

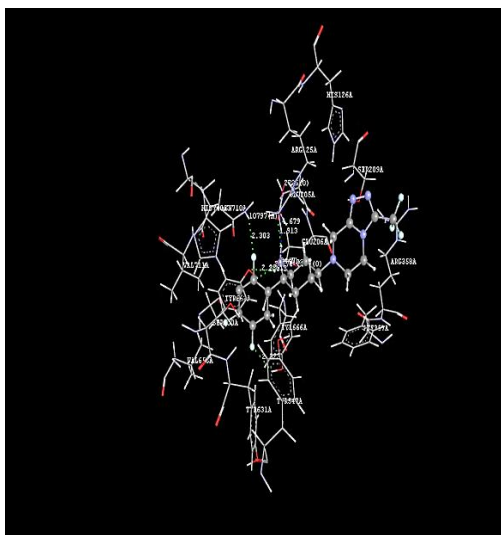
## Docking Studies of Epigallocatechin Gallate as Natural DPP-IV Inhibitor

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### Graphical Abstract



### Abstract.

DPP-IV enzyme is one of the important targets for the anti-diabetic drugs. Natural products like Epigallocatechin Gallate (EGCG) had been reported to have antidiabetic action *vide* multiple mechanisms which also include inhibition of DPP-IV enzyme. However, its mechanism and site of action on DPP-IV enzyme was not thoroughly explored. Thus, the current study was aimed to perform docking studies of EGCG with the DPP-IV enzyme, (PDB ID: 2P8S) using VLife MDS 4.6. Results indicated that EGCG was successfully docked in the DPP-IV enzyme with dock score of -87.584 when compared with standard and co-crystallized drug (cyclohexamine inhibitor) which has dock score of -84.0564. Further interaction analysis suggested that Epigallocatechin Gallate has aromatic interactions with Phe357A and hydrogen bonding with Arg125A, Glu206A and Arg358A. So based on the current study, Epigallocatechin Gallate can be further processed for tailoring and designing of novel DPP-IV inhibitors.

## Introduction

Diabetes mellitus, a chronic metabolic disorder, which is characterized by the abnormal increase in the blood glucose level in blood plasma. Both genetic and environmental factors are responsible for it, which leads to the either deficiency in the insulin production or resistance of cells to the insulin i.e. insulin resistance [1]. Reports indicated that ageing and diabetic history in the family of male are important demographic risk factors where prediction can be done by assessing the low testosterone levels [2,3]. If unchecked or not properly treated, diabetes mellitus will lead to various macrovascular and microvascular complications and could make patients vulnerable to the infectious diseases [4]. Dipeptidyl-peptidase-IV (DPP-IV), a serine exopeptidase, plays a very critical role in the regulation of glucagon like peptide-1 and glucose-dependent insulinotropic polypeptide. Thus, DPP-IV inhibitors are the target search for the treatment of diabetes mellitus [5,6].

Natural products, be it from plants, marine or microbial sources, have been long used for the treatment of various metabolic disorders like diabetes mellitus [7-10]. Epigallocatechin gallate (EGCG) is a natural polyphenol, available in wide varieties of sources which includes, but not limited to, black tea [11, 12], black current [13], cherry [13], forest fruit [13], green tea (Indian) [13], lemon [13], orange [13] and strawberry [13] etc. Literature suggested that EGCG has proven its strong potential for treatment of diabetes by multiple mechanisms which also include inhibition of DPP-IV [14-17].

With the advancement in molecular biology, docking studies and *in silico* pharmacology studies, enzyme modulators and receptors associated with molecular pathogenesis of the disease are being considered as important targets for treatment of diabetes mellitus [18]. Since the mechanism of epigallocatechin gallate as

inhibitor of DPP-IV enzyme was not extensively explored, aim of the current study was to perform docking studies of EGCG with the DPP-IV enzyme and get the insight about the possible site of action.

## Materials and Methods

Structure of EGCG was taken from PubChem and drawn using ChemDraw Ultra software. It was then exported to VLife MDS 4.6 software for energy minimization and docking studies. The structure i.e. PDB file of the DPP-IV enzyme selected was 2p8s and taken from the RCSB website. It will also be exported to VLife MDS 4.6 for processing. Parameters selected for the energy minimization of EGCG were: Force Field: Merck Molecular Force Field; Charge: MMFF Charge; Number of cycles: 10,000 with RMS gradient of 0.01. The parameters fixed for docking simulation was like this: number of placements, 50; rotation angle, 10°; exhaustive method; ligand-wise results: 10; scoring function: dock score [1, 4, 19].

## Results and Discussion

S.No.	Name of the Molecule	Code	Best Placement	Dock Score
1.	Epigallocatechin Gallate	06.	06_opt_opt_C7_LP7	-87.60
2.	Referance Ligand 417	-X-	-X-X-X-X-	-84.10

**Table 1 Docking score of the EGCG when docked in the co-crystallized tracked active site of DPP-IV enzyme, 2p8s. Dock score is PLP scoring function.**

Results indicated that Epigallocatechin Gallate was having strong affinity towards DPP-IV enzyme, with dock score of -87.584 when compared with standard and crystallized drug (cyclohexamine inhibitor) which has dock score of -84.0564 (Table 1). Further interaction analysis suggested that Epigallocatechin Gallate

has aromatic interactions with Phe357A and hydrogen bonding with Arg125A, Glu206A and Arg358A. So based on the current study, Epigallocatechin Gallate can be selected for tailoring and designing novel DPP-IV inhibitors.

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