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Molecular Docking Analysis of Epigallocatechin 3- Gallate [EGCG] on Fatty Acids and Carnitine Transporters Family

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Abstract

EGCG is the main catechin present in green tea. Fatty acids can be categorized as saturated or unsaturated depending on the hydrocarbon chain and terminal carboxyl group they contain, typically with an even number of carbons. EGCG has attracted considerable interest because of its several health benefits, such as its anti-inflammatory, antioxidant, and anticancer characteristics. Yet, the precise molecular targets and mechanisms of action are not fully understood. Exploring the potential interaction of EGCG with fatty acids and carnitine transporters, which play a vital role in lipid metabolism and energy production, could provide insights into its physiological effects. Analysis of molecular docking between EGCG and fatty acid and carnitine transporters, and their interactions. A contact and binding occur between the fatty acid transporters (FABP) and VLCAD and CPTII. EGCG was subjected to molecular docking simulations with active sites of transporter families such as FABP, CPT2, and VLCAD. The docking analysis showed that EGCG has favourable binding interactions with the target transporters, involving important hydrogen bonding and hydrophobic interactions. EGCG showed a strong ability to bind to the active sites of FABP and CPT2, indicating its potential to influence their functions.

Keywords: *Carnitine transporter family, CPT2, EGCG, FABP, Molecular docking, VLCAD.*

Introduction

Epigallocatechin-3-gallate (EGCG) is the primary catechin found in green tea. The health benefits of drinking green tea are believed to stem from its polyphenolic compound and other related catechins [1]. Green tea and EGCG have been associated with antioxidant effects, cancer prevention, improved weight reduction, increased cardiovascular health, and protection of the skin from ionizing radiation, among other possible health advantages [1]. One cup of brewed tea contains 200-300 mg of EGCG [2]. Approximately 16.5% of water-extractable tea includes EGCG, accounting for almost 50% of all green tea catechins [3]. Fatty acids (FAs) may be classified as either saturated or unsaturated based on the presence of a hydrocarbon chain and a terminal carboxyl group, usually containing an even number of carbons. The de novo fatty acid synthesis pathway intricately links the metabolism of glucose and lipids. This process aids cells in adjusting to environmental changes and generates significant quantities of adenosine triphosphate (ATP) via beta-oxidation [4]. The protein carnitine palmitoyl transferase 2 (CPT2), located on the inner mitochondrial membrane, plays a vital role in catalyzing the conversion of acylcarnitine to acyl-CoA. A common reason for recurrent myoglobinuria in adults is a deficiency in the enzyme CPT2. This is an inherited disorder affecting the fatty acid oxidation pathway, often characterized by elevated levels of acylcarnitine [5]. Fatty acid

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binding proteins (FABPs) are intracellular lipid chaperones that regulate cellular lipid responses and trafficking, and stimulate adipocyte lipolysis. Research indicates that mammals have a minimum of nine different isoforms.FABP-4 (A-FABP) is essential in the progression of insulin resistance and atherosclerosis and is mostly found in adipocytes and macrophages. FABP-4, a significant adipokine, is associated with several illnesses such as metabolic syndrome, obesity [6], type 2 diabetes, insulin resistance [7,8], hypertension, cardiovascular disease, and atherosclerosis [9–11].

Diabetes mellitus, a prevalent non-communicable illness, results in many fatalities annually and has an increasing economic influence [12]. Oxidative stress, caused by high blood sugar levels in diabetes, plays a significant role in the development of problems that harm various organs such as the heart, liver, kidneys, retina, and brain. Green tea, derived from the Camellia sinensis plant, is a widely consumed beverage globally due to its many health benefits. Green tea extract (GTE) contains several biologically active compounds, such as epigallocatechin-3-gallate (EGCG), which is a potent antioxidant [13]. Molecular docking is a computer method used to forecast non-covalent interactions between molecules, such as a protein receptor and a ligand [14]. It is often used to virtually filter large compound libraries [15].

Materials and Methods

Protein Target Preparation

Protein targets were obtained from the Protein Data Bank (PDB). We used the Discovery Studio Visualizer 2020 to create the protein of interest. Water molecules inside the protein structures were analyzed and eliminated if needed. Furthermore, bound ligands and ions were omitted. PDB proteins usually do not include hydrogen atoms, thus we added hydrogen atoms to align the protein with the conventional protein structure. The hydrogen atoms are essential for the following docking investigations. Finally, optimization and minimization methods were used to complete the protein's manufacturing [16].

Ligand Preparation

The ligand Epigallocatechin-3 gallate was acquired from the PubChem database. The compounds were built using the Discovery Studio Visualizer 2020, adjusted to ensure the ligand's lowest energy isomer. After reducing energy, the ligand molecules conducted molecular docking tests [17]**.**

Molecular Docking

We brought the protein we created into our workspace and discovered its active site using the Uniprot database in our current study. We found that a grid of around 60Å was needed to include all the active site residues identified by the site map. We kept the default values for characteristics such as the van der Waals radii of non-polar atoms in both the receptor and ligand, which were set at 0.50. We chose the most advantageous structural arrangement by considering criteria including docking score, glide energy, and the existence of hydrogen bonding and hydrophobic contacts [18].

Results

Table 1. Log Table Shows Affinity and RMSD of CPT2 and Epigallocatechin-3 Gallate

	Affinity	**Dist from best mode**	
Mode	**(kcal/mol)**	**rmsd l.b.**	**rmsd u.b.**
1	-8.6	0.000	0.000
2	-8.4	3.860	9.352
3	-8.1	2.221	6.017
4	-7.9	2.467	8.209

5	-7.9	2.522	9.003
6	-7.9	2.603	5.126
7	-7.9	18.786	21.332
8	-7.7	4.982	9.416
9	-7.7	5.019	9.020

Table 2. Log Table Shows Affinity and RMSD of FABP and Epigallocatechin-3 Gallate

Mode	Affinity (kcal/mol)	Dist from best mode rmsd l.b.	rmsd u.b.
1	-8.5	0.000	0.000
2	-7.8	18.242	20.70
3	-7.8	2.364	6.248
4	-7.7	16.973	20.853
5	-7.6	1.448	1.830
6	-7.6	26.904	30.04
7	-7.5	26.574	29.402
8	-7.5	26.586	29.589
9	-7.5	26.446	28.833

Table 3. Log Table Shows Affinity and RMSD of VLCAD and Epigallocatechin-3 Gallate

Mode	Affinity (kcal/mol)	Dist from best mode rmsd l.b.	rmsd u.b.
1	-8.8	0.000	0.000
2	-7.7	35.863	38.682
3	-7.7	28.705	31.993
4	-7.6	2.046	6.797
5	-7.4	1.989	4.78
6	-7.4	21.329	24.924
7	-7.4	2.528	5.339
8	-7.2	2.877	5.568
9	-7.2	27.099	28.424

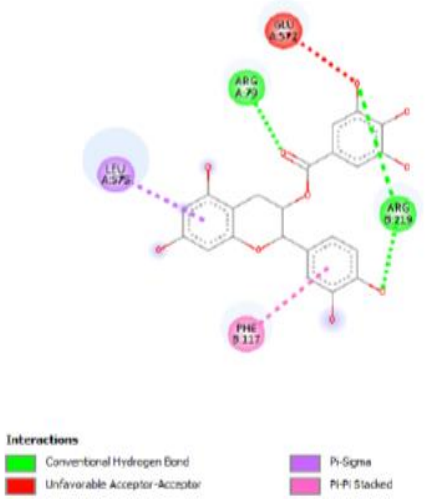

Figure 1. Shows the Interaction Between CPT2 and Epigallocatechin-3 Gallate in a 2D Structure

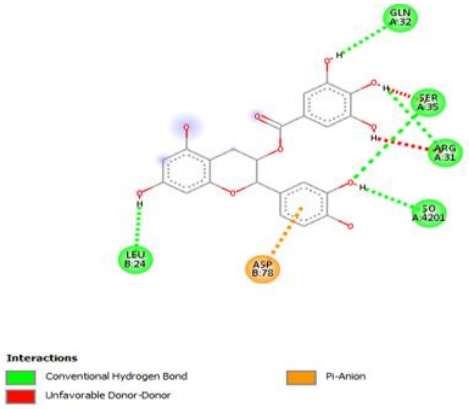

Figure 2. Shows the Interaction Between FABP and Epigallocatechin-3 Gallate in a 2D Structure

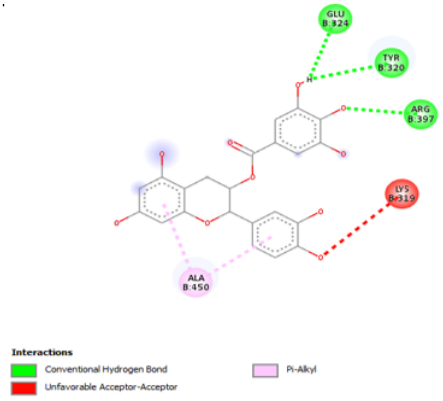

Figure 3. Shows the Interaction Between VLCAD and Epigallocatechin-3 Gallate in a 2D Structure

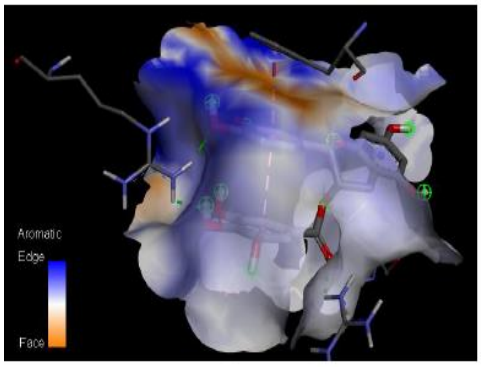

Figure 4. Shows the Interaction Between CPT2 and Epigallocatechin-3 Gallate in a 3D Structure

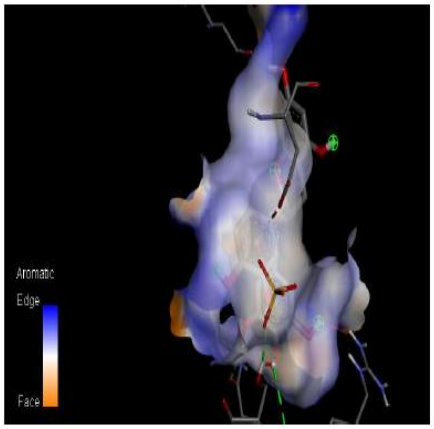

Figure 5. Shows the Interaction Between FABP and Epigallocatechin-3 Gallate in a 3D Structure

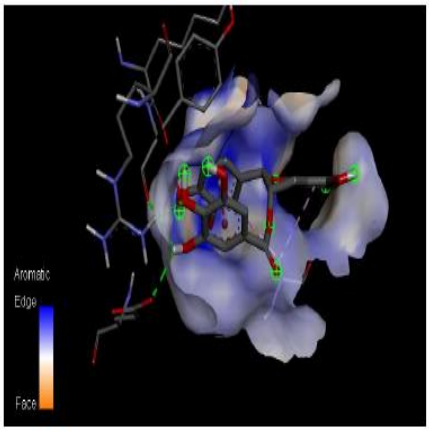

Figure 6. Shows the Interaction Between VLCAD and Epigallocatechin-3 Gallate in a 3D Structure

Table 4. Compare the Molecular Docking Results of EGCG with CPT2, FABP, VLCAD

RESULT ANALYSIS	**VISUALIZATION SOFTWARE**	**PROTEIN**	**LIGAND**	**DOCKING SCORE**	**AMINO ACID RESIDUE**
Auto dock 1.5.7	Discovery software	FABP	Epigallochatechin 3-gallate	-8.5	Conventional Hydrogen bonding:GLN A:32,5ER A:35,ARG A:31,50 A:4201,LEU B:24 Unfavourable Donor-Donor bonding: 5ER A:35,ARG A:31 Pi-Anion bonding: A5P B: 78

		VLFAB		-8.8	Conventional Hydrogen bonding: GLU B:324, TYR B:320, ARG B:397 Unfavourable Donor-Donor bonding: LYS B:310 Pi-Alkyl bonding : ALA B:450
		CPT2		-8.6	Conventional Hydrogen bonding:ARG A: 79,ARG B:219 Unfavourable Donor-Donor bonding: GLU A:572 Pi-Alkyl bonding: PHE B: 117 Pi-Sigma bonding: LEU A:575

Results and Discussion

Diabetes is increasingly becoming a major worldwide health issue, with an estimated 693 million individuals projected to be impacted by 2045. This prevalent condition leads to serious consequences, including macrovascular problems like cardiovascular disease, and microvascular concerns such as diabetic kidney disease, diabetic retinopathy, and neuropathy. The issues mentioned lead to increased mortality rates, eyesight loss, renal failure, and a worse quality of life for those with diabetes [10]. Diabetes mellitus (DM) is mainly categorized into two subtypes: type 1 DM and type 2 DM. Type 1 diabetes mellitus is treated with insulin replacement therapy, whereas type 2 diabetes mellitus is handled with oral hypoglycemic medicines [19].

Molecular docking studies indicate that the breakdown of fatty acids depends on their transportation into mitochondria, which is aided by enzymes called carnitine palmitoyltransferase 1 and 2 (CPT1 and CPT2). These enzymes connect fatty acids to carnitine, and EGCG accelerates this process, perhaps providing a favorable treatment for diabetes[20]. A separate research study used molecular docking analysis to investigate the interactions between substances such as (+)-catechin, (−)-epicatechin, EGCG, B2, and C1 with α-glucosidase. The idea proposes that Lotus procyanidin extract (LPE) might attach to several locations on the enzyme, creating hydrogen bonds and hydrophobic interactions.

This interaction may cause changes in the enzyme's structure, leading to a decrease in its activity. Thus, using EGCG may help to suppress diabetes action [21].Table 1 displays the results of the docking analysis, showing logarithmic values representing affinity and root mean square (RMSD) values of CPTII. The RMSD value is extremely significant at 0.000, while the affinity value is regarded important when it exceeds -4.5. The selected docking score is -8.6, indicating a substantial RMSD value. [22-24]. The docking score is analyzed using visualization tools that provide 2D and 3D picture structures for examination (Figure 1 and 4). Figure 1 displays the Pi-Sigma Bond, Pi-Sigma Stacker Bond, Conventional Hydrogen Bond, and Unfavorable Acceptor-Acceptor Bond in a 2D framework.

Table 2 displays the results of the docking analysis, showing logarithmic values representing affinity and RMSD values. The RMSD value is extremely significant at 0.000, while the affinity value is regarded as important when it exceeds -4.5. The selected docking score is -8.5, indicating a notable RMSD value for FABP. The docking score is analyzed using visualization tools that generate 2D and 3D picture structures for study (Figure 2 and 5). Figure 2 displays a Conventional Hydrogen Bond, Unfavourable Donor-Donor Bond, and Pi-Anion Bond in a 2D arrangement.

Table 3 displays the results of the docking analysis, showing logarithmic values representing affinity and root RMSD values of VLCAD. The RMSD value is extremely significant at 0.000, while the affinity value is regarded as important when it exceeds -4.5. The selected docking score is -8.8, indicating a notable RMS value of VLCAD. The docking score is analyzed using visualization tools that generate 2D and 3D picture structures for study (Figure 3 and 6). Figure 3 displays a Conventional Hydrogen Bond, Unfavourable Donor-Donor Bond, and Pi-Anion Bond in a 2D arrangement.

Conclusion

Analysis of molecular docking indicates that epigallocatechin 3-gallate (EGCG) may interact with fatty acids and carnitine transporters, possibly affecting their function (represented in figure 7). This first inquiry suggests a possible connection between EGCG and these transporters, however a more thorough analysis would be needed for a definitive conclusion. Additional research is required to establish the scope of this interaction, its biological importance, and any possible therapeutic ubses.

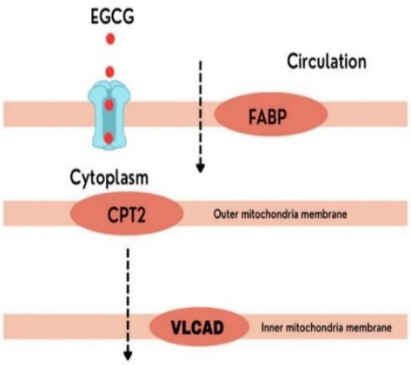

Figure 7. The Above Figure Represents the Alteration of the FABP, CPT2 and VLCAD with EGCG

Conflict of Interest

The authors declare that they have no conflict of interest.

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