Plant Sterols in Diabetes Management

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The plant-based food we consume often contains many sterol-based bioactive compounds. It is well documented that these compounds could effectively manage the processes of insulin metabolism and cholesterol regulation. Insulin resistance followed by hyperglycemia often results in oxidative stress level enhancement and increased reactive oxygen species production. At the molecular level, these changes induce apoptosis in pancreatic cells and hence lead to insulin insufficiency. Studies have proved that plant sterols can lower inflammatory and oxidative stress damage connected with DNA repair mechanisms. The effective forms of phyto compounds are polyphenols, terpenoids, and thiols abundant in vegetables, fruits, nuts, and seeds. The available conventional drug-based therapies for the prevention and management of diabetes are time-consuming, costly, and with life-threatening side effects. Thereby, the therapeutic management of diabetes with plant sterols available in our daily diet is highly welcome as there are no side effects.

Keywords: diabetes ; insulin resistance ; plant sterols ; enriched foods

1. Introduction

Diabetes mellitus (DM), commonly known as diabetes, is an endocrine disorder characterized by elevated glucose levels [1]. The pancreatic cells produce a metabolic peptide hormone called insulin which allows the entry of glucose from the blood to the cells to support them with energy. A lack of adequate insulin functional balance plays a vital role in diabetes development [2]. Diabetes is a chronic disease, and its global prevalence is estimated to be 4.4% in 2030. According to the International Diabetes Federation (IDF) data, it is estimated that by the year 2045, about 693 million people will be affected by diabetes worldwide, and the most badly hit countries will be the USA, China, and India [3]. Diet plays a significant role in the etiology of many diseases such as diabetes, cancer, and cardiovascular illness, even at a younger age. A healthy diet pattern (less salt, sugars, saturated, and industrial trans-fat but with more green and leafy vegetables and fruits) is essential to maintain good health and to prevent many diseases. Having the habit of following an unhealthy and uncontrolled diet is considered one of the fundamental reasons behind the induction of obesity and overweight [4]. The overweight and obese conditions can lead to many unhealthy situations such as cardiovascular diseases, muscular-skeletal disorders, and certain cancers associated with breast, ovarian, colon, and liver. At present, the epidemic death proportion due to obesity-related diseases has reached at least 2.8 million deaths per year globally [5].

Abnormal accumulation of fats results in insulin resistance, impaired glucose tolerance, and even diabetes [6]. In obese conditions, the level of major inflammatory proteins such as interleukin-6 (IL-6) and tumor necrosis factor (TNF-α) increases significantly. Elevated levels of these inflammatory markers induce dyslipidemia by inviting macrophages towards the adipose tissue [6][7]. Various conditions such as programmed cell death in pancreatic β cells due to insulin resistance, hyperglycemia-induced oxidative stress, and enhanced production of reactive oxygen species can lead to diabetes. The phytosterols are natural compounds that include sterol and stanol esters and are abundantly occur in plants' cell membranes. The plant sterols that are commonly present in daily food intake are the β-sitosterol, campesterol, and stigmasterol. Due to the structural similarity with the body's cholesterol, the phytosterols compete with the cholesterol and help in reducing the absorption of dietary cholesterol [8]. The European Foods Safety Authority (EFSA) declared that the daily consumption of plant sterols within the therapeutic dose (1.5–2.4 g/day) is adequate for disease prevention in humans without harmful side effects [9].

2. Plant Sterols and Anti-Cholesterol Activity

The human body requires the waxy substance cholesterol to build healthy cells and synthesize hormones and digestive fluids. Overall, cholesterol within the required range helps our body to function correctly. An imbalance between the two forms of cholesterol, such as low and high lipoproteins, increases the chances of developing heart disease and stroke. The hypocholesterolemic effect of plant sterols was identified in early 1950 [10]. Still, many studies are in line to identify the molecular mechanism behind the anti-cholesterol effect of PS. So far, many studies emphasize that the plant sterol could

regulate the levels of lipid variables such as LDL, HDL, triglycerides, and apolipoprotein B effectively [11]., Many studies have supported the lipid regulatory action of plant sterols; however, a lack of understanding of the mechanism prevents them from being used in clinical trials. Many reports have suggested that the plant sterols and stanols could reduce LDL levels and exert their action in a dose-dependent way [12][13]. Some data also show that the stanols could exert a dose-dependent hypocholesterolemic effect compared to sterols [14]. The efficiency of plant sterol may largely depend on the baseline levels of plasma lipids. Studies have shown that plant sterols could effectively lower the concentration of triacylglycerols and thereby reduce the synthesis of very-low-density lipoproteins. Conversely, a few detailed research studies have highlighted the negative association of phyto compounds with hypercholesterolemia impact [15][16].

3. Plant Sterols and Anti-Diabetic Effects

Plant-based medicines are commonly used to prevent many chronic diseases. They have been in use as a complementary or alternative therapy form since ancient times. For example, the anti-diabetic drug metformin, a derivative from the plant *Galega officinalis*, is widely used to prevent diabetes [17][18]. The other medicinal plants with anti-diabetic properties include *Aloe vera*, Jamun/Indian blackberry, gurmar, bitter guard, basil, yacon, fenugreek, etc. The various parts of the plants, such as leaves, seeds, roots, and fruits are used to treat diabetes [19][20][21][22][23][24]. These medicinal plants regulate many functions such as insulin secretion, insulin resistance, glucose absorption, and regulation (**Table 1**).

Results from animal studies have supported the potent hypoglycemic and hypocholesterolemic effects of plant sterols [25][26][27][28]. However, so far, no clinical research has been conducted to verify the impact of plant products as conventional drugs for diabetic management. The plant sterols could regulate the expression of genes such as glucose-6-phosphatase, phosphoenolpyruvate carboxykinase, and peroxisome proliferator-activated receptor-alpha and influence the rate of metabolism [29]. Misawa et al. reported that the ethanolic extract of *Aloe vera* could increase the production of insulin in Zucker diabetic fatty rats [30]. Research by Patil et al. proved the insulin-secreting efficiency of plant sterols present in cumin oil, cumin aldehyde, and cuminol with the help of the diabetic rat model [31]. The research identified that the plant sterol present in black cumin (*N. sativa*) blocks the sodium-dependent passage of glucose across the jejunum. Long-term treatment of *N. sativa* modulates glucose tolerance and body-weight reduction as equivalent to metformin in a rat model [32]. Indian satinwood (*Chloroxylon swietenia)* shows a significant hypoglycemic effect in streptozotocin-induced diabetic rats [33]. The ethyl acetate extract of fruits of weeping forsythia could effectively enhance the plasma level of insulin [34]. The ethanolic extract of scarlet gourds (*Coccinia grandis)* leaves exerts its hypoglycemic activity by reducing the plasma glucose level and increasing the serum insulin level [35]. These plant compounds are noticed for their ability to induce hypoglycemic impact via improving the mechanism of insulin secretion.

Research using the common nettle (*Urtica dioica*) leaves extract identified the gender-biased working modulation of plant sterols. The study proved that the compound could balance hypoglycemic activities in male Wistar rats. It could effectively reduce the plasma glucose level and fasting insulin resistance index in male rats [36]. The extract of cashew tree (*Anacardium occidentale)* could significantly reduce the blood glucose levels in STZ induced diabetic rats. In this experiment, the compound showed its ability to reduce fasting glucose levels [37]. An oil extracted from garlic (*Allium sativum)* helps to improve insulin secretion and glucose tolerance. It proved that the extract could enhance glycogenesis by increasing GLUT4 expression in the rat model [38]. The bark extract of the Sapphire berry family (*Symplcos cochinchinesis)* has been shown to improve insulin resistance and thus reduce glucose levels [39]. Similar results are observed upon the use of the extract of *Helicteres angustifolia* [40]. Other plant extracts that work by a similar mechanism to reduce the blood glucose level with effective insulin sensitivity modulation include the *Pleurotus ostreatus*, *Afzelia africana*, *Uvaria chamae*, and resveratrol [41][42][43][44].

Some phyto compounds act by inhibiting the α-glucosidase, thereby preventing carbohydrate metabolism. Reduced carbohydrate metabolism results in a decreased rate of glucose assimilation and could lead to a reduced postprandial glucose level in the blood. Many plants such as basil contain phyto compounds that inhibit enzymes such as α-glucosidase and α-amylase, thereby acting as a potent anti-hyperglycemic agent [45]. On chromatographic separation, the basil leaves are found to contain flavonoids, glycosides, steroids, and tannins [46]. The polyphenol compounds isolated from the jute plant exert its potential by inhibiting ACE and lowering the levels of α- glucosidase and α- amylase significantly [47][48]. Certain legumes like soybean have been shown to contain polyphenolic compounds such as isoflavones [49]. The phyto compounds of fig fruits such as vitexin and isovitexin were shown to have glucose reduction properties in sucrose-loaded mice [50]. The figs (*Ficus deltoidea)* are considered an alternative natural remedy for diabetes and are also available in many commercial forms. Plant sterols have been shown to improve insulin production, GLUT4 expression, and insulin sensitivity. As well it inhibits α glucosidase, α amylase, and ACE functions. In addition, the plant-derived compounds also regulate genetic and epigenetic factors to counteract diabetes. More clinical research is necessary to support the therapeutic potential of plant sterols in preventing diabetes.

Table 1. Anti-diabetic activity of different herbs.

Botanical Name	Common Name	Components Used	Animal Studies	Effects	Reference
Aloe barbadensis	*Aloe vera*	Leaves	Diabetic rats	Significant reduction in the levels of the enzymes that facilitate carbohydrate metabolism	[30]
Cuminum cyminum	Cumin	seeds	Diabetic rats	Improves insulin secretion	[31]
Nigella sativum	Black cumin	Seeds	Rats	Improves glucose tolerance	[32]
Chloroxylon switenia	Indian satinwood	Barks	Diabetic albino rats	Decreases blood glucose level	[33]
Forsythia suspense	Weeping forsythia	Fruits	STZ induced Kunming mice	Significant reduction in blood glucose level	[34]
Coccinia grandis	Scarlet gourds	Leaf	Diabetic Wistar rats	Improves insulin-secretagogue and cytoprotective activities	[35]
Afzelia africana	African mahogany	Stem	Diabetic Wistar rats	Reduces hyperglycemia	[42]
Urtica dioica	Common nettle	Leaf	Fructose induced Insulin resistance Wistar rats	Significantly reduces hyperglycemia and insulin resistance	[36]
Anacardium accidentale	Cashew tree	Leaf	Diabetes induced female albino Wistar rats	Significant reduction in the levels of serum glucose, glycosylated haemoglobin, FIRI, and serum insulin	[37]
Pleurotus ostreatus	Oyster mushroom		Diabetes induced male Wistar rats	Significant reduction in blood glucose level	[41]
Uvaria chamae	Bush banana	Root	Diabetes induced albino rats	Significant improvement in the regeneration of islets of Langerhans	[43]
Cinnamomum zeylanicum	Cinnamon	Bark	STZ-induced rats	Significantly diminishes α-glucosidase activity	[22]
Ocimum basilicum	Basil	Leaves		Significantly inhibits α amylase activity in a dose-dependent manner	[46]
Corchorus olitorius	Jute	Leaves		Significantly inhibits the enzymatic activities of α-amylase, α-glucosidase, and ACE	[48]
Ficus deltoidea	Fig	Leaves, Flowers	STZ-induced diabetic rats	Significantly lowers the blood glucose level	[50]
Holarrhena antidysenterica	Bitter oleander	Seeds	Starch-loaded normoglycemic rats	Interferes with starch digestion	[24]
Olea europaea	Olive	Leaves	STZ-induced diabetic rats	Inhibits α amylase activity	[21][23]
Glycine max	Soybean	Soybean		Significantly lowers the levels of α-amylase, α- glucosidase and ACE	[49]

4. Conclusions

Phyto compounds, the naturally obtained formulations from plants, are well known for their effective anti-diabetic properties. They can exert their function directly by interacting with several signaling pathways associated with diabetes. They also have a potent hypocholesterolemic effect, which could indirectly counteract those obesity-related issues connected with diabetes. In conclusion, we strongly support that due to fewer side effects with significant medicinal character, plant sterols and stanols can be widely used to prevent diabetes. More clinical trials are needed to reveal the anti-diabetic benefits of plant compounds to commercialize them as therapeutic agents.

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