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Gymnema sylvestre: An Alternative Therapeutic Agent for Management of Diabetes

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ABSTRACT

Gymnema sylvestre (Asclepiadaceae) also known as 'gurmar' or 'sugar destroyer' is a woody, climbing traditional medicinal herb which has many therapeutic applications in Ayurvedic system of medicine. It is used for lowering serum cholesterol, triglycerides and blood glucose level (hypoglycemic or antihyperglycemic), hypolipidaemic, weight loss, stomach ailments, constipation, water retention and liver diseases, either high or low blood pressure, tachycardia or arrhythmias, and used as aperitive, purgative, in eye troubles, anti-inflammatory, smooth muscle relaxant, prevention of dental caries, cataract and as anticancer-cytotoxic agent. Its flowers, leaves, and fruits contains alkaloids, flavones, saponins, sapogenins, anthraquinones, hentri-acontane, pentatriacontane, α and β-chlorophylls, phytin, resins, d-quercitol, tartaric acid, formic acid, butyric acid, lupeol, β-amyrin related glycosides and stigmasterol having main principle bioactive compunds viz. gymnemic acids, gymnemasides, gymnemagenin, gurmarin, gymnemosides, gymnemanol, gymnemasins, gypenoside, and conduritol which act as therapeutic agent and play vital role in many therapeutic applications. Gymnemic acids are thought to be responsible for its antidiabetic activity and it is the major component of an extract shown to stimulate insulin release from the pancreas. Another anti-sweet agent gumarin is utilized as a pharmacological tool in the study of sweet-taste transduction. The commercial exploitation of this plant and their secondary metabolites are some of the major prospective of this rare medicinal herb. The focus of the present review is to achieve the potential of therapeutic value of this herb and mechanism and action of their secondary metabolites.

INTRODUCTION

Despite the use of several types of oral anti-diabetic drugs, treatment of type-2 diabetes is still a major problem due to therapy failure (DeFronzo, 1999). Such failure is evident in a majority of patients after 10 years treatment with sulfonylurea, a widely used class of drugs that stimulate insulin release by closure of B-cell K-ATP channel (DeFronzo, 1999; Brown *et al.,* 2004). Herbal medicines known to be useful in diabetes treatment may be able to lead to compounds with such a combination of ideal therapeutic properties (Gupta, 1961; Jain and Sharma, 1967; Reddy *et al.,* 1989; Stocklin, 1969; Liu, 1992; Sinsheimer and Manni, 1965). Yet, according to an earlier review of herbs and nutrient supplements that were claimed to improve glycemic control few plants were supported by rigorous clinical evidence. The herbs that did demonstrate positive clinical effects were *Gymnema sylvestre*. Of particular interest was the herb Gymnema, because of its long history as a treatment for diabetes, and its range of unique and varied effects.

G. sylvestre (Asclepiadaceae) a vulnerable species is a slow growing, perennial, medicinal woody climber found in central and peninsular India. Its leaves, called "Gurmar" in India, are well known for their sweet taste suppressing activity (Kapoor, 1990) and are used for the treatment of diabetes mellitus (Dixit and Pandey, 1984; Gupta, 1961; Jain and Sharma, 1967; Reddy *et al.,* 1989) for over 2000 year, hence the name "Gurmar" meaning 'sugar destroying'. It is used in food additives against obesity. *G. sylvestre* is a woody, climbing herb indigenous to the tropical

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forests of central and southern India. The plant belongs to Kingdom Plantae with Division Angiospermae and Class Dicotyledoneae. Gymnema is native to south-Indian forests. It is a large tropical liana native to central and western India and can be also found in tropical Africa and in Australia (Stocklin, 1969). The current review is aimed at providing an overview on ethnomedicinal, pharmacological studies including clinical and experimental studies, hypoglycemic and anti-hyperglycemic activities of plants, active hypoglycemic compounds and constituents along with their available toxicity status.

CHEMICAL CONSTITUENTS AND BIOACTIVE COMPONENTS

The anti-diabetic array of molecules has been identified as a group of closely related gymnemic acids after it was successfully isolated and purified from the leaves of *G. sylvestre* (Liu 1992; Sinsheimer and Manni, 1965). Later, the phytoconstituents of *G. sylvestre* were isolated, and their chemistry and structures were studied and elucidate (Sinsheimer and Manni, 1965; Sinsheimer *et al.,* 1970; Yoshikawa *et al.,* 1989; Yoshikawa *et al.,* 1992). Gymnemic acids, a group of triterpenoid saponins belonging to oleanane and dammarene classes. Oleanane saponins are gymnemic acids and gymnemasaponins, while dammarene saponins are gymnemasides. Gymnemic acids I-VI were isolated and characterized from aqueous leaf extracts and gymnemic acids XV-XVIII from the saponin fraction of the leaves. Gymnemic acids VIII-XII have been elucidated as glucosideuronic acid derivatives of gymnemagenin (Porchezhian and Dobriyal, 2003). Gymnemic acids are thought to be responsible for the antidiabetic activity of *G. sylvestre*; gymnemic acid VIII was the major component of an extract shown to stimulate insulin release from the pancreas (Persaud *et al.,* 1999).

Gymnema saponins I-V, groups of anti-sweet principles with a novel D-glucoside structure are also present in gymnema extracts. Besides this, other plant constituents are flavones, anthraquinones, hentri-acontane, pentatria contane, α and β-chlorophylls, phytin, resins, d-quercitol, tartaric acid, formic acid, butyric acid, lupeol, β-amyrin related glycosides and stigmasterol. The plant extract also tests positive for alkaloids. The structure of gurmarin, another anti-sweet agent found in gymnema, has been elucidated as a polypeptide comprising 35 amino acid residues (Fletcher *et al.,* 1999).

Mechanism of Action of Gymnemic Acids

The main constituent of gymnema is believed to be gymnemic acid, a mixture of at least 17 different saponins. Gymnemic acid formulations have been found useful against obesity, according to recent reports (Yoshikawa *et al.,* 1993). This is attributed to the ability of gymnemic acids to delay the glucose absorption in the blood. The atomic arrangement of gymnemic acid molecules is similar to that of glucose molecules. These molecules fill the receptor locations on the taste buds thereby preventing its activation by sugar molecules present in the food, thereby curbing the sugar craving. Similarly, Gymnemic acid molecules fill the receptor location in the absorptive external layers of the intestine thereby preventing the sugar molecules absorption by the intestine, which results in low blood sugar level (Sahu *et al.,* 1996). Structure of gymnemic acid and gymnemagenin is shown in **Fig. 1 and 2.**

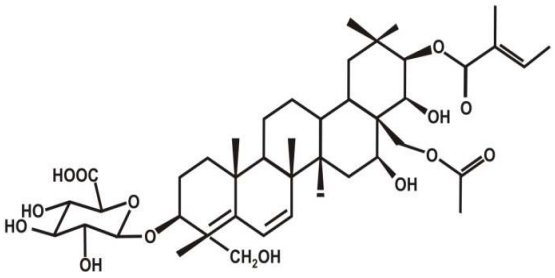

Fig. 1: Structure of gymnemic acid.

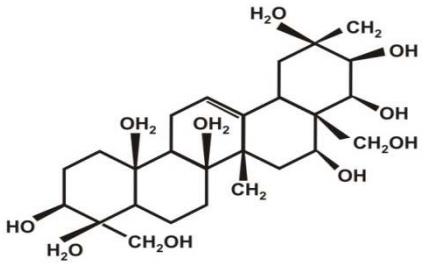

Fig. 2: Structure of Gymnemagenin.

There are some possible mechanisms by which the leaves and especially Gymnemic acids from *G. sylvestre* exert its hypoglycemic effects are:

- It increases secretion of insulin
- It promotes regeneration of islet cells
- It increases utilization of glucose: It is shown to increase the activities of enzymes responsible for utilization of glucose by insulin-dependent pathways, an increase in phosphorylase activity, decrease in gluconeogenic enzymes and sorbitol dehydrogenase and
- It causes inhibition of glucose absorption from intestine, the exact action being unknown. It could be involve one or more mechanisms (Nakamura *et al.,* 1999).

Ethnomedicinal uses

Gymnema has played an important role in Ayurvedic medicine for centuries. Its use has been confined primarily to the management of diabetes mellitus and similar hypo/hyperglycemic conditions. As early as 1930, the pharmacological effect of the plant was investigated. The leaves also have been used for stomach ailments, constipation, water retention, and liver disease. The flowers, leaves, and fruits have been used in the treatment of either high or low blood pressure, tachycardia or arrhythmias. Chewing the leaves destroys the ability to discriminate the sweet taste, giving it the common Hindi name of gurmar, or "sugar destroyer." According to the Ayurvedic Pharmacopoeia of India, both the dried leaf and root of gymnema, depending on dosage

form and formulation, are also used in the treatment of svasa (bronchial asthma), kasa (cough), kustha (leprosy and other skin diseases), and vrana (wounds), among other conditions.

According to Charak Samhita, it removes bad odor from breast milk. It is aperitive. This plant is useful as purgative, in eye troubles. The leaf extract and flower is beneficial for eyes. Bark is given in the diseases caused by vitiated kapha (phlegm). The root bark is useful in piles. According to the Ayurveda it is acrid, alexipharmic, anodyne, anthelmintic, antipyretic, astringent, bitter, cardiotonic, digestive, diuretic, emetic, expectorant, laxative, stimulant, stomachic, uterine tonic; useful in amennorrhoea, asthma, bronchitis, cardiopathy, conjunctivitis, constipation, cough, dyspepsia, haemorroids, hepatosplenomegaly, inflammations, intermittant fever, jaundice and leucoderma. Also it is used for the treatment of dysentery in North Coastal areas of Andhra Pradesh, India (Pragada *et al.,* 2012)

Pharmacological Aspects

G. sylvestre is one of the indispensable medicinal plants used in Ayurvedic system of medicine for the treatment of diverse diseases **(Fig. 3)** and are well known for their sweet taste suppressing activity and are used for the treatment of diabetes mellitus. It is used in food additives against obesity. Authors group previously described some medicinal plants and biological entities (macrofungus) as golden gift for human kind (Thakur *et al.,* 2009; Thankur *et al.,* 2009; Sanodiya *et al.,* 2009). In continuation, *G. sylvestre* has been the subject of extensive phytochemical and bioactive investigations due to its importance in traditional folk and Ayurvedic system of medicine.

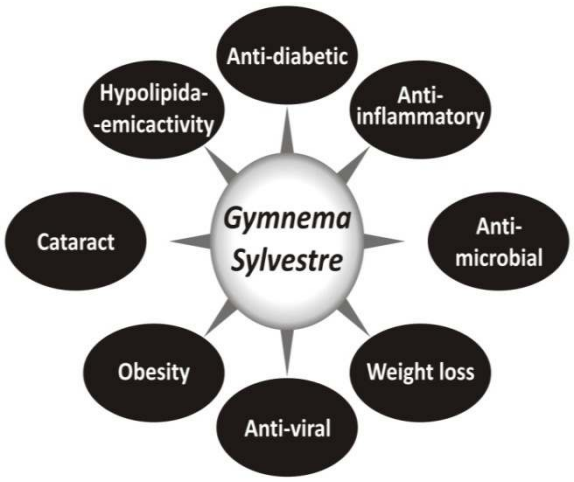

Fig. 3: Medicinal Properties of *Gymnema sylvestre.*

***Gymnema sylvestre* in Diabetes Mellitus**

Experimental studies, for instance, have found that many of the constituents in Gymnema decrease the uptake of glucose from the small intestine. Gymnema has also demonstrated improvements in glycogen synthesis, glycolysis, gluconeogenesis, and hepatic and muscle glucose uptake, as well as the reversal of hemoglobin and plasma protein glycosylation. Some authorities also indicate that gymnema may improve glycemic control by stimulating insulin release from the pancreatic islets of Langerhans.

Hypoglycemic activity or antihyperglycemic activity

Gymnema sylvestre has long been used as a treatment for diabetes (Nakamura *et al.,* 1999; Sahu *et al.,* 1996; Murray, 1999). When Gymnema leaf extract is administered to a diabetic patient, there is stimulation of the pancreas by virtue of which there is an increase in insulin release (Kanetkar *et al.,* 2004). These compounds have also been found to increase fecal excretion of cholesterol (DeFronzo, 1999).

A number of studies have evaluated the effects of *G. sylvestre* on blood sugar in animals (Rahman *et al.,* 1989). In one typical study, diabetic rats received an alcoholic extract of *G. sylvestre* (100 mg/kg/day) for 1 month (Gupta and Seth, 1962). By the second week, the mean blood sugar level was lower among animals receiving the Gymnema extract (74 mg/dL) than among the control group (106 mg/dL).

This difference was maintained throughout the study. A blood glucose-lowering effect of similar magnitude produced by tolbutamide has been demonstrated. It should be noted that the doses used would be equivalent to a 7 g dose for a typical man (Gupta and Seth, 1962). A more dramatic effect was noted when the extract was administered parenterally to rats (Gupta and Variyar, 1964).

Shanmugasundaram *et al.,* (1990) investigated that patients received 200 mg Gymnema powder twice daily in addition to their usual doses of insulin, mean glycosylated hemoglobin (HbA 1c) decreased significantly from baseline (12.8 to 9.5%) at 6 months in a controlled trial of patients with type 1 diabetes. Mozersky, (1999) reported that 22 patients were given *G. sylvestre* extract along with their oral hypoglycemic drugs. All patients demonstrated improved blood sugar control. Twenty-one out of the twenty-two were able to reduce their oral hypoglycemic drug dosage considerably, and five patients were able to discontinue their oral medication and maintain blood sugar control with the extract alone.

The effects of an alcoholic extract of *G. sylvestre* (GS4) on insulin secretion from islets of Langerhans and several pancreatic β-cell lines were examined by Persaud *et al.,* (2009). GS4 stimulated insulin release from β-cells and from islets in the absence of any other stimulus, and GS4-stimulated insulin secretion was inhibited in the presence of 1mM EGTA.

Persaud *et al.,* (2009) examined the effects of a novel Gymnema extract on insulin secretion from the MIN6 –cell line and isolated human islets of Langerhans. Insulin secretion from MIN6 cells was stimulated by OSA in a concentration-dependent manner, with low concentrations (0.06- 0.25mg/ml) having no deleterious effects on MIN6 cell viability, while higher concentrations (0.5mg/ml) caused increased Trypan blue uptake. Normal and streptozotocin-induced diabetic rats were treated with either a 50% ethanolic extract of Gymnema leaves (GS3, 20 mg/day/rat), a purified residue of GS3 (GS4, 20 mg/day/rat), or no intervention for up to 95 days (Shanmugasundaram *et al.,* 1988).

Hypolipidaemic Activity

In a study conducted on experimentally induced hyperlipidaemic rats the leaf extract at a dosage of 25-100 mg/kg administered orally for two weeks reduced the elevated serum triglyceride (TG), total cholesterol (TC), very low density lipoprotein (VLDL) and low density lipoprotein (LDL)-cholesterol in a dose dependent manner. The ability of the extract at 100mg/kg to lower TG and TC in serum and its antiantheroscelrotic potential were almost similar to that of a standard lipid lowering agent clifibrate (Bishayee and Chatterjee, 1994).

In another study a dose-dependent increase in fecal cholesterol and cholic acid-derived bile acid excretion has been demonstrated in rats (Nakamura *et al.,* 1999). A 3-week study showed a decrease in apparent fat digestibility and an increase in excretion of neutral sterols and acidic steroids in rats receiving an extract of *G. sylvestre* leaves and either a normal or high-fat diet. Total serum cholesterol and triglycerides also were decreased significantly (Shigematsu *et al.,* 2001). After 10 weeks, plasma triglycerides were lower in Gymnema-fed rats than in controls, but the difference in plasma total cholesterol levels was no longer significant (Shigematsu *et al.,* 2001). An aqueous extract of the leaf was effective in reducing serum lipids in 27 insulin dependent diabetic patients taking insulin only, when treated with 400 mg/day. Serum levels of lipids returned to near normal.

Weight Loss

An increase in body weight was significantly suppressed in a long-term study of the administration of *G. sylvestre* extract in rats fed a high-fat diet. However, in rats receiving a normal diet, no significant suppression of weight gain was observed (Shigematsu *et al.,* 2001). Use of a dietary supplement containing *G. sylvestre* in combination with glucomannan, chitosan, fenugreek, and vitamin C was investigated in obese adults (body mass index 30 kg/m 2 or more) (Woodgate and Conquer, 2003). Compared with placebo recipients, the treatment group lost significantly more body weight, and percentage of body fat and absolute fat mass were significantly reduced. Reduction in upper abdominal, waist, and hip circumferences also was demonstrated in patients receiving active treatment.

The effect of Gymnema on body weight, glucose absorption and lipid metabolism was examined by using a breed of fatty rats with genetic obese-hyperglycaemia.

Sweet Taste Suppression Activity

The antisweet principles of Gymnema include gymnemic acids, gymnemasaponins and gurmarin. Gymnemasaponins completely inhibited the perception of sweetness induced by a 0.1 M sucrose solution. The reduced sensitivity to sweet substances produced by Gymnema might result from the competition at the receptor sites between glycosides and the sweet substances. An electrophysiological study on taste responses in rats suggests that gurmarin acts on the apical side of the taste cell, possibly by binding to the sweet taste receptor protein (Miyasaka and Imoto, 1995). A gymnemic acid rinse used by human volunteers reduced the intensities of sucrose and aspartame to 14% of their pre-rinse levels (Gent *et al.,* 1999).

Experimental evidence

Effect of Gymnema powder on Blood Glucose Level and Lipid Profile on Human Subjects

The present study was conducted by the authors at Diabetes camp, School of Studies in Biotechnology, Jiwaji University, Gwalior (M.P) to study the effect of gurmar leaf powder intervention on the blood glucose level and Lipid profile of 20 non-insulin dependent diabetic human subjects (n=15), (40-60) years residing in the Gwalior city, Madhya Pradesh. Information regarding name, age, religion, lifestyle pattern, was collected with the help of interview schedule.

All the subjects were divided in to three groups of 15 subjects each (Group I, II, III) whose FBG values were < 200 mg/dl , cholesterol levels were < 200 mg/dl, triglycerides levels were found to be < 150 mg/dl and VLDL levels were found to be < 150 mg/dl. Group I included diabetic control group which received standard allopathic antidiabetic drugs. Group II, which received Gymnema powder (1 gm/day) and the Group III, which received mixture of Gymnema powder and standard allopathic antidiabetic drugs (1 gm/day) for 90 days. It was observed form the study that administration of dosage before meals to these groups reduced the FBG levels by 16.3%, 12.9 %, 26.6% and PP levels by 13.17%, 24.8 %, 47.21% respectively in Group I, II and III. Similarly the lipid levels such as Total Cholesterol, triglycerides, LDL, VLDL, were also found to reduce significantly by 38 %, 31.3 % , 45 % and 31.7 % respectively. Hence, it was concluded form the study that GS supplementation can be advocated to subjects with metabolic syndrome.

GYMNEMA IN OBESITY

Obesity and its effect on human body

Obesity and associated type 2 diabetes mellitus are the emerging epidemic of this new century. It is characterized by the increased storage of triglycerides (fat molecules) in adipose tissue thereby causing insulin resistance. It could also be defined as the condition of a human being in which the body contains more fat than required and which can lead to a disease state.

Resistin, also known as adipocyte-secreted factor and FIZZ3, (Kim *et al.,* 2001; Holcomb *et al.,* 2000) is a 12.5-kDa cysteine-rich protein that is specifically expressed in white adipose tissue. It has been proposed that elevated plasma resistin levels in rodent models of obesity could be causative in the development of insulin resistance and that resistin may be a link between obesity and type-2 diabetes. In keeping with this hypothesis, resistin was shown to be down-regulated by the antidiabetic drug rosiglitazone in white adipose tissue of mice, suggesting that suppression of resistin expression could be one of the underlying mechanisms for the beneficial effects of thiazolidinediones in insulin-resistant states (Steppan *et al.,* 2001). Along the same line, acute hyperglycemia under normoinsulinemic conditions led to up-

regulation of resistin transcription in various adipose depots (Rajala *et al.,* 2002) **(Fig. 4).**

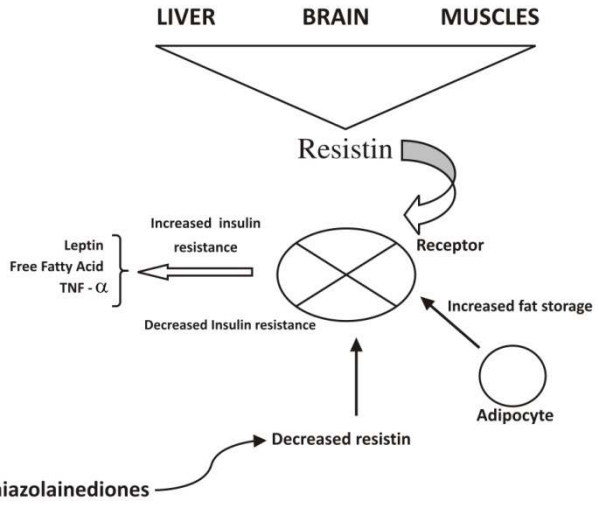

Fig. 4: Resistin and its area of linkage.

Linkage between Obesity, Diabetes and Gymnemic acids

From the above aspects of the diseases i.e. obesity, diabetes mellitus and gymnemic acids, a linkage amongst them is quite clear. The diagrammatic representation shown below will give an idea as to how the three are inter-linked. Hence, it is obvious that same medicine can be used for curing of both the disease. Obesity is the main consequence from the accumulation of the carbohydrates and fats. Gymnemic acids cure the binding of carbohydrates to the receptors in the intestine and hence, the "empty calories" are taken care of so that the body does not go into obese stage. The acids are also useful in curbing of diabetes by a similar mechanism as mentioned above for carbohydrate. Currently, gymnemic acids are being sold in the form of Gymnema Tea, for curing obesity (Flier, 2001) **(Fig. 5).**

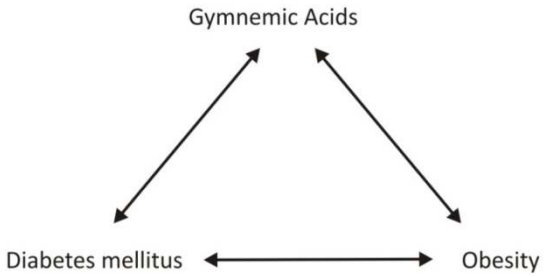

Fig. 5: Linkage between Obesity, Diabetes mellitus and Gymnemic acids.

TOXICOLOGICAL AND SAFETY EVALUATION

No adverse reactions were reported in a long-term study of insulin-dependent diabetic patients (Shanmugasundaram *et al.,* 1990). However, consider the possibility of hypoglycemia. Systolic blood pressure was raised in spontaneously hypertensive rats fed a high sucrose diet. The clinical significance of this finding is unknown (Preuss *et al.,* 1998). In an acute toxicity study in mice, no gross behavioral, neurologic, or autonomic effects were observed. The acute LD 50 was 3990 mg/kg. The safety ratio (LD 50 /ED 50) was 11 and 16 in normal and diabetic rats, respectively (Chattopadhyay, 1999).

CONCLUSION AND FUTURE PROSPECTS

Gymnema Leaves has been used by natural clinics in India for centuries to support healthy blood sugar levels. The taste of Gymnema suppresses the ability to detect sweet tastes. It has an important place among such antidiabetic medicinal herbs. It has shown experimental or clinical anti-diabetic activity and it boosts our insulin level. Since each part of *G.sylvestre* has some medicinal property, it is very much commercially exploitable. During the last few decades considerable progress has been achieved regarding its biological activity and medicinal applications. Hence, it can be chosen as a source for the development of industrial products for treatment of diabetes mellitus. Medicinal value of this herb has become a matter of great significance particularly its antidiabetic action which is reported by several researchers but the mechanism of action of *G. sylvestre* is not yet clearly understood.

However, there are currently no standard protocols for guaranteeing its product for quality and efficacy. From a pharmacological point of view, safety is a relative concept and it should be clear by further appropriate research in this direction. A systematic research should be undertaken to develop a modern drug using compounds isolated from this climbing shrub. A modern effective and safe drug can be developed after extensive investigation of its pharmacodynamics, kinetics, proper standardization and clinical trials. An extensive research should be undertaken on this herb and its products including standardization of various parts and subparts and drug development program using *G.sylvestre* compounds for their better economic and therapeutic utilization. Further research is needed to establish content and bioactivity of the many compounds present, their mode of actions and the effect of preparation and consumption differences on their medicinal activity.

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