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DOCKING STUDIES ON POLYPHENOLS DERIVATIVES WITH INSULIN RECEPTOR TYROSINE KINASE - AN *INSILICO* APPROACH

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Abstract: Objective: Diabetes mellitus, a leading non-communicable disease with multiple etiologies is considered as one of the five leading causes of death in the world. Compounds isolated from plants are safer and have a lot of potential than the chemical drugs. Experimental studies on animals or cultured human cell lines support the role of polyphenols in the prevention of cardiovascular diseases, cancers, neurodegenerative diseases, diabetes and osteoporosis. Polyphenols strongly has a role in the prevention of degenerative diseases. Flavonoids are the best defined group of polyphenols in the human diet. Flavonoids are widely distributed in plants fulfilling many functions. In the present study polyphenols are used as targets against the diabetic receptors. Docking was performed to study the interaction of polyphenols with Insulin Receptor Tyrosine Kinase meant to be a target for diabetes. Cyanidine, myricetin, catechin, quercetin and daidzein were chosen for the study. The molecular structure was taken from PubChem database. The 3D structure of the protein was obtained from PDB databank. Using these structures docking analysis was performed using Glide tool in Schrodinger software.The polyphenols showed a good interaction proving to be a good activator of the receptor molecule. Among the selected polyphenols cyanidine was found to interact with the protein receptor with a glide score of -7.568 and glide energy of -41.199. The docking method explores the ability of polyphenols that bound to the active binding site shows that the inhibitors are the best binder. Through the present study we conclude that polyphenols can be useful as therapeutic agent for the herbal therapy of diabetes.

Keywords: Diabetes mellitus, Flavonoids, Insulin receptor, polyphenols

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INTRODUCTION

Diabetes mellitus is a progressive metabolic disease and it has affected a considerable percentage of populations throughout the world. Epidemiological data indicated that 2.8% of the world's population was diabetic in 2000 and it may progress to 4.4% of the world's population by 2030.It affects all age groups of people and ethnic groups (Xing et al., 2009). The pathogenesis of both type 1 and type 2 diabetes are different, but, hyperglycemia and its associated complications are common in both conditions (Chen et al., 2008). Presently, research is also focused on traditional medicinal plants or herbs to utilize as potential alternative source to treat diabetes due to its multiple pharmacological actions (Chandramohan et al., 2008). Several phyto constituents possessing antidiabetic activity were isolated and studied from many medicinal plants, but still scientists are continues their research on medicinal plants to bring good antidiabetic lead or drugs to the healthcare community. Diabetics have raised levels of glucose in their blood. It has been suggested that the increasing glycation in diabetes can influence the ability of plasma proteins to bind to small molecules (Liu et al., 2012).The blood plasma proteins of diabetic patients reduce the beneficial effects of dietary polyphenols. The diabetic plasma proteins have an affinity 1 to 10 times lower for polyphenols than healthy proteins.

Polyphenolic compounds are abundant in the plant kingdom and are found in a wide variety of human foods (Gee et al., 2001). The flavonoids, which are the best defined group of polyphenols in the human diet, themselves, comprise a large and complex group, all of which contain a three-ring structure with two aromatic centres' and a central oxygenated heterocycle. The main dietary sources of polyphenols are fruits and beverages. Fruits like apple, grape, pear, cherry, and various berries contain up to 200–300 mg polyphenols per 100 g fresh weight.(Scalbert et al., 2005). Their potentially antineoplastic effects include antioxidant activity, induction of Phase II enzyme activity, inhibition of protein kinase and interactions with Type II estrogen binding sites. Naturally occurring polyphenolic compounds may play a role in the protective effects of fruits and vegetables against cancers in general, and they appear to have considerable potential for pharmaceutical uses as chemopreventive agents against neoplastic changes in the alimentary tract.

Five different polyphenols were chosen for the study namely Quercetin, myricetin, cyanidin, catechin and daidzein. Their structures, molecular formula, molecular weight were obtained from pubchem. Chemsketch software was used to draw the structure which was used for the docking studies. The selected polyphenols with its detail are provided in Table 1. Myricetin is a naturally occurring flavonol, a flavonoid found in many grapes, berries, fruits,

vegetables, herbs, as well as other plants. Walnuts are a rich dietary source. Trace amounts can be found as glycosides (Miean et al., 2001). It is one of the phenolic compounds present in red wine (Maggiolini et al., 2005). In vitro research suggests that myricetin in high concentrations can modify LDL cholesterol such that uptake by white blood cells is increased. A Finnish study correlated high myricetin consumption with lowered rates of prostate cancer (Knekt et al., 2002). Three flavonols (kaempferol, quercetin, and myricetin) reduced the risk of pancreatic cancer by 23 percent (Nothlings et al., 2007).

Myricetin increases cell viability and decreased cell apoptosis. Myricetin has the therapeutic value for preventing β-cell death. Myricetin serves as severe acute respiratory syndrome coronavirus (SARS-CoV) chemical inhibitors (Yu et al., 2012).Myricetin possesses signicant analgesic activity with independent of the opioid system. Myricetin may be a cyclooxygenase-1 (COX-1) inhibitor with anti-platelet activity (Tong et al., 2009).Myricetin plays a major role as an antioxidant (Gordon et al., 1998). Myricetin was found to increase insulin sensitivity and normalize blood glucose level. Quercetin is a flavonoid widely distributed in nature. Quercetin is a plant pigment. It is a naturally-occurring polar auxin transport inhibitor (Fischer et al., 1999). It is found in many plants and foods, such as red wine, onions, green tea, apples and berries, Ginkgo biloba. Buckwheat tea has a large amount of quercetin. Quercetin is used for treating conditions of the heart and blood vessels atherosclerosis, high cholesterol, heart disease, and circulation problems. It is also used for diabetes, cataracts, hay fever, peptic ulcer, schizophrenia, inflammation, asthma, gout, viral infections, chronic fatigue syndrome (CFS) and for treating chronic infections of the prostate. Quercetin is also used to increase endurance and improve athletic performance. Quercetin used to sensitize leukemia cell lines and B cells isolated from patients affected by chronic lymphocytic leukemia (B-CLL) (Spagnuolo et al., 2012).Quercetin has antioxidant and anti-inflammatory effects which might help reduce prostate inflammation. Cyanidin is a pigment found in many red berries including but not limited to grapes, bilberry, blackberry, blueberry, cherry, cranberry, elderberry, hawthorn, loganberry, acai berry and raspberry. It can also be found in other fruits such as

apples and plums, and in red cabbage and red onion. It has putative antioxidant and radical-scavenging effects that protects cells from oxidative damage and reduce risk of cardiovascular diseases and cancer (Wang et al., 1999). Cyanidin possesses a promising antiulcer activity by potentiating the defensive barriers of the gastrointestinal mucosa (Magistretti et al., 1988). Catechin is a flavan-3-ol, a type of natural phenol and antioxidant. It is a plant secondary metabolite. Catechin is present in cocoa. It is one of the major phenolic

compounds identified in peach. Catechin is also found in vinegar. Catechin a component of green tea is responsible for the renoprotection (Chennasamudram et al., 2012).Daidzein is found in food such as soybeans and soy products like tofu and textured vegetable protein. Soy isoflavones are a group of compounds found in and isolated from the soybean. Daidzein has cytoprotective properties in neurons, which are due to an increase in PPARγ activity (Hurtado et al., 2012).

MATERIALS AND METHODS

Important Databases Used

PDB (Protein Data Bank): Repository of atomic co-ordinates and three-dimensional structural data of important biological macromolecules, such as, proteins and nucleic acids, maintained in Rutgers and UCSD.

PubChem: Database of chemical molecules and their activities against biological assays, maintained by Nation Center for Biotechnology Information (NCBI) in Bethesda, Maryland.

Qsite finder: Q-SiteFinder is a new method of ligand binding site prediction. It works by binding hydrophobic (CH3) probes to the protein, and finding clusters of probes with the most favorable binding energy.

Software's used

Chemsketch:

It allows drawing of chemical structures including organics, organometallics, polymers, and Markush structures. It also includes features such as calculation of molecular properties and logP prediction.

Schrodinger:

Schrodinger software suite is drug design software using both ligand and structure-based methods. Schrödinger provides accurate, reliable, and high performance computational technology to solve real-world problems in life science research.

Three dimension structure of protein was obtained from protein data bank (Berman et al., 2000). Polyphenol structures were obtained from pubchem. The structures obtained were drawn in chemsketch software. Docking was performed using schrodinger software to find the interaction of polyphenols with insulin receptor tyrosine kinase.

RESULTS

The binding mode and interactions of the selected polyphenols were analyzed. The interactions with the protein, their binding energy, Glide score, hydrogen bond length are given in Table 2.Among the selected polyphenols cyanidin was found to have the best glide score with glide energy -41.199 kcal/mol. Cyanidin was found to interact with active site residues Glu 1108 and Asp 1143 by means of hydrogen bond. Myricetin was found to have four interactions with the active site residue Glu 1108, Phe 1144 and Asp 1143 with glide

energy -41.895. Quercetin was found to be interacted with the three residues of active site Asp 1143, Glu 1108 and His 1057. Catechin was seen with four interactions to the protein active site Asp 1143, His 1057, Glu 1108 and Phe 1144 with glide energy -40.528. Daidzein was found to have only one interaction with the residue Ser 1270 with the glide energy -26.5457.

DISCUSSION

Many plants have been traditionally used in the treatment of diabetes. Polyphenols contained in these plants have various therapeutic activities (Marles et al., 1995; Gray et al., 1997). In the present insilico study the interaction of polyphenols with insulin receptor tyrosine kinase have been analysed. This reveals that polyphenols act as potential activators of insulin receptor tyrosine kinase and they have an antidiabetic activity. These compounds can activate the kinase domain since the phosphorylated tyrosines are bound to the residues located in the activated loop of the protein. The field of molecular docking has emerged during last three decades and now is becoming the integral part in drug discovery and development area. The present study helped to identify the potent of polyphenols attributing to treatment of diabetes. This result clearly demonstrates that the approach used in the study is successful in finding novel antidiabetic compounds from plants. Also, the study states and confirms the importance of small molecules from plants, their use in enhancing protein-ligand interaction studies, insilico and provide vital clues that can be used to design new molecules with improved activity(Sundararajan et al., 2010; Rohit et al., 2011). In the present study we propose that Polyphenols, which are widely, present in plants and herbs can be used as a drug for diabetes. Polyphenols from plant sources are easily available and has a greater effect without any side effects. Thus this study proves that polyphenols can be used as a therapeutic drug for diabetes.

CONCLUSION

The aim of the study was to find out the potent activator of Insulin Receptor. Docking results indicates that the selected polyphenols were found to interact with the functional residues of insulin receptor. Hence they can be considered as potent activators. As these polyphenols are present in various food products and other sources naturally, they can be taken orally either as a supplement or by consuming the food in which they are present and can be used as a remedy to cure diabetes mellitus when there is a deficiency of Insulin, as a substitute or replacement for Insulin. Further study can be carried out in the wet lab.

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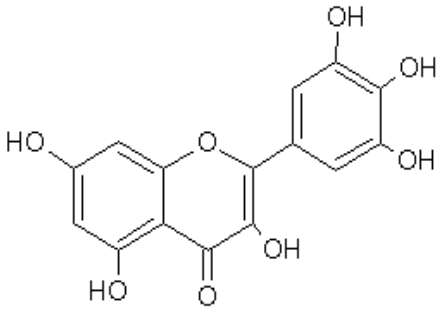
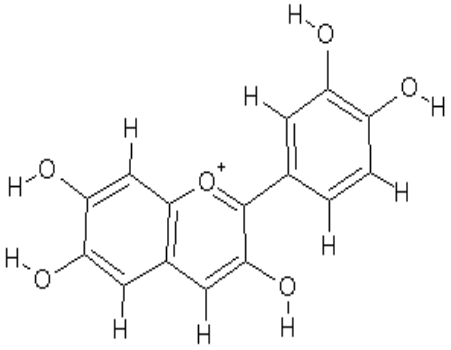
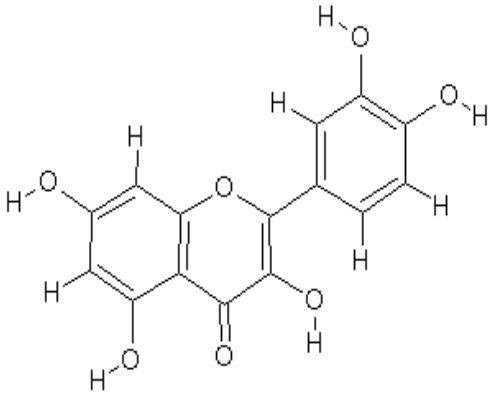
Myricetin



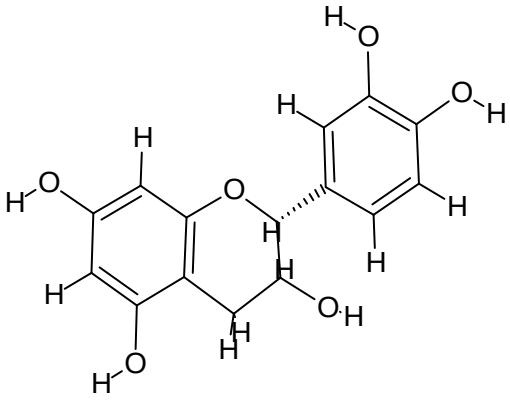
Cyanidine



Quercetin



Catechin



Daidzein

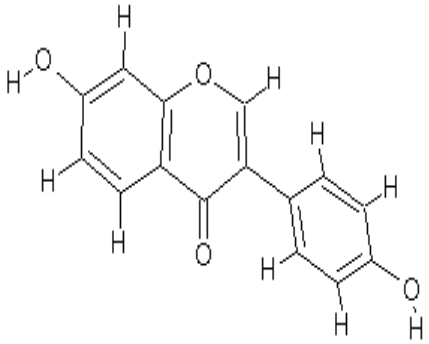


Table 2: Docking results with the Ligand name, Glide score, Glide energy, Hydrogen bond length and the interactions.

Ligand	G Score	G Energy Kcal/mol	H bond Length	Interaction (D-H...A)
Cyanidin	-7.568	-41.199	1.730	Cyan (H) .... (O) Asp 1143
			2.005	Cyan (H) .... (O) Glu 1108
			2.087	Cyan (H) .... (O) Glu 1108
Myricetin	-5.732	-41.895	1.796	Myr (H) .... (O) Glu 1108
			1.958	Myr (H) .... (O) Glu 1108
			2.084	Myr (H) .... (O) Phe 1144
			2.230	Myr (H) .... (O) Asp 1143
Quercetin	-5.617	-41.794	1.777	Quer (H) .... (O) Asp 1143
			2.461	Quer (H) .... (O) Glu 1108
			2.124	Quer (H) .... (O) His 1057
Catechin	-4.387	-40.528	1.643	Cate (H) .... (O) Asp 1143
			2.041	Cate (H) .... (O) His 1057
			2.371	Cate (H) .... (O) Glu 1108
			2.468	Cate (H) .... (O) Phe 1144
Daidzein	-4.262	-26.545	1.801	Diaz (H) .... (O) Ser 1270

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