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In silico molecular GRIP docking studies of antioxidant potentials of black tea compounds

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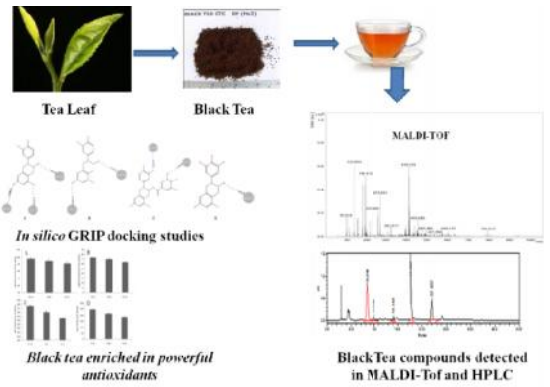
Graphical Abstract



Abstract.

Black tea is a very widely accepted and popular beverage that has attracted the research limelight and has exhibited multifaceted health effects due to the presence of wide range of pharmacologically active molecules. This paper aims to explore the antioxidant potentials of black tea catechins by *in silico* molecular GRIP docking studies. Basing on the result of dock score epicatechin gallate, catechin, epicatechin, epigallocatechin gallate all exhibited significant antioxidant potentials against the targeted enzymes.

Introduction

Tea (*Camellia sinensis*) belonging to family *Theaceae* is one of the most widely consumed beverages of the world and have proven to have multidimensional health potentials due to the actions of several pharmacologically active molecules in it (Sen and Bera, 2013). Black tea is very much preferred in Indian context due to the flavoring contents and astringency. Black tea is rich in several pharmacologically active molecules the catechins, benzotropolone compounds the theaflavins, methyl xanthenes viz. caffeine, theobromine, theophylline etc (Sen and Bera, 2013; Bhandari et al., 2015). *In silico* molecular GRIP docking studies aided in understanding the antioxidant potential of tea catechin molecules at mechanistic level. Rapid escalations in drug development costs, labor intensive screening of innumerable new chemical entities greatly limits the drug development process. More protein target molecules became available with the emergence of proteomics, genomics, bioinformatics, NMR and crystallography. Computational tools like *in silico* modeling is just suitable for the purpose of identification and analysis of the active sites and potential drug molecules binding to such sites (Singla, 2014; Meruva et al., 2014; Jadhav et al.,). Bioinformatic software tools offers a fast and frugal screening of active phytomedicinal compounds thereby diminishing labor, cost and time (Meruva et al., 2014). The aim of protein-

ligand docking is to calculate the binding energy of the protein-ligand reaction complex at given atomic co-ordinates. The key parameters for flexible docking include energy functions, protein catalytic sites and active residues (Meruva et al., 2014). For rapid, accurate protein-peptide and protein-ligand docking, GRIP™ by V Life software is a novel methodology available for rigid as well as flexible docking purposes. It makes use of a set of ligands with its conformers to be docked into the receptor cavity. This software helps to search for the active sites, consists of pre-computation of grids and tries to maximize favorable interaction and minimize unfavorable and repulsive interaction by proving the best possible orientation. GRIP scoring function allows for fast and precise capturing of ligand-receptor interactions in the active sites of proteins. In GRIP docking, unique conformers of a set of ligands are considered as input and offers the advantages of wide range of parameterizations, both ligand guided as well as cavity guided docking options, considers hydrogen bonding, repulsions and dispersion interactions with manual, automated and batch mode operations (Jadhav et al.; De et al., 2017).

Materials and Methods

The Proteins used for GRIP Docking include Copper-zinc superoxide dismutase (4B3E), glutathione peroxidase (3KIJ) and erythrocyte catalase (1DGB) of Homo sapiens were used for the current study. Their PDB structures were taken from RCSB. V life MDS 4.3 is very robust software with inclusion of all the necessary simulation modules. The 2D-structures of catechin (C), epicatechin (EC), epicatechin gallate (ECG), epigallo catechin (EGC) and epigallocatechin gallate (EGCG) the major catechin available in black tea were drawn in the 2D drawing application (2D Draw app) of MDS 4.3, followed by its conversion into 3D form by using default conversion procedure. Their energy minimization was done by using Merck Molecular Force Field (MMFF). MMFF is a class II force field designed to be a transferable force field for pharmaceutical compounds that accurately treats conformational energetics and non-bonded interactions. Molecular docking energy evaluations are usually carried out with the help of scoring function like dock score, PLP score, potential mean force (PMF) score, steric and electrostatic score. PLP score or Piecewise Linear Potential scoring function calculates both the shape and hydrogen bond complementarity of poses to the active site. The PLP score is a pair wise additive scoring function. The PLP function is incorporated by the MDS V Life Science software in the GRIP docking method which calculates the ligand-receptor binding affinity in terms of the PLP score. The PLP score is designed to enable flexible docking of ligands to perform a full conformational and positional search within a rigid binding site. These molecules were docked into the active site of 4B3E (copper-zinc superoxide dismutase), 3KIJ (crystal structure of human peroxidase) and 1DGB (catalase) that can be obtained as co-crystallized with bicarbonate ion or NADPH or by the use of cavities. The parameters fixed for docking simulation were: number of placements is 100, rotation angle at 10o, exhaustive method, ligand-wise results-10, scoring function-PLP score. By rotation angle, ligand would be rotated inside the receptor cavity to generate different poses of ligand inside the receptor cavity. By placements, the method will check all the 100 possible placements into the active site pocket and will result the best placements out of 100. After docking simulation, the best docked conformer of test molecules and reference ligands were then checked for their interactions with targeted proteins like hydrogen bonding, hydrophobic, pi-staking/aromatic, charge and van der Waal's interactions (Singla and Bhat, 2010; Singla et al., 2013; Malleshappa and Patel,

2013; Igoli et al., 2014; Igoli et al., 2014; Singla et al., 2012).

Results and Discussion

Catechin (C), epicatechin (EC), epicatechin gallate (ECG), epigallocatechin (EGC) and epigallocatechin gallate (EGCG) have undergone binding interactions with different amino acid residues by van der waals interactions, hydrophobic interactions, charge interactions with superoxide dismutase, glutathione peroxidase and catalase. All the mentioned catechins exhibited negative dock scores showing their strong binding affinities with the copper zinc superoxide dismutase. The scoring functions of Catechin, epicatechin, epicatechin gallate, epigallocatechin and epigallocatechin gallate were -48.81, -48.08, -61.67, -52.27, and -60.24 respectively. EGCG exhibited the highest negative dock score and can as considered as most potent antioxidant though all catechins showed the activities. The potencies of catechin and epicatechin were found to be almost equivalent in terms of docking score. Considering the binding interactions of the above mentioned black tea catechins with glutathione peroxidase the dock score of the Catechin, epicatechin, epicatechin gallate, epigallocatechin and epigallocatechin gallate were determined to be -60.23, -58.63, -61.19, -57.88 and -60.14 respectively. The potent catechin in terms of dock score was ECG. In this case catechin and EGCG showed to be equipotent in terms of dock score. Considering the case with catalase, ECG was found to be the most potent with a dock score of about -89.64 followed by EGCG with a dock score of -86.79; catechin and epicatechin were found to be equipotent with dock scores of -68.58 and -68.01 respectively followed by EGC (-66.66). From the results of *in silico* GRIP docking studies it is clear that the different catechins of black tea possess significant antioxidant potentials. Oxidative stress is the root cause of several chronic and degenerative diseases. Intake of natural antioxidants that are available in dietary sources and beverages can serve as an effective adjuvant therapy. However epicatechin gallate with highest affinity towards all proteins was found to be most active in comparison to other catecins. Here it is to be mentioned that the homeostatic condition of the body is disturbed due to oxidative stress and the situation is counteracted due to elevated superoxide dismutase (SOD) level. But in due course SOD level depletes and if potent natural antioxidants like EGCG etc present in black tea be supplemented at this stage it can effectively combat the crisis.

Conclusions

In silico molecular GRIP docking studies was helpful in the identification of the potent black tea catechins with antioxidant activities at different levels of potencies.

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