



## In Silico Docking of Polyphenolic Compounds against Caspase 3-HeLa Cell Line Protein

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### Abstract

The present study was carried out using caspase 3, which is a human cervical cancer cell line protein. The current molecular docking shall stand useful for designing and development of future novel compound with higher inhibitory activity against caspase 3-HeLa protein. Further, these compounds can be validated further in wet lab to be nominated as potential drug candidates against HeLa proteins. The highest negative energy value obtained after docking among five compounds with caspase 3 was found to be coumarin (-378.3 KJ/mol), followed by camptothecin, epigallocatechin and quercetin with docking scores -285.3, -258.2 and -236 KJ/mol respectively. The least docking score was in docking of gallic acid with caspase3 and the scoring was -181.3 using Hex 8.0.0 docking software.

**Keywords:** *In silico* docking; Camptothecin; Quercetin; Epigallocatechin; Coumarin; Gallic acid; Autodocking

### Introduction

Cancer is one of the serious threats to humans, causing deaths worldwide in spite of substantial advances in research for its diagnosis and treatment. Almost 20 million new cases are predicted by the year 2020. Disturbingly, the proportion of new cases from the developing countries like India is expected to rise around 70%. The gauge of the problem of cancer in the Indian sub-continent is distressing [1]. Cervical cancer is the commonest cause of death among women in developing countries [2]. According to information center on HPV (human papilloma virus) and cancer in India, every year, 122,844 women are diagnosed with cervical cancer and mortality incidence from this disease is 67,477. In country like India with women population of 432.2 million aged between 15 years and older, are at risk of developing cancer, as it is the second most common cancer found in women aged 15-44 years [3]. Hence, there is a need for search of novel therapeutic drug with minimum side effects against human cervical cancer cell line which is also cost effective. Thus, researchers have turned towards natural products for synthesis of green drug for which, there is a need of knowledge on their interaction with target protein.

Various natural polyphenols have been studied to show cytotoxic effects on human cervical cancer cell lines, thus showcasing new perspectives in drug development against cervical cancer. The five natural compounds considered in this study are the polyphenols. These are a group of chemical substances from natural and herbal extracts which have gained great attention because of their negligible side effects and effective role in anticancer activity. Several studies were carried out to demonstrate the ability of these substances to target viral oncogenes and to inhibit the deregulation and signaling of gene expression of the host cells [4].

The quercetin belongs to the class of flavonoids as inclined to show anti-proliferation, induction of apoptosis against HeLa cell line *in vitro* and also induction of G2/M phase cell cycle arrest and mitochondrial apoptosis [5]. *In vitro* studies on HeLa cell line has proved that epigallocatechin, belonging to class of flavan-3-ols showed anti-proliferation and induced-apoptosis also inhibited telomerase activity [6]. Gallic acid, belonging to the class of phenolic acids studied *in vitro*

on HeLa cell line was proved to induce of apoptosis [7]. Camptothecin, a natural alkaloid was studied as an anticancer drug to have anti-proliferative effect on HeLa cancer cells in low concentrations, through its nature of induction of apoptosis [8]. Coumarin, a naturally occurring substance found in many plants and also their derivatives have tended to induce apoptosis in HeLa cell lines by engaging both extrinsic and intrinsic pathway [9].

The objective of the current study is to analyse the domain and active sites of the caspase 3-hela cell line protein, to perform docking of the polyphenolic compounds and determine their active sites and compound docking so that their potentiality as a therapeutic agent against caspase 3 is assessed.

### Materials and Methods

#### Tools used

Bioinformatics tools: Soft wares like ChemSketch was used for chemical drawing and graphics, Hex 8.0.0; is an Interactive Molecular Graphics Program that calculates and displays possible docking modes of pairs of protein and DNA molecules. Hex can also analyze Protein-Ligand Docking, the ligand is assumed to be rigid, and it superposes several pairs of molecules based only on the knowledge of their 3D shapes [10]. The Spherical Polar Fourier (SPF) correlations were used to enhance the calculations and its one of the few docking programs has built in graphics for interpretation of the result [11].

#### Protein preparation

The three dimensional structure of HeLa cell line protein Caspase-3 was found as a complex with V266F (Figures 1-6). This was retrieved from the PDB (Protein Data Bank) (<http://www.rcsb.org/pdb>). The complexes bound to the receptor molecule, such as non-essential water molecules, including heteroatoms were removed from the target receptor molecule. Finally, hydrogen atoms were added to the target receptor molecule. The PDB was established in the year 1971, which is the worldwide archive of structural data of biological macromolecules, established by Brookhaven National Laboratories [12].

#### Ligand preparation

Five compounds namely Camptothecin, Quercetin, Epigallocatechin, Coumarin and Gallic acid were used for docking

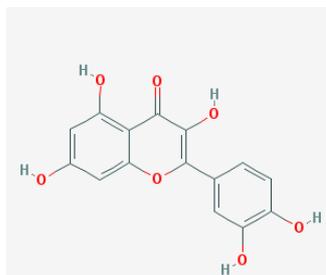


Figure 1: 2D structure of Quercetin.

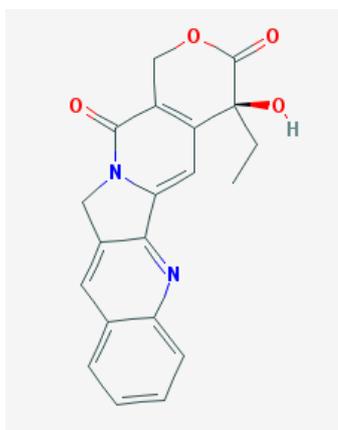


Figure 2: 2D structure of Camptothecin.

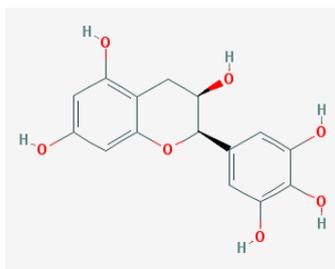


Figure 3: 2D structure of Epigallocatechin.

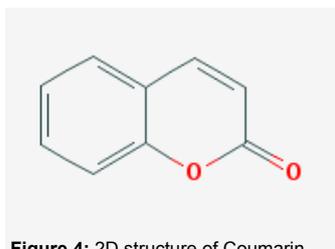


Figure 4: 2D structure of Coumarin.

studies (Figures 1-5). The structure of these compounds were obtained from the Pubmed literature which shows inhibitory effects towards human cervical cancer cell line proteins [13]. The source for three dimensional structures was from PDB and further used for docking studies.

## Docking of receptor with ligands

Caspase 3 receptor was docked with different ligands using Hex 8.0.0 docking software [14,15]. Hex docking was carried out by setting appropriate parameters such as twist range-360, receptor range-180, FFT mode-3D fast lite, ligand range-180, grid dimension-0.6 and distance range-40. The binding energy produced by docking action was tabulated.

## Results and Discussion

Bioinformatics is emerging as an important tool in the field of pharmaceutical and drug development with the prospective to significantly improve the drugs and to check as to how they are originated, carried to the clinical trials and eventually released to the marketplace. This study was performed using HeLa cell line protein caspase-3 and five different compounds, the receptor was derived from Protein Data Bank (PDB) and was used as target for stimulating docking against the five different compounds. These results provide a strong consideration about interactions between the five compounds; camptothecin, quercetin, epigallocatechin, coumarin, gallic acid and caspase 3 which is the human cervical cancer cell line protein. By using Hex 8.0.0 software docking studies were performed and thus their binding model was explored. Further, it is well known that the recognition of binding site between the ligand and the receptor is the beginning point for drug discovery and also to determine the function of protein. In the present study, the active site of HeLa cell line protein caspase 3 was predicted with higher precision figure.

Also the active site of Caspase-3 is comprised of amino acid residues as follows:

ARG64,SER120,HIS121,GLY122,GLN161,ALA162,CYS163,SER205,TRP206,ARG207,ASN208,SER209,TRP214,MET222,GLN225,TYR226,ARG238,ARG241,LYS242,THR245,GLU246,PHE247,GLU248,SE R249,PHE250,SER251,PHE256

## Ligand/Receptor Interaction Studies

The objective of this ligand-protein docking was to explore their predominant binding model of five different ligands with three dimensional structure of a HeLa cell line protein-caspase 3. The intermolecular flexible docking simulation was performed to explore the binding site of the five compounds-camptothecin, quercetin, epigallocatechin, coumarin, gallic acid with HeLa cell line protein Caspase 3. Energy values were calculated from the information obtained while docking the conformations of caspase 3 inhibitor complexes. The crucial interaction information concerning the binding pockets and their orientation of inhibitors in the target protein was obtained. The binding affinity was measured in terms of KJ/mol.

The results of docking and crucial interaction between the ligand and the receptor are shown in figures. The highest negative energy value obtained after docking among five compounds was found between Coumarin with caspase 3 (Figure 7) with value -378.3, followed by camptothecin with caspase 3 (Figure 8), epigallocatechin with caspase 3 (Figure 8) and quercetin with caspase 3 (Figure 9) with docking scores -285.3, -258.2 and -236 respectively. While the least docking score was in docking of Gallic acid with caspase3 (Figures 10 and 11) and the scoring was -181.3 using Hex 8.0.0 docking software (Tables 1 and 2). This prediction on the activities of new inhibitors based on the docking scores gives accurate understanding for ligand and receptor binding interaction, which can be employed for newer drugs against cancer. Higher the negative Etototal value stronger is the interaction between ligand and receptor which leads to activation of receptors.

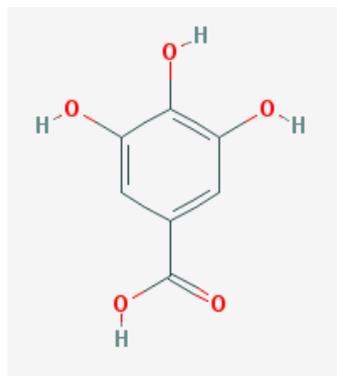


Figure 5: 2D structure of Gallic acid.

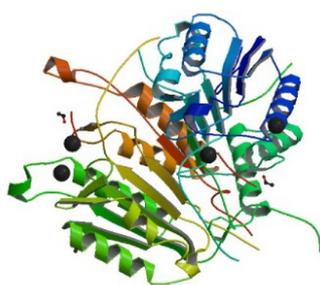
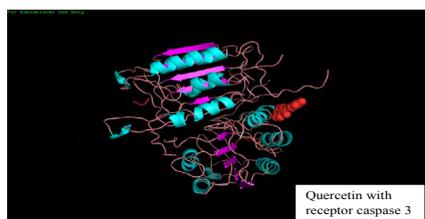
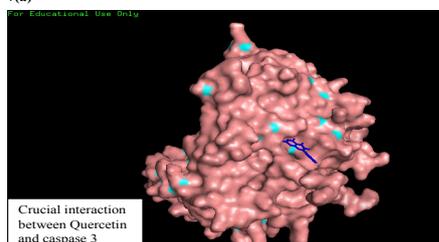


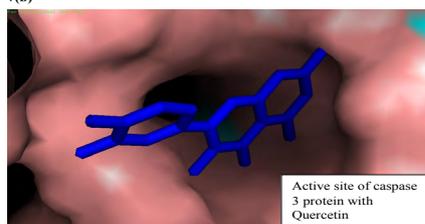
Figure 6: Caspase 3 V266 F retrieved from PDB.



7(a)

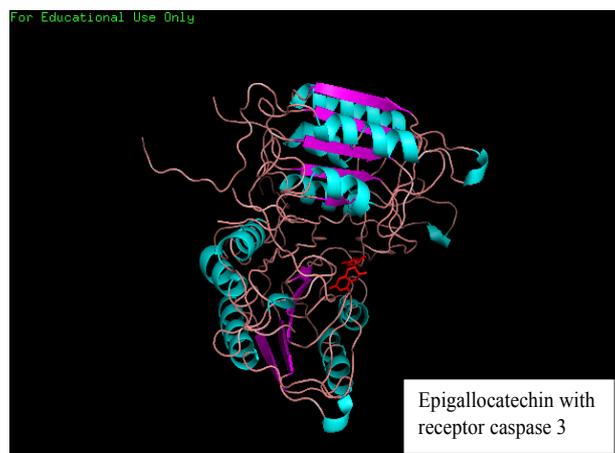


7(b)

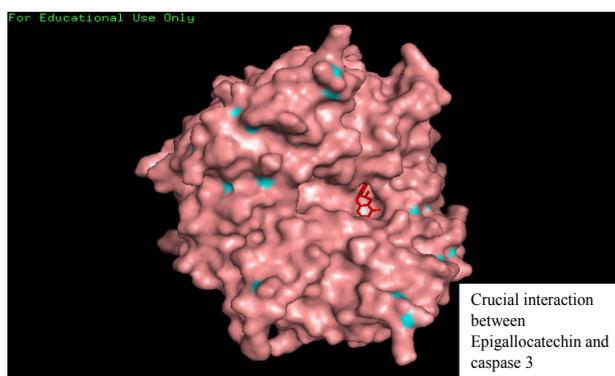


7(c)

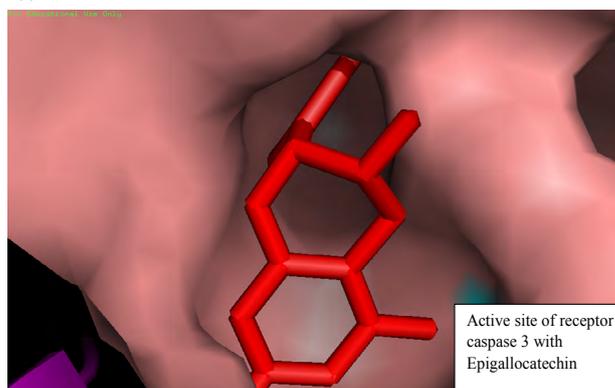
Figures 7: a, b and c) Docking of Quercetin with caspase 3 receptor.



8(a)



8(b)



8(c)

Figures 8: a, b and c) Docking of Epigallocatechin with caspase 3 receptor.

## Conclusion

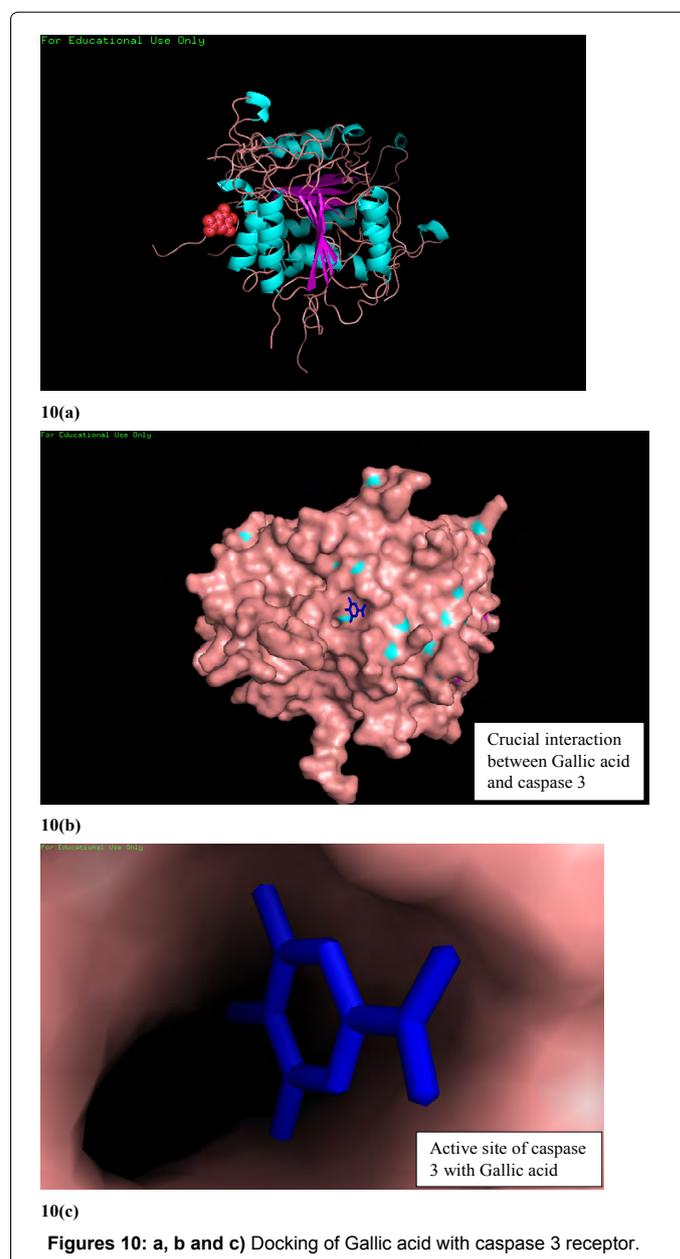
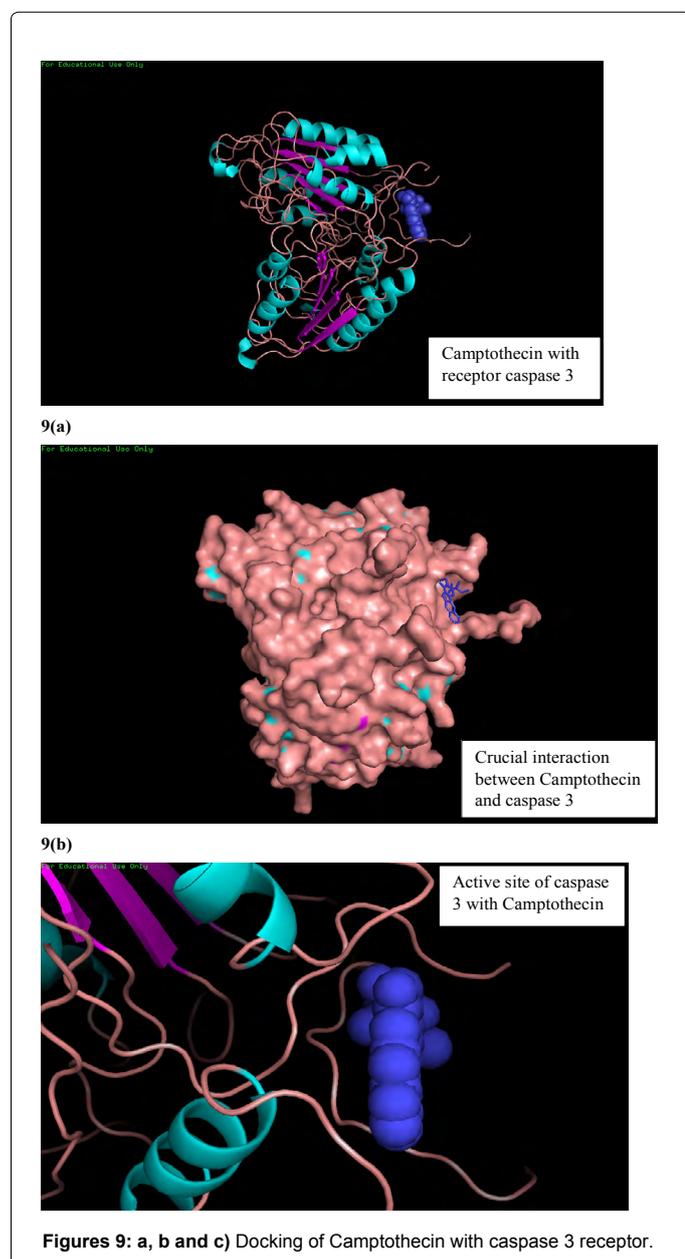
The molecular docking in the current study was concrete enough to discover the binding mechanism and interaction between the five different compounds which are the ligands and the HeLa cell line protein Caspase 3. The results obtained in this study shall be useful for future drug designing and development of novel compounds with higher inhibitory activity against several types of cancer. However, it is necessary to validate these compounds in wet lab studies for establishing them as potential novel candidates.

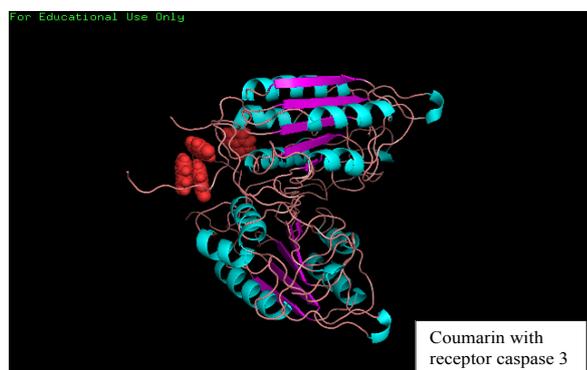
S. No	Name of the compound	Molecular weight	Log P3	H-Bond Donor	H-Bond Acceptor	Complexity
1	Quercetin	302.238 g/mol	1.5	5	7	488
2	Camptothecin	348.358 g/mol	1	1	5	742
3	Epigallocatechin	306.27 g/mol	0	6	7	380
4	Coumarin	146.145 g/mol	1.4	0	2	196
5	Gallic Acid	170.12 g/mol	0.7	4	5	169

Table 1: Compound details from pubchem.

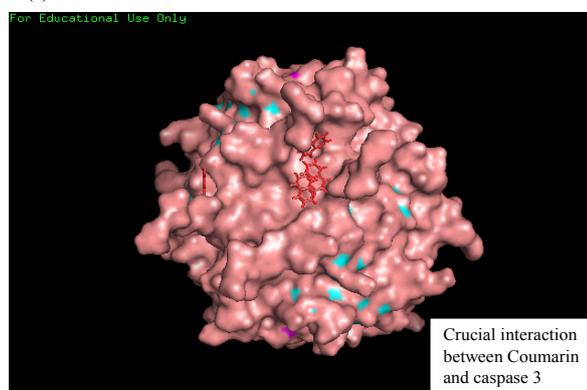
S. No	Ligand	Hela cell line protein	Eforce (binding energy of ligand)	Docking score ETotal Value KJ/mol	Eshape (energy content of the protein)
1	Quercetin	Caspase-3	0	-236.0	-236.0
2	Epigallocatechin	Caspase-3	0	-258.2	-258.2
3	Camptothecin	Caspase-3	0	-285.3	-285.3
4	Coumarin	Caspase-3	0	-378.3	-378.3
5	Gallic acid	Caspase-3	0	-181.3	-181.3

Table 2: Docking results of caspase 3 receptor with five compounds.

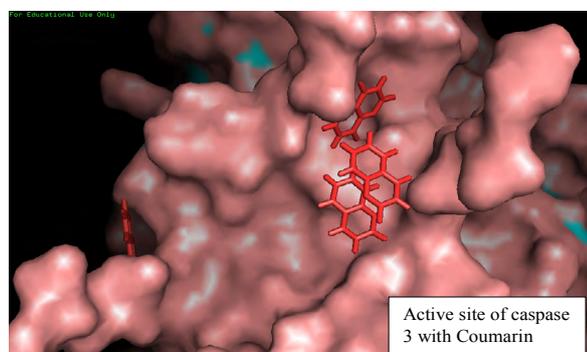




11(a)



11(b)



11(c)

Figures 11: a, b and c) Docking of Coumarin with caspase 3 receptor.

## Acknowledgements

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