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Herbal Medicine in the Management of Diabetes: Current Trends and Evidence

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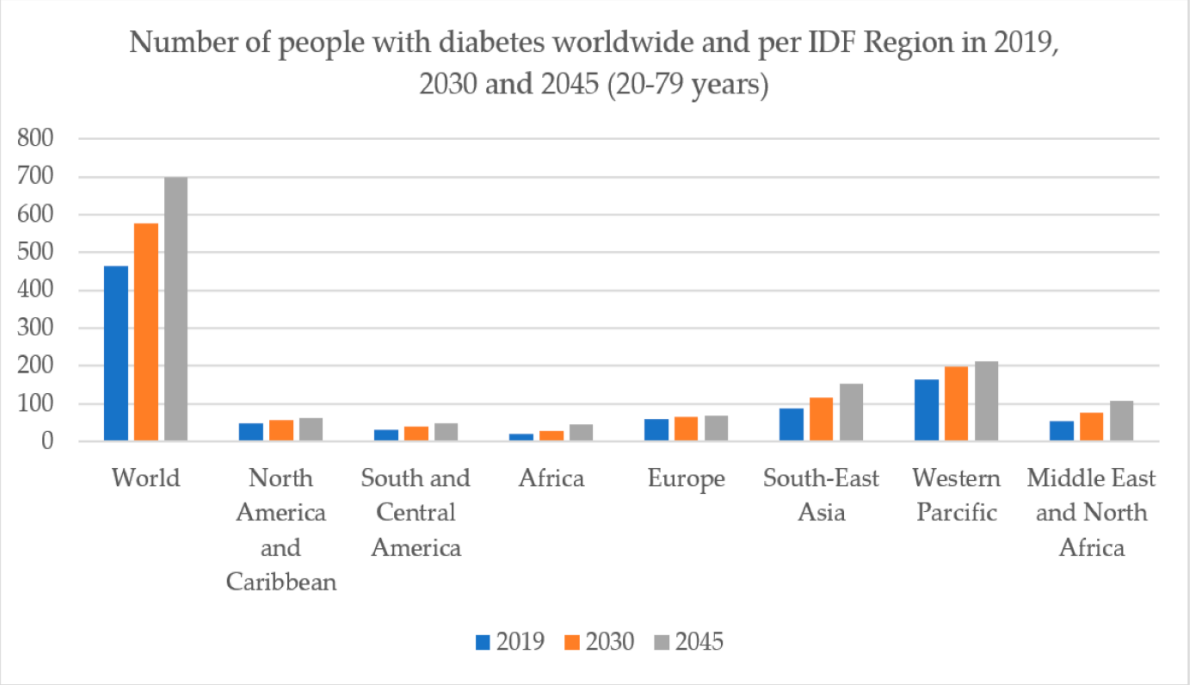
Abstract:
Increased use and popularity of herbal medicine for the treatment of diabetes have recently been reported. As, oxidative stress has been recognized as the key underlying pathophysiology of diabetes and its complication, the aim of the bibliometric analysis is to evaluate the world scientific production analysis and developing its trend in the area of antioxidative hypoglycemic herbal drugs and diabetic nephropathy with emphasis on the numbers of scientific publications, citations, world-wide geographical distribution and identifying the leading journal source in the area.

Keywords: Diabetes mellitus, Management of Diabetes, Medicinal plants, Vitamins.

INTRODUCTION:

Diabetes mellitus (DM) is a multifactorial metabolic disease marked by persistently high blood sugar levels and abnormalities in the metabolism of carbohydrates, fats, and proteins due to deficiencies in either the production or action of insulin, or both. Long-term harm, organ failure, and malfunction are among the consequences of diabetes mellitus. Three primary kinds of diabetes mellitus exist. Insulin-dependent diabetes mellitus, or type 1 diabetes, is an autoimmune disease that arises when the body's insulin-producing cells are damaged, resulting in little to no insulin production from the pancreas. To survive, a person with type 1 diabetes has to take insulin every day. Children any young adults are the ones who develop it most frequently. More than 90% of adult instances of diabetes mellitus are type 2 diabetes, sometimes referred to as "insulin-independent diabetes mellitus". It is a condition where the pancreas secretes sufficient insulin but the body is unable to make use of the insulin, a state referred to as insulin resistance. Gestational diabetes mellitus (GDM) is a level of glucose intolerance with onset or initial recognition in the second or third trimester of pregnancy. GDM is due to the pregnancy hormone or an insulin deficiency. GDM is among the most common metabolic disorders in pregnancy.
Hyperglycemia results in eyes, kidneys, nerves, heart and blood vessels damage. As of 2019, the entire adult population of the age group 20–79 years has been estimated by the ninth edition 2019 of the International Diabetes Federation (IDF) Diabetes Atlas published by the IDF to be 463 million with diabetes, projected to rise to 578 million by 2030. There is a death of one patient due to diabetes mellitus every 6 s, this is more than deaths due to human immunodeficiency virus (HIV) (1.5 million), tuberculosis (1.5 million) and malaria (0.6 million).



According to the statistics of International Diabetes Federation in 2019, the number of adults aged 20 – 79 years is 463 million living with diabetes and this is expected to reach 578 million by 2030. Among these, in 2019, 373.9 million adults between 20 -79 years across the globe,7.5% of adults, are estimated to have impaired glucose tolerance. The majority of those with impaired glucose tolerance are adults below 50 years of age (180.0 million-48.1%). Prevalence of diabetes in men aged 20-79 years is slightly greater compared to women (9.6-% vs 9.0%). The incidence of diabetes is projected to rise in both men and women between the years 2019 and 2030 and 2045. Everywhere across the globe, there exist top 10 nations with population of individuals having diabetes, which are China, the USA, Indonesia, India, Brazil, Mexico, Japan, Pakistan, Thailand, and Nigeria. Even through the risks of GDM among pregnant women have been identified clearly, there remains doubt that the treatment lowers and regulates blood glucose level of pregnant women may minimize those risk or not. Additionally, GDM continues to enhance the risk for the onset of type 2 DM after pregnancy. Cultural and social transition, e.g., aging, population, physical activities reduced, diet, etc. The economic burden related to diabetes involves mounting health services, an economic cost.

Management of diabetes mellitus:

Treatment for diabetes mellitus greatly depends on an understanding of its pathophysiology. A pre-prandial blood glucose level of 80 to 120 mg/dL (4.4 to 6.7 mmol/L), a bedtime blood glucose level of 100 to 140 mg/dL (5.6-7.8 mmol/L), and a HbA1c level of less than 7% are all suggested by the American Diabetes Association as part of glycemic management. Any therapy program for people with diabetes mellitus should focus on weight control, physical activity, and healthy eating. In addition to lowering blood glucose levels, these lifestyle changes also help people lose weight and improve a number of cardiovascular disease risk factors. Patients must rely on drugs for treatment because the majority of them are unable to lead healthy lifestyles.

The goal of current diabetes mellitus treatment is to regulate and bring blood glucose levels in the vasculature down to normal. Both contemporary and conventional medication work by encouraging the

pancreatic islet's beta-cells to release more insulin, blocking hormones that raise blood glucose levels, making the insulin receptor site more sensitive, preventing the liver's glycogen from hydrolysing, and improving the tissues and organs utilization of glucose. There are now two classes of injection and six major classes of contemporary medications used worldwide to regulate blood glucose levels. Alpha–glucosidase inhibitors, thiazolidinediones (glitazone), sulfonylureas, biguanides (metformin), and DPP-4 inhibitors are the names of the tablets. Insulin and incretin mimetics are the kinds of drugs administered by injections. These drugs' mechanism have been documented. But the majority of contemporary medications have a lot of negative side effects, which can lead to some major health issues when the medication is processed. One biguanides medication that can improve insulin sensitivity and prevent the liver from producing glucose molecules is metformin. But metformin also has some major adverse effects, like gastrointestinal problems like dyspepsia, nausea, and diarrhoea in the beginning. people with severe liver disease, decompensated heart failure, severely impaired renal function, and other severe medical conditions should not use metformin. Thiazolidinediones have the advantageous benefits of increasing insulin sensitivity, lowering insulin resistance, lowering cardiovascular risks when used to treat diabetes. However, weight gain and fluid retention-which can result in peripheral edema and heart failure-are the most frequent side effects of thiazolidinediones. Patients with similar conditions, such as heart failure and serious liver problems, were not allowed to use the medications. Rosiglitazone may raise the risk of a heart attack and have cardiovascular side effects. In many nations, pioglitazone has not been made available because of worries about an elevated risk of bladder cancer.

Inverse document frequency (IDF) statistics show that health spending for adults aged 20 to 79 years has grown, rising from USD 232 billion in 2019. It has been projected that the economic effect of diabetes will continue to rise steadily. By 2030, health spending is expected to exceed USD 825 billion, and by 2045, it will reach USD 845 billion. As a result, the cost of medications has grown to be a significant issue for diabetic patients in underdeveloped nations. In addition to contemporary medicine, traditional medicines have been around for a while and are valuable complementary therapies. Around 75-80% of the world's population still relies heavily on plant-based traditional medicine, according to the WHO, especially in developing nations with a wide variety of plants. Because they are more culturally acceptable, more compatible with the human body, and have less side effects than contemporary treatments, traditional medicines are typically the first choice for patients' primary healthcare in underdeveloped nations. Some medicinal plants have recently been utilized empirically as antidiabetic and antihyperlipidemic treatments, with reports of their benefits in diabetes being made all around the world. Over 400 plant species with hypoglycemic activity have been reported in the literature, yet exploring new antidiabetic drug from natural plants has remained appealing since they possess management of diabetes mellitus. The majority of plants possess by active compound, including phenolics, glycosides, alkaloids, terpenoids, flavonoids, carotenoids, etc. which have been enhanced as possessing antidiabetic activities.

Anti-diabetic properties of medicinal plants:

Around the world, diabetes has been prevented and/or treated at a reasonable cost by using medicinal plants or plant-based medication. Actually, a lot of impoverished nations use plant-based therapy to treat diabetes and other illnesses. Traditional medicinal plants contain natural chemicals that are structurally derived from a number of medications utilized today. For instance, the traditional usage of

Galega officinalis to treat diabetes can be linked to the development of the anti-hyperglycemic medication metformin. Vitamins C, D, and E, Hibiscus sabdariffa L. (roselle plant), Momordica charantia (bitter melon), Zingiber officinale Rosc (ginger), and Allium sativum (garlic) are the most often used medicinal plants and vitamins with hypoglycemic properties to boost the immune system and control blood sugar levels in humans. Many developing nations and a few affluent nations employ medicinal plants to address their healthcare demands since they are readily available, affordable, and effective in managing diabetes.

***Allium sativum*:**

Garlic, scientifically known as Allium sativum, is a plant species belonging to the Amaryllidaceae family. Numerous health advantages of garlic are well documented, including improved blood pressure, decreased cholesterol, and strengthened immunity. Additionally, studies have indicated that garlic may help those with diabetes. According to research, garlic may help enhance insulin sensitivity and reduce blood sugar, both of which are advantageous for people with diabetes. Among the main phytochemicals found in garlic are: (1) allicin, which is one of the most well-known and gives it its strong smell; (2) sulphur compounds, such as diallyl disulfide and diallyl trisulfide, which have anti-inflammatory, anti-cancer, and antioxidant qualities; (3) flavonoids, such as quercetin and kaempferol, which are known for their antioxidant qualities; (4) saponins, which are natural detergents with cholesterol-lowering qualities; and (5) fructans, a class of carbohydrates that may serve as prebiotic candidates.

Figure: 1 Garlic may help enhance insulin sensitivity.

Anti-inflammatory, immunomodulatory, cardioprotective, hypolipidemic, hypoglycemic, antioxidant, antibiotic, antifungal, antibacterial, antiseptic, antiviral, and anticancer properties are some of garlic's positive health effects. Clinical research has shown that using garlic supplements together with common anti-diabetic medications helps people with type 2 diabetes manage their condition. Furthermore, studies have shown that garlic and its compounds effectively lower insulin resistance. Garlic also helps regulate type 2 diabetes by acting as a hydrogen sulfide donor. Garlic has been shown in another study to lower glucose and lipid profiles, including haemoglobin A1c (HbA1C) and fasting glucose levels, in diabetic patients.

***Allium cepa* (Allium):**

Allium cepa Linn. belongs to the Liliaceae family, which is also known as onions. Many nations, including China, Egypt, and Vietnam, use it as a culinary element. Because of its ability to withstand extreme environments, such as cold or drought, this plant can be kept for an extended period of time without losing its phytonutrient composition.

***Momordica charantia*:**

Both wealthy and developing nations employ Momordica charantia, or bitter melon, as an alternative or supplemental medication to manage diabetes mellitus. It contains substance that help diabetic individuals control and reduce their blood glucose levels. By increasing insulin sensitivity and decreasing the liver's synthesis of glucose, it controls and lowers blood glucose in diabetics. Anti-inflammatory, immunomodulatory, hypolipidemic, hypoglycemia, antioxidant, antifungal, antibacterial, antiviral, and anticancer properties are some of the health benefits of bitter melon. Amino acids, carbohydrates, flavonoids, glycosides, minerals, phenols, phytosterols, saponins, tannins, and vitamins are found in bitter melon leaves, fruit, and seeds according to phytochemical analysis. These substances have anti-oxidant, anti-inflammatory, immunomodulatory, hypolipidemic, and anti-hyperglycemic properties. According to studies, hypoglycemic herbs improve glucose intake by muscle or adipose tissues, boost insulin secretion, and prevent the liver from producing glucose and the intestines from absorbing it. Bitter melon has hypoglycemic properties that promote glucose absorption into skeletal muscle cells and boost insulin release, according to a number of in vivo experiments conducted on animals. In a similar vein, certain clinical studies have demonstrated that bitter melon successfully decreases blood sugar levels in people with type 2 diabetes. Kim and associates, for instance, conducted a randomized, placebo-controlled research. Following a 12-week course of treatment, lipid profiles, blood glucose levels, and adverse events were examined. The final analysis of bitter melon's ability to reduce glucose involved 90 participants. Age, sex, and glycated haemoglobin (HbA1C) levels did not change between the bitter melon extract and placebo groups, according to the results. The HbA1c levels of the bitter melon and placebo groups did not change following a 12-week course of bitter melon extract treatment; however, the average fasting glucose level of the bitter melon group dropped ($p = 0.014$). Throughout the course of treatment, no significant side effects were noted. The findings demonstrated that bitter melon lowers blood sugar levels in those with type 2 diabetes. Comparing diabetic rats to healthy rats, another study revealed that bitter melon permanently restored normal blood glucose levels.

Figure: 2 Supplemental medication to manage diabetes mellitus.

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***Hibiscus sabdariffa L*:**

A member of the Malvaceae family, Hibiscus sabdariffa L. (roselle) grows wild in tropical regions across numerous nations. Its high concentration of pharmacologically active chemicals and beneficial therapeutic qualities have led to its long-standing usage in traditional medicine. The anti-hypertensive, anti-inflammatory, body fat mass reduction, immunomodulatory, hypoglycemic, antioxidant, lipid-lowering, anticancer, and anti-xerostomic properties of Hibiscus sabdariffa L. (roselle) are the most often reported health benefits. The presence of bioactive and functional substances such phenolic acids, flavonoids, anthocyanins, organic acids, and dietary fiber has been linked to the medicinal benefits of Hibiscus sabdariffa L. (roselle). Oral treatment of Hibiscus sabdariffa L. (roselle) at doses of 72 mg/200 g body weight and 288 mg/200 g body weight for 21 days decreased blood glucose levels in rats with chronic diabetes, according to an animal study. For six days in a row, Harrison and associates assessed how well Hibiscus sabdariffa tea (10 g of powder in 500 mL of boiling water) controlled one volunteer's postprandial blood glucose (60 min) levels. They discovered that drinking tea made from Hibiscus sabdariffa lowers blood glucose levels and postprandial hyperglycemia.

Figure: 3 They have immunomodulatory effects.

***Zingiber officinale*:**

Zingiber officinale, or ginger, is a common flavour used for many foods and beverages. It has been utilized as an herbal medicine to cure numerous diseases across the globe since ancient times. Phytochemicals analysis showed that Zingiber officinale contains phenolic compounds like gingerols, shogaols, paradols, and non-volatile compounds like zingiberone, zingiberole, and zingiberene.

The benefits of health due to ginger consist of its anti-inflammatory, immunomodulatory, antioxidant, hypolipidemic, hypoglycemic, and antiemetic properties as well as reducing blood pressure and blood sugar. Numerous experiments in animals and human beings have shown that ginger is a hypoglycemic food adjunct with potential for the treatment of type 2 diabetes in human beings. Ginger activates its action through its ability to influence insulin secretion, enhancing glucose clearances within the insulin-sensitive peripheral tissues, important in sustaining homeostasis in blood glucose levels. Additionally, 6-gingerol was found to augment the glucose uptake at the insulin-responsive adipocytes and demonstrate enhanced insulin-responsive glucose uptake with enhancement of diabetes within cells exposed to gingerol. A study had previously shown that the use of 50% ethanolic extract of ginger rhizomes prevents the onset of obesity and insulin resistance in rats inter alia by controlling the PPAR receptors.

Figure: 4 They act as reducing blood sugar.

Antidiabetic effect of vitamins:

Vitamins have a significant impact on diabetes mellitus risk, development, and consequences. Consuming vitamin C, vitamin D, vitamin E, or a combination of these vitamins has been linked to a lower incidence of diabetes in the general population. By controlling insulin secretion or insulin sensitivity, for instance, vitamins C, D, or E may have anti-diabetic effects. They may also have immunomodulatory, antioxidant, hypolipidemic, and hypoglycemic effects.

Vitamin D:

A fat-soluble vitamin, vitamin D (calciferol) is involved in the regulation of bone formation, the improvement of the immune system, and the absorption of calcium, iron, magnesium, phosphate, and zinc. Ergocalciferol (Vitamin D2) and cholecalciferol (Vitamin D3) are the two forms of vitamin D. It is

naturally present in meat (beef liver), dairy products (milk), green vegetables, fish and meat. Vitamin D3 was created by skin exposure to UVB radiation from the sun, while plants produced vitamin D2. A lack of vitamin D has been linked to insulin resistance and the impairment of pancreatic beta cells, but vitamin D receptors are present in most tissue or organs and play a variety of biological roles, including promoting calcium absorption in the gut, maintaining adequate serum calcium and modulating various processes, including cell growth, immune function, glucose metabolism, and insulin sensitivity. According to recent studies, low vitamin D levels are linked to obesity, hypertension, glucose intolerance, and the onset of type 2 diabetes. Because vitamin D aids in the conversion of proinsulin to insulin secretion, and improves insulin action by regulating the calcium pool, preclinical research has shown that pancreatic beta cells function normally when vitamin D also plays a role in transcription regulation, which includes the down regulation of pro-inflammatory cytokine genes like interleukin-2 and interleukin-12, the production of anti-inflammatory cytokines, the prevention of beta-cell destruction, and tumor necrosis factors-alpha. When diabetic patients took 4000 IU of vitamin D supplements for six months, their insulin sensitivity significantly improved when compared to a placebo, according to randomized control double-blind intervention research. A related study also found that, in comparison to controls, vitamin D supplements have an impact on insulin secretion in prediabetic patients. Additionally, vitamin D supplements are linked to lower levels of metabolic markers such as triglycerides, glycated haemoglobin, total cholesterol, low-density lipoprotein, and diabetic complications.

Vitamin E:

Plant based oils (peanuts, olive, soybean oil), nuts (almonds), seeds (sunflower seeds), fruits (red bell pepper, mango), and vegetables (collard green, spinach, and beets green) are the main source of vitamin E. The eight isoforms of this collective set of fat-soluble substances can be divided into tocopherol and tocotrienol isoforms have a saturated side and chain on the chromanol ring and are categorized as alpha, beta, gamma, and delta. Tocoprienol isoforms, on the other hand, have an unsaturated side chain. The two types can be further divided into alpha, beta, gamma, and delta, with alpha tocopherol most suited to human nutritional needs. Vitamin E is a potent antioxidant that inhibits the creation of ROS generated when fat oxidizes and, thus, prevents or retard chronic diseases linked with free radicals. In research, it has been proven that a high concentration of vitamin E decrease biomarkers of oxidative stress and enhances immune defense. A randomized trial in patients with diabetic nephropathy revealed that 12 weeks of supplementing 800 IU vitamin E increased significantly the glutathione peroxidase levels when compared to the placebo. A parallel prospective study on type 2 diabetics with or without complications receiving 4000 IU vitamin E as a supplement to hypoglycemic medication daily for 9 months demonstrated a progressive decline in fasting blood sugar, serum glycated haemoglobin (HbA1C), and BMI in comparison with control. Overall, the antioxidant effect of vitamin E can potentially postpone diabetic complications.

Vitamin C:

Vitamin C or ascorbic acid is an antioxidant and serves multiple roles like enzyme cofactors, scavengers of free radicals, donors of electrons during transport, or receptors in the plasma membrane. Vitamin C deficiency result in collagen, blood vessel, and bone connective tissue formation defects, dentine, cartilage, skin, and oxidative stress tends to result in glucose metabolism and hyperglycemia induces the

oxidation of glucose to yield free radicals. The generation of free radicals in excess of the scavenging capacity of endogenous antioxidants could lead to macro-and microvascular dysfunction. Vitamin C biomolecules can guard against oxidation by being involved in oxidation-reduction reactions, wherein dehydroascorbic acid will be oxidized and reduced back to ascorbate. Fresh fruits, vegetables, and aromatic herbs are the primary sources of vitamin C. Vernacular names for fruits with significant levels of vitamin C are Australia's Kakadu plum, camu-camu of south America, fruit star, guava, kiwi, strawberry, orange, lemon, and pear. Cruciferous vegetables and aromatic herbs conveying high levels of vitamin C are broccoli, kale, pepper, cabbage, parsley, chives, and coriander. Temperature is significant in the stability and preservation of vitamin C. The soft approach to retain vitamin C content, and prevent potential leaching out into water, destruction, and pH alteration, is steaming or boiling in a small amount of water for extremely short-time and deep freezing for long storage. Since most fruits and vegetables are rich in vitamin C, a potential cohort study involving 23,953 diabetic-free men as baseline found that 1741nof the men who developed type 2 diabetes consumed more vegetables and fruits to the extent of 1.6 servings per week. In a study established that type 2 diabetic patients taking ascorbic acid showed a decrease in blood sugar as well as blood pressure after 4 months when compared to placebo. Besides, a cross-sectional study of the relationship between Vitamin C serum concentration and fasting blood glucose, glycated haemoglobin, serum malondialdehyde, and lipid profiles in diabetic patients observed that low vitamin C levels strongly elevate the systolic blood pressure, glycated haemoglobin, and malondialdehyde, resulting in oxidative stress biomarker elevation. The report also identified an inverse correltion between fasting blood sugar, total cholesterol, and vitamin C concentrations. The same outcome was identified in a retrospective study investigating Vitamin C concentration, renal impairment, and obesity in type 1 diabetes and type 2 diabetes patients. In conclusion, these observations recommend vitamin C therapy to improve glycemic and blood pressure in diabetic patients.

Conclusion:

Hyperglycemia brought on by deficiencies in insulin secretion, action, or both is a hallmark of diabetes mellitus (DM), a dangerous chronic metabolic condition. The maintenance of an average blood glucose level depends on insulin. Hyperglycemia results from diabetes patients' either nonexistent or reduced insulin production. Serious long-term consequences like blindness, heart failure, stroke, vision issues, nerve damage, dental disease, and kidney failure can result from uncontrolled diabetes mellitus. Over the past few decades, DM treatment methods have improved. Anti-diabetic medication has major adverse effects, including hypoglycemia coma and liver and renal problems, even if the condition of DM patients has improved over the past few decades. The therapeutic qualities of Allium sativum, Momordica charantia, Hibiscus sabdariffa L., Zingiber officinale, and vitamins C, D, and E-all of which have antidiabetic effects are highlighted in this review paper. The inclusion of coumarins, flavonoids, polyphenols, terpenoids, and other bioactive chemicals that lower blood glucose levels is thought to be responsible for the antidiabetic benefits of these vitamins and medicinal plants. When taken in the right amounts, medicinal plants and vitamins have been shown to increase blood circulation, encourage wound healing, reduce fasting blood sugar levels in diabetics, and lessen problems related to the disease. As a result, considerable efforts should be made to raise knowledge of the health advantages of vitamins and medicinal plants in the economical prevention and treatment of DM patients, particularly those in developing nations who cannot pay the exorbitant expenses of contemporary medication.

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