Available online www.jocpr.com

Journal of Chemical and Pharmaceutical Research, 2014, 6(9):278-281

Research Article

ISSN : 0975-7384
CODEN(USA) : JCPRC5

Computational studies on the antiobesity effect of polyphenols from pomegranate leaf

Sudeep H. V.* and Shyam Prasad K.

Department of Biomedicinal Research, Vidya Herbs Pvt. Ltd, #101, Jigani II phase, Bangalore, Karnataka, India

---

ABSTRACT

Different polyphenols present in Pomegranate leaves were docked into validated drug targets of obesity which include enzymes pancreatic lipase and fat mass and obesity associated protein (FTO). The in silico calculations predicted that lowest energy docked poses of phenolic compounds can interact with catalysis-dependent residues, thus making them possible catalytic inhibitors and of course physiologically active. Compounds that possess a number of hydrogen-bond-accepting and/or -donating groups like phenolics and quinones show extensive interactions with the targets. Based on the ligand-protein interaction we can conclude that phenolic principles like Punicalagin, corilagin, punicalin and apigenin thus offer profound promise as anti-obesity drugs. This study has immediate applications in development of non-toxic drugs/nutraceuticals that may safeguard human populations against severe complications associated with obesity.

Key words: Docking, Obesity, Pomegranate, Polyphenols

INTRODUCTION

Weight gain and obesity are major risk factors for the health complications ranging from insulin resistance and type 2 diabetes mellitus to atherosclerosis and the sequelae of nonalcoholic fatty liver disease[1]. Physiologically, obesity is a disarray of energy balance and primarily considered as a disorder of lipid metabolism[2]. The condition is associated with a growing number of enzymes involved in lipid metabolic pathways. They represent a rich pool of potential therapeutic targets for obesity[3][4].

Pancreatic lipase is a key enzyme involved in obesity responsible, in conjunction with a pancreatic colipase, for the breakdown of dietary triglcerides into the absorbable fatty acids and monoglycerides. Orlistat is anti-obesity drug that binds to the active site of lipase and inhibit its activity. The complex induces a conformational change in the enzyme that leads to a lid-like structure on the lipase, hence exposing the catalytic active site. This operation leads to acylation of a hydroxyl group on serine residue burden on the active site of the enzyme making it inactive as lipase. The inactivated lipase is unable to hydrolyse fats into fatty acids and monoglycerides, which lead to their passage with faeces. This inhibition decrease the absorption of fats by >30 % [5].

Fat mass and obesity associated protein also known as alpha-ketoglutarate-dependent dioxygenase (FTO) is another enzyme that appears to be correlated with obesity in humans [6]. FTO contributes to the regulation of the global metabolic rate, energy expenditure and energy homeostasis. FTO contributes to the regulation of body size and body fat accumulation.

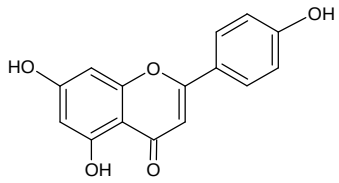
Pomegranate (*Punica granatum* L.) is a shrub cultivated in India, Mediterranian countries, Malaysia, tropical Africa and to some extent in United States [7]. The plant has been valued since ancient times to treat many conditions such as diarrhea, dysentery, hemorrhage, parasitic infections, ulcers and microbial infections [8]. Pomegranate is a rich source of polyphenols and possesses an array of compounds that have been attributed to the pharmacological

activities such as anti-tumor, astringent and antidiarrheal activities. The present research carried out at Vidya Herbs Pvt Ltd encompasses the evaluation of therapeutic potentials of phenolic compounds from *P. granatum* leaves by *in silico* molecular docking with key regulatory enzymes involved in lipid metabolism viz., pancreatic lipase and FTO.

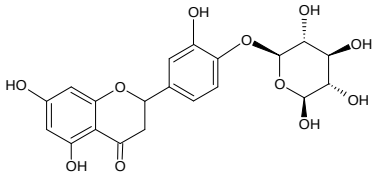
EXPERIMENTAL SECTION

AutoDock tools was utilized to generate grids, calculate dock score and evaluate the conformers of inhibitors bound in the active site of enzymes pancreatic lipase and FTO as targets for antiobesity activity. Automated docking is a graphical user interface. AutoDock 4.2 was employed to get docking and binding scores; which is implemented by Lamarckian genetic algorithm method. The ligand molecules i.e., the phenolic compounds from pomegranate leaf (Figure 1) and standard drug Orlistat were designed and the structure was analyzed using ACD/Chemsketch. The PRODRG server was used to minimise energy of drug compounds and 3D coordinates were prepared. The protein structure files (PDB ID: 1LPB and 3LFM) were taken from PDB and edited by removing the hetero atoms using Python molecule viewer. The grid map was centred at particular residues of the protein and was generated with AutoGrid. As per genetic algorithm all the torsions were allowed to rotate during docking. The Lamarckian genetic algorithm and the pseudo-Solis and Wets methods were applied for minimization, using default parameters [9].

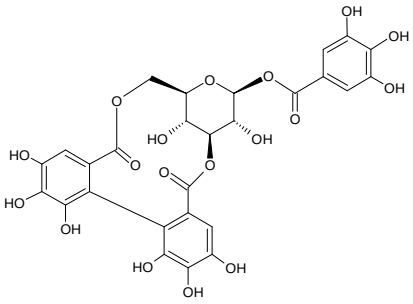
Figure 1. Structures of docked polyphenols discussed in this work



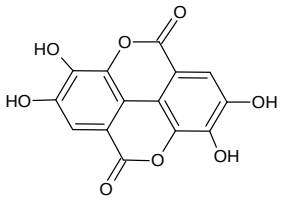
Apigenin



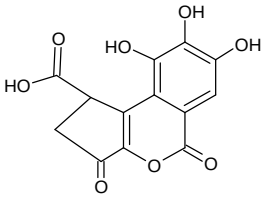
Luteolin 4-O-glucopyranoside



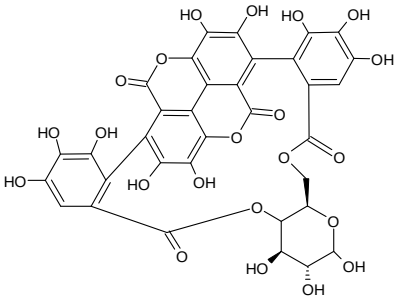
Corilagin



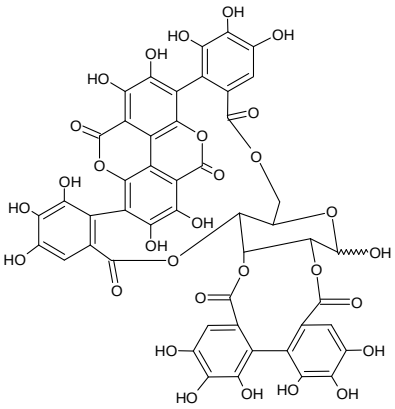
Ellagic acid



Brevifolin carboxylic acid



Punicalin



Punicalagin

RESULTS AND DISCUSSION

Extracts of pomegranate leaves have been previously documented to possess anti-obesity activity [10]. Phytochemically it is a rich source of polyphenols. Further it is well known that flavanoids and tannins are major

group of secondary metabolites in plant kingdom and attribute to the medicinal claims of the plants [11][12]. This work presents the molecular docking of polyphenols from pomegranate leaves with the key metabolic enzymes responsible for obesity with a view of obtaining structural motifs that preferentially interact with these molecules. The docking results revealed compounds with more favorable interactions with the targets and also indicated that some of the compounds present certain structural motifs that could make them form extensive Van der Waals interactions and hydrogen bonding with targets. After comparative docking analysis it was learnt that punicalagin and corilagin showed better inhibition of enzymes in comparison to other compounds.

All the test compounds showed favourable interactions with pancreatic lipase better than the standard drug orlistat (Table 1). Extensive interactions were observed between punicalagin and Asn residues 229, 384, Arg residues 337, 339, Asp 387 and Tyr369 residues of pancreatic lipase with a value of -11.85 and seven hydrogen bonds (Figure 2). The orientation of polyphenols in the catalytic site of FTO indicated profound interaction in the form of protein-ligand hydrogen bond formation (Table 2). Among the tested molecules, corilagin exhibited top pose with low binding energy (-9.44 kJmol^{-1}) and forming nine hydrogen bonds with active pocket residues; Asp467, Gln468, Arg80, Pro93, Ser95 and Ala466 (Figure 3).

Figure 2. (A) Predicted hydrogen bonding interactions (green spheres) can be seen between punicalagin and active residues of pancreatic lipase (B) Binding of Punicalagin with active pocket of Pancreatic lipase

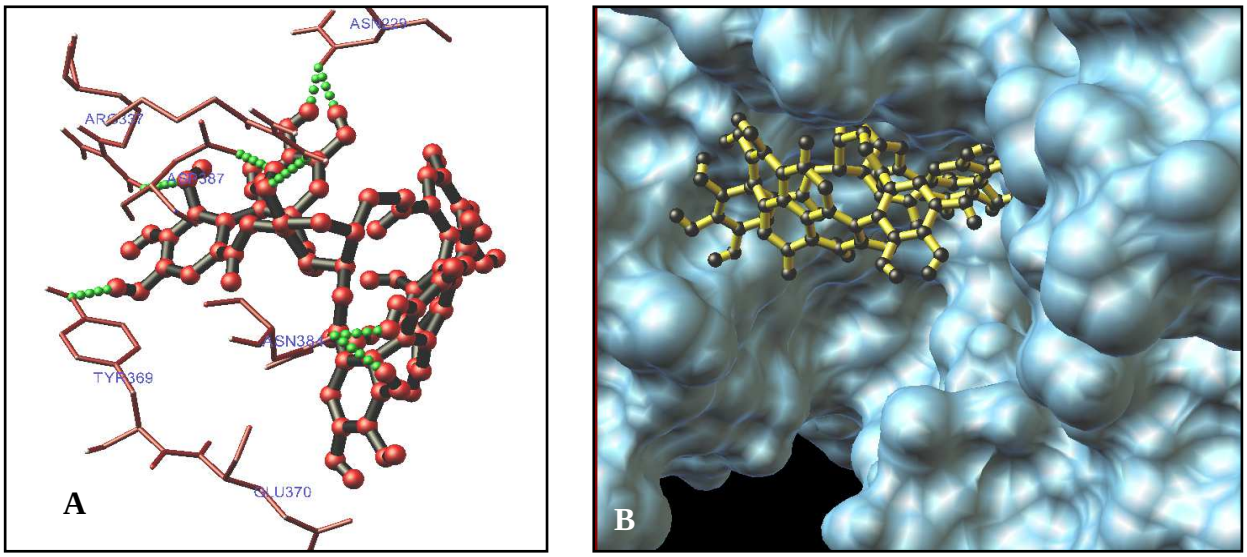


Figure 3. (A) Some predicted interactions (blue spheres) between Corilagin (green and white) and active site residues Asp467, Gln468, Arg80, Pro93, Ser95, Ala466 of FTO; (B) Corilagin in the active site of FTO

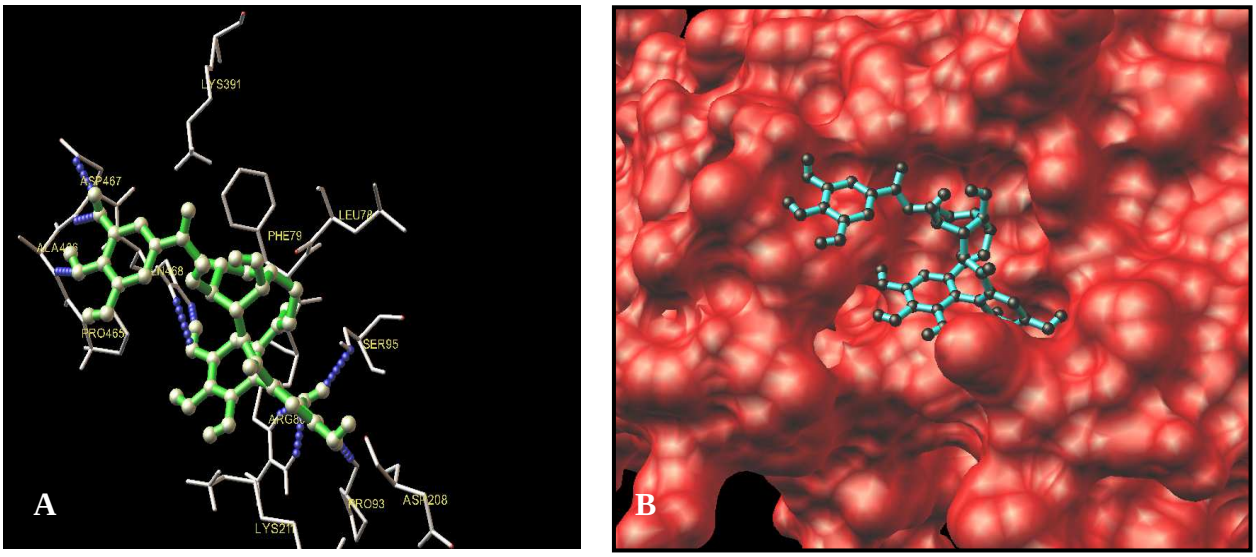


Table1. *In silico* docking score of polyphenols from *P. granatum* leaf and Orlistat with Pancreatic lipase

Molecule	Binding Energy (kJ/mol)	Ligand Efficiency (kJ/mol)	Inhibitory constant (µM)	H-Bond	Interaction
Punicalagin	-11.85	-0.15	2.06	7	Asn384, Tyr369,Arg337, Asn229, Asp387, Arg339
Ellagic acid	-7.07	-0.32	6.59	5	Glu370, Arg339, Asp387, Asn384
Corilagin	-7.81	-0.17	1.9	6	Asn229, Lys238, Glu15, Cys237, Asn10
Brevifolin COOH	-6.44	-0.31	19	5	Glu370, Asn384, Asp387, Arg339
Punicalin	-8.2	-0.15	971.98	7	Asp387, Asp328, Glu13, Glu370, Arg339
Eapigenin	-7.11	-0.36	6.13	5	Arg44,Cys39, Glu48
Luteolin 4-O-glucopyranoside	-8.18	-0.26	1.01	4	Gln368,Asn384, Asp328,Thr292
Orlistat (Std)	-1.03	-0.03	176.96	2	Lys238

Table 2. *In silico* docking score of polyphenols from *P. granatum* leaf and Orlistat with FTO

Molecule	Binding Energy (kJ/mol)	Ligand Efficiency (kJ/mol)	Inhibitory constant (µM)	H-Bond	Interaction
Punicalagin	-8.63	-0.11	469.14	4	Gln468, Asp208, Lys391, Ser95
Ellagic acid	-7.21	-0.33	5.18	4	Asp208, His73, Arg80, Pro93
Corilagin	**-9.44**	**-0.21**	**119.39**	**9**	**Asp467, Gln468, Arg80, Pro93, Ser95, Ala466**
Brevifolin COOH	-6.52	-0.31	16.63	3	Arg80, Ser95
Punicalin	-7.97	-0.14	1.44	4	Arg80, Ser95, Pro95
Apigenin	-8.54	-0.43	555.9	4	Pro93, Leu78, His73, Ser95
Luteolin 4-O-glucopyranoside	-10.41	-0.34	23.2	5	Asp208, Arg80, Pro93, Ser95
Orlistat (Std)	-4.65	-0.14	390.87	3	Arg80, Ser95

CONCLUSION

Inhibitor selectivity remains an important issue when being considered for chemotherapy. Nevertheless, many pharmacologically active natural polyphenols can contribute as drugs against complications such as obesity and diabetes, structural differences are now being exploited in drug designing. The docking calculations in this study revealed that most of the phenolic and quinone compounds with top poses are strong inhibitors of pancreatic lipase rather than FTO. Although these compounds have been shown to have inhibitory action against the tested enzymes, target-based experimental screening of the compounds will provide information about selectivity and mechanism of action.

REFERENCES

[1] SE Shoelson; L Herrero; A Naaz, *Gastroenterology*., **2007**, 132(6), 2169-80.
[2] CD Strader; JJ Hwa; M Van Heek; EM Parker, *Drug Discovery Today*., **1998**, 3, 250–256.
[3] Y Shi; P Burn, *Nature Reviews Drug Discovery*., **2004**, 3, 695–710.
[4] I Melnikova; D Wages, *Nature Reviews Drug Discovery*., **2006**, 5, 369–370.
[5] PA Hollander; SC Elbein; IB Hirsch; B Kelly; J McGill; T Taylor, *Diabet Care*., **1998**, 21, 1288-301.
[6] TM Frayling; NJ Timpson; MN Weedon; E Zeggini; RM Freathy; CM Lindgren; JR Perry; KS Elliott; H Lango; NW Rayner; B Shields; LW Harries; JC Barrett; S Ellard; CJ Groves; B Knight; AM Patch; AR Ness; S Ebrahim; DA Lawlor; SM Ring; Y Ben-Shlomo; MR Jarvelin; U Sovio; AJ Bennett; D Melzer; L Ferrucci; RJ Loos; I Barroso; NJ Wareham; F Karpe; KR Owen; LR Cardon; M Walker; GA Hitman; CN Palmer; AS Doney; AD Morris; GD Smith; AT Hattersley; MI McCarthy, *Sci*., **2007**, 316(5826), 889–94.
[7] M Viuda-Martos; J Fern_andez-L_opez; JA Perez-Alvarez, *Compr Rev Food Sci Food Saf*., **2010**, 9, 635–54.
[8] YG Lihua Zhang; Y Zhang; J Liu; J Yu, *Sci Horticult*., **2010**, 123, 543–6.
[9] A Rodriguez; D Infante, Characterization *in silico* of flavonoids biosynthesis in Theobroma cacao L. *Net Biol*., **2011**, 1, 34-45.
[10] IK Adnyana; EY Sukandar; Ari Yuniarto; S Finna, *Int J Pharm Pharmaceut Sci*., **2014**, 6(4), 626-631.
[11] V Koleckar; K Kubikova; Z Rehakova; K Kuca; D Jun; L Jahodar; L Opletal, *Med Chem*., **2008**, 8, 436-447.
[12] T Hirano; M Gotoh; K Oka, *Life sci*., **1994**, 55, 1065-1069.