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Research Article

In Silico Antidiabetic Activity of Linalool Isolated From *Coriandrum Sativum* Linn Fruit - a

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ABSTRACT

Background and aim: Diabetes Mellitus [DM] is a metabolic disorder characterized by disturbances in carbohydrate, protein and lipid metabolism and by complications like micro vascular (retinopathy, neuropathy and nephropathy) and macro vascular (heart attack, stroke and peripheral vascular disease) complications. *Coriandrum sativum* Linn has been claimed to possess antidiabetic properties in Traditional System of Medicine. This study aimed to evaluate molecular interaction of linalool in *C.sativum* and targeted protein related to Type 2 DM.

Material and Methods: Isolation of Linalool from the methanol extract of fruit of *C.sativum* was done by column chromatography. Evaluation of hypoglycemic activity through an in silico docking approach with molecular target such as glutamine: fructose- 6-phosphate amidotransferase was performed. Molecular docking study was performed with Autodock docking software.

Results: The docking studies of the ligand linalool with target protein showed that this is a good inhibitor, which docks well related to diabetes mellitus with -2.0297kJ mol^{-1} Van der waal energy and -5.9265 kJ mol^{-1} as docking energy. Hence linalool can be considered for developing into a potent anti-diabetic drug.

Conclusion: Management of diabetes is challenge to the medical treatment. This leads to increasing demand for natural products with antidiabetic activity with fewer side effects. This work establishes *C.sativum* extract as a potential inhibitor for diabetes. Thus enabling a possibility of this plant extract as a new alternative to existing diabetic treatment.

Keywords: *Coriandrum Sativum*; Diabetes Mellitus; Molecular Docking; In Silico; Linalool

INTRODUCTION

Diabetes mellitus is a metabolic disorder characterized by disturbances in carbohydrate, protein and lipid metabolism and by complications like micro vascular (retinopathy, neuropathy and nephropathy) and macro vascular (heart attack, stroke and peripheral vascular disease) complications [1]. A worldwide survey has reported that diabetes mellitus affects nearly 10% of the population. It has been predicted that the prevalence of diabetes in adults will increase from 135 million in 1995 to 350 million in 2030 as given by International Diabetes Federation [2,3]. Currently available synthetic antidiabetic agents produce serious side effects like hypoglycemic coma and hepatorenal disturbances [4,5]. Patients are therefore using herbal medicines which have fewer side effects and have the potential to impart therapeutic effect in complicated disorders like diabetes and its complication [6]. Following the WHO's recommendation for research on the beneficial uses of medicinal plants in the treatment of diabetes mellitus, investigations on hypoglycemic agents derived from medicinal plants have also gained momentum. Traditional medicinal plants with various active principles and properties have been used from ancient times by physicians and laymen to treat a great variety of human diseases such as diabetes, coronary heart disease and cancer. Antidiabetic agents from medicinal plants could serve as a good source for drug design and much attention has been fixed on formulation of herbal medicine [7].

Plants are well known in traditional herbal medicine for their hypoglycemic activities and available literature indicate that there are more than 800 plant species showing hypoglycemic activity. There has been increasing demand for the use of plant products with antidiabetic activity due to low cost, easy availability and lesser side effects. Therefore, plant materials are continuously scrutinized and explored for their effect as hypoglycemic agents. One such plant is *Coriandrum sativum* which has been used in Traditional System of Indian Medicine for treating diabetes.

Coriander [*Coriandrum sativum* Linn.] an annual of the Apiaceae family is one of the valuable medicinal and seasoning plant. This species comes from the Mediterranean region and it is grown all over the world. The coriander fruit and essential oil isolated from it are used for medicinal purpose [8,9]. *C.sativum* is widely used in traditional medicine to treat anxiety, dizziness, headache, edema, fever, digestive disorders, respiratory diseases, allergies, and burns [10,11]. The fruits are used as astringent, anthelmintic, emollient, stomachic, antibilious, digestive, appetizer, constipating, diuretic, antipyretic, refrigerant, tonic, expectorant, anodyne, antidiabetic and dyspepsia. The phytochemical screening of *Coriandrum sativum* showed that it contained essential oil, tannins, terpenoids, reducing sugars, alkaloids, phenolics, flavonoids, fatty acids, sterols, glycoside, wide range of minerals, trace elements and vitamins. The previous pharmacological studies revealed that it possessed anxiolytic, antidepressant, sedative-hypnotic, anticonvulsant, memory enhancement, improvement of orofacial dyskinesia, neuroprotective, antibacterial, antifungal, anthelmintic, insecticidal, antioxidant, cardiovascular, hypolipidemic, anti-inflammatory, analgesic, antidiabetic, mutagenic, antimutagenic, anticancer, gastrointestinal, deodorizing, dermatological, diuretic, reproductive, hepatoprotective, detoxification and many other pharmacological effects[12-17].

Silver nanoparticles were synthesized using methanol and aqueous extract of fruit of *C.sativum* and its antioxidant activity were reported [18]. We have reported better activity with 75 % methanol extract of fruit of *C.sativum* and HPTLC data also showed that 75 % methanol extract has more number of phytoconstituents than all other extract [13]. The 75 % methanol extract showed significant decrease in blood glucose level at a dose of 100 mg/kg and 200 mg/kg. It also decreased the lipid parameters such as total cholesterol, total triglycerides, total bilirubin, SGOT, SGPT and ALP when compared with diabetic control. 75% methanol extract at 100 mg/kg was better in controlling diabetes when compared to 200 mg/kg bw suggesting that *C.sativum* possess antidiabetic activity [19,20].

Molecular docking is an important computational tool to predict the plausible interactions between the drug and protein in a non-covalent fashion. An in silico docking procedure have been carried out to examine whether the compound is a good ligand with diabetic target Glutamine: fructose-6-phosphate amidotransferase. Glutamine: Fructose-6-Phosphate Amidotransferase (GFAT) is a rate-limiting enzyme in the hexoamine biosynthetic pathway and plays an important role in type 2 diabetes. The enhanced activity of human GFAT has been implicated in insulin resistance in cellular and animal models. Thus, human GFAT is recognized as an interesting

potential target for type 2 diabetes complications. Glutamine-Fructose-6-Phosphate Amidotransferase (GFAT or GFPT) is the first and rate-limiting enzyme of the hexosamine pathway. GFAT controls the flux of glucose into the hexosamine pathway and catalyzes the formation of glucosamine 6-phosphate. The majority of glucose will enter the glycolysis pathway, with a small percentage entering the hexosamine pathway. GFPT or GFAT regulate the hexosamine pathway products. Therefore, this enzyme involved in a therapeutic target against Type 2 DM [21].

The aim of present study was to isolate Linalool from methanol extract of *C.sativum*. To the best of our knowledge, this is the first report on docking studies of the compound Linalool isolated from *C.sativum* for antidiabetic activity.

MATERIALS AND METHODS

Plant material

The *Coriandrum sativum* fruits were collected from local market in Bangalore, Karnataka, India and it was identified and authenticated by Botanist, Natural Remedies Pvt Ltd., Bangalore. A voucher specimen was deposited in The Oxford College of Pharmacy, Bangalore. The fruits were dried in shade and powdered coarsely, passed through sieve no. 40 and stored in air tight container for further use.

Preparation of fruit extract

Coarsely powdered fruits of *C.sativum* 200 g was extracted with 75 % methanol [1500 ml] in soxhlet apparatus till the complete exhaustion, filtered. The methanol extract was concentrated by rotary vacuum evaporator and evaporated to dryness.

Chemicals used

All chemicals and solvents used were of analytical grade and procured from SD fine Chemicals Ltd, Mumbai.

Isolation of Linalool

75% methanol extract was subjected to column chromatography using solvents of increasing polarity as eluent and Silica gel as stationery phase. Fraction from 68-79 from petroleum ether: Benzene (98:2) yielded colorless liquid [100 mg; 0.5 %] which was found to be linalool and confirmed by Co-TLC and already it was observed in Gas chromatography [22].

Sequence retrieval

Authentic structures for Ligands were retrieved from Protein data bank. The three dimensional structure of target protein was downloaded from PDB (www.rcsb.org/pdb) structural database. This file was then opened in SPDB viewer edited by removing the heteroatoms, adding C terminal oxygen. The active pockets on target protein molecule were found out using CASTp server. The ligands were drawn using ChemDraw Ultra 6.0 and assigned with proper 2D orientation (ChemOffice package). 3D coordinates were prepared using PRODRG server.

Ligand binding site prediction

Ligand binding sites were calculated using Q site finder http://www.modelling.leeds.ac.uk/ qsitefinder/, surface topology and the pocket information were also analyzed by the cast P server http://sts-fw.bioengr.uic.edu/castp/calculation.php. Pocket detection and occupancy of the protein was set up using Q-Site Finder. Clefts were tarnished in the protein-surface using Q-SiteFinder. The Solvent Available Surface Area (SASA) was found by the software server GETAREA http://curie.utmb.edu/getarea.html. The atomic Solvent Accessible Surface Area (SASA) enclosed by each cleft was calculated by utilizing radius of water probe 1.4 A^0 and the area/ energy per residue was also designed. Dielectric constant was set to a value of 80.0, and Poisson-Boltzmann method of computation for 20 cycles was used for calculating the electrostatic potential in SWISS-PDB viewer. All the ligand binding residues were amongst hotspots as predicted by Meta-PPISP. Furthermore, PIC was made to use to calculate the nature of interaction occurring in the ligand binding residues.

Docking studies

Autodock V3.0 was used to perform Automated Molecular Docking in AMD Athlon (TM)2x2 215 at 2.70 GHz, with 1.75 GB of RAM. AutoDock 3.0 was compiled and run under Microsoft Windows XP service pack 3. For docking, grid map is required in AutoDock, the size of the grid box was set at 102, 126 and 118 Å (R, G, and B), Comparative availability of 3D structures was checked in NCBI Entrez, along with PDB and SWISSPROT databases [23].

Assessment of protein-ligand interaction

Hydrogen bond interactions were calculated by using Discovery studio (http://accelrys.com/products/discovery-studio) and ligand map was generated using MOLEGRO (http://molegro-molecular-viewer.software.informer.com/2.5/).

RESULTS AND DISCUSSION

Linalool was isolated from 75% methanol extract of *C.sativum* fruits. The structure is given in the (Figure 1). It was obtained as colorless liquid, bp:198^{0}C [lit bp: 198-199^{0}C], refractive index: 1.460[lit refractive index: 1.463]. Molecular formula: $C_{10}H_{18}O$ and molecular weight: 154. It was confirmed to be Linalool by Co-TLC.

Linalool is a major and common terpenoid contained in most herbal essential oils and teas, including both green and black teas, and has been implicated in aroma and flavoring [24]. Oral exposure to linalool from formulated food products, including beverages, was estimated at up to 140 µg/kg/day, including the dietary intake of linalool from natural sources such as vegetables and spices [25]. Linalool has been traditionally used for medicinal purposes because of its potent antioxidative activities [26,27]. Recent studies have suggested that linalool may have a novel biological activity in TG metabolism, as the oral administration of fragrant herbal essential oils containing linalool, including *Plantago asiatica* and *Melissa officinalis* essential oils, was shown to improve dyslipidemia by reducing plasma TG concentrations [28].

In silico molecular docking studies

In order to investigate the binding capacity of Linalool in *C.sativum* on proteins related to diabetes in humans, we docked the

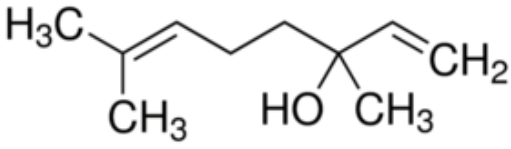

Figure 1: The structure of Linalool [Synonym: (±)-3, 7-Dimethyl-1, 6-octadien-3-ol, (±)-3, 7-Dimethyl-3-hydroxy-1, 6-octadiene].

compound to the target protein. Results showed that docking of the molecule with -2.0297kJ mol^{-1} Vander waal energy and -5.9265 kJ mol^{-1} as docking energy (Table 1). High binding affinity of the ligand to the receptor was explained clearly by interaction analysis in (Figure 2, Figure 3 and Figure 4).

Glutamine: fructose-6-phosphate amidotransferase (GFAT) is the key enzyme in the hexoamine biosynthetic pathway and plays an important role in type 2 diabetes [29]. In our study, docking of novel compound with 2ZJ3 showed van der Waal interaction with ALA 674, CYS 373, THR 425, GLY 374, SER 376, THR 375, SER 473, SER 676, VAL 471, LYS 675 and GLU 560.

GFAT plays a key role in hexosamine biosynthetic pathway, which is involved in glucose-induced insulin resistance and the induction of the synthesis of growth factor. The hexosamine pathway is the sensor

Table 1: Molecular docking results of linalool with 2zj3.

Molecule	Initial potential energy	Potential Energy	Initial RMS gradient	RMS gradient	Van der Waals energy	CDocker Energy
Linalool	50.9046	20.0971	12.1566	0.09716	-2.0297	-5.9265

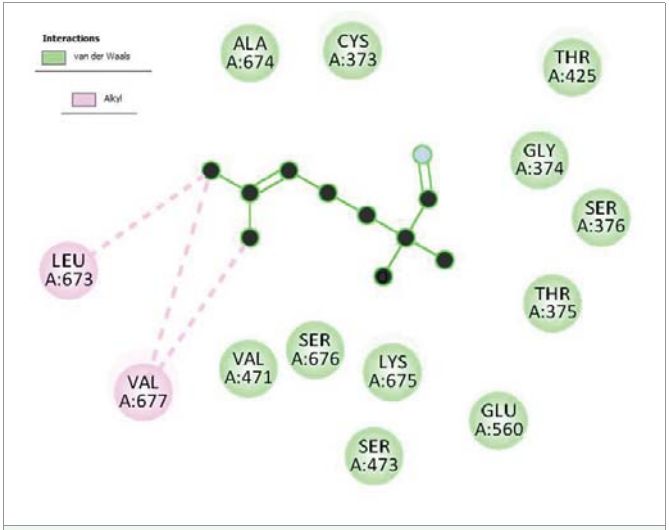

Figure 2: Linalool interactions with the active site amino acids of the 2zj3 protein.

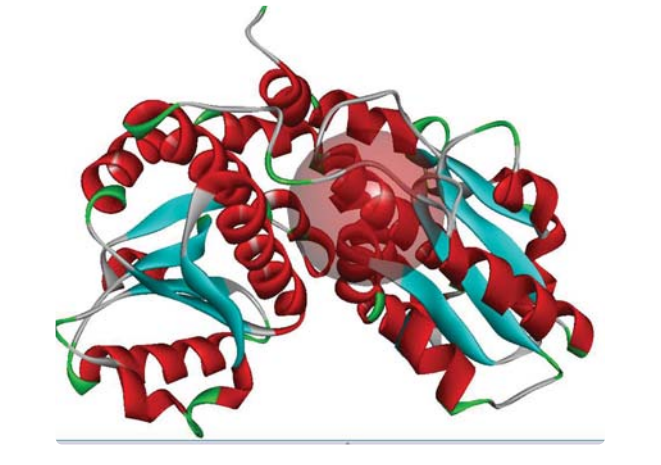

Figure 3: Secondary structure and binding site of the 2zj3 protein.

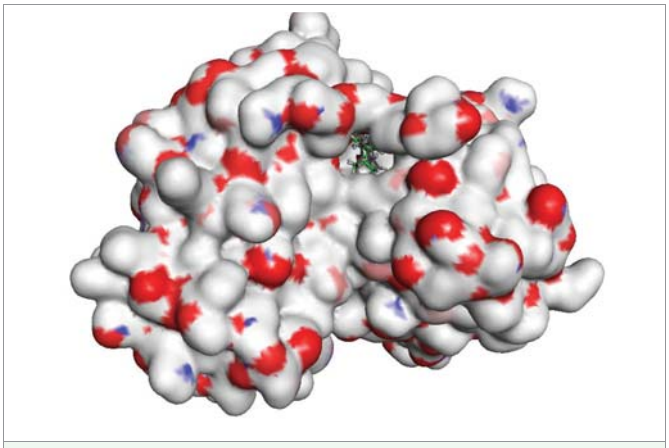

Figure 4: Surface view and docked ligand inside the 2zj3 protein.

of the glycoglysis pathway, in the reaction of fructose-6-phosphate (F6P) with the NH2 donor amino acid, a glutamine which is converted to Glucosamine-6-Phosphate (GlcN6P) by the Glutamine Fructose-6-Phosphate Amidotransferase (GFA) enzyme. Subsequent reactions result in the formation of uridine diphosphate N-acteylglucosamine (UDP-GlcNAc) which is utilized as a substrate for N- and O-linked glycosylation. It is intracellular protein O-Glycosylation Mediated By O-Linked Glcnac Transferase (OGT) which has been postulated to contribute to glucose toxicity by altering gene expression. The synthesis of glucosamine begins with the transport of glucose into the cell and its conversion to glucose-6-phosphate by hexokinase and then isomerization to fructose-6-phosphate by the enzyme phosphofructose kinase I of the glycolysis pathway. Then fructose-6-phosphate can go through the normal metabolic pathway as previously described in glucose metabolism. Due to the hexosamine pathway, 2–5% of fructose-6-phosphate formed in glycolysis is converted to glucosamine. Fructose-6-phosphate is isomerized and aminated by glutamine and GFAT (L-glutamine, D-fructose-6-phosphate amidotransferase) to yield glucosamine- 6-phosphate. First, Acetyl-Coenzyme (CoA) from either glucose metabolism or fatty acid oxidation transfers its acetyl group to glucosamine-6-phosphate to produce N-acetylglucosamine-6-phosphate. Then, a Uridine Nucleotide (UDP) is added to the glucosamine yielding Uridine 50-Diphospho-N-Acetylglucosamine (UDP-GlcNAc). Overall the production of UDP-GlcNAc requires glucose, glutamine, acetyl-CoA, uridine, and ATP. Studying the interaction of GFAT with UDP-GlcNAc and its 3D structure will provide more chances to develop a new strategy for treatment of type 2 diabetes. The majority of glucose will enter the glycolysis pathway, with a small percentage entering the hexosamine pathway. Hexosamine biosynthesis is known to contribute to insulin resistance and the induction of the synthesis of growth factor. GFPT or GFAT regulate the hexosamine pathway products. Therefore, this is involved in a therapeutic target against type 2 diabetes [21].

CONCLUSION

Renewed interest on the use of herbal products is gaining importance. Globally, many herbal products are being used as food supplements for prophylaxis of common ailments such as diabetes, hypertension etc.

Prior to the pharmacological investigation of any herbal product it is mandatory to investigate the safety profile of these herbal products.

It is documented that if an herbal substance is free from side effects or adverse effects up to 2000 mg/kg, it is considered safe for clinical use, the absence of acute toxicity is observed thus proving the safety profile of *C.sativum.*

The 75 % methanol extract showed significant decrease in blood glucose level at a dose of 100 mg/kg and 200 mg/kg. It also decreased the lipid parameters such as total cholesterol, total triglycerides, total bilirubin, SGOT, SGPT and ALP when compared with diabetic control. 75% methanol extract at 100 mg/kg was better in controlling diabetes when compared to 200 mg/kg bw suggesting that *C.sativum* possess antidiabetic activity. This was further confirmed by isolating Linalool from the methanol extract. This compound was found to interact the target protein which can be related to DM with -2.0297kJ mol^{-1} Vander waal energy and -5.9265 kJ mol^{-1} as docking energy. Docking studies of the linalool with target protein showed that this is a promising candidate which docks well with the target related to diabetes mellitus. Thus Linalool can be considered for developing into a potent antidiabetic drug.

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