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ROLE OF ALPHA AMYLASE INHIBITOR IN DIABETES MELLITUS

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ABSTRACT

The prevalence of diabetes mellitus globally and in the Indian subcontinent has become a serious medical and pharmacological issue that needs to be managed and prevented as it has become the major cause of death due to the complications associated with this disorder. The commercial anti-diabetic medications with alpha-amylase inhibition property presently in clinical use has several side effects which led to the finding of natural antidiabetic agents or alpha-amylase inhibitors from various plants extracts that are known for medicinal properties. The antidiabetic agents used are alpha-amylase inhibitors that act upon alpha-amylase enzyme which is involved in the digestion of dietary starch and delays the glucose release in the blood after the meal and thus prevent postprandial hyperglycaemia. The antidiabetic agents from plant extracts are known to be the best and safer therapeutic approaches for the prevention and management of diabetes mellitus and postprandial hyperglycaemia. In this review, various natural plant extracts and phytochemical compounds used in the treatment of hyperglycaemia via alpha-amylase inhibition as an antidiabetic agent are discussed.

Keywords: Alpha amylase, Diabetes Mellitus, Alpha amylase inhibitor, post-prandial hyperglycaemia

INTRODUCTION

Diabetes mellitus commonly known as diabetes is a chronic metabolic disease characterized by both postprandial and fasting hyperglycaemia with disturbed carbohydrate metabolism, fat metabolism and protein metabolism **[1]**.

Diabetes mellitus which is noninsulin dependent is commonly occurring disease caused due to the endocrine system where the insulin secretion is decreased by the pancreatic Langerhans beta cell or when because of excessive glucose absorption, a reduction in insulin resistance is followed **[2]**. Indian Council for Medical Research, Evaluation and Public Health Foundation, and Institute for Health Metrics, reported recently that diabetes prevalence in India has increased by 64% over 25 years. Recently, in India diabetics is a serious health concern among citizens as India represents 49% of the world's diabetes burden **[1]**. Diabetes mellitus disorder will affect approximately 366 million people worldwide by 2030 as per prediction **[3]**. Diabetes to become the seventh leading cause of death according to world health organisation (WHO) by 2030. The increased diabetes prevalence is caused by various factors which are increasing population, aging, urbanization, physical inactivity and obesity. There are three types of diabetes known are: insulin-dependent diabetes mellitus, and malnutrition-related diabetes mellitus, non-insulin-dependent diabetes mellitus **[4]**. A therapeutic approach for management of diabetes effectively is to reduce hyperglycaemia by inhibiting the digestion of ingested carbohydrates. Inhibition of the enzymes involved in carbohydrate digestion could significantly decrease the blood glucose level after a meal if starch hydrolysis gets delayed **[5]**. The source of energy that is starch is the most abundant storage carbohydrates found in crops like rice, wheat, maize, and also in potato, and tapioca. The starch obtained from the various crops is harvested and used as it is or modified chemically or enzymatically into different products such as starch hydrolysates, cyclodextrins, fructose, and glucose syrups. The enzyme amylases known for hydrolysing the starch belong to multidomain proteins **[6]**. Amylases represent 30% of the enzyme produced in the world belongs to a class of industrial enzymes and are widely used in various industries such as food, fermentation, textile, paper, detergent, and sugar industries. The amylases are also used in the biotechnology field for environmental pollutant removal, breakdown of starch into desired products using microorganisms, and also its application has expanded into various fields, such as clinical, medicinal, and analytical chemistry. Amylase was the first enzyme produced at an industrial

level from a fungal source in the year 1894, used as a pharmaceutical strategy in digestive disorder treatment **[7]**. The carbohydrate digesting or hydrolysing enzyme known as pancreatic alpha-amylase is the enzyme responsible for conversion of starch into glucose or maltose **[1]**. The pancreatic alpha-amylase is the key hydrolysing enzyme present in the digestive system responsible for the generation of glucose from the diet. α-Amylase enzyme (E.C. 3.2.1.1) hydrolyses the alpha-1,4-glycocidic bonds and breakdown the starch components amylose and amylopectin into smaller units that is maltose and glucose **[8]**. The breakdown or hydrolysation of the dietary starch or carbohydrate occurs rapidly which leads to the sudden increase in the post prandial glucose level in the blood known as post prandial hyperglycaemia. Thus, the control of the activity of Human Pancreatic α-amylase present in the small intestine becomes the most important aspect to treat the diabetes as the enzyme is associated with an increase in post-prandial glucose level in the blood **[3]**. Thus, inhibition of pancreatic alpha amylase present in the small intestine, could inhibit the rate of starch hydrolysis which delays the process of digestion. This delayed digestion process lowers the glucose level in the blood and hence the effective approach in reducing the postprandial hyperglycaemia **[5]**. Inhibitors of human pancreatic α-amylase reduce the glucose levels by slowing down the rate of starch to the conversion of glucose. Therefore, inhibitors can be used as drug targets for the development of anti-diabetic drugs. Alpha amylase inhibitors which are currently in the clinical trial are acarbose and miglitol are synthetic hypoglycaemic and non-specific agents have various side effects like diarrhoea, bloating, abdominal discomfort , and flatulence and unable to treat diabetic complications **[1]**. Therefore, the natural extracts can be better and safer agents for the treatment of diabetes such as natural extracts found in numerous medicinal plants can be studied as antidiabetic agents. There are around 800 medicinal plants according to the Ayurveda in the Indian subcontinent which have antidiabetic properties **[3]**. There are several bioactive compounds that are known as nutraceuticals for e.g., polyphenols, these compounds can manage the cellular mechanism involved in the diabetes pathogenesis that causes oxidative stress and inflammation. The polyphenolic compounds are found in

various plants that are used as conventional sources of antidiabetic agents and mostly some of the edible spices rich in polyphenolic compounds are given much importance due to their no adverse side effects **[9]**. The plant polyphenols are known to have various potential benefits to human health according to recent research and are capable of decreasing the oxidative stress along with inhibiting enzymes involved in the breakdown of carbohydrate which prevent hyperglycaemia **[2]**. Thus, the polyphenols can be used in the management of diabetes mellitus along with changes in lifestyle as these compounds can lower the blood glucose level **[8]**. The phytochemicals found in the spices are coumarins, flavonoids, terpenoids, glucosides, phenolics, saponins, alkaloids and other extracts that are involved in the alpha amylase inhibition **[1]**. The molecules like polyphenols, flavonoids, tannins, and cinnamic acid derivatives have antidiabetic properties as they are involved in alpha amylase inhibition and thus, natural plant extracts or products are of much interest to study as alpha amylase inhibitors. These plant extracts obtained naturally have low cost and side effects which makes them more acceptable as antidiabetic agent to prevent hyperglycaemia **[10]**.

Role of insulin in diabetes:

Insulin is a peptide hormone secreted by the β cells of islets of Langerhans which is a group of cells present in the endocrine gland of the pancreas. Insulin is known to maintain the normal glucose levels of blood by promoting cellular glucose uptake, controlling carbohydrate metabolism, lipid, and protein metabolism, and supporting cell division and growth by its mitogenic effects **[11]**. A deficiency of insulin, or an inability to appropriately respond to insulin, can drive the development of the symptoms associated with diabetes and leads to hyperglycaemia and hypoglycaemia **[12]**. Insulin maintains glucose levels of blood by signaling the liver cells, muscle cells, and fat cells to bring in glucose from the blood. Therefore, insulin stimulates the cells to transport glucose from the blood for providing energy to the body and if adequate energy is present in the body, insulin sends signals to the liver to convert the glucose from the blood into glycogen and store it in the liver. The liver is known to store glycogen up to approximately 5% of its total mass and few cells of the body can get glucose from the blood without the help of insulin, although most of the

cells do need the presence of insulin **[12]**. Simultaneously with facilitating cells for glucose absorption, insulin also helps in the metabolism of the body. Insulin is accountable for a decision taken by cells to store glucose in the form of fat or use it as glucose. For blood glucose level management, insulin signals the fat cells to absorb the blood glucose, and if there is excessive blood glucose, then insulin signals fat cells to store the excess glucose in the form of triglycerides **[13]**. The body with type 2 diabetes does not respond adequately to insulin and this condition is known as insulin resistance where the body is unable to take glucose from the blood efficiently. In the initial levels of type 2 diabetes, the body produces more insulin than normally it requires to produce. If type 2 diabetes prolongs for years, the demands on the pancreas increase for the production of insulin which can lead to a loss of pancreatic beta cells that are known as insulin-producing cells because they wear out. Type 2 diabetes patients require to inject insulin depending on their level of insulin resistance for the management of their blood sugar levels **[12]**. The factors responsible for insulin resistance are increased levels of fat and free fatty acids in the blood which occurs due to overeating which causes weight gain and obesity. Visceral fat and inflammatory hormones are factors that are also associated with insulin resistance. Other reasons are high fructose intake, increased oxidative stress, lack of physical activity, inflammation, and destruction of gut microbiota **[14]**.

Role of alpha amylase in digestion and diabetes:

The α 1, 4 -glycosidic bonds of starch get broken down by salivary alpha-amylase and get convert into short fragments. As the alpha salivary amylase enzyme reaches the stomach area, it gets inactivated because of the acidic pH of the stomach. Hydrolysis of starch further occurs in the presence of pancreatic alpha-amylase present in the pancreas. Pancreatic juice reaches the duodenum and pancreatic α-amylase there further breaks down the starch to generate maltose, maltotriose, and other oligosaccharides. The oligosaccharides are known as dextrins, which are amylopectin fragments involving α-1, 6 branch bonds. The epithelial of the microvilli present in the intestinal cleaves maltose and dextrins into glucose units, which becomes assimilated within the circulatory system. Glycogen similar to starch also follows a similar digestive pathway for

the yield of glucose by hydrolysis **[15]**. The regulation of α-Amylase occurs through plenty of inhibitors which are classified based on the tertiary structures into six categories. The active site of the alpha-amylase gets blocked in the presence of inhibitors and these inhibitors regulate the starch conversion and convert into simple sugars post-meal during glucose peaks to control the rate of glucose breakdown. This is an approach especially essential in diabetes mellitus, where low quantities or inhibition of α-amylase are required to control glucose levels. These inhibitors of alpha-amylase function as a defense mechanism by plants for the inhibition of α-amylase in insects and thus able to protect themselves from herbivorous agents **[15]**. Alpha-amylase inhibitors presently in clinical use are acarbose and miglitol **[16]** and voglibose, sitagliptin, nojirimycin and 1- deoxynojirimycin **[17]**, that inhibit the carbohydrates digestion and present short-term control of glucose levels in the blood. The shortcoming of such inhibitors is non-specificity in targeting various glycosidase enzymes. Moreover, these alpha-amylase inhibitors have severe side effects that restrict their use as therapeutic medications. Hence, natural extracts obtained from traditional medicinal plants are essential for investigation including high potential for new antidiabetic drug discovery. Various plants are known to confer α-amylase inhibitory activity which may be applicable in the treatment and management of diabetes **[16]**.

Natural antidiabetic agents as alpha-amylase inhibitors:

A glycoprotein known as Phaseolamin was identified in the year 1975, found in white and kidney beans scientifically termed as *Phaseolus vulgaris* contains an α-amylase inhibitor. Further, phaseolamin is a dietary supplement and utilized in pharmaceutical products sold in the market as protein concentrates for the management of weight **[18]**. The plant from Iran named *Urtica dioica* plant is traditionally used in the treatment of diabetes there. In a study, the ethanolic extract obtained from the leaf of the *Urtica dioica* plant showed significant α-amylase inhibitory activities which were concentration-dependent. Another plant named *Juglans regia* has medicinal applications and its leaves have been utilized worldwide frequently in traditional medicines. The seed and methanolic leaf extracts of this plant *Juglans regia* showed the antidiabetic effect **[16]**. A plant widely distributed in southeast Asia

named *Ruellia tuberosa* L. and also found in Indonesia. According to traditional medicine, this plant has antidiabetic, antihypertensive, antipyretic, and analgesic properties. *Ruellia tuberosa* L. showed a vital blood glucose-lowering effect in alloxan-induced diabetic rats and rabbits. The ethyl acetate fraction of methanolic extracts of *Ruellia. tuberose* L. showed five flavonoids according to a report named cirsimaritin, cirsimarin, cirsiliol 4-glucoside, sorbifolin, and pedalitin accompanying Betulin, vanillic acid, and indole-3-carboxaldehyde and these flavonoids were isolated from the plant. Also, some other flavonoids were also reported in this plant such as Apigenin, luteolin, 3,5-diglucoside, apigenin-7-O-glucuronide, apigenin glucoside, apigenin rutinoside, luteolin glucoside, and flavone glycoside. But, the hypoglycaemic mechanism of these bioactive compounds has not been studied so far. The potent inhibitor of alpha-amylase in rats and human models according to the *in-silico* study of bioactive compounds of *Ruellia. tuberosa* L. is Betulin **[19]**. Alpha-amylase inhibitors from diverse indigenous medicinal plants have a great potent inhibitory activity and one such plant is *Phyllanthus amarus.* This plant has been used as traditional medicine worldwide for various diseases including jaundice, constipation, diarrhoea, kidney infirmities, ringworm, ulcers, malaria, genitourinary diseases, haemorrhoids, and gonorrhoea and also explicated potent antiviral effect according to a study against hepatitis B virus. The study including *in vitro* inhibitory effect of different extracts found in *Phyllanthus amarus* which are ethanol and hexane revealed an alpha-amylase inhibitory effect on porcine pancreatic alpha-amylase **[20]**. *Senna surattensis* plant which belongs to the family Caesalpiniaceae is generally named Glaucous cassia found all over India as a small tree or large shrubs. The leaves of this plant are tender and utilized as a vegetable long with rice. The bark and leaves of this plant are beneficial in the treatment of diabetes and gonorrhoea, and the aerial parts are employed in treating diabetes whereas the beads formed from the wood of this plant are wrapped around the neck used as a remedy for jaundice. The phytoconstituents found in this plant are anthraquinone, flavonol glycosides, chrysophanol, kaempferol, and quercetin and it has been widely used as traditional diabetes medicine. The ethanolic extract of *S. surattensis* showed an inhibitory effect on

postprandial blood glucose levels in vitro which helps in the treatment and management of diabetes **[2]**. Secondary plant metabolites widely distributed in plant species are phenolic phytochemicals and polyphenols are among one of them and these are strong antioxidants present in green tea and black tea. The significant phenolic compounds existing in green tea are flavonols which are catechins. The content of catechin in black tea is decreased by almost 85% as compared to green tea and modified into teaflavin-3-30 -digallate and thearubigin, which are known as catechin polymerization products. These polyphenolic compounds can hinder glucose absorption by the inhibition of alpha-glucosidase and alpha-amylase in the digestive organs that inhibit carbohydrate digestion. Therefore, inhibitors of alpha-glucosidase can delay the glucose production and absorption from dietary complex carbohydrates which result in decreased blood glucose levels after a meal and suppresses hyperglycaemia after a meal. Thus, this could be a treatment method for the prevention and management of type 2 diabetes **[8]**. The solvent extracts of *Azadirachta indica A. Juss., Bixa orellana L., Bougainvillea spectabilis Willd., Cinnamomum verum J. S. Presl, Curcuma longa L., Ficus bengalensis L., Ficus racemosa L., Momordica charantia L., Murraya koenigii L. Spreng., Syzygium cumini L. Skeels, and Tribulus terrestris L*. plants possess hypoglycaemic property and exhibit potent inhibitory activity on human pancreatic alpha-amylase, which is even more beneficial than acarbose. The inhibitory activity is possible due to the presence of phytochemicals in the extracts which are alkaloids, proteins, tannins, cardiac glycosides, flavonoids, saponins, and steroids **[3]**. The Indian spices such as cinnamon, cumin, fenugreek, clove, and nutmeg possess α-amylase inhibitory properties. The chemical profile of Indian spices explicated the presence of several phytochemicals such as glucosides, phenolics, saponins, flavonoids, alkaloids, coumarins, and terpenoids, and these phytochemicals present pharmacological properties to spices. The Indian dietary spices are known to stimulate various metabolic and physiological responses in the gastrointestinal system, cardiovascular system, reproductive system, and nervous systems, and thus provides significant health effects. The extracts of spices containing benzene extract of

cinnamon, clove, fenugreek, and nutmeg and chloroform extract of cumin displayed potent alpha-amylase inhibitory effect **[1]**. The bark of the black wattle tree scientifically named *Acacia mearnsii* contains tannins and has enzyme (alpha-amylase, glucosidase, and lipases) inhibitory properties, also rich in unusual catechin-like flavan-3-ols, such as robinetinidol and fisetinidol. *Araucaria angustifolia* is a regional conifer of South America, found in southern and south-eastern Brazil and north-eastern Argentina, and the seed of this plant is known as pinhão, which is produced in April to August as a seasonal product. The tannin content of the pinhão coat is rich in procyanidins as compared to the tannin of the Acacia plant and is an effective inhibitor of the human salivary alpha-amylases and the porcine pancreatic α-amylases. Hence, the tannin from the pinhão coat also useful in reducing blood glucose levels and in the treatment of diabetes **[10]**. Several plants of the western ghats in the western region of India such as *Aloe vera (L.) Burm.f., Adansonia digitata L., Allium sativum L., Casia fistula L., Catharanthus roseus (L.) G. Don., Cinnamomum verum Persl., Coccinia grandis (L.) Voigt., Linum usitatisumum L., Mangifera indica L., Morus alba L., Nerium oleander L., Ocimum tenuiflorum L., Piper nigrum L., Terminalia chebula Retz., Tinospora cordifolia (Willd.) Miers., Trigonella foenum-graceum L., Zingiber officinale Rosc.* are extremely recognized in Ayurveda to hold anti-diabetic properties and are identified to reduce blood glucose levels **[21]**. The 'wonder tree' local to the Indian subcontinent named Neem scientifically *Azadirachta indicia A. Juss.; Meliaceae*, recognized for its various therapeutic applications for longer than 2000 years. The aqueous extract of Neem leaves showed lower blood sugar levels in streptozotocin-induced diabetic rats according to earlier studies. It is the richest source of secondary metabolites in the environment, particularly tetranortriterpenoids commonly known as limonoids and they have been examined to hold a broad range of pharmacological activities and insecticidal potency. Neem limonoids are divided into two groups based on their skeletal or structure which is basic limonoids (4,4,8-trimethyl-17-furanylsteroidal skeleton such as azadirone, azadiradione, gedunin) and C-seco limonoids (with modified and rearranged C-ring such as azadirachtin, salannin, nimbin). The

tetranortriterpenoid meliacinolin and azadirachtolide isolated from *A. indica* leaves, and swietenine from *Swietenia macrophylla* is able to inhibit the alpha-amylase activity in streptozotocin induced diabetic rats according to a recent study **[5]**. Various studies related to plant-derived flavonoid-rich foods showed strengthen life expectancy through the prevention of persistent lifespan-shortening diseases such as diabetes, cancer, and cardiovascular diseases. Flavonoid-rich foods possess extraordinary health benefits and are characterized as superfoods. All plant origin foods like tea, fruit, vegetables, grains, legumes, nuts, and wine are superfoods. The primary flavonoid sources from dietary items are tea and wine found mostly in eastern societies and western societies, respectively. Furthermore, leafy vegetables, onions, apples, berries, cherries, soybeans, and citrus fruits are also regarded as an influential source of flavonoids belonging to dietary food items **[22]**. Traditionally used agents from natural sources like plants in the treatment of diabetes mellitus are rich sources of polyphenolic compounds. Amidst all polyphenolic compounds from plants, considerable attention has been given to few edible species because of their negligible antagonistic consequences. The most popular polyphenolic compound known as Curcumin has a surplus of therapeutical effects like antioxidant, antiviral, anticancer, anti-inflammatory and, many more. Curcumin is supposed to be safe regarding its extensive uses in conventional medication and modernized medication, along with culinary uses. Inclusive data has illustrated the promising role of curcumin in the treatment of diabetes and complications associated with it through accentuating various cellular mechanisms **[9]**. A carotenoid named lactucaxanthin found in lettuce scientifically named *Lactuca sativa* is known to inhibit the α-amylase activity and α-glucosidase activity. These inhibitors for the intestine and pancreas alpha-amylase enzyme and glucosidase enzyme thus helps in lowering the blood glucose levels after the meal by delaying the starch hydrolysis during digestion. Therefore lactucaxanthin can significantly inhibit the alpha-amylase and also alpha-glucosidase activity and could be involved in the medical and nutritional significance for the treatment and prevention of diabetes mellitus **[23]**. A traditional spicy flavouring substitute known as Garlic (*Allium sativum L.*,

Liliaceae) presented an anti-diabetic effect by administration of garlic ethanolic extract in diabetic rats. *Brassica juncea* seeds commonly called Rai in India are used as a spice in various food items and these were studied in alloxan-induced diabetic albino rats and displayed a notable antihyperglycemic effect. A woody climber named *Gymnema sylvestre* belonging to the family Asclepiadaceae founds in central and southern India's unkempt tropical forest has been employed as a supplement for the treatment of diabetes mellitus. Water-soluble extract of leaves from *Gymnema sylvestre* was found to reduced blood glucose levels by restoration of the islets and beta cells of the pancreas in diabetic rats. In tropical Africa, the plant *Mangifera indica* belonging to the family Anacardiacea is used medicinally and aqueous extract of its Linn stem bark exhibited anti-inflammatory, analgesic, and anti-diabetic properties because of the presence of various chemical constituents, like the polyphenolics, flavonoids, triterpenoids, mangiferin. Intra-peritoneal treatment of mangiferin secluded from *Mangifera indica* displayed influential antioxidant effects and enhances glycosylated haemoglobin levels in animals induced with diabetes **[4]**. An Indian subcontinent vegetable named *Momordica charantia* belonging to the family Cucurbitaceae is regularly known as karela and its extract displayed hypoglycaemic and strong hypolipidemic activities in streptozotocin-induced diabetic rats. The peptide found in the aqueous extract of *Momordica charantia* exhibited hypoglycaemic activity in alloxan-induced diabetic rats and during the treatment body weight increased and blood glucose levels decreased. The water-soluble extracts of *Momordica charantia* and *Eugenia jambolana* for fifteen days considerably inhibited hyperglycaemic and hyperinsulinemia in fructose-fed rats. Also, the Oral feeding of *Momordica charantia* extract showed the beta cells regeneration in streptozotocin-diabetic rats. Alcoholic extract of *Momordica charantia* displayed hypoglycaemic activity because of the stimulation of the production of glycogen in the liver of streptozotocin-induced diabetic rats **[4]**. An Indian aromatic downy shrub or small tree is ordinarily known as ‘curry patta’ named *Murraya koenigii* (L.) Spreng belongs to the family Rutaceae and its water-soluble extract administration orally reduces plasma lipid levels correlated with diabetes mellitus. The ethanolic extract of leaves

of *Murraya koenigii* displayed anti-hyperglycaemic along with antioxidant activity during treatment in rats and the antioxidant potential of *Murraya koenigii* was found to be accountable for the anti-diabetogenic properties of *Murraya koenigii.* The ethanolic leaf extract and aqueous extract of *Murraya koenigii* significantly reduced the blood glucose level and displayed hypoglycaemic activity in experimental diabetic rats and in normal and alloxan diabetic dogs respectively **[4]**. The jamun belonging to the family Myrtaceae is named *Syzygium cumini* local to India and flourishes efficiently in the tropical climate and distributed in many parts of the Indian sub-continent along with Asian and Eastern African countries. Ethanolic extracts and water extracts of *Eugenia jambolana* pulp gave less significant anti-hyperglycaemic activity in diabetic rabbits whereas alcoholic extracts and aqueous extracts of seeds of *Syzygium cumini* showed reduced tissue damage in the brains of diabetic rat. Oral administration for six weeks of the water-soluble extract of seeds of *Syzygium cumini* displayed hypoglycaemic activity and antioxidant property and powder of seeds of *Eugenia jambolana* exhibited antidiabetic action in streptozotocin-induced diabetic rats. *Eugenia jambolana* seed kernel's ethanolic extract produces reduced oxidative stress in streptozotocin-diabetic rats, which occurred due to the hypoglycaemic property of it. Administration of water-soluble extract of bark of *Syzygium cumini* orally manifested an advantageous impact on glycoproteins associated with its anti-diabetic activity in streptozotocin-induced diabetes rats **[4]**.

The *Trigonella foenum graecum* is a leguminous annual plant included in the family Fabaceae and its seeds generally known as fenugreek or methi in the Indian sub-continent and Mediterranean countries and are used as an herb or seasoning. Oral administration of seed powder of *Trigonella foenum graecum* around 5% in the food for three weeks in alloxan-induced diabetic rats displayed remarkable antidiabetic results in experimental Type-1 diabetes with negligible complexities. *Trigonella foenum graecum* seed paste and spent turmeric named *Curcuma longa* confirmed anti-diabetic effects in streptozotocin-induced diabetic rats and the paste of fenugreek seed was more effective as compared with spent turmeric in improving diabetic state. The

soluble dietary fibre portion of fenugreek seeds conferred anti-hyperglycaemic effects and has the ability to diminish aggregation of platelet in diabetic rats. *Trigonella foenum graecum* seed powder in the regular diet of the patients enhances glucose tolerance level, serum insulin levels along with the decreased level of 24-hour sugar excretion in the urine **[4]**. *Olea europaea L.* commonly known as olive is rich in phenolic compounds, including leaves and the additional virgin olive oil whose salubrious qualities are associated with the phenolic fraction. The treatment of diabetes has been practiced using olive oil since old times and few phenolic compounds present in olives act as an inhibitor for carbohydrate-hydrolysing enzymes. The hot water and ethanolic extract of olives during in vitro pancreatic alpha-amylase inhibitory action of olive leaves gave a notable decrease in blood glucose levels when various doses of olive leaf powder and secluded compounds were administered to diabetic rats. The genus *Salvia* commonly known as sages and its different types of species has been employed as traditional medicine in the treatment of hyperglycaemia induced due to diabetes mellitus **[17]**. *Castanea sativa* is generally known as chestnut possesses various health benefits which have a preventive role in cardiovascular diseases and shows a reduction in type 2 diabetes uncertainty and metabolic syndrome. The concrete impacts accomplished with enhanced chestnut consumption are associated with its high organic acid content and phenolic compounds. In regard to the significance of chestnut for the treatment of diabetes, extract of Chestnut astringent skin has been found as an amylase inhibitor. In the study of Chestnut astringent skin, it was able to hinder the absorption of carbohydrate and reduces postprandial hyperglycaemia because of the presence of active polyphenolic compound in diabetic rats through alpha-amylase inhibition activity **[17]**. A Mediterranean plant containing strong antioxidant activity named *Rosmarinus officinalis* commonly known as rosemary is recognized as a spice that possesses anti-diabetic properties. In a recent analysis of the pancreatic alpha-amylase inhibitory action of various extracts of spices, an aqueous extract of rosemary showed efficient inhibitory activity and found to be the richest in phenolic compounds. *Moringa oleifera* which is generally called as Drumstick tree is a tropical tree possessing various inherent pharmacological activities

along with the diabetes mellitus treatment and also, aqueous extract of leaves of *M. oleifera* has been found to decrease blood glucose levels in normal glycaemic rats and diabetic rats **[17]**. Various cereals such as wheat (*Triticum aestivum*), barley (*Hordeum vulgareum*), sorghum (*Sorghum bicolor*), rye (*Secale cereal*), and rice (*Oryza sativa*) are known to contain alpha-amylase inhibitors. Interestingly, amylase inhibitors found in wheat showed higher inhibitory action against human pancreatic alpha-amylase. The enduring herb *Curcuma longa*, usually recognized as turmeric, comes under a medicinal plant extensively grown in tropical areas of Asia. The main active compound of *Curcuma longa* named curcumin which is a yellow-pigmented fraction of *C. longa* includes curcuminoids related to curcumin chemically known to produce the anti-hyperglycaemic effects **[17]**. *Ocimum basilicum* is a prevalent culinary herb commonly called basil employed in various traditional medicines worldwide. Bactericidal, anti-inflammatory, antioxidative, antiulcer, hypolipidemic, radiation protective, and hypoglycaemic are their salubrious properties related to health. In an in vitro analysis of the porcine pancreatic alpha-amylase inhibitory activity of *Ocimum basilicum* extracts, aqueous leaf extracts showed a substantial alpha-amylase inhibitory action containing active flavonoids and polyphenol content **[17]**. The cocoa tree named *Theobroma cacao L*. is a food rich in polyphenol comprises monomeric flavanols ((-)- epicatechin and, in lower quantities, (+)-catechin, (+)- gallocatechin, and (-)-epigallocatechin) in a 10% of the entire content whereas 90% of the content includes oligomeric and polymeric C4β-C8 linked B type procyanidins, along with anthocyanins and other flavonol glycosides. The benefits of cocoa associated with health in animal models involve antiobesity and antidiabetic properties and the bioactive compounds of cocoa have been known to decrease blood glucose levels **[17]**. The antidiabetic effect of various *Vaccinium* species was studied including the alpha-amylase inhibitory action of berry extracts which contains phenolic phytochemicals has various health beneficial effects such as in glycaemic control. Raspberries (*Rubus idaeus*) and Rowanberries (*Sorbus aucuparia*) were found to be the most effective berries for inhibitory activity and the phytochemical analysis including raspberry extracts showed, less amylase inhibitory activity with low levels of

anthocyanins but high ellagitannins levels showed high amylase inhibitory activity. On other hand, the amylase inhibitory activity of the extracts of rowanberry with the proanthocyanidins-rich fraction was reported as great alpha-amylase inhibitors **[17]**.

CONCLUSION

Diabetes mellitus is the most prevalent metabolic disorder found in a large population globally and in India which is becoming a life-threatening disease worldwide. Diabetes mellitus occurs due to insufficient insulin production or due to insulin resistance which leads to the increase in blood glucose level after the meal is known as postprandial hyperglycaemia. Various complications are associated with diabetes mellitus which makes the disorder more prevalent and thus it requires effective therapeutic approaches. The enzymes involved in the hydrolysis of dietary carbohydrates into glucose are alpha-amylase and alpha-glucosidase and therefore, to inhibit the rate of glucose production in diabetic patients after the meal, the agents known as alpha-amylase inhibitors are required that slows down the release of glucose in the blood after a meal and prevents postprandial hyperglycaemia. The synthetic antidiabetic agents with alpha-amylase inhibitory activity or synthetic alpha-amylase inhibitors currently in clinical use are acarbose, miglitol, voglibose, sitagliptin, nojirimycin, and 1- deoxynojirimycin associated with various risk factors and side effects. The side effects that occur due to these synthetic antidiabetic drugs are diarrhoea, bloating, abdominal discomfort, and flatulence, therefore, it is required to adopt natural therapeutic approaches and discover natural antidiabetic agents for the prevention and management of diabetes mellitus. Various natural extracts from plant sources and phytochemical compounds have been extracted for the inhibition of alpha-amylase to control the post-prandial hyperglycaemia and so the control of diabetes mellitus. These natural antidiabetic agents are cost-effective, possess low-risk factors and negligible side effects which makes them the best and safe medications for the treatment of diabetes mellitus.

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