Original Article

FENUGREEK TREATMENT OF POLYCYSTIC OVARIAN SYNDROME: AN IN-SILICO EVALUATION TO EXPLORE THE THERAPEUTIC EFFICACY OF QUERCETIN

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ABSTRACT

Background: Polycystic ovarian syndrome **(**PCOS) is a fairly common condition that affects both endocrine and metabolic systems. It affects women of reproductive age of all ethnicity and race. Only a small number of females are diagnosed with it. There is a good percentage of people who are still not diagnosed because of a lack of good diagnostic criteria and varying symptoms among different individuals. Fenugreek is an herb that contains many constituents including Quercetin. It helps in the regulation of steroidogenesis.

Material and Methods: Molecular docking of Quercetin with insulin receptor substrate 1, follicle-stimulating hormone receptor and androgen receptor was performed using Autodock4. The ADME (absorption, distribution, metabolism and excretion) properties were calculated by using smile notation in the Swiss ADME web-based tool. The Bioavailability Score was calculated using Mol-inspiration web-based tool.

Results: The study shows that Quercetin is having best binding capacity with the androgen receptor and also shows good binding affinity with FSH receptors and Insulin receptors. This indicates Quercetin can have a positive effect on PCOS.

Conclusion: We can conclude that Quercetin is helpful for the treatment of PCOS.

Key Words: Quercetin, Polycystic ovarian syndrome, Diabetes mellitus

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INTRODUCTION

Poly Cystic Ovarian Syndrome (PCOS), a major endocrinopathy, is a common condition that affects both the physical and emotional well-being of many women across the world. PCOS is characterized by increased androgen production and Insulin resistance along with increased insulin protection which can result in Type 2 Diabetes Mellitus.[1]

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PCOS is known to affect 2-20% of reproductive-aged females worldwide of all ethnicity and race. Increased level of androgens prevents the edition of progesterone from ovaries which is important for the maturation of eggs. As a result, numerous small cysts (fluid-filled sacs) form in the ovaries. PCOS is considered a syndrome because the signs and symptoms vary from woman to woman. The cause of PCOS is a combination of many factors including obesity and hormonal change but the exact cause of PCOS is still unknown.[2] PCOS is characterized by increased androgen production and Insulin resistance along with increased insulin protection which can result in Type 2 Diabetes Mellitus. Complications

of this syndrome include, infertility, insulin resistance, obesity, depression, increased risk of development of type 2 diabetes, hyper-triglyceridemia, gestational diabetes and metabolic syndrome. Obesity is associated with PCOS and can worsen the complications of this disorder. PCOS etiology is heterogeneous. It is caused by a combination of reproductive and metabolic disorders.[1]

Ovaries contain immature eggs stored in small fluid-filled follicles. FSH (Follicle stimulating hormone) and LH (Luteinizing hormone) are secreted by anterior pituitary gland that causes increase in size of follicle and maturation of eggs and secretion of estrogen. Once a certain level of estrogen is secreted, a Luteinizing hormone surge from the pituitary gland towards the ovaries causes ovulation. The left-out follicles and eggs dissolves and the egg travels in the fallopian tube where it awaits fertilization, If the egg fails to fertilize then the endometrium of uterus sheds causing menstruation and cycle the repeats.[3] In PCOS, normal menstrual cycle is disturbed as pituitary gland releases excess amount of Luteinizing hormone. Hence follicle doesn't mature, and ovulation doesn't occur leading to anovulation. The follicle that didn't mature persists as fluid filled sacs or cysts. These cysts secrete increased amount of testosterone causing an-ovulation and hence infertility.[2]

Treatment of PCOS is still a challenge. Over the past few years, the use of natural products to treat diseases has become common, for the treatment of PCOS, fenugreek is one of them. Fenugreek (Trigonella foenum-graceum L.) is known to treat Diabetes mellitus. Constituent of Fenugreek that is important with respect to treatment of PCOS is Quercetin. Quercetin has antioxidant and anti-inflammatory roles.[4] Much research has been conducted on Quercetin and its benefits. Quercetin decreases insulin resistance.[5] Quercetin exerted protective effect against PCOS in the rat model by enhancing levels of antioxidant enzymes, also helps in the prevention of weight gain and causes significant decline in serum glucose level.[6,7] This study was aimed to evaluate the activity of phytochemicals of the herbal substance Fenugreek on Androgen Receptors (AR), Follicle Stimulating Hormone Receptors (FSHR) and Insulin Receptor (IR).

MATERIAL AND METHODS

This In-silico study was conducted in CMH Lahore Medical College between March 2022 to June 2022. The three-dimensional crystal structure of insulin receptor substrate 1(IRS 1), follicle stimulating hormone (FSH) receptor and androgen receptor (PDB ID 1IRS, 1XUN & 1E3G) was downloaded from the RCSB Protein Data Bank.

The chemical structure of the ligands was obtained from PubChem compound database. It was prepared by Chem-Bio Draw and MOL SDF format of this ligand was converted to PDBQT file using PyRx tool to generate atomic coordinates.

Molecular docking of Quercetin with insulin receptors substrate 1, follicle stimulating hormone receptors and androgen receptors were performed using Autodock4. The 3D structure of androgen receptor, insulin receptors substrate 1(IRS 1) and follicle stimulating hormone (FSH) receptor (PDB ID 1E3G, 1IRS & 1XUN) were acquired from RCSB (Research Collaborator for Structural Bioinformatics).

The ADME (absorption, distribution, metabolism and excretion) properties were calculated by using smile notation in Swiss ADME web-based tool.[8]

Molecular docking is used to recognize and optimize drug candidates by examining and modelling molecular interactions between ligand and target macromolecules. Molecular docking is used to generate multiple ligand conformations and orientations and the most appropriate ones are selected.[9]

RESULTS

Using computer-based methods like ADMET tools the molecular descriptors and drug likeliness properties was studied. Annexure I give the pharmacokinetic properties of the drug Quercetin.

The docking score of the compound shows good binding affinities with the given

receptors. The docking score of Quercetin with the three receptors are shown in the table 1.

Table 1. Results of Molecular Docking of Quercetin

Receptor	Binding Energy kCal/mol
Androgen receptors	-13.82 (KI = 74.69pM)
Follicle Stimulating Hormone receptors	-5.96 (kI = 42.64uM)
Insulin Receptors	-3.33 (kI = 3.62mM)

Figures 1, 2 and 3 illustrate the interactions of Quercetin with the given receptors.

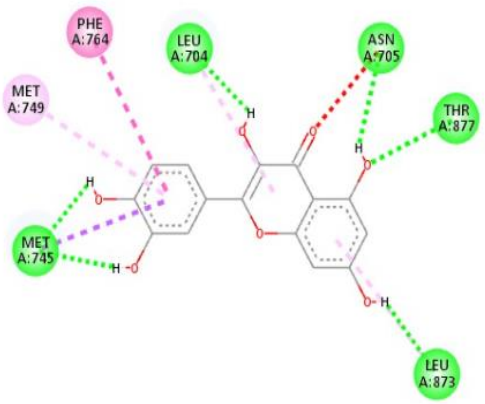

Figure-1: Interaction of Quercetin with Androgen Receptors (Note 6 hydrogen bonds in Green)

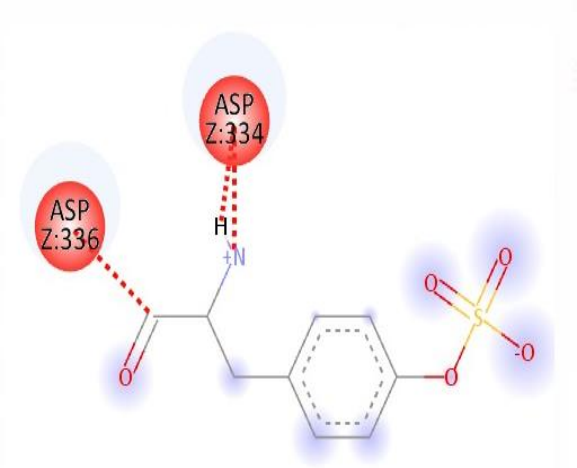

Figure-2: Interaction of Quercetin with FSH Receptor

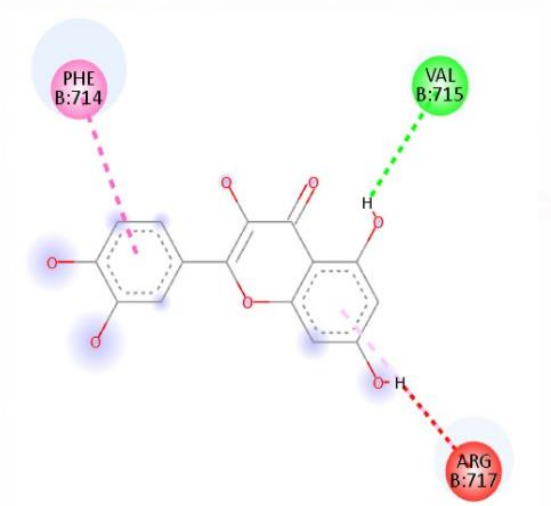

Figure-3: Interaction of Quercetin with Insulin Receptor

DISCUSSION

PCOS can cause insulin resistance in 50-70% cases, dyslipidemia in 70% cases and is associated with metabolize disorder/ syndrome. As technology is progressing, many new protein targets are being discovered which results in a need for processing systems that can identify and analyze active sites and put forth drugs that can react with active sites. Docking is such a processing system that determines the binding affinity among molecules. If we are given a ligand and a protein, we can analyze their binding affinity by docking them. Swiss ADME web tools are used to determine molecular weight (MW), molecular refractivity (MR), polar surface area and count of specific atom types. Annexure I explains that Quercetin has 1 rotatable bond and 7 H-bond acceptors. Lipophilicity is described by partition coefficient between n octanol and water (log Po/w). Lipophilic character of the drug and predictive models were determined by Swiss ADME. The predictive models are; WLOGP has its basis on fragmental system of Wildman and Crippen, it is an atomistic method; XLOGP3 constitutes corrective factor and knowledge-based library, it is an atomistic method; iLOGP based on free energy of solvation in n-octanol and water determined by GB/SA (Generalized-Born

and solvent accessible surface area), it is a physics based method .Two drugs or drugs like external sets were cross reacted with iLOGP; MLOGP based on relationship with 13 molecular descriptors, it is a topological method; SILICOS-IT based on 27 fragments and 7 topological descriptors, it is a hybrid method. Lipophilicity of Quercetin is shown in Annexure I.

Formulation and handling of a drug is made easy by a soluble compound. Also, soluble compound facilitates absorption for oral administration, parenteral administration also requires high solubility to provide appropriate quantity of active ingredient in small volume. Swiss ADME constitutes a couple of topological methods to predict solubility. Annexure I defics that quercetin is soluble in all areas. To analyze active transport through biological membrane e.g., from GIT wall to lumen requires information if the compound is a substrate or not a substrate of permeability glycoprotein (most significant member among ABC transporter or ATP binding cassette transporter as P-gp suggested). Examination if a chemical can be a substrate of P-gp or important CYP isoenzymes inhibitors is done by Swiss ADME. Annexure I makes it clear that Quercetin is not a P-gp substrate. Swiss ADME provides five rule-based filters with wide range of properties which can determine if a molecule is drug like or not. The pioneer is the Lipinski (Pfizer) filter the other four rules are Ghose (Amgen), Veber (GSK), Egan (Pharmacia) and Muegge (Bayer). Output panel explains any violation of any rule.

Quercetin shows no violation of the rules mentioned above and its bioavailability score is 0.55. Significant aspect of structural based drug designing is estimating the binding affinity among a small molecule docked on a binding site of a receptor. Drug discovery, virtual screening, molecular docking, offering multicore capability, high performance and enhanced accuracy and ease to use are the properties provided by an open-source program AutoDock Vina. If structure of ligand-protein is known, then the docking tool's ability to remake the binding mode of protein and a ligand is analyzed by the parameters chosen for docking. Table 1 shows that Quercetin and androgen receptors have the best docking abilities. Quercetin also has binding affinity with FSH receptors and IRS1 receptors. These findings support the results of previous studies which suggest the protective role of Quercetin against PCOS.[10-15] Our study provides a probable mechanism of functioning of quercetin in the protection of insulin resistance in PCOS.

CONCLUSION

Computational tools may be helpful in finding the cause of this syndrome. Nowadays PCOS has become a major issue, that's why we are in a dire need for effective and efficient treatment. Quercetin helps in regulation of steroidogenesis. The study shows that Quercetin is having best binding capacity with the androgen receptors and also shows good binding affinity with FSH receptors and Insulin Receptor this indicates Quercetin can have positive effect on PCOS. Thus, we can infer that Quercetin might be helpful for the treatment of PCOS. Further studies and trials are required to assess its actions.

Conflict of Interest

The authors declare no conflict of interest.

Funding

None to declare

AUTHOR'S CONTRIBUTION

IB: Conception of the idea, devising the methodology and data analysis
MZ: Article writing, referencing and rephrasing
AM: Article writing and referencing
BM: Article writing and data collection
AM: Article writing and referencing
HI Article writing and referencing
FI: Devised the methodology and overall supervision
RKA: Devised the methodology and overall supervision

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Annexure I: Pharmacokinetic Properties of Quercetin

1. Physicochemical Properties of Quercetin	
Molecular Formula	$C_{15}H_{10}O_7$
Molecular weight	302.24 g/mol
Num. heavy atoms	22
Num. aromatic heavy atoms	16
Num. rotatable bonds	1
Num. H-bond acceptors	7
Num. H-bond donors	5
Molar Refractivity	78.03
Topological Polar Surface Area (TPSA)	131.36 Å²
2. Lipophilicity of Quercetin	
Log Po/w (iLOGP)	1.63
Log Po/w (XLOGP3)	1.54
Log Po/w (WLOGP)	1.99
Log Po/w (MLOGP)	-0.56
Consensus Log Po/w	1.23
3. Water Solubility of Quercetin	
Log S (ESOL)	-3.16
Solubility	2.11e-01 mg/ml ; 6.98e-04 mol/l
Class	Soluble
4. Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-glycoprotein substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	Yes
CYP3A4 inhibitor	Yes
Log Kp (skin permeation)	-7.05 cm/s
5. Drug Likeness of Quercetin	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
6. Bioavailability Scores of Quercetin	
GPCR ligand	-0.06
Ion channel modulator	-0.19
Kinase inhibitor	0.28
Nuclear receptor ligand	0.36
Protease inhibitor	-0.25
Enzyme inhibitor	0.28