Journal of Advanced Scientific Research

Available online through https://sciensage.info

ISSN
0976-9595
Review Article

MECHANISMS OF ACTION OF ALKALOIDS IN THE MANAGEMENT OF DIABETES MELLITUS

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Received: 01-10-2021; Revised: 22-02-2022; Accepted: 18-03-2022; Published: 30-04-2022

https://doi.org/10.55218/JASR.202213302

ABSTRACT

The aim of the diabetes treatment is primarily to save life and alleviate symptoms and secondary to prevent long term diabetic complications and, by eliminating various risk factors. The inability of current therapies to control all the metabolic defects of the disease and their pathological consequences, cost effect, there is a need for the alternative strategies for diabetes therapy. The mechanism of action of herbal antidiabetic could be; stimulation of insulin secretion from beta cells, reduction in insulin resistance, stimulation of glycogenesis and hepatic glycolysis, activation of PPAR γ, etc. This review summarizes the specific mechanism action of different alkaloids that target the various metabolic pathways in human body.

Keywords: Diabetes mellitus, Alkaloids, Antidiabetic medicinal plants, Mode of action.

1. INTRODUCTION

Type-2 diabetes mellitus (T2DM) leads to various other diseases. Current therapies of T2DM have various side effects and ultimately lead to insulin resistance, along with financial burden [1]. Since ancient times, plants and their derived products have been used to treat human ailments in various parts of the world where access to modern medicine is limited. Lot of medicinal plants have been reported for anti-diabetic activity [2]. The antidiabetic activity of medicinal plants follow several mechanisms of action:increased insulin secretion; inhibition of glucose production in the liver; inhibition of glucose absorption by the intestinal; the inhibition of diabetes-related complications [3]. Study of naturally occurring alkaloids along with their mechanisms has been discussed here, which may lead toward the better understanding about their efficacy and selection of future anti-diabetic drugs. Alkaloids are secondary plant metabolites. On the basis of ring structure, these can be classified into 14 sub classes [4]. Alkaloids are classified as true alkaloids e.g., nicotine, atropine, morphine; protoalkaloids e.g., mescaline, adrenaline, ephedrine; polyamine alkaloids e.g., putrescine, spermidine and spermine; pseudoalkaloids e.g., caffeine, theobromine, theophylline etc, peptide and cyclopeptide alkaloids [5]. Many alkaloids have been isolated and studied for their antidiabetic activity [6]. Thus, this review discusses the mechanisms of action plant derived alkaloids.

2. MECHANISM OF ACTION OF ALKALOIDS

The alkaloid berberine, extracted from *Tinospora cordifolia*, induce glucose transport, carbohydrate digestion and absorption [7]. The effective treatment for diabetes is α-glucosidase inhibition because it will delay the time of absorption of glucose [8]. During gluconeogenesis, barberine reduces the glucose-6-phosphatase enzyme activity which modifies the conversion of d-glucose from glucose-6-phosphate [9]. Alkaloids like berberine, catharanthine, vindoline and vindolinine, Sotolon [4,5-dimethyl-3-hydroxy-2 (5H)-furanone], trigonelline, gentianine, carpaine, ginkgolides, allylpropyldisulfide, aegelin, marmesin, marmelosin, β-carbolines (harmine, nor-harmine, pinoline), betaine, achyranthine, β-ecdysone, castanospermine, epifagomine and fagomine [10-24] are the chief phytoconstituents isolated from various plant sources, their mechanism of action is discussed in Table 1.

Piperine, pipernonaline, and dehydropipernonaline alkaloids are isolated from *Piper retrofractum* fruits. These alkaloids act as potential antidiabetic agents [32]. Tecomine is isolated from *Tecoma stans Linn*. The antidiabetic activity of ethanolic extract of *T. stans* stem may be due to potentiation of insulin secretion from β-cells of pancreas, i.e., pancreatotropic action [33].

Sharma et al., (2009) studied anti-diabetic activity of an alkaloid from *Capparis deciduas*, the mechanism of the alkaloid was reported as improvement of GLUT 4, glucokinase activity and peroxisome PPARγ [34]. Patel et al., (2015) studied that koenidine increased insulin activity, glucose uptake and GLUT 4 translocation in L6-GLUT4 [35].

In another study, Punitha et al., (2005) studied administration of benzyl tetra isoquinoline alkaloid-berberine in diabetic rats suppressed oxidative stress parameters, reduced elevated lipids, ameliorated glycosylation of haemoglobin [36].

Table 1:Different metabolic pathways of alkaloids

Sl. no	Alkaloids	Specific mechanism of action	Plant Sources	References
1	Barberin	Carbohydrate digestion and carbohydrate absorption	*Tinospora cordifollia, Barberis aristata*	[10,11]
2	Catharanthine, vindoline, vinblastine, vincristine	Free radical scavenging Action	*Cathanthrus roseus, Vincarosea*	[12-14]
3	Sotolon[4,5-dimethyl-3- hydroxy-2(5H)-furanone], trigonelline, gentianine, carpaine compounds	Glucose transport, carbohydrate digestion and absorption	*Trigonella foenumgraecum*	[15]
4	Ginkgolides	Insulin secretion	*Ginkgo biloba*	[16]
5	Allylpropyldisulfide	Glycogensynthesis, insulinsecretion	*Alliumsativum*	[17, 18]
6	Aegelin, marmesin, marmelosin	Regeneration o fpancreatic βcells and insulin Secretion	*Aegle marmelos*	[19, 20]
7	Harmine, pinoline	Insulin secretion and β-cell regeneration	*Tribulus terrestris*	[21, 22]
8	Betaine, achyranthine, β- ecdysone	Carbohydrate digestion andabsorption	*Achyranthusaspera*	[23]
9	Castanospermine, epifagomine, fagomine	Carbohydrate digestion and absorption, insulin secretion	*Xantho cercis zambesiaca*	[24]
10	Castanospermine, australine	DPP-IV inhibition	*Castanospermum australe*	[25]
11	Caffeine (1,3,7-trimethylxanthine)	Insulinse cretion and β-cell Regeneration	*Camellia sinensis*	[26]
12	Jatrorrhizine, magnoflorine, palmatine	By stimulating insulin secretion	*Tinospora cordifolia*	[27]
13	Lepidine and Semilepidine	Potentiate pancreatic secretion of insulin from islet β-cells	*Lepidinum sativum*	[28]
14	Javaberine A, Javaberine A hexa acetate, Javaberine, B hexa acetate	Inhibitors of TNF-α	*Talinum panicalatum*	[29, 30]
15	Cryptolepine	Decrease in blood glucose level	*Cryptolepis sanguinolenta*	[31]

3. ALKALOID RICH EXTRACTS

Alkaloid rich fraction of *Capparis deciduas* contains spermidine alkaloids i.e., cadabicine, isocodonocarpine, codonocarpine, and capparidisinine inhibited the elevation of blood glucose level, also decrease the total cholesterol and triglyceride levels. It was found to be effective to control T2DM condition by reducing effect of G6Pase, PEPCK, aldose reductase and TNF-α expression. At the same time, it increased the expression of GLUT-4, PPAR-γ and glucokinase [34]. *Morus spp. (Moraceae)* latex has been reported to have antidiabetic activities due to very high concentrations of 1,4-dideoxy-1,4-imino-D-arabinitol, 1-deoxynojirimycin, and 1,4-dideoxy-1,4-imino-D-ribitol [37]. Alkaloids rich fraction of *Aervalanata Linn. (Amaranthaceae)* contains major amounts of alkaloid; canthin-6-one showed significant antidiabetic activity [38].

The therapeutic impact of natural alkaloids against blood glucose pathogenesis is mediated through a variety of signalling cascades and pathways, shown in Fig. 1 [39].

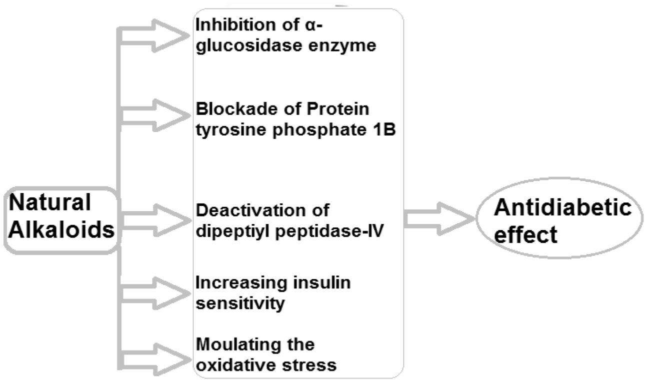

Fig. 1: Therapeutic impact of natural alkaloids against blood glucose pathogenesis is mediated through a variety of signalling cascades and pathways

4. CONCLUSION

Treatment of T2DM requires multidisciplinary approaches and beside the medicinal treatment, it requires dietary and lifestyle management. Natural products are being used from a long time to treat various kinds of disorders including T2DM. A very vast literature is available that describes number of anti diabetic plants and their compounds with different types of mechanism of action. Compounds isolated from various herbs and plants have been reported for their selective activities toward specific targets. Synthesis of these compounds may reduce the cost and increase their availability for further research. However, more investigations must be carried out to explore the anti-diabetic mechanism of action at cellular and molecular level for future applications.

5. ACKNOWLEDGEMENT

Authors sincerely thanks to Dr. S. Chandra Mohan, Research Director, Shanmuga Centre for Medicinal Plants Research, Thanjavur, Tamil Nadu, India.

Conflict of interest

None declared

Source of funding

None declared

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