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HERBAL DRUGS ENHANCING THE TREATMENT OF DIABETES MELLITUS

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Abstract:
Diabetes mellitus is becoming a common metabolic disorder which has serious threat to public health in the world. There are chemicals and biochemical agent that helps in controlling diabetes but there is no permanent remedy available which helps to get recovered completely from this disorder. By conducting large number of research work, numerous traditional medicines have been found for diabetes. Substances and extracts isolated from different natural resources especially plants have always been a rich arsenal for controlling and treating diabetes problem and complication arising due to it. So this review helps the reader to understand the importance of various types of herbal and polyherbal formulations present traditionally which can be used to treat diabetes mellitus.

Keywords: Diabetes mellitus, Herbal drugs

1. INTRODUCTION:

Diabetes mellitus is that the most typical endocrine disorder which currently affects quite 100 million people worldwide and thus the amount of people with diabetes is increasing because of increase , aging and increasing prevalence of obesity and physical inactivity(1) .India is that the world's second most populous country, having more people with type 2 diabetes than in the other nation because the disease prevails in both genders and every one age groups Plants are wont to treat non-insulin dependent diabetes since past (2) . Numerous investigators have taken great interest in plants as possible sources for brand spanking new hypoglycemic agents and lots of plants have already been screened (3). Today, quite 800 plants are identified as potential treatments Indian traditional health care system uses variety of medicinal plants traditionally over 1000 years in herbal preparations(4). Medicinal plants, minerals and organic matter cover a serious a part of traditional medicines. Most of the Indian traditional medical practitioners formulate and dispense their own recipes (5). 21,000 plants are listed by the WHO, which are used for medicinal purposes around the world. Among these, 2500 species are in India, out of which, 150 species are used commercially on a fairly large scale (6). India is that the largest producer of medicinal herbs and is named the arboretum of the planet Ethnology botanical information reports about 800 plants which possess anti-diabetic potential within the developed

countries, the use of herbal medicine for the sufferers of diabetes is inspired by the priority about the adverse effects and price associated with chronic use of synthetic drug (7). There are wide ranges of phyto constituents useful within the treatment of diabetes (8). These include alkaloids, glycosides, peptidoglycan, hypoglycan, steroids, guanidine, glycopeptides, terpenoides, amino acids and inorganic ions. consistent with ethno botanical survey, there are about 800 plants which possesses anti diabetic potential(9). DM may be a group of metabolic alterations characterized by hyperglycemia II. Type I diabetes often mentioned as type I diabetes (10), is insulin dependent and known to affect only 5% of the diabetic population. the sort II, which is non-insulin dependent, usually develops in adults over the age of 40(11). it's already been established that chronichyperglycemia of diabetes is related to future damage, dysfunction and eventuallythe failure of organs, especially the eyes, kidneys, nerves, heart and blood vessels .It has an adverse effect on carbohydrate, lipid and protein metabolism resulting in chronic hyperglycemia and abnormality of lipid profile(12). These cause series of secondary complications including polyurea, polyphasia, ketosis, retinopathy also as cardiovascular disorder the traditional drugs are wont to treat diabetes by improving insulin sensitivity increasing insulin production and decreasing the number of glucose in blood(13). The adverse effect of drug treatment aren't always satisfactory in maintaining normal levels of blood glucose and this view many medicinal plants are provided a possible source of anti-diabetic principle which are widely used for the treatment of DM in various traditional system of drugs worldwide and lots of of them are known to be effective against diabetes(14). The hypoglycemic effect of pharmacologically active component of plant decrease the effect on α-amylase and various direct and indirect effects of varied blood parameters responsible for development of diabetes (15) an outsized number of antidiabetic medicines are available within the pharmaceutical marketplace for diabetes and its related complications; however, currently no effective therapy is out there to cure the diseaseHowever, thanks to unwanted side effects the efficacies of those compounds are debatable and there isa demand for brand spanking new compounds for the treatment of diabetes(16). within the previous few years, there has been a growing interest within the herbal medicine in care and management of diabetes both in developing and developed countries, thanks to their natural origin and fewer side ffects.In this review , an effort has been made to compile the reported hypoglycemic plants available in several scientific journals and should be useful to the health professionals,scientists and students working within the field of pharmacology and therapeutics to develop evidence based medicine to cure different sorts of diabetes in man and animals. This review shows the importance and therefore the refore the interest placed on medicinal plants within the drive to demonstrate their antidiabetic effects and the responsible bioactive agents (17).

A progression of survey papers are delivered managing the use of metabolomics research in T2DM and other metabolic problems All things considered, a specific audit article on the utilization of metabolomics approaches concerning the roles of therapeutic plants in diabetes treatment has not been distributed up so far(18). it might presumably guide specialists, doctors and researchers to seek out the simplest therapeutic plant or new drug details for imminent improvements in diabetes the board and treatment(19). Accordingly, this paper means to feature and survey the present metabolomics considers, which have demonstrated expected biomarkers of natural examples and residential grown medication in vivo tries (20). Around 800 plant species are accounted for to possess antidiabetic properties (21). A couple of plant animal varieties are utilized for avoidance or the executives of diabetes by the Local Americans, Chinese, South Americans and Asian Indians.

In this audit article, an attempt has been made to rearrange the detailed hypoglycemic plants accessible in various logical diaries and could be valuable to the wellbeing experts, researchers and researchers working within the field of pharmacology and therapeutics to make proof based elective medication to repair various sorts of diabetes in man and creatures (22). This audit shows the importance and therefore the refore the premium placed on restorative plants within the drive to exhibit their

antidiabetic impacts and the capable bioactive specialists (23). This survey additionally covers the regular name of a plant, the parts that are generally utilized as a cure sources, concentrates, dosages, and a test model(24).

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1.1 Anti Debetic effect and role of natural products :

1.1.1 Vine tea

Antidiabetic effect of (Vine itea) Extraction of Vine tea leaves using boiling Water in High fat diet iand streptozotocin-induced T2DM (25). The methanolic extracts were fed to the animals at a dosage of 250 and 500 mg/kg weight(26) .

1.1.2 Centella asiatica

Pegaga is a conventional Malay solution for a wide scope of protests (27). Among the 'pegaga', Centella asiatica has been utilized as a solution for diabetes mellitus (28). Along these lines, we chose to approve this case by assessing the in vivo antidiabetic property of C. asiatica (CA) on T2DM rodent model utilizing the comprehensive 1H NMR-based metabolomics approach (29).

1.1.3 Genipin

Genipin possesses a good spectrum of biological activities together with amelioratory effects on polygenic disease , however the definite mechanism of this impact remains unknown (30). to research the medicine activities of genipin and explore the organic chemistry changes of humor endogenous metabolites on diabetic rats evoked by alloxan, 1H proton magnetic resonance spectrum analysis let alone variable knowledge analysis was want to (32).

1.1.4 Gegen Qinlian

Metabonomic profiles of the sort a pair of diabetic rats evoked by streptozotocin and high-sugar, high fat diet on the treatment of Gegen Qinlian stewing (GQD) for nine weeks were investigated (33). Rats were arbitrarily divided into 5 groups: traditional management (NC), sort a pair of polygenic disease (DM), Glucophage hydrochloric, GQD in high and low dosages (34). Plasma samples for 1H NMR-based metabolomic analysis, bodily fluid samples for clinical organic chemistry, and liver and duct gland tissues for histopathology take a look at were collected. Symptom effectualness of GQD and its ability to ameliorate the diabetic symptoms in a very world scale (35). NMR-based metabonomics approach is useful for the additional understanding of diabetes-related mechanisms (36).

1.1.5 Curcuma longa

Curcuma longa, at a nutritionally relevant dose with human use, administered in conjunction with Associate in Nursing unbalanced diet (37). Indeed, ancient food supplements are long wont to counter metabolic impairments elicited by unbalanced diets (38). Curcuma longa has been provided by nuclear magnetic resonance metabolomics and GC-MS lipidomics of the liquid body substance (39). Curcuma longa extract (1% of curcuminoids within the extract) for 10 weeks (40). Orthogonal projections to latent structures discriminant analysis (OPLS-DA) on the liquid body substance nuclear magnetic resonance profiles and carboxylic acid composition (determined by GC/MS) showed a transparent discrimination between HFS teams and controls. (41)

1.1.6 Ge Gen Qin Lian

Changes in endogenous metabolites within the plasma of streptozotocin (STZ)-induced diabetic rats treated with Ge Gen Qin Lian Decoction (GGQLD) were studied (42). The endogenous mixtures in plasma were identified utilizing ultra superior fluid chromatography combined with quadrupole-season of-flight couple mass spectrometry (UHPLC-Q-TOF-MS). Reflux extraction using ethanol (50 %) Ge Gen Qin Lian Decoction (GGQLD fruits is very good Antidiabetic effect. with Ge Gen Qin Lian Decoction (GGQLD belong to chinese medicinal plan(43).

1.1.7 Huangbai-Zhimu

Antidiabetic effect of alcoholic extract Huangbai-Zhimu herb-pair Huangbai (the dried bark of Phellodendron chinense Schneid) Zhimu (the dried rhizome of Anemarrhena asphodeloides Bge) Reflux extraction using ethanol (50 i%) Alcoholic leaves extract 200 and 500 mg/kg bw was used for these studies (44). Huangbai-Zhimu have significant antidiabetic activity in induced diabetic High fat diet and streptozotocin-induced T2DM. (45)

1.1.8 Ipomoea iaquatic

Hypoglycaemic effect Ipomoea aquatic Sonication of the aerial part of I.aquatic using ethanol High fat diet and streptozotocin induced T2DM (46). Obese diabetic rats group were administered with Ipomoea aquatic ethanolic extract (n=5) 4 weeks treatment (47).

.No S.No	Specific medicinal plant treatment	Biological Sample	Study population and duration of treatment	Analytical platform (s)	Biomarkers and metabolic pathways identified	Diabetes type	Statistical method	Ref Ref
1	Ampelopsis grossedentata (Vine itea) Extraction of Vin tea leaves using boiling Water	Serum	Sprague Dawley rats were divided into five groups: Normal group, High-fat-diet group, High-fatdiet group treated with Pioglitazone, High-fatdiet group treated with 500 mg/L Vine itea, High-fat-diet group treated with 2000 mg/L Vine itea.	LC-MS	Acetyl-CoA, phosphoenolpyruvic acid, cis-aconitate, fructose-1,6-phosphate, glucose-6-phosphate, fructose 6-phosphate, i6-phospho-gluconate, uric acid, allantoin, hypoxanthine and inosine (↓)	High fat diet induced T2DM	PLS-DA ANOVA	(48)
2	Centella asiatica Maceration of the freeze dried leaves with ethanol (70 %) followed by ultrasonication	Urine	47 male Sprague Dawley rats were divided into five groups norml group (n=10) Obesive groups (n=10) Obese-diabetic group (n=5) Obese-diabetic group treated with 300 mg/kg Metformin(n=8) 4 week itreatment	1H-NMR	Valine, leucine and isoleucine biosynthesis, the TCA cycle, phenylalanine, tyrosine and tryptophan biosynthesis, glutathione metabolism, energy metabolism, purine metabolism Serum isamples: Choline, succinate, lactate, pyruvate, glutamate and alanine (↑)	High fat diet and streptozotocin-induced T2DM	PCA	(49)
3	Coptis chinensis (berberine	Serum	116 patients with newly diagnosed T2DM and	UPLC-Q-TOF MS	The concentration ofi13 fatty acids in ipatients after	T2DM and	PLS-DA	50

			dyslipidemia,		3months berberine administration decreased significantly.Berberine may imediate glucose metabolism via participation in lipid metabolism and regulation of insulin scretion and insulin sensitivity by down-regulating fatty acids imetabolism, thereby enhancing glucose iutility iand iglycolysis.	dyslipidemia	OPLS-DA ANCOVA	
4	Curcuma long Maceration iof Curcuma longa rhizome with hot water (80 i°C), and evaporation iof the aqueous extract then, the rhizome residue was re-extracted with ethanol at 60 °C.	Serum	30 imale Sprague Dawley were divided into three groups: Normal group (n=6)	1H-NMR GC-MS	Glutamine, glycoproteins (acetyl), C20:5n-3 Eicosopentaenoic acid, C22:6n-3 Docosahexaenoic iacid, C24:1n-9 Nervonic acid (↓)	High fructose	PCA	(51)
5	Gardenia jasiminoides Ellis fruit (genipin)	Serum	36 male Sprague Dawley rats were divided Normal group (n=6)	1H-NMR 2D-NMR	Glucose, valine, isoleucine, trimethylamine-N-oxide, glutamate, betaine and dimethylamine (↓)Pyruvate, choline, arginine, glycerol, alanine, trimethylamine, 3-hydroxybutyrate, N-acetylglycoproteins,	Alloxan-induced T1DM	PCA PLS-DA ANOVA	(52)

					succinate, acetone and glutamine (↑)			
6	GenGen Qin Lian (GGQLD) consists of four herbs, Pueraria Lobatae Radix, Scutellariae Radix, Coptidis Rhizoma, and Glycyrrhizae Radix et Rhizoma Praeparata cum Melle, in ia weight ratio of 8:3:3:2. Immersing of Herb pieces iin distilled water and then extraction by refluxing	Serum	70 male Sprague–Dawley rats were randomly divided into five groups Normal group (n=10) Diabetic group (n=13), iDiabetic group treated with imetformin (n=13), Diabetic group treated iwith GGQLD (n=13), Diabetic group treated with fermented GGQLD (n=13). 8 weeks treatment	LC-MS	30 ipotential chemical markers contributed ito the separation of Ge Gen Qin Lian (GGQLD) and Fermented Ge-Gen-Qin-Lian (FGGQLD). Deglycosylation reaction by stepwise cleavage of the sugar moieties was considered the main metabolic pathway. The increasing trends of flavone aglycones (daidzein and liquiritigenin) and isoflavone C-glycosides (puerarin), as well as other homologous compounds, might be helpful for explaining the greater antidiabetic effects of FGQD, which occur partially via regulation of the levels of ISI, TC, TG, and HDL	High fat diet and streptozo tocin-induced T2DM	PCA OPLS-DA ANOVA	(53)
7	GeGen Qin Lian (GGQLD) Reflux extraction using iethanol (50 %)	Plasma	Male Sprague Dawley rats were divided into five groups: Normal group Diabetic group	1H-NMR	Glucose, glycerol, unsaturated lipids, lipoprotein iand Isoleucine, ieucine, valine,β-	High fat diet and streptozo tocin-induced T2DM	PCA PLS-DA ANOVA	(54)

			Diabetic group treated with 4 g/kg GGQLD Diabetic group treated with 8 g/kg GGQLD Diabetic group treated with 300 mg/kg Metformin Diabetic group treated with 4 g/kg GGQLD Heat map Diabetic group treated with 8 g/kg GGQLD analysis Diabetic group treated with 300 mg/kg metformin 9 weeks treatment		hydroxybutyrate, alanine, lactate, arginine, N-Acetyl groups, succinate, glutamate, dimethylamine, creatine, creatinine, tyrosine and trimethylamine-N-oxide (↑)The results confirmed the hypoglycemic efficacy of GGQLD and its ability to ameliorate the diabetic symptoms in a global scale.			
8	Ge Gen Qin Lian (GGQLD)	Plasma	18 male Sprague Dawley rats were divided into three groups Normal igroup (n=6) Diabetic igroup (n= i6) Diabetic group treated with 4.95 g/kg of GGQLD (n=6)	UHPLC-QTOF-MS	Phytosphingosine, dihydrosphingosine (↑) Cholylglycine, niacinamide pantothenic acid, (↓) Sphingolipid metabolism, CoA biosynthesis, primary bile acid biosynthesis, nicotinate and nicotinamide Metabolism.	Streptozotocin-induced T2DM	PCA ANOVA	(55)
9	Huangbai-Zhimu herb-pair Huangbai (the dried bark of Phellodendron chinense Schneid)	Urine	Male C57BL/6 J mice were divided into three group Normal group Diabetic group	GC-MS	Glucose, hexadecanoic acid, octadecanoic acid, propanoic acid, 3-hydroxybutyric acid, and 2,3-	High fat diet and streptozotocin-induced T2DM	OPLS-DA	(56)

	Zhimu (the dried rhizome of Anemarrhena asphodeloides Bge) Reflux extraction using iethanol (50 %)				dihydroxybutanoic acid (↓)			
10	Ipomoea aquatic Sonication of the aerial part of I. aquatic using ethanol (95%)	Urine	Sprague–Dawley irats: Normal group (n=6) Obese diabetic group (n=5) Obese diabetic rats group were administered with Ipomoea aquatic ethanolic extract (n=5) 4 weeks treatment	1H-NMR	potential biomarkers were iidentified: Creatinine/ creatine, carnitine, 1-methyl nicotinamide, trigonelline, leucine and lysine,3-hydroxybutyrate (3-HB), formate (↑)Glucose, succinate, citrate and 2-oxoglutarate (↓)Glucose metabolism, energy metabolism lipid metabolism, amino acid metabolism, gut microbiota and nicotinate/nicotinamide metabolism	High fat diet and streptozotocin induced T2DM	PCA PLS-DA	(57)

Table 1.2: Investigating the effect of herbal medicines on blood metabolites of diabetic animals

Biological isource	Family	Parts iused	Phytochemicals	Anti idiabetis iactivity [In ivitro In ivivo]	Reference
Acacia Arabica	Fabaceae	Seed, Bark	Polyphenol, Tannin	Alloxon diabetic rat	(58),(59)
Acacia Arabica	Fabaceae	Seed, Bark	Polyphenol, Tannin	Alloxon diabetic rat	(60)
Cassia auriculata	Fabaceae	Flower	Sterol, Triterpenoid, Flavonoid, Tannin	STZ rat	(61)
Glycine max	Fabaceae	Seed	3-O-methyl-D-chiro-inositol	Type II diabetic patient	(61)
Tamarindus indica	Fabaceae	Seed, Fruit	3-O-methyl-D-chiro-inositol	STZ rat	(62)
Xanthocercis zambesiaca	Fabaceae	Leaf	Flavonoid, Polysaccharide	Alloxan rat	(63)
Retama raetam	Fabaceae	whole plant	Fagomine, 4-O-beta-Dglucopyranosylfagomine, Castanospermine	Alooxan mice	(64)
Butea monosperma	Fabaceae	Fruit	Butein, Palasonin, Stigmasterol-3 β-D-glucopyranoside	Stz rat	(65)
Aegle marmelos	Rutaceae	Leaf, Seed, Fruit	Aegeline 2, Coumarin, Flavonoid, Alkaloid	Type II diabetic	(66)
Citrus reticulate	Rutaceae	Fruit	Essential oil	STZ rat	(67)
Feronia elephantum	Rutaceae	Fruit	Bioflavonoid, Triterpenoid, Stigma sterol, Bergapten		(68)
Murraya koenigii	Rutaceae	Leaf, Fruit	Carbazole, Alkaloid		(69)
Limonia acidissima	Rutaceae	Fruit	Polysaccharide	STZ rat	(70)

Allium cepa	Alliaceae	Bulb	Allyl propyl disulphide, S-methyl cysteine sulphoxide		(71)
Allium sativum	Alliaceae	Root	Diallyl disulphide oxide, Ajoene, Allyl propyl disulfide, S-allyl cysteine, S-allyl mercaptocysteine		(72)
Aloe barbadensis	Asphodelaceae	Leaf	Lophenol, 24-methyl-lophenol, 24-Ethyllophenol	STZ rat	(73)
Azadirachta indica	Meliaceae	Leaf, Seed	Nimbidin		(74)
Melia dubia	Meliaceae	Whole Plant		STZ rat	(75)
Beta vulgaris	Chenopodiaceae	Whole Plant	Sugar beet pectin, Polydextrose		(76)
Biophytum. Sensitivum	Oxalidaceae	leaf	Liminoid	STZ rat	(77)
Averrhoa bilimbi	Oxalidaceae	Seed, Leaf	Sugar beet pectin, Polydextrose	STZ mice	(78)
Brassica juncea	Brassicaceae	Leaf	Isorhamnetin diglucoside		(66),(67)
Raphanus sativus	Brassicaceae	Whole plant			(45),(66)
Lepidium sativum	Brassicaceae	Seed			(48),(66)
Cajanus cajan	Leguminosae	Leaf	(7R*,9as*)-7-phenyloctahydroquinolizin-2-one	STZ mice	(49),(54)
Withania Somnifera	Solanaceae	Fruit	Withanolide, Alkaloid	STZ rat	(50),(57)
Lycium barbarum	Solanaceae	Fruit	Polysaccharide	STZ rat	(51),(34)
Withania Coagulans	Solanaceae	Whole Plant	Milk-coagulating enzyme, Esterase, Fatty oil, Essential oil, Alkaloid	STZ rat	(52),(56)
Physalis alkekengi	Solanaceae	Leaf, Bark	Polysaccharide		(53),(45)
Capsicum Frutescens	Solanaceae	Fruit	Capsaicin	STZ rat	(54),(56)

Catharanthus Roseus	Apocynaceae	Leaf	Vinculin, Alkaloid		(55),(45)
Cinnamomum Zeylanicum	Lauraceae	Seed	Cinnamaldehyde		(56),(48)
Persea americana	Lauraceae	Root	Fat, Protein, Vitamin, Mineral		(57),(46)
Coriandrum Sativum	Apiaceae	Bulb	Alanine	STZ mice	(58),(56)
Cuminum cyminum	Apiaceae	Leaf	Aldehyde		(59),(61)
Psidium guajava	Myrtaceae	Leaf, Fruit	Terpen, Flavonoid, Strictinin, Isostrictinin, Pedunculagin, Polysaccharide	STZ mice	(60),(43)
Baccharis trimera	Myrtaceae	Leaf	Polysaccharide		(61),(56)
Syzygium jambolanum	Myrtaceae	Fruit	Polysaccharide	Alloxan rat	(62),(57)
Egyptian Morus Alba	Moraceae	Bark	Polysaccharide	STZ rat	(63),(55)
Gymnema sylvestre	Asclepiadaceae	Leaf, Fruit	Gymnemic acid, Gymnema, Saponin	STZ rat	(64),(45)
Hordeum vulgare	Poaceae	Seed	Beta-glucan	Alloxan rat	(65),(70)
Triticum vulgare	Poaceae	Whole 26] plan	Albumin	STZ rat	(66),(61)
Hygrophila Auriculata	Acanthaceae	Whole plant	Unknown	Alloxan rat	(67),(70)
Strobilanthes Crispus	Acanthaceae	Leaf	Albumin	Alloxan rat	(68),(67)
Ibervillea sonorae	Cucurbitaceae	Root	Monoglyceride (MG), Fatty acid	STZ rat	(69),(65)
Momordica Charantia	Cucurbitaceae	Whole plant	Charantin, Momordicin, Galactosebinding lectin Non-bitter, Diosgenin, Cholesterol, lanosterol, β-sitosterol, Cucurbitacin glycoside	Alloxan rat STZ mice STZ rat	(70),(66)
Cucumis Metuliferus	Cucurbitaceae	Fruit	B-carotene, Fatty acid	STZ rat	(71),(74)
Momordica	Cucurbitaceae	Fruit	Steroidal glycoside or phenolics	STZ rat	(72)

Momordica balsamina	Cucurbitaceae	Fruit	Momordicin, Vitamin C, Resin acid, Fixed oil, Carotene, Aromatic volatile oil, Alkaloid	Alloxan rat	(76)
Jatropha curcas	Euphorbiaceae	Whole plant	Diterpene	Alloxan rat	(76),(4),(77)
Mangifera indica	Anacardiaceae	Stem Bark,	Mangiferin, Phenolics, Flavonoid	STZ rat	(78)
Asteraceae	*Eugenia jambolana*	Fruit pulp, Seed	Pandanus odorus	Alloxan rat	(78)

2. Conclusion:

Diabetes mellitus is a most common endocrine disorder, affecting millions of people worldwide. It is a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The increase in resistance and populations of patients at some risk, in conjunction with the restricted number of commercially available drugs for diabetes that still present have many side effects and also problems like unwanted hypoglycemic effect are the cause to shift the research towardstraditionally available medicine which have low side effect and wide range of bio activity and do not require laborious pharmaceutical synthesis seems highly attractive. From this review article, it may be useful to the healthprofessionals, scientists and scholars to develop evidence-based alternative medicine to cure different kinds of diabetes problem using herbal preparation. Substances and extracts isolated from different natural resources play very important role to design medicine and treat hyperglycemic problem in diabetes mellitus.

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