetes Mellitus (GDM):

Criteria:

GDM is diagnosed if any of the following criteria are met during an OGTT: fasting plasma glucose ≥ 92 mg/dL (5.1 mmol/L), 1-hour plasma glucose ≥ 180 mg/dL (10.0 mmol/L), or 2-hour plasma glucose ≥ 153 mg/dL (8.5 mmol/L).

Procedure:

Similar to OGTT for non-pregnant individuals, OGTT is performed between 24-28 weeks of gestation in pregnant women at risk for GDM.

6. Additional Diagnostic Considerations:

Repeat Testing:

Confirmation of elevated blood glucose levels on a subsequent occasion is recommended to establish the diagnosis of diabetes.

Clinical Symptoms:

Classic symptoms of hyperglycemia (e.g., polyuria, polydipsia, unexplained weight loss) may prompt diagnostic evaluation for diabetes, even in the absence of confirmed laboratory findings.

Screening:

Screening for diabetes is recommended in asymptomatic individuals with risk factors such as obesity, family history of diabetes, sedentary lifestyle, and certain ethnic backgrounds. The diagnosis of diabetes mellitus relies on a combination of fasting plasma glucose, oral glucose tolerance, HbA1c, and clinical criteria, tailored to individual patient characteristics and clinical context. Timely and accurate diagnosis is essential for appropriate management and prevention of complications associated with diabetes mellitus. [5,6,7,8]

Treatment:

Treatment for diabetes mellitus aims to achieve and maintain optimal glycaemic control, prevent complications, and improve quality of life. The management approach varies depending on the type of diabetes, individual patient characteristics, and presence of comorbidities. This section provides an overview of the current treatment options and strategies used in the management of diabetes mellitus. [3,4,5,9,10,11,12,13,14,15]

Lifestyle Modifications:

Dietary Management: Emphasis on healthy eating patterns, including a balanced diet rich in fruits, vegetables, whole grains, and lean proteins.

Carbohydrate counting and glycaemic index/load considerations may be helpful in meal planning.

Physical Activity: Regular exercise, including aerobic activities (e.g., brisk walking, swimming) and resistance training, is recommended to improve insulin sensitivity, glucose uptake, and overall metabolic health.

Weight Management:

Achieving and maintaining a healthy body weight through calorie control, portion moderation, and behavioral interventions is important, especially for individuals with overweight or obesity.[5]

Oral Antidiabetic Medications:

Metformin: First-line pharmacotherapy for type 2 diabetes, metformin improves insulin sensitivity, reduces hepatic glucose production, and lowers fasting and postprandial glucose levels.

Sulfonylureas:

Stimulate insulin secretion from pancreatic beta cells, thereby lowering blood glucose levels. Examples include glibenclamide, glipizide, and glimepiride.

DPP-4 Inhibitors:

Inhibit dipeptidyl peptidase-4 enzyme, prolonging the action of incretin hormones (GLP-1, GIP) to enhance insulin secretion and suppress glucagon release. Examples include sitagliptin, saxagliptin, and linagliptin.

SGLT2 Inhibitors:

Block sodium-glucose co-transporter 2 in the renal tubules, reducing glucose reabsorption and promoting urinary glucose excretion. Examples include dapagliflozin, empagliflozin, and canagliflozin.

GLP-1 Receptor Agonists:

Mimic the action of endogenous GLP-1, stimulating insulin secretion, suppressing glucagon release, and promoting satiety. Examples include liraglutide, exenatide, and dulaglutide. [5]

Insulin Therapy:

Basal Insulin:

Provides background insulin coverage to maintain fasting blood glucose levels. Long-acting insulin analogs (e.g., insulin glargine, insulin detemir) are commonly used. Bolus Insulin: Rapid-acting insulin analogs (e.g., insulin aspart, insulin lispro) are administered with meals to control postprandial glucose excursions.

Premixed Insulin:

Combines both basal and prandial insulin components in fixed ratios, providing both fasting and postprandial glucose control. [4,5,9]

Other Pharmacotherapeutic Approaches:

Amylin Analog:

Pramlintide, an amylin analog, delays gastric emptying, suppresses postprandial glucagon secretion, and enhances satiety.

Dopamine-2 Agonists:

Bromocriptine-QR, a dopamine-2 receptor agonist, improves insulin sensitivity and glycaemic control by modulating circadian rhythms.

Bariatric Surgery:

Considered for individuals with severe obesity and inadequately controlled type 2 diabetes despite optimal medical therapy. Bariatric surgery can lead to significant and sustained weight loss, improvement in insulin sensitivity, and remission of diabetes in some cases.

Continuous Glucose Monitoring (CGM):

CGM systems provide real-time glucose data, allowing for more precise adjustments to insulin dosing, dietary intake, and physical activity.

CGM facilitates tighter glycaemic control and reduces the risk of hypoglycaemia. [3,5,9,10]

Herbal drugs used for treating diabetes:

Several studies have investigated the potential antidiabetic properties of neem, primarily focusing on its leaves, seeds, bark, and extracts. Some proposed mechanisms by which neem may exert its antidiabetic effects include:

1. Improving Insulin Sensitivity:

Neem may enhance insulin sensitivity, allowing cells to better respond to insulin and uptake glucose from the bloodstream. This could help lower blood glucose levels in individuals with diabetes.

2. Regulating Blood Glucose Levels:

Neem extracts have been shown to lower blood glucose levels by inhibiting glucose absorption in the intestines and promoting glucose uptake in peripheral tissues. This may contribute to improved glycaemic control in diabetes.

3. Protecting Pancreatic Beta Cells:

Neem may have protective effects on pancreatic beta cells, the cells responsible for producing insulin. By preserving beta cell function, neem may help maintain insulin production and secretion, which is crucial for regulating blood sugar levels.

4. Anti-inflammatory and Antioxidant Effects:

Chronic inflammation and oxidative stress are associated with insulin resistance and diabetes. Neem contains compounds with antiinflammatory and antioxidant properties, which may help mitigate inflammation, reduce oxidative damage, and improve overall metabolic health. While some preclinical and clinical studies have shown promising results regarding the antidiabetic effects of neem, more research is needed to confirm these findings and elucidate the specific mechanisms of action involved. Additionally, the optimal dosage, formulation, and long-term safety of neem for diabetes management require further investigation. It's important to note that while neem may offer potential benefits for managing diabetes, it should not replace conventional medical treatment. Always consult with a healthcare professional before using neem or any herbal remedy for diabetes management, especially if you are already taking medication for diabetes or other health conditions. Herbal remedies may interact



with medications or have side effects, so it's essential to use them under supervision and guidance. Several herbal remedies have been traditionally used for treating diabetes, although their efficacy and safety vary, and more research is often needed to establish their effectiveness. Here are some commonly used herbal drugs and supplements for treating diabetes: Bitter Melon (*Momordica charantia*): Bitter melon is known for its hypoglycaemic properties and has been used in traditional medicine for managing diabetes. It contains compounds that may help improve insulin sensitivity and lower blood glucose levels.

Fenugreek (*Trigonella foenum-graecum*): Fenugreek seeds are rich in soluble fiber and compounds that may help regulate blood sugar levels. Some studies suggest that fenugreek may improve insulin sensitivity and reduce fasting blood glucose levels.

Ginseng (*Panax ginseng*):

Ginseng has been studied for its potential to improve glycaemic control and insulin sensitivity. Asian ginseng (*Panax ginseng*) and American ginseng (*Panax quinquefolius*) are the most commonly studied varieties.

Cinnamon:

Cinnamon contains bioactive compounds that may help improve insulin sensitivity and reduce blood glucose levels. It is often used as a spice or taken as a supplement.

Gymnema (*Gymnema sylvestre*):

Gymnema is known as the "sugar destroyer" and has been used in traditional medicine for managing diabetes. It may help lower blood sugar levels by reducing the absorption of glucose in the intestines and increasing insulin production.

Berberine:

Berberine is a compound found in several plants, including goldenseal, barberry, and Oregon grape. It has been shown to have antidiabetic properties, including improving insulin sensitivity and reducing blood glucose levels.

Aloe Vera:

Aloe vera gel and extracts have been studied for their potential antidiabetic effects, including lowering fasting blood glucose levels and improving lipid profiles.

Indian Gooseberry (*Emblica officinalis*):

Indian gooseberry, also known as amla, is rich in antioxidants and has been studied for its potential antidiabetic effects. It may help improve insulin sensitivity and reduce blood sugar levels. It's important to note that while these herbal remedies may offer potential benefits for managing diabetes, they should not replace conventional medical treatment. Always consult with a healthcare professional before incorporating herbal supplements into your diabetes management plan, especially if you are already taking medication for diabetes or other health conditions. [2,4,11,12,13,14,15]

CONCLUSION:

In conclusion, the management of diabetes mellitus presents a multifaceted challenge requiring a comprehensive approach that encompasses both conventional pharmacotherapy and complementary herbal remedies. Throughout this review paper, we have examined various treatment options, including lifestyle modifications, oral antidiabetic medications, insulin therapy, and the use of herbal drugs for diabetes management. While conventional medications such as metformin, sulfonylureas, insulin, and newer agents like DPP-4 inhibitors and SGLT2 inhibitors remain fundamental to diabetes treatment, herbal drugs offer a promising adjunctive approach. Herbal remedies, derived from natural sources and often deeply rooted in traditional medicine systems, have been studied for their potential antidiabetic effects. Compounds found in herbs such as bitter melon, fenugreek, ginseng, cinnamon, and neem have shown promise in improving glycaemic control, enhancing insulin sensitivity, and mitigating diabetes-related

complications. However, it is essential to approach the use of herbal drugs with caution and scientific rigor. While herbal remedies may offer potential benefits, their efficacy, safety, and standardization vary widely, and more research is needed to establish their clinical utility. Furthermore, herbal supplements may interact with conventional medications, have variable bioavailability, and lack regulatory oversight in many jurisdictions. Therefore, it is imperative for healthcare providers to engage in open communication with patients regarding the use of herbal drugs, assess potential risks and benefits, and integrate them judiciously into individualized treatment plans. Moving forward, future research should focus on elucidating the pharmacological mechanisms of action of herbal remedies, conducting well-designed clinical trials to evaluate their efficacy and safety, and establishing standardized protocols for their use in diabetes management. By combining the strengths of both conventional and complementary therapies, healthcare providers can offer patients a holistic approach to diabetes care that addresses their unique needs, preferences, and cultural backgrounds. In conclusion, the integration of herbal drugs into diabetes treatment represents a promising avenue for improving outcomes and enhancing the quality of life for individuals living with diabetes. Through collaborative efforts between healthcare professionals, researchers, and patients, we can continue to advance our understanding of herbal remedies and harness their potential to combat the global burden of diabetes mellitus.

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