Plant-Based Bioactive Constituents as an Antidiabetic Agent

CHAPTER 13

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SUMMARY

As diabetes mellitus is one of the common metabolic disorders, several synthetic anti-diabetic drugs and insulin preparations are available but still there is a need for the development of novel anti-diabetic drugs with minimal side effects. With the passage of time, medicinal or herbal products have gained much more importance all around the world. Now a days, several medicinal plants have been used effectively for the management of diabetes mellitus.

INTRODUCTION

Diabetes is a Greek word that means 'to pass through' and mellitus is a name of honey in Latin. Diabetes is characterized by reduced production of insulin from β-cells of Islets of Langerhans or when the pancreas can't efficiently utilize the insulin. Insulin (hormone) is produced by β-cells of the pancreas and it controls the level of blood glucose in the body. High blood glucose level (hyperglycemia) is the commonly known problem of uncontrolled diabetes2. Diabetes is a chronic metabolic disorder with persistent high glucose levels in the blood that disturbs the metabolism of carbohydrates, fat, and protein (Kaul et al., 2013; Rais et al., 2021). Diabetes has no definite treatment, but the use of medicinal plants seems to be an appropriate solution to control and manage this problem. The hypoglycemic activities of many plants have been reported during the last twenty years. Numerous medications are available to relieve the symptoms of diabetes. But, these medicines are expensive and linked with several complications. Herbal medicines attain importance as they are cost-effective and also show better therapeutic effects with minor side effects (Al-Goblan et al., 2014; Jacob & Narendhirakannan, 2019).

According to the International Diabetes Federation (IDF), diabetes prevalence rate was about 3.2% in 2004. Obesity and overweight increase the risk of diabetes mellitus. Diabetes is now increasing day by day as the epidemic of the latest century. It will overpower the health framework in the coming days. Diabetes mellitus is a global epidemic disease that is caused by the devastation of the beta cells with consequent insulin deficiency and results in an increase in the level of glucose, neurological, cardiovascular, retinal and renal complications. Symptoms of marked high blood glucose levels comprise an increase in uric acid, weight loss and blurred vision (Maina et al., 2010). Diabetes mellitus affects people of different age groups and disturbs people's normal lives globally. Several synthetic oral anti-diabetic drugs and insulin preparations are available for diabetes mellitus, still there is need for the development of novel anti-diabetic drugs. As synthetic drugs have side effects and develop resistance in long term usage, herbal medicines gain more importance with the passage of time all around the world (Alam et al., 2022).

Diabetes mellitus is one of the most abundant metabolic disorders around the globe affecting 2.8 % of the population worldwide and is expected to rise to 4.4% by 2030 year which is an alarming situation. It is known as one of the five major morbidities around the globe (Kharroubi & Darwish 2015). Different genetic and non-genetic factors may be responsible for the development of diabetes. According to the American Diabetes Association (ADA) in 1997, diabetes types comprise type 1, type 2, and gestational diabetes mellitus (Wild et al., 2004; Cakan et al., 2012; American Diabetes Association, 2014).

Oxidative stress is linked with the development of many diabetes associated complications such as kidney, eye, nervous and vascular disorders and even stroke (Sabu et al., 2002). Patients suffering from diabetes are all time at risk of various

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complications, these complications may be macrovascular, microvascular or both. The morbidity and mortality rates in older people are more linked with macrovascular complications than microvascular (Ullah et al., 2016).

THERAPEUTIC ACTIVITY OF MEDICINAL PLANTS

Medicinal plants play a significant role in the treatment of various illnesses due to the occurrence of beneficial vital phytochemicals. Traditional plants are known to have noteworthy anti-diabetic activity due to their constituents such as phenolic, flavonoids, alkaloids, and tannins that are responsible for improvement in the pancreatic tissue efficiency via improving the secretion of insulin and reducing the glucose absorption in the intestine (Kooti et al., 2016; Jacob & Narendhirakannan, 2019). These compounds have fascinating biological actions and medicinal potential. Numerous herbs, fruits, and grains have important biological actions like antioxidant, antidiabetic, anticancer, antitumor, anti-analgesic, anti-inflammatory, antimicrobial, and antimalarial. Now a days there has been increasing interest in the use of medicinal herbs for the cure of diabetes but it is also required to provide a scientific basis used for treatment and the active principles of plants (Ansariet al., 2023).

It is estimated that the range of herbal plants worldwide is 30,000 to 75,000 and they are used for targeting infectious and life threatening diseases. Previous studies suggest that there are roughly 410 confirmed medicinal plants that are used against diabetes mellitus. Extracts of numerous medicinal plants have the activity to modulate the different metabolic pathways such as glycogen synthesis, Krebs cycle, glycolysis, gluconeogenesis, cholesterol synthesis, synthesis and release of insulin, carbohydrate metabolism and absorption (Al-Goblan et al., 2014; Jacob & Narendhirakannan, 2019). Medicinal plants were also used for the treatment of secondary complications arising from diabetes mellitus and also showed cholesterol lowering and antioxidant activity. Complications are still associated with the use of natural plants and herbs so attention is diverted toward the development of synthetic compounds of natural plants (Rozmer & Perjési, 2016).

Medicinal plants are important because of the occurrence of various secondary metabolites like alkaloids, tannins, phenolics, terpenoids and essential oils. Literature indicates that 80 % of the world population used various plant formulations and their metabolites as traditional medications (Anand et al., 2019; Tran et al., 2020; Cherrada et al., 2024). Plants are used as a source in many industries like pharmaceuticals, cosmetics, perfumery, and flavor. As modern drugs show more resistance, researchers are now searching for better options as alternatives for the treatment of different diseases (Jamshidi-Kia et al., 2017). Several bioactive constituents possess anti-diabetic effects.

BIOACTIVE CONSTITUENTS THAT ACT AS INSULIN

Momordica charantia, known as bitter melon, or bitter gourd, is one of the common vegetables of the family Cucurbitaceae, used as a vegetable and also as herbal or folk medicine. It possesses different phytochemicals such as fatty acids, amino acids, alkaloids, saponins, phenolics, carbohydrates, minerals, and vitamins, that exhibit antidiabetic, antioxidant, anti-inflammatory, anti-cancer, anti-viral, and anti-bacterial activities (Saeed et al., 2018; Tran et al., 2020). Insulin like proteins are present in the seeds, fruits, and the callus of *Momordica charantia* (MC) that are homologus to human insulin, and exhibited anti-hyperglycemic (Fig.1) action when tested on humans, rats, langurs, and gerbils. Various research stated that bioactive compounds of MC have significant antidiabetic activity and enhance glucose tolerance. Additionally, MC has been used for diabetes management for thousands of years (Tan, 2014; Dandawate et al., 2016).

PLANT CONSTITUENTS THAT ACT AS INSULIN-LIKE PROTEIN

Ginseng (*Panex ginseng*) has been the most popular traditional plant for a long period of time belonging to the family Araliaceae. Many bioactive constituents are present in the roots of ginseng that includes panaxans, triterpene glycosides, or saponins, salicylates, and vanillic acid (Tran et al., 2020). The most important phytochemical present in ginseng is saponins known as ginsenosides. Among them, Ginsenosied Rb2 is responsible for decreasing blood glucose levels. In general, saponins are responsible for controlling glucose metabolism and insulin secretion (Park et al., 2005; Ratan et al., 2020).

BIOACTIVE CONSTITUENTS UPSURGE INSULIN SECRETION

Allium cepa (family Liliaceae) known as onion, is a valuable ingredient for cooking in several countries. Phytocompounds present in this plant are amino acids, phenolics, flavonoids, essential oils, thiosulf inates and vitamins, etc. *Allium cepa* possesses several activities, such as antidiabetic, antioxidant, and anti-inflammatory etc. The major biochemical constituents are quercetin, allicin, S-methyl L-cysteine S-oxide, alliin, propanethial S-oxide, and diallyl disulfide. These constituents can decrease blood glucose levels and have powerful antioxidant action which might be responsible for its hypoglycemic activity. Various studies

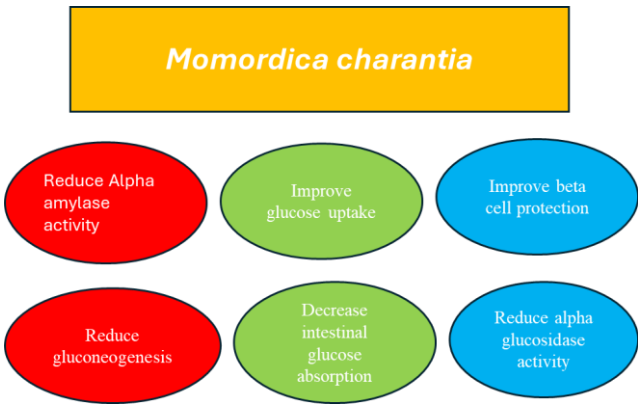

Fig 1. Antihyperglycemic effects of *Momordica charantia*

reported the hypoglycemic activity of *Allium cepa*. *Allium sativum* also has the same properties (Kumari & Augusti, 2002; Lakshmi et al., 2012).

Aloe vera is a healing plant and is frequently used in diabetes management (Singh & Kumar, 2017). The notable phytoconstituents are flavonoids, tannins, phenols, alkaloids, saponins, carbohydrates, vitamins and minerals. These complexes have beneficial actions, such as antioxidant, antimicrobial, antihyperglycemic etc. Scientists constantly inspecting the beneficial properties of this herb to yield new modern and traditional medicines. Literature proposes that the extract of *Aleo vera* decreases blood glucose levels extensively (Gaber et al., 2020; Nasir et al., 2020).

Allium sativum is a usual herb, titled garlic that relates to the family Allium, appears in Asia, Africa and Europe (Singh & Kumar, 2017). Garlic is acknowledged as an effective medicinal herb for the treatment of different diseases. Corresponding to the literature, garlic take over several biological actions like antibacterial and hypoglycemic (Gaber et al., 2020). As garlic represses several phytoconstituents like steroids, flavonoids, cardiac glycoside, alkaloids, terpenes and resin. It also has sulfur complexes e.g. allicin, alliin (Chauhan et al., 2010; Gaber et al., 2020). According to scientific studies, garlic has antidiabetic activity by showing different mechanisms like enhancing glycogen synthesis and glucose tolerance (Adinortey et al., 2019).

BIOACTIVE CONSTITUENTS FOR REGENERATION OF B-CELLS

Pterocarpus marsupium

Pterocarpus marsupium (*P. marsupium*) is a big tree belonging to the family Fabaceae, extensively used in the system of 'Ayurveda' for the management of several metabolic illnesses like hyperglycemia. This plant contains abundant phenolic and flavonoid compounds. Literature suggests that *P. marsupium* contains alkaloids, tannins, terpenoids, proteins, steroids and amino acids, etc. (Gupta & Gupta, 2009). The probable antidiabetic constituents identified include epicatechin. Previous studies indicated that this plant contains polyphenolic constituents such as pterosupin, and marsupsin, and also flavonoids like carsupin, marsupol, and pteroside. These constituents have numerous activities e.g., antidiabetic, anti-inflammatory, and anti-oxidant (Rahman et al., 2018).

The *P. marsupium* ethyl acetate extract was tested on diabetic rats. The studies on *P. marsupium* ethanolic extract decreased the blood sugar level reported. The epicatechin, obtained from *P. marsupium*, shows the capability to regenerates β-cells of the pancreas. Furthermore, various studies indicated that the *P. marsupium* aqueous extract stimulates insulin secretion and improves the uptake of glucose, so it can be used as an antidiabetic remedy (Halagappa et al., 2010; Tran et al., 2020).

Gymnema sylvestre

Gymnema sylvestre (*G. sylvestre*) of the family Apocynaceae, is commonly used in numerous countries around the globe for treating many diseases, particularly diabetes. It contains several bioactive constituents but the major active ingredient is Gymnemic acids. Numerous studies have described that the main therapeutic function of *G. sylvestre*is is its antidiabetic activity (Tiwari et al., 2014). Literature suggests that *G. sylvestre* leaf water extract possesses hypoglycemic activity. Other research recommended that *G. sylvestre* extract stimulate the secretion of insulin. Numerous mechanisms have been involved to elucidate the hypoglycemic activity of *G. sylvestre* (Fig. 2). Many studies described that the use of Gymnemic acids in diabetes management due to stimulation of pancreatic cell production, thus increases the insulin production, sensitivity and activity of insulin which ultimately help to control blood

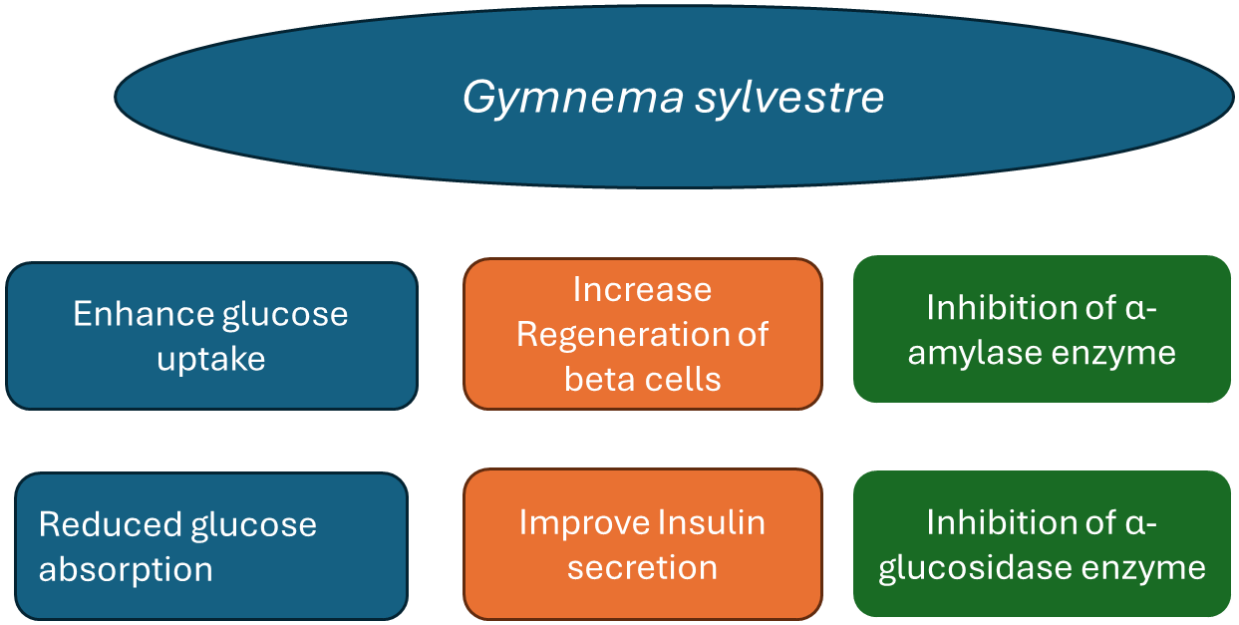

Fig 2. Mechanism of *Gymnemasylvestre sylvestre* in controlling glucose level

glucose concentration (Khan et al., 2019; Laha & Paul 2019; Ananda et al., 2020).

Tinospora cordifolia

Tinospora cordifolia (*T. cordifolia*) has been usually identified as "Amrita" or "Guduchi" and belongs to the family Menispermaceae. For a long period of time, this drug has been known to be a vital drug of Indian systems of medicine. It is usually present in India, and is described as the chief source of treatment for various illnesses like fever, urinary diseases, and dyspepsia (Tiwari et al., 2018; Sharma et al., 2019). It has been investigated that *T. cordifolia* contains many constituents that belong to various classes of secondary metabolites like glycosides, alkaloids, phenols, steroids, essential oils, and polysaccharides. Its leaves contain various compounds like alkaloids, flavonoids, proteins, and glycosides. These active constituents have several activities, including anti-diabetic, anti-cancer, antiseptic, anti-inflammatory and antimicrobial activities (Rajalakshmi & Anita, 2016; Geethanjali et al., 2017). According to studies, *T. cordifolia* root extract promotes insulin secretion and inhibits glycogenolysis in diabetic rat models ultimately improving the blood glucose level (Sangeetha et al., 2011; Patel & Mishra, 2011).

BIOACTIVE CONSTITUENTS THAT REDUCE THE GLUCOSE ABSORPTION

Cyamposister tragonoloba

Cyamopsis tetragonoloba L. is usually identified as Cluster Bean or Guar, (family Fabaceae) and was stated to contain a huge amount of carbohydrates and fiber. Some phytochemicals in leaves are carbohydrates, fibers, proteins, galactomannans, condensed tannins, caffic acid, gentisic acid, gallic acid, coniferyl alcohol, and p-hydroxycinamyl. Flavonoid contents present in this plant are quercetin, daidizein, and kaemferol. Additionally, other polyphenolic compounds are gallotannins, gallic acid and their derivatives (Sharma et al., 2011). The phenolic and flavonoid compounds of Cyamopsis tetragonolo showed hypoglycemic effect on experimental rats. Another research reported that this plant improved the release of insulin and reduced the HbA1c level. Henceforth this plant can be effectively used in the treatment of diabetes mellitus (Gandhi et al., 2014).

***Ocimum sanctum* L.**

Ocimum sanctum is a tiny tree, usually called as 'Sacred basil. It relates to the family Lamiaceae and has a enjoyable aroma. Numerous active ingredients are present in this plant (Rahman et al., 2011; Verma, 2016; Singh & Chaudhuri, 2018). Leaf extract of *O. sanctum* confines volatile oil, eugenol, methyl eugenol and p -caryophylen. *O. sanctum* comprises various bioactive mixtures, such as terpenoids, esters, aliphatic aldehydes, phenolics. It also have metabolites, involving flavonoids, phenolics, fatty acids. These ingredients are mainly studied for beneficial purposes involving antioxidant, anti inflammatory, antibacterial and antidiabetic (Rahman et al., 2011).

BIOACTIVE CONSTITUENTS HAVING OXYGEN-RADICAL SCAVENGING ACTION

As discussed overhead, the fruit juice of *Momordica charantia* has antioxidant potential due to its radical scavenging effect. Literature also demonstrated other activities like the cell-protective activity of M. charantia extract. The effectiveness of certain Indian Ayurvedic plant extracts, like *Momordica charantia*, *Eugenia jambolana*, *Tinospora cordifolia*, and *Mucuna pruriens* was examined for diabetic cataract prevention in vivo (Kim et al., 2013; Tsaiet al., 2014).

BIOACTIVE CONSTITUENTS THAT INCREASE THE UTILIZATION OF GLUCOSE

Certain medicinal plants such as *Cyamospsis tetragonolobus*, *Grewia asiatica* and *Zingiber officinale* Rosc were testified of their anti-hyperglycemic activity by controlling the utilization of glucose in the body.

Zingiber officinale

It is a traditional flowering plant of family Zingiberaceae. All portions of the plant, like rhizome, roots are extensively used as vital food spices and/or as traditional medicine. The phytoconstituents of ginger rhizome have the efficiency to reduce free-radical. They contain volatile oils, phenolic compounds, and many others. The volatile oils, also documented as ginger vital oils, are a combination of terpenoid compounds, like sesquiterpene hydrocarbons, carbonyl compounds, alcohols, and esters. Particularly, the phenolics present in ginger are the utmost vital phytochemicals and were categorized into two groups: gingerol- gingeron and shogaol linked group and diarylheptanoids. It also comprises multiple of amino acids, like glutamate, glycine, aspartic acid, threonine, and serine, etc. Furthermore, ginger comprises polysaccharides as well as organic acids like oxalic acid, and tartaric acid, etc (Nasry et al., 2013; Wei et al., 2017).

Various studies stated that ginger juice is very effective in controlling the blood glucose level in normal fasting rats as well as in alloxan-induced diabetic rats. Other studies also confirmed that ginger can effectively control the glycogen amount in the tissues of diabetic animals by improving the peripheral utilization of glucose and restoring the weakened liver (Imtiyaz et al., 2013). Furthermore, *Zingiber officinale* rhizome also showed that its bioactive constituents can augment the uptake of glucose. Additional surveys showed that the mixture of the fresh ginger displayed inhibition against alpha-amylase, alpha-glucosidase, and angiotensin-converting enzyme. Also, powder of ginger can reduce the glucose level and trigger inflammatory action which is linked to the progress of insulin resistance (Akinyemi et al., 2014; Sahardi & Makpol, 2019; Liu et al., 2019).

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