IJBPAS, September, 2020, 9(9): 2303-2314

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

PLANTS WITH ANTIDAIBETIC ACTIVITY: AN IN-SILICO BASED STUDY

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Received 24th Jan. 2020; Revised 26th Feb. 2020; Accepted 2nd April 2020; Available online 1st Sept. 2020

https://doi.org/10.31032/IJBPAS/2020/9.9.5185

ABSTRACT

From ancient times, plants as drugs have been used for different type of disease and disorder or any illness. Raw plant or its formulations were used in different medicinal systems. The phytoconsitituents present in the plants play imperative role in the treatment. Plants extract and formulations supposed to be having few or no side effects. About 800 plants may possess anti-diabetic potential. Diabetes is an epidemic disorder spread worldwide. It is estimated that number of patient increase day by day globally. By 2025 it may be cross the number 300 million as per WHO. Currently used drugs for the treatment of diabetes causes several adverse effects. It is the time of challenge and opportunity for the scientist to develop such drugs that has minimum side effects with max efficacy. So the further advance in the development of new drugs becomes the need of future. Now a day's many scientific approaches like molecular docking utilise in the development drug discovery field. It is an emerging tool now days. This technique utilizes some scoring function for the prediction of binding affinity between two molecules. Phytoconstituents studied with different type of programme for their affinity for particular target/ protein provides great knowledge about the efficacy of molecule. In the present review it is concluded that querecetin, Sitosterol, Stigmasterol, Catechin hydrate, Epigallocatechin, Rutin, Betulin and lupeol shows good binding affinity towards α-Amylase and α-Glucosidase.

Keywords; Diabetes, Medicinal Plants, Docking Studies, Phytoconstituents, antidaibetic

INTRODUCTION

Herbal medicines may be defined as naturally occurring, plant-derived compounds with minimum or without industrial processing that have been used for the treatment of any illness. These medicine and their formulations utilized from enormous number of years. These medicines initially took the form of crude drugs such as teas, tinctures, powders and poultices **[1]**. Many modern drugs like aspirin, codein, digitoxin, diosgenin, ephedrine, ipecac, quinine and reserpine are derived from traditional medicinal plants used frequently used to treat pain, inflammation, cough, cardiovascular complications, nasal congestion, malaria, blood pressure respectively **[2]**. The term diabetes has been originated from Greek word as dia (through) and bêtes (pass) **[3]**. It is a metabolic disorder of carbohydrate, protein and fat. Diabetes is a bundle of metabolic disorder characterized by hyperglycemia (chronic), due to faulty insulin secretion, their action or both. **[4]**. There are mainly four types of diabetes Type 1 diabetes, Type 2 diabetes, Gestational diabetes mellitus, Drug or chemical-induced **[5]**.

Recent study shows that number of case of diabetic patients increased three fold between 1990 and 2010. Globally the counts of new patients doubled per annum **[6]**. As per WHO it estimated that by 2025 counts of diabetic patients may likely to cross 300 milllions. For the treatment of diabetes Insulin, Sulfonylureas, Glinides and Biguanides are the popular choice but due to a number of adverse effects shown by many of these drugs, it is the need of future to search safer and effective drugs for diabetes. Plants has been observed to be a good source of drugs. Many modern drugs derived from plants and their derivatives. In approximation 800 plants may possess anti-hyperglycemic potential **[7]**.

The process of docking involves in determination of ligand orientation and conformation within the target **[8]**. Molecular docking determines the preferred orientation of one molecule to another when they form a stable complex. By knowing the preferred orientation, it may be used to determine the strength of binding affinity between two molecules. Docking can be performed between Protein- protein, Protein-peptide, Protein- nucleotide and Protein-small ligand. To perform docking it requires structures of protein (receptor) and a ligand **[9]**.

Phytoconstituent Responsible For Antidiabetic Activity as Predicted By Docking Studies

In the present review it is found that plant constituents like querecetin, sitosterol, stigmasterol, catechin hydrate, epigallocatechin, epigallocatechin gallate, rutin, betulin and lupeol shows good binding affinity towards α-Amylase and α-Glucosidase when docked with different softwares, Whereas enzyme DPP4 and GLP1 shows good affinity for Catechin, Charantin, Cucurbitacin, Kuguacin A, D, G, B, H and Omarigliptin extracted from different parts of plants. Studies also suggest that quercetin increase the amount of insulin plasma concentration and decrease sugar level in urine in the treated diabetic rats **[10]**. Phytoconstituents like chrysin, isoquercitrin involved in insulin secretion. Similarily silymarin, silybin, silychristin and silidianin shows insulinomimetic activity. A number of compounds as caffeic acid, fenugreekine, inulin, glucosamines, corosolic acid, p-coumaric acid taraxacosides, kaempferol, 3-O-methylprotocatechuic acid 4-hydroxybenzoic acid actively participate in carbohydrate (digestion, absorption) insulin secretion and glucose transport **[11]**.

Research Methodology

This review is a summary of the current knowledge of various plants and their constituents exhibiting hypoglycaemic activity. To prepare this review article, authors have searched the literature using PubMed, SCOPUS and Google scholar with the key words diabetes, antidiabetic plants, docking analysis. The literature search included only articles written in the English language. Reviews and original research articles published between 2018 and 2020 were included in this review as references. Many plants like *Azadirachta indica*, *Clinacanthus Nutans, Calotropis procera, Morus indica L.*and *Momordica charantia L* shows good affinity. Moreover the various constituents from different parts of plants were studied extensively. So summarize list is prepared of different plant which includes Compounds, Receptor and different types of software involved in these studies.

Table 1: List of plants studied by docking for antidiabetic potential

Sr. no.	Plant (Family)	Chemical Constituents (Docked)	Receptor/Target	Software	Ref.
1.	*Azadirachta indica* (Meliaceae)	Campesterol, Methoxypodocarpa,11,13-trien-3-ol,Nimbiol,12-hydroxy-13-isopropylpodocarpa-8,11,13-trien-3-one, 12-hydroxy-13-isopropylpodocarpa, 11,13-trien-7-one , 13-isopropyl-12-Squalene, Sitosterol, Stigmasterol	α-Amylase, α-Glucosidase, AMPK	AutoDock 1.5.4	[12]
2.	*Clinacanthus nutans* (Acanthaceae)	Glycerol monostearate ,Heptadecanoic acid, Hexadecenoic acid 1-linolenoylglycerol, 1-Monoplamitin, A-tocospiro B, Pentadecanoic acid,Phytol,Palmitic acid,Quercetin,Stigmast-5-ene, Stigmasterol	α-Glucosidase and α-Amylase	AutoDock 1.5.6	[13]
3.	*Calotropis procera* (Apocynaceae)	Myrciacitrin IV, Gluconic acid, Hydroxybenzoic acid, Quinic acid, 4-O-β-d-Galactopyranosyl-d-fructose	α Glucosidase	M O E	[14]
4.	*Cinnamomum camphora* (Lauraceae)	Cynidine	α Glucosidase	Autodock vina	[15]
5.	*Cornus capitata*	Betulinic acid, Arjunolic acid, Epibetulin, Maslinic acid, Betulin,	α-glucosidase	AutoDock4	[16]

	Wall. (Cornaceae)	Lupeol			
6.	*Crassocephalum rubens* (Asteraceae)	6-Hydroxy-2-cyclohexen-one-carboxylate, 3,4-Methylene dioxybenzoic acid, 8-Methoxy-6,7-methylenedioxycoumarin and Sanguisorbic acid dilacton.	α Glucosidase	AutoDock Vina	[17]
7.	*Dictyopteris hoytii* /algae (Dictyotaceae)	2-Bromoethylmethylbenzene, 1,4-dioate fucosterol cerotic acid n-octacos-9-enoic acid 11-eicosenoic acid	α-Glucosidase	M O E	[18]
8.	*Dryopteris cycadina* (Dryopteridaceae)	β-Sitosterol, β-Sitosterol 3-O-β-D-glucopyranoside, 3, 5, 7-trihydroxy-2-(p-tolyl) chorman-4-one, Quercetin-3-0-β-D-glucopyranoside (3/→0-3///) β-D- Quercetin -3-0- β –D-galactopyranoside, 5, 7, 4-Trihydroxyflavon-3-glucopyranoid	α-Glucosidase	M O E	[19]
9.	*Elaeagnus umbellata* Thunb. (Elaeagnaceae)	Catechin hydrate, Epigallocatechin, Epigallocatechin gallate, Rutin, Quercetin	α-Amylase and α-Glucosidase.	Glide	[20]
10.	*Ficus racemosa* Linn. (Moraceae)	α- Amyrin, β- sitosterol Friedelin , Lupeol	Human Maltase GlucoAmylase	Cdocker	[21]
11.	*Gardenia jasminoides* Ellis (Rubiaceae)	Geniposide, Gardenoside	α-Glycosidase	Vina	[22]
12.	*Gracilaria edulis* /marine macro alga (Florideophyceae)	11-methoxy-2-methyltridecane4-ol	α-Amylase	Autodock 4.2.6	[23]
13.	*Ipomoea sepiaria* (Convolvulacae)	Erucic amide, 10-Heneicosene, 9-Hexacosene, 1-Monolinoleoylglycerol trimethylsilyl ether, Phytol Quercetin, 3,7,11,15-Tetramethyl-1-hexadecen-3-yl acetate, Z-9-Hexadecen-1-ol , Octadecamethylcyclononasiloxane, Tetracosamethyl-cyclododecasiloxane, Hexasiloxane, , Icosamethylcyclodecasiloxane , Linoleic acid, Heptadecane, 2E,9Z,12Z-octadecatrienoic acid, Lauric acid Octasilaheptadecane, 9-cis-Oleamide, Supraene, Tetracosapentaen, Campesterin, Lycopen-16-ol, Stigmasterin, Triacontan, 2,3-Dimethylheptadecane,	TCF7L2	Hex8.0.0	[24]
14.	*Ipomoea mauritiana jacq* (Convolvulceae)	Chloroacetic acid , Dodecanoic acid, Hexanoic acid, Nonacosane , Octacosoic acid,Octadec-1-ene, Octadecan-1-ol, Octadecanoic acid, Scopoletin ,Sitosterol β, Taraxerol, Tetradecanoic acid,Taraxerol acetate,Tetracosane, Tetradecanal	GFAT, and PPAR Gamma	Dock	[25]
15.	*Ipomoea purpurea* (Convolvulaceae)	Cairicoside, Purgin III, Pescaprein(I and V) ,Purginoside II	α-Glucosidase Maltase GlucoAmylase	Autodock 4.2	[26]
16.	*Lycium barbarum* (Solanaceae)	trans-N-feruloyloctopamine, cis-N-caffeoyltyramine, Lyciumamide A, trans-N-caffeoyltyramine	PPAR -γ	Schrodinger	[27]
17.	*Lycium chinese* (Solanaceae)	trans-N-feruloyloctopamine, Dihydro-N-caffeoyltyramine, trans-N-caffeoyltyramine, Lyciumamide A, cis-N-caffeoyltyramine	PPAR -γ	Schrodinger	
18.	*Momordica Charantia* L. (Cucurbitaceae)	Gentisicacid5-O-β-dxyloside, Momordicoside F_1, F_2 G, I, K and Karaviloside XI	α-Amylase and α-Glucosidase	Autodock 4.2	[28,29, 30]
		Charantal, Charantoside XI, IDG, TCD	α-Amylase, α-Glucosidase	Autodock 4.2	
		Catechin,Charantin, Cucurbitacin,Kuguacin A, D,G, B,H and Omarigliptin	DPP4 and GLP1	Autodock vina	
19.	*Musa balbisiana* (Musaceae)	Apiforol	Isomaltase and α- Glucosidase	Schrodinger suite	[31]
20.	*Michelia alba* DC (Mangoliaceae)	Eugenol methyl ether, β-Linalool, Linalool oxide, Indole, Pyran Linalool oxide	human pancreatic α-Amylase	Autodock 4.2	[32]
21.	*Morus indica* L. (Moraceae)	Aminoguanidine, Apigenin	aldose Reductase	Autodock 4.2	[33]
		Estragole, Linalool	α-Amylase ,PPA,Lipase	AutoDock Vina	
22.	*Ocimum basilicum* (Lamiaceae)	Estragole, Linalool	α-Amylase ,PPA and Lipase	AutoDock Vina	[34]
23.	*Prangos pabularia Lindl* (Apiaceae)	Menthone,5-Pentyl-1,3-cyclohexadiene, (E)-1,3-Nonadiene,1-Decanol, 2-Methoxy-3-(1-methylpropyl)pyrazine, 3-Dodecyn-2-ol, Osthole, trans-α-Bergamotene, (3E)-2-Methylocten-5-yne, cis-Piperitone epoxide, Pulegone,1-Tridecyne	PTP-1B.	Molegro Virtual Docker	[35]
24.	*Pelliciera rhizophorae* (Tetrameristaceae)	Betulin, lupeol	α-Glucosidase	Molegro Virtual Docker 6.0.1	[36]
25.	*Quercus serrata*	Rosmarinic acid	α– Glucosidase	AutoDock	[37]

	/Fagaceae			4.2.6	
26.	*Quisqualis indica* (Combretaceae)	Linolenic acid, Phytol 9,12-Linoleic acid, Pentadecanoic acid,	α-Amylase	AutoDock Vina	[38]
27.	*Rubus chingii* Hu (Rosaceae)	Bine, Chingiitannin A	α-Amylase	AutoDock Vina 1.1.2	[39]
28.	*Ruellia tuberosa* L (Acanthaceae)	Daidzein, Hispidulin	α-Amylase	HEX 8.0	[40]
29.	*Syzygium cumini* (Myrtaceae)	Gallic acid, Glycitin Hesperetin, Hydroxydimethoxy flavones,Kaempferol ,Luteolin,Naringenin, Propionic acid , Quercetin ,Thermopsoside,	α-Amylase α-Glucosidase	Autodock 4.2	[41]
30.	*E. bicyclis, E. stolonifera, E. maxima, and E. cava*/ seaweed (Lessoniaceae)	Eckol,Dieckol, Dioxinodehydroeckol, Phloroglucinol,7-Phloroeckol, Phlorofucofuroeckol-A	α-GlucosidasePTP1B	Autodock Vina	[42]
31.	*Sideritis L* (Lamiaceae)	Acetoside, Lavandufolioside	Tyrosine Phosphatase 1B		[43]
32.	*Silybum marinum* (Asteraceae)	SilybinA,B, Isosilybin A, B, Silychristin A, B, Silydianine	α-Glucosidase	Autodock 4.2	[44]
33.	*Trigonella foenum-graecum* (Fabaceae)	Canagliflozin, Galactomannan, Galactomannan, Hydroxyisoleucin	1GFY	Cdocker	[45,46]
		Gallic acid	DPP IV	Auto Dock	
34.	*Wedelia calendulacea* (Compositae)	Wedelolactone	DPP4, GLUT1, PPAR γ	Schrodinger	[47]
35.	*Withania coagulans* (Solanaceae)	Ajugin A, Withanolide A, Withacoagulin	PPAR- α- Glucosidase, DPP-4	Glide-Maestero	[48]

CONCLUSION

Herbal medicines have no side effects and can be used as drug for the diabetes. Diabetes Mellitus is epidemic disorder throughout the world. So, effective medicines without lesser (no side effects) and toxic effects is the need of future. More in-silico work is needed to be done on formulation of plants derived products. Modern scientific studies like docking, focus on the bioactive compounds become more popular in recent times. From various in-silico studies carried on plants, it is suggested that the herbal compounds shows significant binding properties with different target proteins and hence can be used for development of newer drugs. The present review provides more than thirty plants studied by docking methods for anti diabetic properties in recent two years. Most of the studies were performed on autodock software. Targets for the docking studies as alpha amylase alpha glucosidase, PPAR used very frequently. Beside plants, some algae also studied for their antidiabetic poteintial. Docking studies suggests that plants from family like Moraceae, Convolvulceae Solanaceae, Combretaceae, Lamiaceae are good candidate for treatment of diabetes. Docking studies also suggest that the phytochemicals have good affinity for the different types of receptors involved in metabolic disorders. These may be used for design of novel lead molecules for diabetes. Further these lead may be used for

synthesizing more safe and effective molecules.

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