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Review Article

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Role of Phytoconstituents of Medicinal Plants in Curing Type 2 Diabetes

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Abstract

Type 2 diabetes (T2D) is a group of disorders when the level of glucose in the blood increases beyond the requirement of the body. The increase in blood glucose is mainly due to the reasons if body does not produce an appropriate amount of insulin, or the body is unable to respond to the insulin produced by the pancreas. The prior symptoms of the diabetic patient are polyuria, polydipsia, and polyphagia. The reason for this disease is a stressed life, change in lifestyle, very little physical exercise, and related activities due to modernization, industrialization, and urbanization. As the glucose accumulation increases in the body, it starts affecting all the organs and tissues. It causes many serious diseases, which are curable up to its first stages, but with time, these diseases become more dreadful and lead to tissue and organ failure. Many discoveries have been there for many years but still, the disease is a panic and has life-ending effects. Nowadays, the use of herbal medicine is more in trend for curing diabetes either type 1 or type 2 due to their low side effects and cost-effectiveness. The use of medicinal plants proves to be the best alternative for curing these diseases, as these are best for health consciousness, cost-effectiveness, and reliability. Recent studies have suggested that nanoparticles have emerged as an ascending and promising factor in their role in herbal medicine including to control diabetes. The preparation of nanoparticles from the various extracts of the herbal plants also led to the increased efficiency of the herbs against diabetes and enhanced shelf life. In conclusion, medicinal plants can be used either in pure form or in the form of metal-coated nanoparticles to control diabetes in humans.

Keywords

Glucose accumulation, Type 2 diabetes, Phytoconstituents, Herbal medicines, Insulin resistance

Introduction

Diabetes is spreading at an alarming rate in all societies, especially in the working age population. It is most prevalent in those persons whoever has more sitting hours either in job or at home [1]. The disease is spreading eternally at its peak point, mainly in developing countries. The disease has been increasing more in adults at an alarming rate up to 422 million cases per year since 1980 [2]. This unexpected promotion in diabetes is due to lethargic nature, deficiency of exercises, outdoor activities, desk-bound lifestyle, and inappropriate eating habits, which leads to obesity, that is directly linked with modernization, mechanization, automation, mass production and expansions. Tension in the working environment or working area is the key factor for many people due to desk-bound workloads, overtime work in shift, lack of sleep due to excessive workload and pugnacious working atmosphere. For overcoming this situation, stress hormones

are released in increased quantity, which is the reason of the cause [3]. According to a report, 69.2 million (8.7%) people are already suffering from diabetes [2]. Many cases of diabetes are not diagnosed properly due to lack of knowledge. Around 1.5 million deaths are caused due to diabetes per year on a global scale.

Day by day, the cases of diabetes are increasing in India. It is estimated that the cases of diabetes will rise to 109 - 110 million approximately by 2035 [2]. The study and appraisal of social economic influence of diabetes in India is very imperative because India is known as the diabetes capital of the world [4]. The total expenditure on diabetes is very much more as compared to any other disease. It may vary between 3000 to 10000 INR yearly (World Economic Forum Report). Due to its high cost, people with less income sources find it difficult to meet our expenses, which leads them to further poverty. Therefore, the cost effectiveness and safe alternative is to switch or move towards folklore medicine, which is better in all aspects to the synthetics. Besides, using traditional medicines, we can also conserve endangered species and our ancestor's knowledge. An emerging technology such as nanotechnology is rapidly extending in various fields such as medicine, health, cosmeceuticals, drug delivery, etc. Nanoparticles (metal-based) have garnered attention as they possess certain properties like anti-bacterial, anti-cancerous, anti-fungal and anti-leishmaniasis [5].

Now-a-day's many medicines against diabetes have been developed but are not very effective, or some chemical medicines, which have adverse side effects. After medicines intake for a continuous period, the patient came to a stage when the doses increased and use of insulin injection started, ultimately leading to the damage of tissues and organ failure. After that, this disease proves to be fatal to a particular person suffering from any type of diabetes [6]. Ethnomedicinal plants are still used by the persons residing in rural areas. Plant remedies, which have medicinal importance against diabetes, are prescribed all over the world. Traditional plants as medicine are used and still recommended. In addition to this, the active principles present in them have been extracted like steroids, alkaloids, glycosides, terpenes, and flavonoids. Nevertheless, this is not sufficient as more studies are required to produce clinically ancillary remedies. In this review, we have compiled 15 medicinal plants, which showed antidiabetic properties as per the previous reports. This review is important for getting knowledge of antidiabetic folklore medicines for controlling diabetes.

Nature consists of many wonders, in which plants are one of them. Maximum numbers of plants are beneficial for mankind in one or the other way. The plants prove themselves as good and healthy source of medications and many commercial drugs have their origin from the plant sources. As evidenced from the available ethnomedicinal data, it can be established that around 800-900 plants may hold anti-diabetic properties. Some plants like *Momordica charantia*, *Pterocarpus marsupium*, and *Trigonella foenum greacum,* show mind blowing results against the control of T2D [7, 8]. Table 1 comprises botanical name, common name, family, plant parts used, solvent used for extraction purpose and their pharmacological activity. Some plants are mentioned in the table 1 given wherein nanoparticles showed enhanced antidiabetic activities.

Diabetes control is noticed in an increasing rate using natural phytoconstituents by traditional medicines. Various traditional plants phytoconstituents are tested and approved having antidiabetic properties mainly alkaloids, imidazoline, polyphenols (flavones, flavonoids, and flavonol), tannins, terpenoids, and saponins [34, 35].

Diabetes can occur in the body when there is deficiency of insulin secretion or its resistance. Normally in a human body when food is taken then automatically the level of glucose is increased which mixed with the blood in the glucose, and the blood sugar level increases. There is a gland present in the human body called pancreas, which secretes the digestive juices and hormones like insulin and glucagon. When the blood glucose rises, insulin is automatically released by the beta cell of the pancreas, which is responsible for assimilation and metabolization of glucose. Also, if the blood glucose level gets low the pancreas secretes glucagon to stimulate the discharge of glucose from the liver [36]. Diabetes is of two types viz. type 1 and type 2.

Type 1 diabetes (T1D): This type of diabetes is found in all but mainly in children and young adults. The main cause of this is the destruction of beta cells of the pancreas by the body immune system that is only responsible for insulin formation or secretion to regulate blood glucose [37].

T2D: This is the most common type. It cannot be caused by one factor. Many factors are responsible for its cause. It can occur genetically or can also be environmentally like beta cells dysfunction, insulin sensitivity, etc. In this, the body is either unable to produce adequate amount of insulin or it does not respond to the insulin (insulin resistance), leading to the increased need of insulin to metabolize glucose and the pancreas fails to produce it [38]. Once the glucose level rises, it cannot be digested and causes many health implications like nerve impairment, cardiovascular diseases, and kidney damage [39]. Diabetes is one of the main reasons for kidney damage.

Diabetes can only be prevented by a healthy lifestyle mainly by change in diet and inclusion of physical activities. Moreover, even if it cannot be handled then try a healthy way to control instead of a synthetic way i.e., the use of herbal medicine as much as possible.

Obesity and T2D

Obesity and T2D are public health problems, with health consequences and economic costs that have raised concern worldwide. Obesity and diabetes are emerging pandemics in the 21st century affecting a very large amount of mankind of every age group. Both are major public health problems throughout the world and are associated with significant, potentially life-threatening co-morbidities and enormous economic costs. Both obesity and T2D are interconnected with each other and is a topic of serious health concerns. Both the diseases are interlinked because if a person is suffering from obesity there are 75% chances of that person to become dia-

Table 1: List of plants with their family, plant parts used, solvent used, and pharmacological activity.

S. No.	Scientific names	Vernacular names	Family	Forms used	Solvent used	Medicative activity	Ref.
1	*Acacia arabica*	Babul, Indian Gum Arabic tree	Fabaceae	Powdered seeds	Ethanol	Seeds of *A. arabica* are used in coarsely powdered form against the rabbit, which is diabetic; can be able to release of insulin by beta cells of pancreas when given at set time at regular intervals without having adverse effect not in health neither in behavior	[9]
2	*Acacia nilotica*	Babul, Indian gum Arabic tree	Fabaceae	Nanoparticles of bark extract	DW	Strong inhibitor for α-glucosidase enzyme activity	[10]
3	*Achillea schischkinii*	Yarrow	Asteraceae	AP, CA, FL, LE	DE, IN, PW	Hyperglycemia, piles, invigorating wounds, flatulence, and gynecological diseases	[11]
4	*Allium sativum*	Lahasun and garlic	Amaryllidaceae	Garlic oil	Ethanol, petroleum ether, ethyl ether extract	It is reported that glucose level is lowered when diabetic mice is treated with the ethanolic extract of *A. sativum* according to body weight at regular intervals	[12]
5	*Allium cepa*	Pyaz, onion	Amaryllidaceae	Silver nanoparticles	DW	α-amylase and α-glucosidase inhibitory activities	[13]
6	*Artemisia pallens*	Davana	Asteraceae	Aerial parts	Methanol extract	Reduced diabetes reports can be noticed when hyperglycemic and alloxanized rats are treated with methanolic extract of *A. pallens*. The disease can be completely cured if the diseased rat is treated with the higher dose of plant extract	[14]
7	*Catharanthus roseus*	Sadabahar, periwinkle	Apocynaceae	Zn based nanoparticles	DW	Inhibition of α-amylase activities	[15]
8	*Crataegus tanacetifolia*	Hawthorn	Rosaceae	BR, FR, FB, FL, LE, YSH	BO, DE, EF, IN, PW	Kidney diseases, hypertension, stress, cholesterol, insomnia, respiratory diseases, throat infection, stone in kidney, body infection	[16]
9	*Dianthus carmelitarum*	Peacock-eye pink	Caryophyllaceae	FL	IN	Diabetes	[17]
10	*Dioscorea bulbifera*	Air potato	Dioscoreaceae	Copper nanoparticles	DW	Inhibitor for α-amylase enzyme activity	[18]
11	*Equisetum arvense*	Horse pipe	Equisetaceae	Aeration organ	Boiled	Antidiabetic	[19]
12	*Erodium cedrorum salmoneum*	Redstem filaree	Geraniaceae	AP, LE	BO, IN, R	Diabetes, carminative	[20]
13	*Gymnema sylvestre*	Gurmar	Apocynaceae	Starch nanoparticles	Methanol	Strong inhibitor for α-amylase enzyme activity	[21]
14	*Lonicera japonica*	Juhee, honeysuckle	Caprifoliaceae	Silver nanoparticles	DW	Strong inhibitor for α-amylase enzyme activity	[22]
15	*Myristica fragrans*	Nutmeg	Myristicaceae	Silver nanoparticles	Ethanol	Inhibitor for α-amylase enzyme activity	[23]
16	*Origanum hypericifolium*	Marjoram	Lamiaceae	AP	IN	Diabetes, prostrate diseases	[24]
17	*Origanum saccatum*	Marjoram	Lamiaceae	AP, FL, LE, JU, SH	IN, DW, PW	Cholesterol, high glucose level, gastric diseases, cold, flu, ulcers, and respiratory diseases	[25]
18	*Origanum sipyleum*	Marjoram	Lamiaceae	FL, LE, SH	AT, DW, IN	Flatulence, diabetes, cholesterol, arthritis, gastro-intestinal diseases, back pain, hypertension, sprains, body ache, headache, cold, flu, etc.	[26]
19	*Psoralea corylifolia*	Babchi	Fabaceae	Silver nanoparticles	Methanol and DW	Inhibition of protein tyrosine phosphatase 1B	[27]
20	*Salvia canescens*	Anatolian sage, woody sage	Lamiaceae	AP	DE	Diabetes	[28]
21	*Scorzonera semicana*	Armenian daisy	Asteraceae	AP, RO	PU, R	High BP, infertility, hyperglycemia, ESKD and ESRD	[29]
22	*Sideritis albiflora*	Ironwort	Lamiaceae	AP	IN	Hyperglycemia, gastrointestinal diseases, respiratory diseases, cold and flu	[30]
23	*Tamarindus indica*	Imli	Fabaceae	ZnO nanoparticles	DW	Reduces α-amylase and α-glucosidase activity	[31]

24	*Taraxacum farinosum*	Turkish cırtlık	Asteraceae	LE	AT, R	Diabetes, gastro-intestinal disorders	[32]
25	*Tephrosia tinctoria*	Orange tephrosia	Fabaceae	Silver nanoparticles	DW	inhibition of carbohydrate digestive enzymes (α-glucosidase and α-amylase) and enhancement of glucose uptake rate	[33]

Note: Plant part used: AP: Aerial part; BL: Basal leaf; BR: Branches; BU: Bulb; CA: Capitula; CO: Cones; FB: Flowering branches; FL: Flower; FR: Fruit; GD: Gall dust; GU: Gum; JU: Juice; LA: Latex; LE: Leaves; RB: Root bark; RE: Resin; RO: Root; SB: Stem bark; SE: Seed; SH: Shoots; ST: Stem; TU: Tuber; VO: Volatile oil; WP: Whole plant; YB: Young branches; YSH: Young shoots.
Composition: AT: As tea; BO: Boiled; BT: Burnt; CH: Chewing; CO: Cooked; CR: Crushed; DE: Decoction; DR: Dried; DW: Distilled water; EF: Eaten fresh; IN: Infusion; MA: Mash; PI: Pill; PU: Poultice; PW: Powdered; R: Raw; SY: Syrup.

betic. According to World Health Organization (WHO) and the new International Association for the study of obesity/International Obesity Task Force Analysis (2010), around 1 billion adults are suffering from obesity, as they are overweight: their Body Mass Index (BMI) 25-29.9 kg/m^2. Despite clear epidemiological and pathophysiological links between obesity and T2D, the actual mechanisms are complex given that some people with obesity appear to be protected in some way from developing T2D, and T2D can develop in a minority of thin people [40]. Obesity and T2D form part of the metabolic syndrome, which combined with hypertension and dyslipidaemia result in premature mortality from cardiovascular disease in millions of people globally each year. Long-term microvascular sequelae from T2D and multiple co-morbidities associated with obesity (including psychological, musculoskeletal, respiratory, and reproductive) also have a major adverse impact on quality of life and pose an enormous fiscal burden on global health authorities. Major factors contributing towards 'diabesity' include chronic overconsumption of energy-dense foods and lack of physical activity [41].

Both obesity and T2D, feature insulin resistance and atherogenic lipid profiles such as increased triglycerides and decreased HDL-C. The genetic basis of human obesity that led to insulin resistance and T2D is multigenic rather than monogenic [42]. Current clinical guidelines acknowledge the therapeutic strength of exercise intervention for prevention and treatment of diabetes.

There is a close relation between BMI and risk of having T2D. If a person can gain weight of 1 kilogram each year continuously for ten years, then there is 49% of risk of developing T2D. Similarly, in the same way if a person can loose 1 kilogram annually continuously for ten years then there is 33% reduction of risk of developing T2D. Weight loss was useful for long-term T2D outcomes and risk of having T2D. Deposition of fat in the body due to unhealthy eating habits, sedentary life style, more sitting jobs and no physical activity make the body obese and if the weight is not reduced or loose with the due course of time than this permanent obesity led to the 100 % highest risk of causing T2D. When 21,205 adults were surveyed in US, 2,894 (13.6%) had found to have T2D. Amongst those with T2D, 80.3% were overweight having weight more than BMI range and 49.1% were obese, the chance of T2D is increasing according to severity of obesity [43]. There are so many studies which prove that gaining weight led to cause of many more diseases, mainly the risk of developing T2D increases to a very large extent. Clinically significant weight-loss up to 1-year in T2D was associated with improved diabetes control [44].

That is the reason that the word 'diabesity' best suited for the association of these two diseases as one is the cause of the other. Moreover, both these diseases are directly proportional to each other as with increase of one (obesity), other may increases (T2D) and with the decrease of one (obesity) other again decreases (T2D).

There are many reasons, which show the association of obesity and diabetes. Those are FFAs and ectopic fat in the development of obesity-related T2D, adipocytokines in the development of obesity-related T2D, leptin, adiponectin, resistin, visfatin, and inflammation in the development of obesity-related T2D [45, 46].

Despite having evident pathophysiological crosstalk between diabetes and obesity, the choices of drugs suitable for the combined treatment of diabetes and obesity are limited in modern medicine [47]. Further, accurate molecular drugs have not been designed or are unavailable for diabetes and obesity are associated with side effects like insomnia, headache, constipation, hypoglycemia, weight gain, and renal complications [48, 49]. As an alternative, integrating complementary and alternative medicines popularly called CAMs with modern medicine would have promising applications in managing lifestyle disorders like diabetes and obesity. However, inadequate scientific evidence plus the use of indigenous languages and epistemologies in CAMs limits their global acceptance.

Impact of obesity on T2D

With the increase in BMI increase above 23, the risk of developing T2D increases. Also, this association was more prevalent in younger age groups as per the Asia-Pacific Region study. Therefore, the gain in weight during early adulthood led to a higher risk of onset of T2D between the 40 and 55 years of age group. Therefore, it is proved that with the increase in BMI and waist circumference the prevalence of developing T2D increases. The risk of diabetes increases linearly with BMI; the prevalence of diabetes increased from 2% in those with a BMI of 25 to 29.9 kg/m^2, to 8% in those with a BMI of 30 to 34.9 kg/m^2, and finally to 13% in those with a BMI greater than 35 kg/m^2 [50]. In a review of 17 prospective and 35 cross-sectional studies in adults aged 18 - 74 years, either BMI or WC was predicted or was associated with T2D independently [51]. An increase in BMI is a better predictor of diabetes than an increase in weight.

Impact of childhood obesity on T2D

T2D in children and adolescents is a global problem, which led to the epidemic of childhood obesity. The sensitivity of insulin can be adversely affected if the rate of obesity in the youth generation increases as it increases the risk of T2D.

Both T2D and rates of obesity run in a parallel direction [52]. Obesity in young people with IGT is mentioned by marked peripheral insulin resistance and hence failure of beta-cells [53]. There is a very high prevalence of metabolic syndrome in youngsters who are obese and there are so many diseases that are associated with obesity in children such as T2D, hypertension, hyperlipidemia, gallbladder disease, nonalcoholic steatohepatitis, sleep apnea, orthopedic complications [54-58].

Benefits of weight loss in T2D and obesity

The tendency to acquire obesity-related diseases can be decreased by 5% to 10% loss in weight due to which glycemia control can be improved and the risk of developing cardiovascular diseases decreases. Path physical studies show that the therapeutic benefit rises with increasing weight loss, but that losses as low as 0.45 - 4 kg (1 - 9 lb) have positive effects on metabolic control, cardiovascular risk factors, and mortality rates. Data on obesity continued to focus on weight loss, including moderate weight loss, as a key component of good care for overweight patients with T2D [59]. The most effective interventions include comprehensive behavioral management, dietary modification, exercise, pharmacotherapy, and bariatric surgery. The most widely investigated drugs, sibutramine and orlistat, result in modest weight loss with demonstrable improvements in co-morbidities, among which is T2D [60].

Nutrition in the management of obesity and T2D

Studies including observational and interventional studies show that T2D can be reduced or prevented by changing lifestyle measures, use of modern techniques with less use of energy in weight reduction, change in diet, more use of fibred rich diet and low-calorie intake [61]. Reduction in weight results in improved insulin sensitivity and improved functioning of β-cell [62]. In both short-term as well as long-term studies inclusion of a low carbohydrate diet in obese patients with T2D has improved readings of glucose profiles, insulin sensitivity, and decreased plasma triglyceride and cholesterol levels [63].

Prevention of T2D by weight reduction

Weight reduction could lead to a decreased incidence of progression to T2D. There are so many studies, which show that with the reduction in body weight, the prevalence of developing risk factors of T2D decreases. The names of the studies are as follows:

Finnish study [64].
Diabetes prevention program [65].
Da Qing study [66].

Medicinal plants with their active phytoconstituents and their effects on diabetes control

Traditional plants of medicinal value with their active principle play an important role in controlling diabetic conditions and the drugs extracted from these medicinal plants are used to cure obesity up to a level. Obesity is one of the reasons for diabetes. A high-fat diet leads to obesity in a person that with time leads to diabetes [66-68].

Some medicinal plants having diabetes-controlling properties are mentioned below

Aegle marmelos

A. marmelos methanolic extract is experimented on and proven to treat hyperglycemia in alloxan diabetic rats. It also decreases lipid peroxidation, conjugated diene, and hydroperoxide levels in serum as well as in the liver. The enzymes, catalase, glutathione peroxidase, superoxide dismutase, and glutathione showed increased activities in blood and liver [69].

Aloe vera

A. vera if taken in large molecular fraction amount then it seems to decrease the level of glucose in blood and serum triglycerides without causing any side effects to the kidney and liver [70].

Annona reticulata

Blood sugar level can be reversed by using residual fractions of hydro-alcoholic extract of *A. reticulate* considerably declined the blood glucose level. Hyperglycemia can also be managed if residual and methanolic fractions are used non-significantly [71].

Azadirachta indica

A. indica extract when tested in rats can affect both the pancreas and islet of Langerhans and reverse the effects of hyperglycemia. The number of β-cells increases after curing with *A. indica* [72].

Calotropis procera

Obesity and diabetes can be treated when the oral latex of *C. procera* is taken. It also does not affect the kidneys because daily water intake is reduced while we are medicated with the extract of *C. procera* during diabetes control [73].

Carica papaya

The level of glucose in the blood, cholesterol level, and obesity can be lowered using aqueous *C. papaya* extract when it is tested in diabetes rats [74].

Catharanthus roseus

Glucose levels in different forms like phospho fructose can be decreased when the extract of *C. roseus* is inoculated in the diabetic rat at regular intervals. Also, the Level of β-cells has increased. Glycogen and lipids are also decreased with the use of this extract. Both the pancreas and islet of Langerhans and reverse the effects of hyperglycemia [75].

The dietary intake of single medicinal plants may not provide a higher degree of safety and efficacy than mixed medicinal plant preparations [76]. Ayurveda, an Indian traditional and folklore medicine system, prescribes various poly-herbal formulations for the treatment of diabetes and obesity. Studies are showing the antidiabetic properties of various formulations such as Arogyavardhini vati, Chandraprabha vati, Naga bhasma, Nishamalaki, and Shilajatu [77-82]. Ayurvedic therapeutics has come out with specific formulations and methodologies to treat 'diabesity' patients [83]. Besides, seaweeds especially algae are considered a good food to control diabetes as these have low calorie and higher nutritious content [84, 85]. Generating scientific evidence and understanding their modes of action in contemporary scientific language would essentially help in expanding their global acceptance as convincing complementary strategies for

managing the dual burden of obesity and diabetes.

These findings support World health organization recommendations regarding the regular consumption of vegetables and selected herbs, such as turmeric, capsicum, ginger, and green tea. Improving knowledge on the use of anti-obesity medicinal preparations and encouraging obese patients to consume them along with an enhanced exercise regimen and a healthy diet should be continued. Additional chemical, biological, and clinical studies are needed on the effectiveness of selected medicinal plants, particularly those used as spices and condiments, in ameliorating and treating obesity in humans. Such anti-obesity data would be useful for food and drug manufacturers as new products are developed, and to governments in the regulation of food products to promote and enhance public health.

Conclusions

Chemical drugs can be replaced by herbal medications for the treatment of many fatal diseases. Diabetes is one of those types of disease, which has a lot of medications but still, the disease is spreading at an alarming rate. Not only the old people, but the youngsters and even children are suffering from this disease. Neonatal babies can even get this disease when they are in their mother's womb. Diabetes can be prevented or delayed by a change in lifestyle, mainly a change in food habits. Healthy food and more physical activities can prevent the onset of diabetes.

Our current understanding of diabesity however does not explain the whole picture given that T2D can develop in lean adults, and not all obese adults develop T2D. Further research is required to gain a clearer understanding of the pathogenesis of T2D, and the complex mechanisms involved that fully explain how obesity and T2D are linked. Diabetes is the fastest-growing disease in the world. The health consequences and economic costs of the overweight, obesity, and T2D epidemics are enormous. Daily use of chemical medicines can one day adversely affect the body and harm the body. So, these synthetic medicines can be replaced by folklore herbal medicines that have no side effects and are economical. Related to this, nanotechnological approaches can lead to the formulation and development of herbal drugs to cure diabetes. The present review is all about the use of traditional plants as medicine and comprises a list of anti-diabetic plants whose phytoconstituents and active principle have alkaloids, polyphenols, terpenoids, tannins, saponins, and imidazoline, which is used to treat hyperglycemia. The review concludes the synthesis of nanoparticles from various extracts as the inhibitor for α-amylase enzyme activity. Diabetes can be prevented or delayed by a change in lifestyle, mainly a change in food habits. Healthy food and activities that are more physical can prevent the onset of diabetes.

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Conflict of Interest

None.

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