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Review Article

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Nutraceuticals in the management of diabetes mellitus

Abstract

Recent years witnessed an upsurge in the use of nutraceuticals, nutritionals and naturals in therapeutics at global level. Conventional treatment options available as synthetic drugs does not meet properly the therapeutic needs for treating diabetes and the herbal drugs provide a better therapeutic hope with lesser side effects. Nutraceuticals are non-specific biological therapies including botanicals, vitamins, antioxidants, minerals, amino acids and fatty acids, which are used to promote wellness, prevent malignant processes and control symptoms. Nutraceutical agents have multidimensional therapeutic benefits and have been claimed to have effective disease preventing, curative and health promotive virtues. Several nutraceuticals used in clinical practice have been shown to target the pathogenesis of diabetes mellitus, metabolic syndrome and their complications and to favourably modulate a number of biochemical and clinical endpoints. Hypoglycaemic drugs are widely used in several traditional systems of medicine to prevent diabetes mellitus. This review attempts to display and remark some of the most popular nutraceuticals being use as anti-diabetic.

Keywords: Nutraceuticals, Diabetes Mellitus, Herbal drugs, Macronutrient, Micronutrient, Oxidative stress, Vitamin

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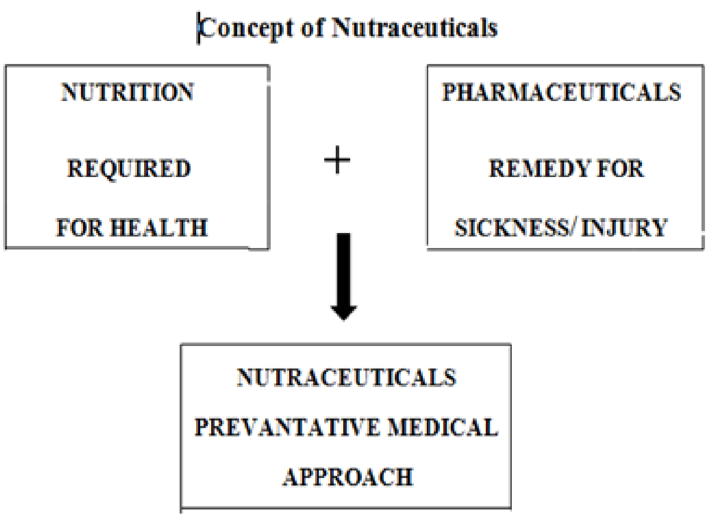
Introduction

Diabetes Mellitus is a complex metabolic disorder associated with developing insulin resistance, impaired insulin signalling and β-cell dysfunction, abnormal glucose and lipid metabolism, sub-clinical inflammation and increased oxidative stress; It was estimated to affect 2.8% of the worldwide population in the year 2000, and it is expected to affect 4.4% in 2030 due to the population aging and a constant increase in obesity; these metabolic disorders lead to long-term pathogenic conditions including micro-vascular and macro-vascular complications, neuropathy, retinopathy, nephropathy, and a consequent decrease in quality of life and an increase in the rate of mortality.[1–3] Among the multiple risk factors underling the incidence and progression of type 2 diabetes mellitus, diet is the main modifiable factor. An increasing number of epidemiological investigations show that diet rich in foods with high content of phytochemicals, high total antioxidant capacity and polyphenolic compounds may be related to lower risk of diabetes and predisposing factors.[4–9] Based on the current understanding of pathophysiology of insulin resistance and type 2 diabetes mellitus, multiple pharmacological and non-pharmacological interventions have been developed with the aim of improving glycaemic control and prevention of diabetes complications; in this area, recently the use of functional foods and their bioactive components have been considered as a new approach in the prevention and management of diabetes and its complications.[10] A nutraceutical is a food with a medical-health benefit, including the prevention and treatment of disease. Nutraceuticals also refer to natural functional/medical foods or bioactive phytochemicals that have health promoting, disease preventing or medicinal properties.[11]



These nutraceuticals normally contain the required amount of vitamins, lipids, proteins, carbohydrates, minerals, or other necessary nutrients, depending on their emphases.[12] Traditional medicinal plants are used throughout the world for a range of diabetic presentations. Herbal drugs are prescribed widely because of their effectiveness, less side effects and relatively low cost.[13] Therefore, investigation on such agents from traditional medicinal plants has become more important.[14] The present review, deals with some selective Herbal medicinal plants having pharmacologically established hypoglycaemic potential.

Categories of nutraceuticals and their role in diabetes

Nutraceuticals are non-specific biological therapies used to promote wellness, prevent malignant processes and control symptoms. These can be grouped into the following three broad categories.[15]

Nutrients: Substances with established nutritional functions, such as vitamins, minerals, amino acids and fatty acids.

Herbals: Herbs or botanical products as concentrates and extracts.

Dietary supplements: Reagents derived from other sources (e.g. pyruvate, chondroitin sulphate, steroid hormone precursors) serving specific functions, such as sports nutrition, weight-loss supplements and meal replacements (Figure 1).

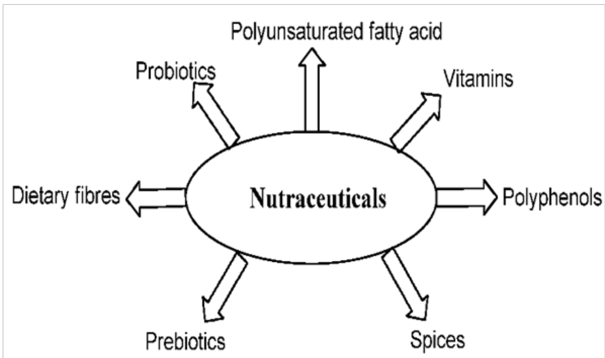


Figure 1 Need for diabetes-preventive nutraceuticals.

The purpose of this review is to discuss these issues and provide a methodological framework for the clinical investigation of nutraceuticals in diabetes mellitus and metabolic syndrome.

Antioxidant of vitamins

Animal studies have shown that an adequate supply of dietary antioxidants may prevent or delay diabetes complications including renal and neural dysfunction by providing protection against oxidative stress.[16] However, clear evidence in humans is lacking.[17]

Vitamin C

Vitamin C (ascorbic acid) is a chain-breaking antioxidant, scavenging ROS directly, and preventing the propagation of chain reactions that would otherwise lead to a reduction in protein glycation.[18] In animals, vitamin C also reduces diabetes-induced sorbitol accumulation and lipid peroxides in erythrocytes. Vitamin C (800 mg/day) partially replenishes vitamin C levels in patients with type 2 DM and low vitamin C levels but does not improve endothelial dysfunction or insulin resistance.[19]

Calcium/vitamin D

One of the first large prospective studies to examine the role of habitual diet on diabetes risk identified high calcium intake as protective; women in the top quintile of calcium intake, as contrasted to those in the bottom quintile, were 30% less likely to develop diabetes over a 6 year follow up, after correction for various potential confounders.[20] Surprisingly, it appears that no subsequent studies have followed this lead. No prospective studies have examined the implications of habitual vitamin D intake (or sunlight exposure) for diabetes risk. Yet there are theoretical grounds for suspecting that, by suppressing secretion of parathyroid hormone (PTH), good calcium/vitamin D status may help to preserve insulin sensitivity and thus help prevent diabetes mellitus.[21]

Vitamin E

Vitamin E is an essential fat soluble vitamin and functions primarily as an antioxidant. Low levels of vitamin E have been associated with increased incidence of diabetes and some research suggests people with diabetes have decreased levels of antioxidants. Additional evidence indicates that people with diabetes may also have greater anti-oxidant requirements, due to increased free radical production secondary to hyperglycaemia. Doses of vitamin E up to 400 IU are generally believed to be safe. Doses over 800 IU may alter blood clotting although supplement trials that have monitored Prothrombin times in subjects have noted no increases.[22]

Carbohydrates

Carbohydrates are the energetic substrate related to the greatest impact on glycaemia levels. The total amount of carbohydrates is the main factor responsible for the post-prandial response, but there are other variables, such as type of carbohydrate, richness in fibre, the way of cooking, degree of maturity, etc., that can play a role.[23] Moreover, there are other factors that can also influence post-prandial glycaemia such as pre-prandial glycaemia, macronutrient distribution of the whole meal (fats and proteins) and the hypoglycaemic treatment administered: oral tablets or insulin.[24] Most scientific societies recommend the individualization of carbohydrate contribution, agreeing with the fact that the diet should provide carbohydrates in the form of fruits, cereals, pasta, legumes, vegetables and tubers. Although there are no long-term studies, it seems that eating starches of legumes has a positive effect on glycaemia, because of the persistent effect on post-prandial glycaemia, with no sudden increases; it may prevent both post-prandial hyperglycaemia and late hypoglycaemia.[25]

Fats

Numerous studies indicate high-fat diets can impair glucose tolerance and promote obesity, dyslipidemia and atherosclerotic heart disease. Research also shows these same metabolic abnormalities are reversed or improved by reducing saturated fat intake. Current recommendations on fat intake for the general population apply equally to people with diabetes: reduce saturated fats to 10% or less of total energy intake and cholesterol intake to 300 mg/d or less.[26] Scientific debate continues over which alternative is preferable to saturated fat polyunsaturated fat, monounsaturated fat or carbohydrate calories.[27] Research suggests monounsaturated fat such as canola, olive and peanut oils may have beneficial effects on triglycerides and glycaemic control in some individuals with diabetes, but care must

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be taken to avoid weight gain.[28,29] Omega-3 fatty acids, found in fish such as salmon and mackerel may reduce serum triglycerides without impairing glycaemic control.[30]

Fibre

Foods rich in fibre, such as fruits and vegetables, are still recommended; special mention is made of whole cereals.[31] Although the protective effect of fibres against some chronic diseases is well established the effectiveness of fibres in lipid and glycaemic metabolism remains uncertain. For the general population, an intake of 26 g/day and 38 g/day is recommended, for women and men, respectively. There is no reason to increase the fibre dose in diabetic patients.[32]

Chromium

Chromium is a trace element that may be deficient in persons with diabetes.[33] It has been suggested that chromium supplements may increase insulin sensitivity and improve glucose tolerance in patients with type 2 diabetes mellitus. A meta-analysis of randomized controlled trials investigating the effects of chromium supplementation on glucose and insulin response in healthy individuals and those with diabetes showed a modest but significant improvement in glycaemic control in the latter, but not in the former.[34] The American Diabetes Association's official position is that there is inconclusive evidence for the benefit of chromium supplementation in diabetes.[35]

Magnesium

Prospective epidemiology links magnesium-rich diets to decreased risk for diabetes, with an inverse correlation between magnesium intake and fasting insulin levels, suggesting an improvement in insulin sensitivity. This view is supported by limited clinical data, as well as by animal studies demonstrating that magnesium helps preserving adipocyte insulin sensitivity.[36] The retina is particularly vulnerable to oxidative damage because of its abundance of polyunsaturated fatty acids, predominantly found in photoreceptor outer membranes, which are readily oxidized.[37] Nutritional supplementation for age-related macular degeneration (AMD) has been investigated in the Age-Related Eye Disease Study that reported a 25% reduction in the risk of progression to advanced AMD in people who had later stages of AMD and were supplemented with a high-dose zinc plus antioxidants formulation.

α- Lipoic Acid

α- Lipoic acid is a naturally occurring antioxidant with potent Reactive oxygen species ROS-scavenging activity. It has the unusual property of being a Reactive oxygen species ROS scavenger in its oxidized state, quenching several radicals. α- Lipoic acid and dihydrolipoic acid work in a redox couple (an electron donating molecule and its oxidized form), and together have other antioxidant properties including chelation of transition metals and the regeneration of other antioxidants such as glutathione, Vitamin C and Vitamin E.[38] α- Lipoic acid has been shown to protect the retina against ischemia-reperfusion injuries *in vivo* and *in vitro*. Ischemic injury to the retina is considered to be one of the major causes of visual loss and occurs in diabetic retinopathy. α- Lipoic acid increases insulin sensitivity by approximately 18–20% in patients with type 2 diabetes mellitus. A review of the clinical trials of α- Lipoic acid in the treatment of diabetic neuropathy reported beneficial effects on acute symptoms and disease progression.[39]

Vanadium

Research indicates that this mineral acts similarly to insulin in transporting glucose into the cells, and is therefore valuable for both type 1 and Type 2 diabetes mellitus. Vanadium supplementation also decreased fasting blood glucose levels, Haemoglobin A1c levels and cholesterol levels 50.[40–42] Dosages ranging from 45-150 mg/day can be useful for improving fasting glucose levels (how much sugar is in the blood when one wakes up in the morning). Toxicity studies show these dosage levels to be safe and well tolerated by most people. Some individuals experience mild gastrointestinal distress, either during the first week of use or at higher dosage levels (up to 400 mg/day).[43]

Protein

Current evidence indicates people with diabetes have similar protein requirements to those of the general population-about 0.86 g/kg per day.[44] Although protein plays a role in stimulating insulin secretion excessive intakes should be avoided as it may contribute to the pathogenesis of diabetic nephropathy.[45] Some evidence suggests eating vegetable protein rather than animal protein is better for reducing serum cholesterol and managing nephropathy.[46] There are a number of different types of protein supplements include liquid protein supplements, protein powders and liquid protein shots. There are a number of sources for protein supplements. Some of these sources include: Whey, Casein, Soy, Rice, and Egg.[47]

Coenzyme Q10

The importance of this nutrient cannot be overstated, primarily because many of the drugs that are needed for management of diabetes and or its complications deplete Coenzyme Q10. Coenzyme Q10 is a promising nutritional intervention for insulin resistance, at least among subjects with hypertension. Singh et al conducted an eight week randomized, double-blind trial comparing the use of a water soluble form of CoQ10 (60 mg twice daily) to a vitamin B complex in 59 hypertensive patients. Their results indicated CoQ10 at this dose lowered glucose and fasting insulin levels, suggesting possible improved insulin resistance.[48]

L-carnitine

L-carnitine (β-hydroxy-γ-trimethylaminobutyrate), a natural vitamin like compound, is an ubiquitous constituent of mammalian plasma and tissues, mainly distributed among skeletal and cardiac muscles. L-carnitine is supplied through dietary sources (e.g., meat, dairy products), and by biosynthesis from lysine and methionine.[49] Supplementation studies have shown that L-carnitine promotes insulin sensitivity and has lipid-lowering actions. L-carnitine performs a number of essential intracellular and metabolic functions, such as fatty acid transport across the inner mitochondrial membrane into the matrix for β-oxidation, detoxification of potentially toxic metabolites, regulation of the mitochondrial acyl-Co A/CoA ratio, and stabilization of cell membranes.[50] L-carnitine facilitates the elimination of short- and medium-chain fatty acids accumulating in mitochondria as a result of normal or abnormal metabolism. L-carnitine also has effects on oxidative metabolism of glucose in tissues. L-carnitine could improve insulin action in the fructose- fed rat model of insulin resistance. Skeletal muscle is an insulin-sensitive tissue, which is also a site of insulin resistance in the fructose-fed rat and it is vulnerable to oxidative damage. Considering this, these authors evaluated the role of L-carnitine in mitigating oxidative stress and lipid accumulation in

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the insulin sensitive skeletal muscle in a well-characterized model of insulin resistance. The effects of L-carnitine in this model suggest that its supplementation may have some benefits in patients suffering from insulin resistance.[51]

Anti-diabetic claims of herbs

Diabetes mellitus is a worldwide menace and exponentially growing metabolic disease in India,[52] affecting the lipid and carbohydrate metabolism and affecting the person physically as well as mentally.[53,54] The knowledge on the heterogeneity of this order is advanced, the need for more appropriate therapy increases. Traditional herbal medicines are used as a safe alternative for conventional hypoglycaemic agents, because synthetic drugs in Non-insulin dependent diabetes mellitus (NIDDM) or insulin in Insulin dependent diabetes mellitus (IDDM) have a limited role to play, and have high risk of drug tolerance, thereby causing a raise in dosage or a change of drug.[55] By virtue of richness in essential phytonutrients, ayurvedic herbs may help as "Potentiators" for these drugs and play a supportive role to maintain the quality of the diabetic life.[56,57] There is vast potential of selected medicinal plants from Ayurveda and Indian folk role medicine. Several works have been attempted by CSIR, ICMR, DBT, and academia on role of herbal nutraceuticals, nutritionals and naturals in metabolic disorders like diabetes (Table 1).

Table 1 Plants and their action of mechanism

Name of the plant	Reported mechanism of action
Acacia arabica (Lam.) Muhl. Common name: Babul [Family: *Fabaceae*]	Acts through release of insulin from pancreatic beta cells, which accounts for the hypoglycaemic activity (Singh, 1975; Wadood, 1989)
Aegle marmelos (L.) Correa Common name: Wood apple [Family: *Rutaceae*]	Increases utilization of glucose; either by direct stimulation of glucose uptake or via the mediation of enhanced insulin secretion and also decreases the elevated glucose and glycosylated haemoglobin levels (Kamalakkanan, 2003)
Allium cepa L. Common name: onion [Family: *Liliaceae*]	Lowers blood glucose level and has potent antioxidant activity, which may account for the hypoglycaemic potential (Augusti, 1973)
Allium sativum L. Common name: garlic [Family: *Alliaceae*]	Has strong antioxidant activity and rapid reactivity with thiol containing proteins responsible for the hypoglycaemic property (Rabinkov, 1998)
Aloe vera (L.) Burm.f. Common name: Aloe [Family: *Aloaceae*]	Maintains glucose homeostasis by controlling the carbohydrate metabolizing enzymes and stimulates insulin release from pancreatic beta cells (Ajabnoor, 1990)
Annona squamosa L. Common name: Sugar apple [Family: *Annonaceae*]	Lowers blood glucose level (Shirwaikar, 2004)
Artemisia pallens Wall. Ex DC. Common Name: Davana [Family: *Compositae*]	Inhibits glucose re-absorption or increase in peripheral glucose utilization (Subramaniam, 1996)
Azadirachta indica A.Juss. Common name: Neem [Family: *Meliaceae*]	Inhibits action of epinephrine on glucose metabolism, resulting in increased utilization of peripheral glucose and exhibits hypoglycaemic activity without altering the serum cortisol concentration (Chattopadhyay, 1999; Gholap and Kar, 2004)
Andrographis paniculata Nees Common name: King of Bitter. [Family: *Acanthaceae*]	Prevents glucose absorption from gut. Has hypotriglycaeridemic effect and antioxidant activity which may be responsible for beneficial effect in the diabetic state (Zhang, 2000 a,b)
Biophytum sensitivum (L.) DC. Common name: Life Plant [Family: *Oxalidaceae*]	Stimulates pancreatic beta cells to release insulin (Puri, 1998)
Beta vulgaris L. Common name: Garden beet [Family: *Chenopodiaceae*]	Lowers blood glucose level (Yoshikawa, 1996)
Brassica juncea (L.) Czern. Common name: Brown Mustard[Family: *Brassicaceae*]	Increases the concentration of hepatic glycogen and glycogenesis and suppressed the activity of glycogen phosphorylase and gluconeogenic enzymes, lead to reduction in glycogenolysis and gluconeogenesis (Khan, 1995)
Cassia auriculata L. Common name: Tanner's Cassia [Family: *Leguminosae*]	Suppresses enhanced gluconeogenesis during diabetes and enhance utilization of glucose through increased glycolysis in addition to pronounced alpha-glucosidase inhibitory actions resulting in a significant and potent lowering of blood glycaemic response (Latha 2003; Abesundara, 2004)

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Boerhavia diffusa L. Common name: Tar vine [Family: *Nyctaginaceae*]	Increases plasma insulin levels and improves glucose tolerance, produces significant antioxidant activity (Pari, 2004; Satheesh, 2004)
Caesalpinia bonducella (L.) Roxb. Common name: Chinese Cinnamon [Family: *Caesalpiniaceae*]	Increases the release of insulin from pancreatic cells (Sharma, 1997)
Citrullus colocynthis (L.) Schrad. Common name: Bitter apple [Family: *Cucurbitaceae*]	Exerts an insulinotropic effect (Abdel-Hassan, 2000)
Cajanus cajan (L.) Millsp. Common name: Pigeon pea [Family: *Fabaceae*]	Lowers plasma glucose level (Amalraj, 1998)
Coccinia indicaWight & Arn. Common name: Ivy gourd [Family: *Cucurbitaceae*]	Suppresses glucose synthesis, through depression of the key gluconeogenic enzymes glucose-6-phosphatase and fructose-1, 6-bisphosphatase and enhances glucose oxidation by shunt pathway through activation of its principal enzyme glucose- 6-phosphate. Also has an insulin secretagogue effect and acts like insulin by correcting elevated enzymes in glycolytic pathway (Kamble, 1998)
Casearia esculenta Roxb. Common name: Carilla Fruit[Family:*Flacourtiaceae*]	Exhibits significant reduction in blood glucose level, a decrease in the activities of glucose-6- phosphatase and fructose-1,6-bishosphatase and an increase in the activity of liver hexokinase, resulting in potent hypoglycaemic activity (Prakasam, 2002)
Catharanthus roseus (L.) G. Don Common name: Madagascarperiwinkle[Family: *Apocynaceae*]	Increases metabolization of glucose and enhances secretion of insulin either from the beta cells of Langerhans or through extra pancreatic mechanism (Nammi, 2003)
Camellia sinensis Kuntze. Common name: Green tea[Family:*Theaceae*]	Epigallocatechin gallate, present in tea increases insulin activity and prevents oxidative damages, responsible for the hypoglycaemic activity (Anderson, 2002)
Enicostemma littorale Blume Common name: Nahi[Family: *Gentiaceae*]	Enhances glucose-induced insulin release from isolated rat pancreatic islets, mediated through K (+)-ATP channel-dependent pathway (Maroo, 2002)
*Eugenia jambolana Lam. (syn. Syzygium cumini L.)*Common name: Indian black berry [Family: *Myrtaceae*]	It enhances serum insulin activity and exhibits norm glycaemia and better glucose tolerance (Ravi, 2004)
Helicteres isora L. Common name: Screw tree[Family: *Sterculiaceae*]	Acts through insulin-sensitizing activity (Chakrabarti, 2002)
Ipomoea batatas (L.) Lam. Common name: Sweet potato[Family: *Convolvulaceae*]	Reduces insulin resistance and possibly acts by maltase inhibition (Matsui, 2002)
Morus alba L. Common name: White mulberry [Family: *Moraceae*]	Acts by increasing glucose uptake (Chen, 1995).
Scoparia dulcis L. Common name: Sweet Broomweed [Family: *Scrophulariaceae*]	Suppresses glucose influx into the polyol pathway leading to increased activities of antioxidant enzymes and plasma insulin and decreases activity of sorbitol dehydrogenase. Also potentiates insulin release from pancreatic islets (Latha, 2004)
Murraya koenigii (L.) Spreng. Common name: curry-leaf tree [Family: *Rutaceae*]	Increases glycogenesis and decreases glycogenolysis and gluconeogenesis (Khan, 1995)
Ocimum sanctum L. Common name: Holy Basil [Family: *Lamiaceae*]	Acts by cortisol inhibiting potency (Gholap, 2004)
Punica granatum L. Common name: Pomegranate [Family: *Punicaceae*]	Inhibits intestinal alpha-glucosidase activity, leading to anti-hyperglycaemic property (Li, 2005)

Conclusion

Among many disease or disorders of carbohydrate, fat and protein metabolism, diabetes is a serious disorder effecting large population of the world. It is associated with decreased insulin production or resistance towards its action. Plants have been traditionally used to treat diabetes patients, both insulin dependent & non-insulin dependent diabetes. Nutraceuticals are food supplements and have nutritional value. All the nutrients discussed in this review have exhibited significant clinical & pharmacological activity. The potency of herbal drugs is significant & they have negligible side effects than the synthetic anti-diabetic drugs. There is increasing demand by patients to use the natural products with anti-diabetic activity. The efficacy of hypoglycaemic herbs is achieved by increasing insulin secretion, enhancing glucose uptake by adipose and muscle tissues, inhibiting glucose absorption from intestine and inhibiting glucose production from hepatocytes. A place for nutraceuticals in clinical practice is emerging, but important pharmaceutical and clinical issues need to be addressed by further research.

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Conflict of interest

None.

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