Journal of Applied Pharmaceutical Science Vol. 5 (12), pp. 042-047, December, 2015
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2015.501207
ISSN 2231-3354

In silico investigation of black tea components on α-amylase, α-glucosidase and lipase

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ARTICLE INFO

Article history:
Received on: 14/06/2015
Revised on: 22/08/2015
Accepted on: 11/09/2015
Available online: 27/12/2015

Key words:
Blacktea, Diabetes, Obesity, Molecular Docking, PreADMET.

ABSTRACT

Black tea is one of the most widely consumed beverages in the world and traditionally known for its antidiabetic and antiobesity property. However, the underlying mechanisms of these properties are not studied widely. In this work, we hypothesize that the reason could be because of the inhibition of gut enzymes by the tea derived phytochemicals. Molecular docking was used to explore the efficacy of tea components to inhibit the key enzymes related with Type II diabetes and obesity; α-glucosidase, α-amylase and lipase. Autodock4.2 molecular docking software that applies Lamarckian Genetic Algorithm was used. The ligand structures were retrieved from PubChem and KNApSAcK-3D database. PreADMET web server was used for Toxicity and ADME predictions. Based on this analysis, it has been found that 8-c-ascorbyl-(-)-epigallocatechin, rutin and orientin could be the putative molecules for amelioration of post-prandial hyperglycaemia whereas 8-c-ascorbyl-(-)-epigallocatechin,8-c-ascorbyl epigallocatechin 3-o-gallate and schaftoside could be used to reduce fat absorption in obese persons. It can be concluded that these phytochemicals or their derivatives can be used for further in-vitro and in-vivo studies to design valuable drugs.

INTRODUCTION

Obesity and Diabetes mellitus have become an ever-growing pandemic affecting millions of people worldwide. Type II diabetes (non-insulin dependent diabetes) occurs in genetically susceptible individuals and is favored by obesity (Zhao, 2006). Obesity has increased at an alarming rate in recent years(Hossain *et al.*, 2007). Decreasing the absorption of dietary energy molecules such as fats and carbohydrates can reduce these metabolism related disorders. This can be achieved by inhibiting the enzymes that are responsible for metabolism of carbohydrates and lipids, which mainly include α-amylase, α-glucosidase and pancreatic lipase(Puls *et al.*, 1977). Commercially available drugs like acarbose, miglitol, voglibose and orlistat are known to have inhibitory effect on these enzymes (Bischoff *et al.*, 1985). However, the use of these drugs has imparted side effects such as abdominal distention and pain, flatulence, yellow eyes and diarrhoea (Gardner *et al.*, 2007). Currently, plant-based medicines have gained importance in the prevention and cure of obesity and diabetes with fewer side effects (McKay & Blumberg, 2007). Tea, one of the most common ancient beverages is a rich source of phytochemicals (catechins, flavonols, theaflavin, thearubigins etc.) with many medicinal benefits. Several studies suggest that tea and its components possess various pharmacological effects such as anti-hypertensive, hypercholesterolemia (Kitani *et al.*, 2007) , reduced risk of cancer (Yang *et al.*, 2009), low risk of stroke and blood pressure (Liang *et al.*, 2009), prevention of dental cavities(Hamer, 2007), enhanced immune functions and inhibition of enzymes involved in diabetes and obesity *in-vitro* (Zheng *et al.*, 2005). Although tea has been known traditionally as anti-obese (Tsuneki *et al.*, 2004) and antidiabetic (Morris *et al.*, 1998), yet there has not been sufficient study to prove its mechanism.

In this study, *in-silico* docking of the enzymes such as α-amylase, α-glucosidase and pancreatic lipase were carried out with tea components to analyse their potency. The computational methodology, involving molecular docking analysis could be an easy gate-way for searching effective drugs of natural origin against these diseases.

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MATERIALS AND METHODS

Protein structure retrieval

The three-dimensional structures of the target enzymes were retrieved from Protein Data Bank (PDB) (http://www.rcsb.org/pdb/). The enzymes selected for targeting the diseases have been compiled in Table 1. Miscellaneous ligands and other heteroatoms such as water, ions, etc. were removed from the protein models for active site predictions and further docking studies using Argus Lab Software.

Table 1: Potential Drug targets with their respective target diseases.

Disease	Enzyme	Organism	PDB Id
Diabetes mellitus Type II	α –amylase	Homo sapiens	1HNY
Diabetes mellitus Type II	α -glucosidase	Homo sapiens	2QMJ
Obesity	Lipase	Homo sapiens	1LPB

Protein Active Site Predictions

The active sites of targeted enzymes were predicted by using CASTp calculations (Computed Atlas of Surface Topography of proteins). Among the predicted sites, the ones having catalytic amino acids were chosen for docking with the ligand. The catalytic amino acids of each protein were analysed using UniProt (http://www.uniprot.org/).

Ligand selection

After extensive literature search on the components of back tea, a database of 150 phytochemicals were created. The three dimensional structure of these phytochemicals were screened from KNApSAcK-3D, PubChem and ChemSpider databases. Ligand optimization and energy minimization was done using Argus lab software. The three-dimensional structures of standard inhibitors for all the proteins were retrieved from PubChem database and used as reference inhibitory molecules.

Molecular Properties and Drug likeness

The tea components were further examined for its drug likeness and molecular properties using FAF-Drug2 (http://mobyle.rpbs.univ-paris-diderot.fr/cgi-bin/portal.py?form= FAF-Drugs#forms::FAF-Drugs2) and PreADMET (http://preadmet.bmdrc.org/).

Molecular Docking

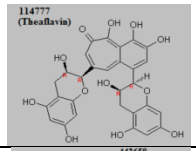
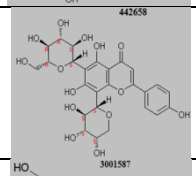
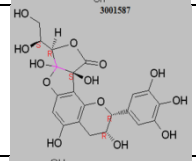
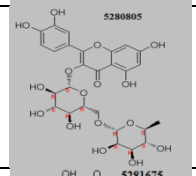
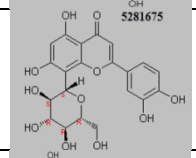
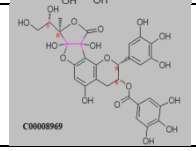
The computational docking of tea components and standard inhibitors was performed at the active site of corresponding protein models using AutoDock4.2 software (version 1.5.6). Lamarckian genetic algorithm (LGA) is used as a default search function in Auto Dock 4.2. LGA is a hybrid of genetic algorithm and local search algorithm that uses a parameterized free energy scoring function to estimate binding energy with standard docking protocol on the basis of a population size of 150 randomly placed individuals; a maximum number of 2.5*107 energy evaluations, a mutation rate of 0.02, a crossover rate of 0.80 and an elitism value of 1(Morris *et al.*, 1998). Fifteen independent docking runs were carried out for each ligand and results were clustered according to the 1.0 Å rmsd criteria. The grid maps representing the proteins were calculated using auto grid and grid size was set to 60*60*60 points with grid spacing of 0.375 Å. While docking, polar hydrogens were added to protein models using the hydrogens module and thereafter Kollman united atom partial charges were assigned. The coordinates of the docked protein along with the ligand were visualized using UCSF chimera and LigPlot+ (Goddard *et al.*, 2007). The softwares and methodology used in the study is similar to our earlier published works (Asthana *et al*., 2014; Asthana *et al*., 2015).

RESULTS AND DISCUSSION

Molecular Properties and Drug likeness

After analyzing the ADMET (Absorption, Distribution, Metabolism, Elimination, and Toxicity) properties, of all the 150 chosen compounds only 19 were found to be non-mutagenic and non-carcinogenic.

Table 2: Molecular Properties of six best selected ligands.

Ligand	Structure	Molecular weight	cLogP	Solubility (Log S)	Drug likeness	Drug score
Theaflavin (114777)		564	-1.88	-3.16	2	0.56
Schaftoside (442658)		564	-1.9	-1.81	-5.83	0.12
8-c-ascorbyl-(-)-epigallocatechin (3001587)		480	-0.75	-1.25	1.82	0.72
Rutin (5280805)		610	-0.95	-2.4	3.31	0.22
Orientin (5281675)		448	-0.24	-1.97	-0.71	0.32
8-c-ascorbyl epigallocatechin 3-o-gallate (C00008969)		646	-0.66	-2.05	-1.39	0.5

These 19 molecules were docked and in accordance with the results, 6 best molecules were selected for their higher affinity

as compared to others and were tested for their drug likeness as shown in Table 2. cLogP value is a measure of hydrophilicity of ligand molecule and high logP value is a result of low hydrophilicity because of poor permeation or absorption. For compounds to have a rational probability of being well absorbed their logP value must not be greater than 5.0 (http://www.organic-chemistry.org/prog/peo/). All the best selected ligands show value less than 5.0 and thus have good permeability. LogS value greater than -4.0 is a good indication of the aqueous solubility of the compounds necessary for its absorption and distribution which were found in our results. In drug likeness test, a positive value indicates that a molecule contains predominantly fragments commonly present in commercially available drugs, though a negative score does not necessarily mean that the molecule cannot be a potential drug. The drug score obtained from the combined outcome of drug likeness, cLogP, solubility, molecular weight and toxicity risks, is used to determine the molecule's overall probability for use as a drug.

Docking Analysis

In the study, oriented towards the design and development of effective drug against obesity and diabetes, we determined the best tea components that could serve as lead molecules for drug design.

Diabetes type II

Diabetes mellitus is a chronic metabolic disorder characterized by hyperglycaemia, and elevated blood sugar levels (Arana *et al.*, 2006). A therapeutic approach to treat diabetes mellitus is by inhibition of carbohydrate hydrolysing enzymes like α-amylase and α-glucosidase (Chhetri *et al.*, 2005).α-amylase breaks the carbohydrates into smaller clusters of saccharides and α-glucosidase acts on the 1,4-α-bonds of starch and disaccharides thereby breaking them down to glucose(Scheen, 2003). The inhibition of these enzymes can slow down the absorption of glucose from intestine, considerably decreasing the postprandial increase of blood glucose level after a rich carbohydrate diet and therefore is a vital strategy in the management of type II diabetes(Subramanian *et al.*, 2008).

Inhibition of α-amylase may not only alleviate diabetes mellitus. but also attenuates other problems such as dental caries and periodontal diseases(Sales *et al.*, 2012). Inhibition efficiencies of commercially available α-amylase and α-glucosidase inhibitors as standards were compared with that of test ligands by docking studies as tabulated in Table 3.

The inhibitory potential of the phytochemicals can be assessed by their binding energies (B.E). The estimated free binding energy of α-amylase with the standard inhibitor acarbose (Chen *et al.*, 2012) was found to be -5.04 kcal/mol. A comparison between the binding energy of the standard and the test molecules such as8-c-ascorbyl-(-)-epigallocatechin, rutin and theaflavin showed that they had better binding affinities with values-8.69,-8.58,-8.41 kcal/mol. The variation in binding energies of the test molecules may be attributed to the intermolecular interaction energy between the α-amylase and ligand molecule. The number of intermolecular interactions, namely hydrogen bonds, and hydrophobic interactions in the docked complexes were shown in Table 3. Since the binding affinity is higher, the inhibition constant (K_i) was relatively low with values of, 0.4289 0.5177and 0.6827 µm for 8-c-ascorbyl-(-)-epigallocatechin, rutin and theaflavin.

Similarly, the standard α-glucosidase inhibitors such as acarbose (Kim *et al.*, 2000), migiltol (Coniff and Krol, 1997) and voglibose (Mitrakou *et al.*, 1998) showed binding energy of +7.03, -6.82 and -9.26 kcal/mol respectively. The positive value of B.E. for acarbose indicates that it does not bind with α-glucosidase for inhibition. Comparing the docking results of test ligands with that of representative inhibitors it was found that orientin and 8-c-ascorbyl-(-)-epigallocatechin with B.E. -8.92 and -7.57 kcal/mol exhibited better inhibition affinity and molecular interaction on the target protein. The K_i values of the selected test ligands were found to be 0.29 and 2.8 µm for orientin and 8-c-ascorbyl-(-)-epigallocatechin respectively, in opposition to K_i values of standard, viz. 9.98 µm for migiltol and 0.1634 µm for voglibose.

Obesity

Obesity is a multifactorial disease characterized by an excessive weight to height proportion owing to enlarged fat deposition that is attributed to a higher calorie intake as compared to the energy expenditure. Pancreatic lipase (PL) plays a key role in the efficient digestion of dietary fats by hydrolysing them into mono-acylglycerol and fatty acids, thus minimising the intestinal absorption of triglycerides (Birari & Bhutani, 2007). This enzyme has been widely used for determination of the potential efficacy of natural products as anti-obesity agents (Sugiyama *et al.*, 2007).
Orlistat, the saturated derivative of lipstatin is the only Food & Drug Association (FDA) approved anti-obesity drug that has been shown to act through the inhibition of pancreatic lipase(McClendon *et al.*, 2009). In this work, orlistat was considered as a standard inhibitor and docked with PL. When docked in the SER-HIS-GLU catalytic pocket, the result shows a binding energy value of -5.9 kcal/mol andK_i value of 47.38 µm (Table 3). The docking studies for nominated test ligands reveals that their free binding energy varies from -3.65 to -10.14 kcal/mol while 8-c-ascorbyl-(-)-epigallocatechin, 8-c-ascorbyl epigallocatechin 3-o-gallate and schaftoside show best binding affinity with values -8.91, -10.14 and -9.78 kcal/mol respectively. Accordingly, the inhibition constant values 0.296, 0.0371 and 0.068 µm respectively are very less in comparison to the standard inhibitory drug orlistat (Table 3). Lower binding energy of the ligands indicates better inhibition affinity and thuslowK_i value. From the docking analysis it is observed that theaflavin, 8-c-ascorbyl (-)-epigallocatechin, rutin and orientin could be used for the inhibition of type II diabetes. Comparing the molecular properties tabulated in Table 2 it was observed that rutin has a better solubility, permeability and drug likeness than the others four ligands but has a low overall drug score that may be due to high molecular weight (M.W.). Optimization of compounds for

Table 3: Comparative analysis of Binding Interactions of standard inhibitors and selected test ligands – Docking and Chimera Analysis.

Enzyme	Name of test Inhibitors	Binding Energy (kcal/mol)	IC (µm)	Hydrogen Bonds	Interacting Amino acid
α-amylase (1HNY)	8-c-ascorbyl(-)-epigallocatechin	-8.69	0.4289	6	HIS201, GLU233, ASP197, ARG195, Intramolecular
	Rutin	-8.58	0.5177	6	GLU233, HIS305, HIS201, LYS200, TRP59
	Theaflavin	-8.41	0.6827	5	ASP300, LYS200, HIS201, THR163
	Acarbose *	-5.04	202.91	8	ASP300, THR163, TYR151, GLY306, ALA307, Intramolecular
α-glucosidase (2QMJ)	Orientin	-8.92	0.2898	5	GLN603, ASP327
	8-c-ascorbyl(-)-epigallocatechin	-7.57	2.8	7	ASP203, ASP327, TYR605, GLY604, Intramolecular
	Acarbose**	+7.03	-	-	-
	Miglitol**	-6.82	9.98	6	ASP327, ASP542, Intramolecular
	Voglibose**	-9.26	0.1634	3	ASP203, ARG526, Intramolecular
Lipase (1LPB)	8-c-ascorbyl epigallocatechin 3-o-gallate	-10.14	0.0371	5	SER237, HIS236, GLY161, ASP164
	Schaftoside	-9.78	0.0677	6	ASP164, SER137, ILE163, Intramolecular
	8-c-ascorbyl(-)-epigallocatechin	-8.91	0.2956	4	ASP164, HIS348, Intramolecular
	Orlistat***	-5.9	47.38	1	SER237

Standard inhibitor of α-amylase, **Standard inhibitors of α-glucosidase, * Standard inhibitor of pancreatic lipase*

Table 4: Molecular Interactions of LigPlot$^+$ Analysis.

Protein	Ligand	Amino acid interaction via	
		Hydrogen bond	**Hydrophobic interaction**
α-amylase (1HNY)	Theaflavin	HIS201, ASP300, HIS299, THR163, LYS200	TYR62, TRP58, TYR151, ILE235, LEU162, ASP19, GLU233
	8-c-ascorbyl-(-)-epigallocatechin)	HIS305, GLU233, ASP195, ASP356	TYR62, TRP58, TYR151, ILE235, LEU162, LYS200, HIS201, TRP59, ASP300, HIS299.
	Rutin	GLU233 (2), HIS201, LYS200, HIS305, TRP59, ASP356	TYR62, TRP58,TYR151,ILE235,LEU162, ASP19,GLU63, ALA198, GLY306
Pancreatic Lipase (1LPB)	Schaftoside	ARG341, PHE162, SER237	PHE300, ILE163, LEU349, ALA345, ALA344, TYR199, HIS348, GLY161,ALA263,ILE294,ASP164
	8-c-ascorbyl-(-)-epigallocatechin	HIS348, HIS236, ASP261, ASP64	PHE300, ILE163, ALA345, ALA344, PHE162, GLY161, ARG341,SER237
	8-c-ascorbyl epigallocatechin 3-o-gallate	SER237, HIS236, ASP164, ARG341	PHE300, ILE163, LEU349, PHE162, HIS348, TYR199, PRO265, LEU298
α-glucosidase (2QMJ)	8-c-ascorbyl-(-)-epigallocatechin	ASP327, GLN603, ASP203, MET144	TYR605, TRP406, ILE364, TRP441, ASP542, ASP443,TYR299, PHE575, TRP539, ARG526, HIS600,
	Orientin	GLN603, ASP327	TYR605,TRP406,ILE364, TRP441, ASP542, ASP443, TYR299, PHE575, PHE450, MET444, ASP203, ALA576, GLY602

their activity on a biological target often increases with the M.W. On the other hand, though orientin has an appropriate M.W., solubility and permeability; its overall drug score is low due to the fact that it has a low drug likeness value. Hence, considering all the properties 8-c-ascorbyl (-)-epigallocatechin was found to be the best molecule with drug score of 0.72 preceding 8-c-ascorbyl epigallocatechin with drug score 0.5 and hence can be used for anti-obesity drug formulation.

Interaction study

The inhibitory activities of the test ligands against the target enzymes like pancreatic lipase, α-amylase and α-glucosidase were poorly revealed by docking studies and thus, only the binding affinity of the ligands is not sufficient to describe the enzyme-ligand complex stability. Hence, molecular interactions such as H-bond & hydrophobic interaction of ligands were studied using UCSF chimera and Ligplot+. Only the best pose of each nominated potential molecules were considered as presented in Table 4. For each ligand molecule a Ligplot+ figure gives a schematic depiction of the hydrogen bonds and non-bonded interactions between it and the residues of the protein with which it interacts. The binding affinity will be higher if the ability of ligands to form hydrophobic interactions with the binding site hydrophobic amino acids is higher. Fig.1 shows the result of interaction study. The left side figure show the UCSF chimera post-docking analysis, the green colored molecule represent ligand and yellow colored ones are the neighboring amino acids in 5 Å region that are interacting with ligand.

The right side figures depicted the Ligplot+ result. In the LigPlot result; green dotted line represents the H-bond of the ligand with the amino acid of the protein represented in green. Red spikes on the arcs show the hydrophobic interaction with the amino acids presented in black. It can be seen that the ligand molecules are surrounded by very hydrophobic amino acids with more than seven hydrophobic interactions for each selected ligand. For α-amylase, we can see that TYR62, TRP58, TYR151, ILE235, LEU162 and ASP19 form hydrophobic interaction with all the three screened ligands, thus contributing to the stable inhibition of the protein.

Similarly, TYR605, TRP406, ILE364, TRP441, ASP542, ASP443, TYR299 and PHE575 contribute to the stability of α-glucosidase-ligand complex.

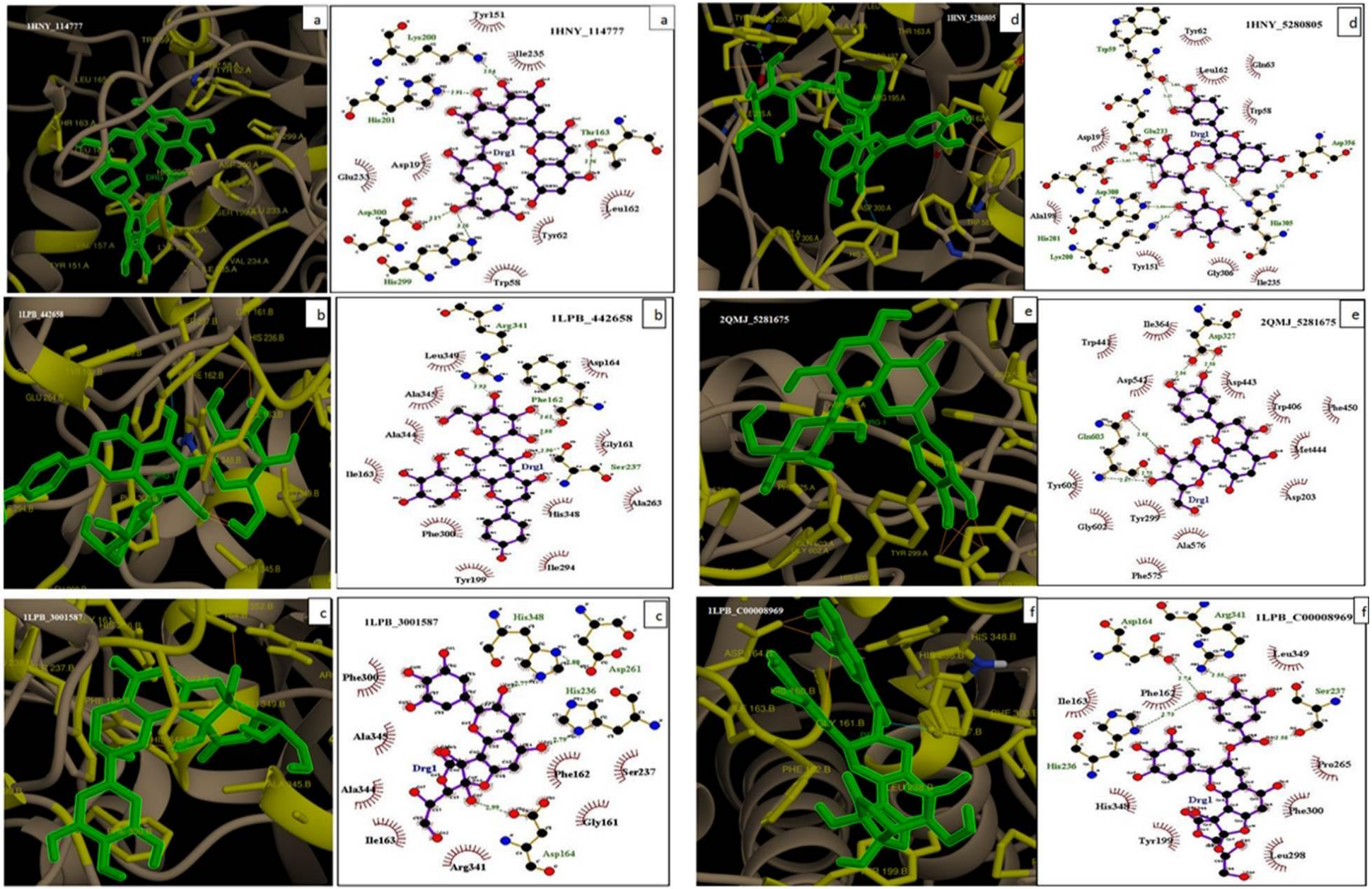


Fig. 1: UCSF chimera post-docking analysis (left) and Ligplot+ result (right) (a) Theaflavin (b) Schaftoside (c) 8-c-ascorbyl-(-)-epigallocatechin (d) Rutin (e) Orientin (f) 8-c-ascorbyl(-)-epigallocatechin 3-o-gallate.The green colored molecule represent ligand and yellow colored ones are the neighboring amino acids in 5 Å region that are interacting with ligand. The right side figures exhibits the Ligplot+ result. In the LigPlot result; green dotted line represents the H-bond of the ligand with the amino acid of the protein represented in green. Red spikes on the arcs show the hydrophobic interaction with the amino acids presented in black.

In case of pancreatic lipase, PHE300 and ILE163 mainly add to stability through hydrophobic interaction as both present in all three selected ligands. LEU349, ALA345, ALA344, TYR199, HIS348, GLY161, ILE163, PHE162 also contribute to the stability for lipase inhibition. Minor variation in hydrogen bond interactions can be seen in the results. The number of hydrogen bonds formed varies in Ligplot and chimera result. This is due to the intramolecular hydrogen bonds formed within the ligand molecule, which can be identified by chimera analysis but not Ligplot results. We can see there is small dissimilarity in the amino acids forming hydrogen bonds for instance, in α-amylase-theaflavin interaction an extra H-bond is formed by HIS299. These alterations may be due to the default cut-off distance of 2.5 Å or to the HBPLUS program used to calculate H-bonds in LigPlot.

As inferred from the post-docking analysis, the chemical structures of all the screened molecules promote hydrophobic interactions and good hydrogen bonding with the surrounding amino acids, and as a consequence impart greater ligand-protein complex stability and augment enzyme inhibition.

CONCLUSION

In our study, it was concluded that theaflavin, 8-c-ascorbyl-(-)-epigallocatechin, rutin and orientin could be potential lead molecules for inhibition of post prandial hyperglycemia whereas 8-c-ascorbyl-(-)-epigallocatechin, 8-c-ascorbyl epigallocatechin 3-o-gallate and schaftoside could efficiently inhibit pancreatic lipase thus serve as anti-obesity drug. The study also revealed that 8-c-ascorbyl-(-)-epigallocatechin emerged as a potential inhibitor of all the selected enzymes, and hence can be used as a common template for designing anti-diabetic and anti-obesity molecules. The enzyme ligand complex interactions provided an insight into the molecular basis that corroborated the existing evidences for anti-diabetic and anti-obesity properties of black tea components. The computational methodology manifested the future prospects of *in vitro* and *in vivo* drug development with the aid of tea components.

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How to cite this article:

Mohapatra S, Prasad A, Haque F, Ray S, De B, Ray SS. *In silico* investigation of black tea components on α-amylase, α-glucosidase and lipase. J App Pharm Sci, 2015; 5 (12): 042-047.