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INSILICO DOCKING AND INTERACTION ANALYSIS OF ELLAGIC ACID AND CURCUMIN DERIVATIVES AGAINST HUMAN CANCER

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ABSTRACT

Despite intensive effort all over the world cancer is still continuing to be a major cause of death. Development of safer and more effective drug is necessary to improve cancer therapy. Plants are a major source of anticancer compounds. Many phytochemicals have been reported as tumor suppressors or inhibitors. In an effort to develop potent anticancer drug from plants this study aim to evaluate the inhibition activity of phytochemicals *ellagic acid* and *curcumin* derivatives against cancer by computational docking studies. The Docking studies were performed with the target protein Cyclin dependent kinases 2 (pdb id-1GII) by glide module of schrodinger suite. Cyclin dependent kinases are important molecules that control cell cycle progression from one phase to the other. The cyclin dependent kinase 2 proteins (1GII) are the key target of human cancers. The molecular docking studies of *ellagic acid* and *curcumin* derivatives with target protein exhibited binding interactions. The result showed that ellagic acid and its derivatives has high desirable potential to bind with the active site of the target protein than *curcumin* and its derivatives. From this *insilico* analysis we propose that both polyphenolic compounds shows inhibition activity with 1GII which is a potential target for cancer therapy and results of these studies are important in the development of plant based drugs for cancer therapy.

KEYWORDS: Phytochemicals, Insilico Analysis, Docking, Schrodinger, Cyclin Dependent Kinase2, Curcumin, Ellagic Acid

Cancer is characterised by the uncontrolled growth of abnormal cells that are capable of spreading to other cells in the vicinity and organs. In spite of the availability of effective chemotherapy and effective drugs, cancer remains a leading dreaded disease world-wide. It has been reported that about 6.7 million people die from cancer. One third of the world population is asymptomatically affected by cancer. However, even with it being a very common disease no effective drug has been developed to fight against cancer.

The failure of potential drug candidates in clinical trials and side effect of already approved drugs has the reason to look for new strategies for developing drugs from naturally occurring medicinal plants. There are many medicinal plants that are known to have goodanti cancer properties (Shu-Yi Yin et.al 2013). The bio active components of the medicinal plants called phytochemicals are responsible for their therapeutic effects in human body. There have been many studies on therapeutic application of these phytochemicals against cancer. In recent years natural products with good anticancer activity and less side effects, have gained increasing scientific attention. Computational analysis of the phytochemicals can helps to develop new potential molecule against the target of cancer. Present study on phytochemical was designed to develop better alternative agent against cancer. curcumin and ellagic acid derivatives were used for the present study because these are belongs to the group of bioactive polyphenols and their promising role in cancer. Curcumin is a naturally occurring polyphenol derived from the plant curcuma longa. It is a potent anticancer agent (Preetha Anand et. al., 2008). Ellagic acid is also a polyphenol present in most of the fruits. It is an antioxidant and anti proliferative compound (Prakash S bisen et.al 2012).

Computational biology and bioinformatics have very important role to pinpoint the drug designing process. To speed up the rational drug designing process there involves a variety of methods to identify the novel compound. Docking is one such which predict the preferred orientation of small molecule drug candidates to their protein target (Shainda Laeeq et.al 2014). Computational method such as molecular docking is one of the best method for predicting the bioactive components from plants.

Insilico based drug discovery is one of the most recent promising stratergy for the development of therapeutic for many disease including cancer. Due to the large data available on protein structure and small molecule the computational drug discovery has increased the efficacy of drug designing processs. There are basically two method involved in computational drug discovery. Structure based drug discovery and Ligand based drug discovery. Here we use structure based drug discovery to identify the potential drug candidates against human cancer. Cyclin dependent kinase-2 is selected as a target for the present study. Nowadays CDK'S, their regulators are the key target of many human cancers (Mary E Law et.al 2015). We need

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the 3 dimensional structural information of protein inhibitor complex for the development of potent and safe new inhibitor.

The objective of the present work is to evaluate the anticancer activity of Curcumin and ellagic acid derivatives by insilco based method. The methods include molecular docking of some selected derivatives of both ellagic acid and Curcumin derivatives with cyclin dependent kinase protein using Schrodinger software.

MATERIALS AND METHOD

Molecular docking calculation were performed using maestro 9.2 version Schrodinger software (Schrodinger maestro v9.2 2015). Schrodinger is one of the most important automated docking tool. It is designed to predict how the ligand molecule or drug candidates can bind to the active site of the target protein. Glide XP module of schrodinger software is used for the docking purpose.

Target identification and preparation

The three dimensional crystal structure of cancer receptor were obtained from RCSB protein data bank (http://www.rcsb.org/pdb/.) .The crystal structure of CDK2 receptor (1GII) were reported to complex with CDK4 inhibitor and have a resolution of 2.0 A^0 shown in fig 1. After identification of the protein, the protein preparation wizard of Schrödinger suite has been used for protein preparation. Preprocess of the target protein was done by the removal of metal ion, cofactor and water molecule outside 5A0 and addition of hydrogen atom. Energy minimization and hydrogen bond optimization was also done.

Ligand identification and preparation

The 2D structure of the selected ligands was identified from the literatures. All the selected compound were download from pubchem data base available in NCBI server and listed in table 1(http://pubchem. ncbi.nlm.nih.gov). The geometry of the selected molecules were optimized by using Ligprep module of Schrodinger suite (Schrodinger Ligprep3.4v 2015). The ligprep is a module of Schrodinger suite to generate a single low energy 3D conformer with acceptable bond lengths and angles for each 2D structure in the initial databases and to generate tautomers and steric isomers and geometry minimization of ligands.

Docking by Glide XP mode

First a grid box is generated around the active site of the internal ligand and is used to find the electro static and vander walls potential of binding pocket. Glide is a complete solution for ligand-receptor docking. Glide offer good accuracy from high-throughput virtual screening of millions of compounds to extremely accurate binding mode prediction. The interaction were calculated using glide sore (Schrodinger Glide5.5v 2015)

Qikprop calculation

The docked compounds are selected and they are subjected to undergo qikprop. After completion of qikprop programme the properties of these structures are analysed and selected the most suitable lead compounds using the table of qikprop descriptors and properties.

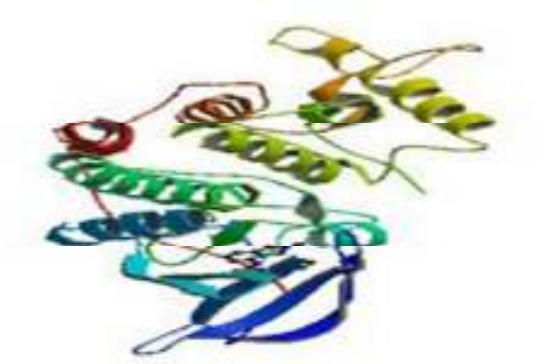
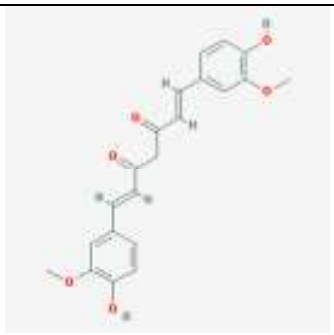
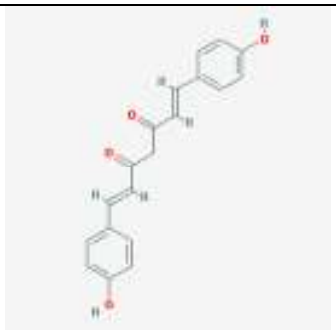
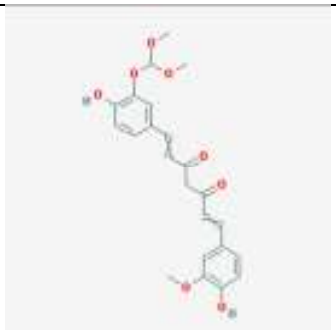
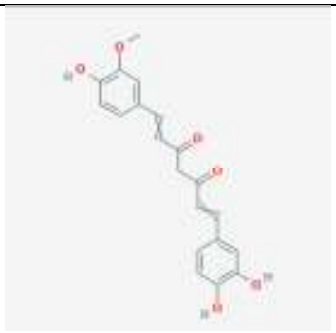
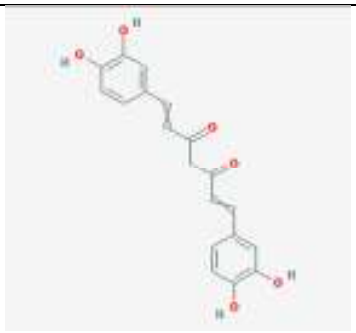
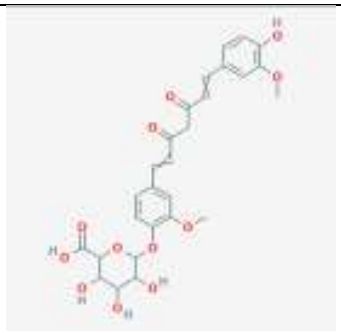
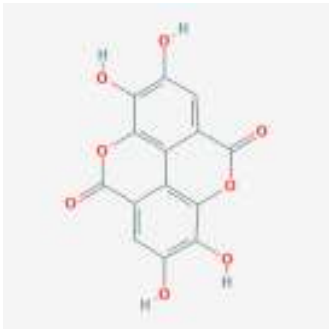
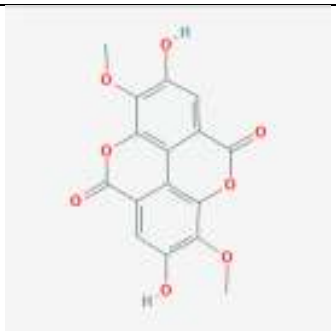
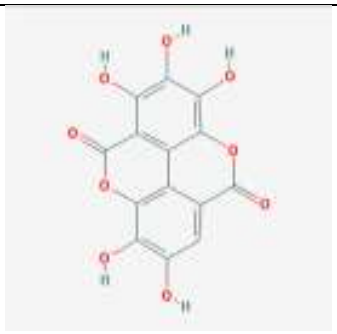
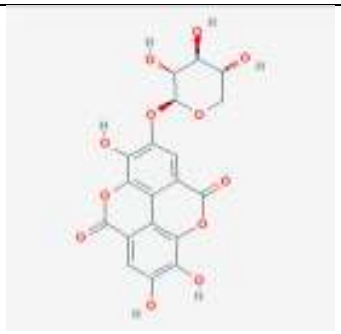
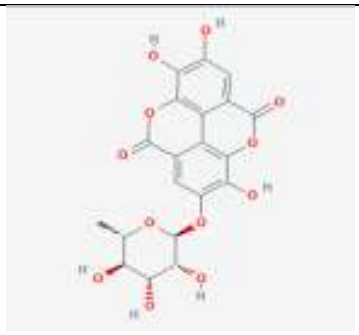


Figure 1: Structure of CDK2 protein

Tab1e 1: 2D structure of phytochemical used for the study

 curcumin	 Bisdimethoxycurcumin	 Dimethoxycurcumin
 Demethylcurcumin	 Didemethylcurcumin	 Curcumin beta d glucuronide
	 Ellagic acid	 3,4 di-0 methylellagic acid
 3,3’ di-o-methylellagic acid	 Flavellagic acid	 Ellagic acid 5-o -xylopyranoside



4-(alpha-Rhamnopyranosyl)ellagic acid

RESULTS

The current investigation showed the behavior of protein-ligand complex of CDK2 receptor with selected phytochemicals. The crystal structure of the CDK protein (1GII) was derived from PDB and used as a target for docking simulation shown in Figure 1.The docking analysis was performed with target protein and curcumin and ellagic acid derivatives using Glide xp module of Schrodinger software. The docking result of the phytochemicals with target protein is shown in table 2a and 2b.

Table 2a: Docking result of ellagic acid and its derivatives with the target protein1GII

No.	Name of compounds	Docking score	Amino acide residues involved	Rule of five	Star value
1	4-(alpha-rhamnopyranosyl) ellagic acid	-12.067	HIS82 HIE84 VAL83	2	4
2	Flavellagic acid	-10.589	VAL83 GLN131	0	1
3	Ellagic acid 4-0-xylopyranoside	10.302	VAL83 ASH145 LYS129	2	4
4	Ellagic Acid	-9.899	VAL83 GLN131	0	0
5	3,4 di-0 methylellagic acid	-9.862	VAL83	0	0
6	Ellagic acid 5-o – xylopyranoside	-8.836	VAL83 ASP86	0	0
7	3,3’ di-o-methylellagic acid	-8.660	VAL83 ASH145	0	0
8	Natural inhibitor	-7.191	HIS82 ASH145	0	0

Table 2b: docking result of curcumin and its derivatives with target protein 1GII

No	Name of compound	Glide score	Amino acid residue	Rule of five	Star value
1	Curcumin beta-D-glucuronide	-8.145	HIS82 LYS20 GLN85	4	2
2	Curcumin	-8.131	VAL83 ASH145	0	0
3	Didemethylcurcumin	-7.719	GLU8 ASH145	1	0
4	Demethylcurcumin	-7.580	HIS82	0	0
5	Bisdemethoxycurcumin	-7.343	Val83	0	0
6	Demethoxycurcumin	-5.687	ASH145	0	0
7	Curcumin 4,4 di acetate	-5.238	VAL83 ASH145	0	0
8	Natural ligand	-6.784	HIS82 ASH145	0	0

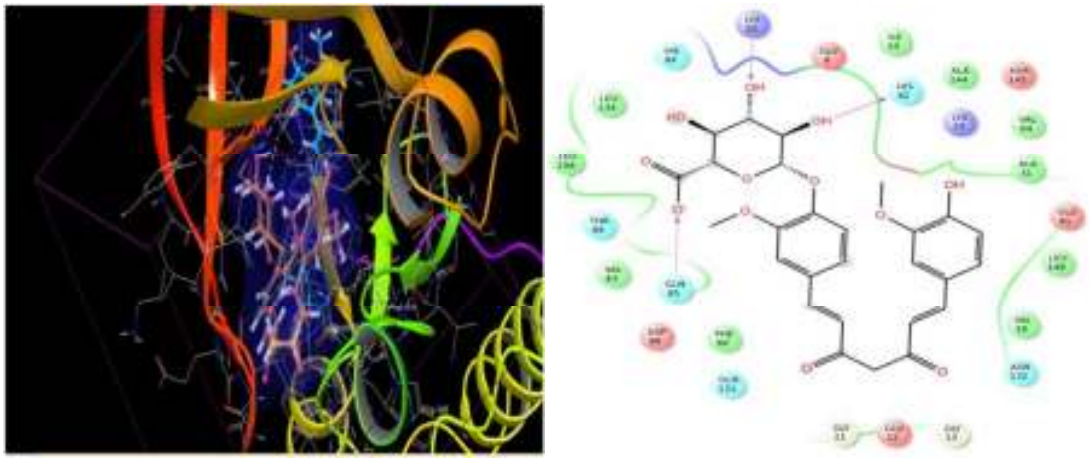


Figure 2: 3D and 2D interaction of Curcumin beta-D-glucuronide with the target receptor 1GII

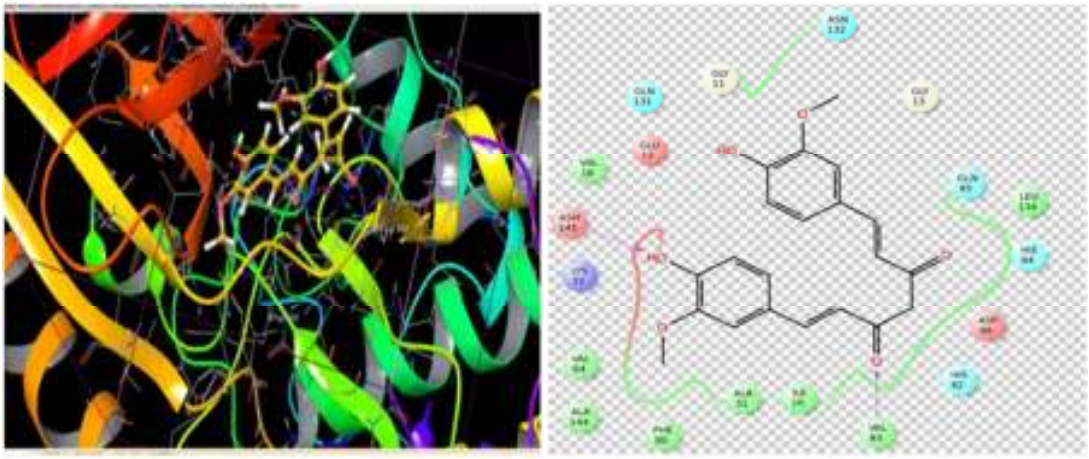


Figure 3: 3D and 2D interaction of curcumin against target protein 1GII

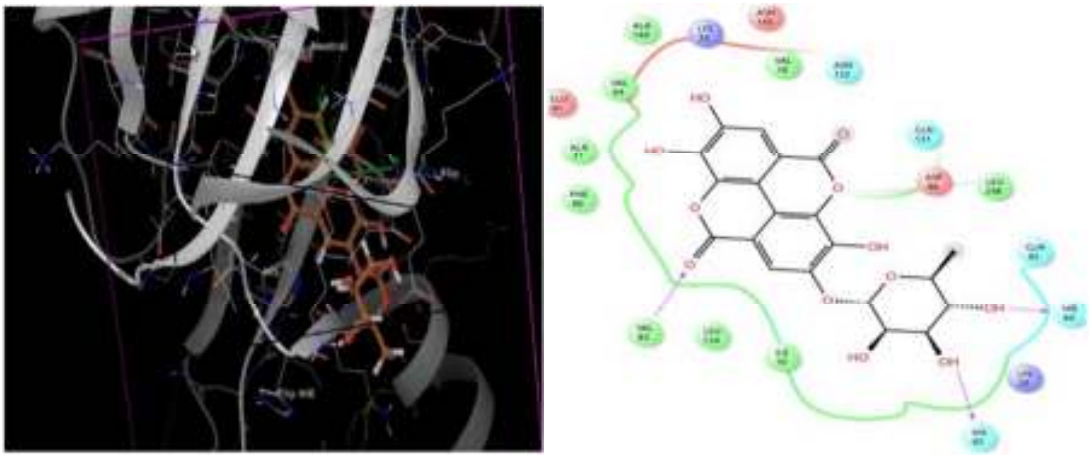


Figure 4: 3D and 2D interaction of 4-(alpha-rhamnopyranosyl) ellagic acid derivative with the target protein 1GII

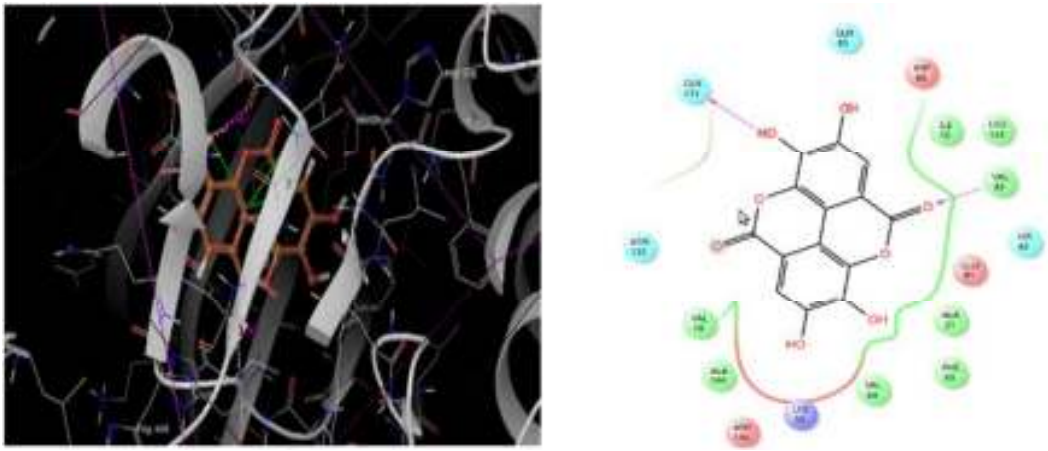


Figure 5: 3D and 2D interaction of ellagic acid with target protein 1GII

DISCUSSION

From the docking result it is evident that all the tested compound show favorable interaction with target protein.

When the receptor (1GII) was docked with ellagic acid and its analogoues the glide score ranging from -12.067 to -8.660kcl/mol which indicate good interaction with the target protein. Higher the negative value of glide score indicate good binding affinity. From this concept among ellagic acid and its derivatives, 4-(alpha-rhamnopyranosyl) ellagic acid has good glide score and better interaction with CDK2 protein. The extensive interaction observed between the two OH groups of 4-(alpha-rhamnopyranosyl) ellagic acid with HIS82, HIE84 and it form hydrogen bond at a distance 1.93A^{o} and 1.90A^{o} and also one of the oxygen atom form a hydrogen bond with the amino acid residueVAL83 at distance 2.009A^{o} respectively fig 4.ellagic acid form two hydrogen bond interaction with the amino acid residues present in the active site of the CDK protein shown in Fig 5. All other derivatives also show good glide score and interaction with the target receptor than the natural ligand.

From the docking result of curcumin and its analogues it is observed that Curcumin beta-D-glucuronide is the most potent hit against the target receptor. The glide score was ranging from -8.145 to -5.238 kcal/mol. All the tested derivatives of curcumin has better glide score than the natural ligand and are capable of inhibiting the target receptor. The Curcumin beta-D-glucuronide has the best glide score and show hydrogen bond interaction of OH group with HIS82 and LYS20 having a bond length of 2.11 and 2.59 A0 respectively. And also form a hydrogen bond between the O atom of the compound and the amino acide residue GLN85 Fig 2. These interactions lead to better binding affinity. Curcumin form hydrogen bond interaction with amino acid residues VAL83 and ASH145 of CDK2 protein with

a glide score of -8.131 kcal/mol Fig3.Toxicity analysis of all the selected phytochemicals were calculated and listed in table 2a and 2b.All the tested compound satisfy Lipnski's rule of five and ADMET properties, those were the qualities of less toxic traded drugs. Star value is an important quikprop descriptor. For less toxic drug molecule the star value must be 0-5 range.

CONCLUSION

In the present work we have used the SCHRODINGER software for finding the anticancer effect of the ellagic acid and curcumin analogues. From the in-silico based docking study it can be concluded that both polyphenolic compounds ellagic acid and curcumin derivatives show activity against the target protein. Computational method provide information on the interaction and binding affinity between the phytochemical and the CDK2 protein. The present study reveal that all the selected compounds could be potential lead molecule for the inhibition of CDK2 receptor. VAL83, HIS82, GLN85, ASH145 and LYS20 are the important residues for potent drug target. These amino acid residues present on the active site of the target CDK2 protein are the main contributors to the protein-ligand interaction. The protein-ligand interaction play an key role in the structure based drug discovery. Qikprop calculation also show that all the tested compound are nontoxic and have drug like properties as they obey lipnski's rule of five. Compound which don't obey this rule may have problem with bioavailability.

By compairing the docking result and interactions in docking method it is found that ellagic acid and its analogues are more promising against cancer than curcumin and its analogues. The result of the current study can be helpful for the designing and development of new CDK2 inhibitors that can consequently be used to cure cancer.

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