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COMPUTATIONAL APPROACH TOWARDS EXPLORING POTENTIAL ANTI- HERPES SIMPLEX VIRUS TYPE 1 ACTIVITY OF SELECTED PHYTOCOMPOUNDS FROM CINNAMOMUM ZEYLANICUM

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Abstract: Herpes simplex (more commonly known as herpes) is classified into two types: Herpes simplex Virus Type 1(HSV-1) and Herpes simplex Virus Type 2(HSV-2). HSV-1 usually causes mouth and lip sores (also called cold blisters). HSV-1 may cause genital herpes, but HSV-2 in the vaginal herpes is most common. Hence, discovering an effective compound to combat herpes infections is essential. The aim was to predict possible interactions between Thymidine Kinase (TK) as one of the most important viral elements in intracellular HSV-1 replication and 5 potential phytochemicals from *Cinnamomum zeylanicum* by using a computational approach. 3-Dimensional Structure of Thymidine Kinase (TK) has been retrieved from the Protein Data Bank, prepared and docked with Rutin, Quercetin , Kaempferol , Isorhamentin and Catechin as ligands with Autodock vina. The highest ligand binding affinity to the targeted protein based on minimal binding energy was calculated. More research was carried out in order to identify the protein active site interacted with the ligands examined and all intermolecular bonds that exist. By showing best related affinity (−9,2 kcal / mol) compared to the other ligands, Rutin was described as the most possible inhibitor of viral activity. Rutin can be considered a promising compound for further evaluation as a potentially efficient antiviral compound against HSV-1.

Keywords: HSV-1, Thymidine Kinase,Autodock Vina, antiviral.

1.Introduction

Herpesviruses are a group of double-stranded human DNA viruses. [1] There are three subfamilies of herpesviruses: alpha-, beta- and gamma-herpesviruses.[2]Herpes simplex virus type-1 (HSV-1), HSV-2, and varicella- virus (VZV) are the human viruses included in the alpha subfamily.[2]The alpha subfamily is separated from other viruses because it has the widest variety of host and a fairly short replicative period. [2] HSV-1 and -2 infect as many as 90 percent of the world's adults. [1] HSV-1 alone infects 66 percent of the population worldwide. HSV-1 seropositivity was registered among 65 percent of Americans and over 50 percent of Europeans.[3, 4] HSV-1 and HSV-2 may cause serious illness in immunocompetent adults and newborns, such as life-threatening sequelae encephalitis, despite antiviral theraphy.4 Such viruses may also cause eye infections that lead to vision impairment: HSV-1 is currently the primary cause of infectious blindness in developing countries.[5] There are currently some commercially available antivirals for treating lesions of the skin caused by HSV-1 and HSV-2. However, these drugs are somewhat inadequate for this form of clinical manifestation, as in most cases they only shorten the recovery time of the lesions within 1–2 days.[6] Several natural products have antiviral activity against HSV-1 and HSV-2, such as fractionated compounds and isolated molecules from microorganism and plants.[7]Additionally, several herbal medicinal plants worldwide have been reported to have antiviral activity against HSV-1 and HSV-2.[8] Interestingly, various forms of natural compounds, such as alkaloids, polysaccharides and proteins display antiherpetic activity.[9] Plant-derived flavonoids are polyphenolic compounds with a broad variety of biological benefits for human health, including anti-inflammatory, antioxidant, antibacterial and antiviral activity. [10] That the number of drug-resistant microorganisms has brought natural compounds such as flavonoids to the fore as an essential natural resource for overcoming this problem. Broad studies have shown that different forms of flavonoids such as rutin, naringin, baicalein, quercetin and kaempferol [11] are potential antivirals against a wide range of important viruses like dengue virus. [12] *Cinnamoum zeylanicum* (Family Lauraceae), commonly called cinnamon, is included in the Magnoliophyta botanical group, Magnoliopsida class.[13] In the Ayurvedic method, cinnamon is used as the flu prevention medication, indigestion and flatulence. Bark is commonly used for preparation of medicine and Mouthwashes. [14] *Cinnamomum zeylanicum* is also used to treat dyspeptic conditions, such as mild gastrointestinal conditions, fullness and loss of appetite. This is also used to treat stomach pain with diarrhoea, amenorrhea and

dysmenorrhoea pain. Cinnamon is used in impotence remedies, colds, dyspnosis. inflammation of the eye, leucorrhoea, vaginitis, rheumatism, neuralgia, trauma, toothache and diabetes.[15] The different parts of the plant (bark, roots, leaves, seeds, fruit stalks, and buds) produce essential oils, which are variable in composition. The biological properties of Cinnamon are mainly due to its biological composition. The bioactive compounds present in Cinnamon bark were identified by Gas Liquid Chromatography and it does mainly contain volatile oils and Phenolic Compounds. The major Phenolic compounds present in Cinnamon are Rutin, Quercetin, Kaempferol, Isorhamentin and Catechin.[16]

Thymidine kinase (TK) is an enzyme which plays a key role in the synthesis of the DNA in HSV-1 virus, and its inhibition by antiviral drugs prevents the propagation of the virus. [17, 18]

Herpes simplex (HSV), a thymidine kinase (TK), is a multi-substrate enzyme with both TK and TMPK activity. [19] Herpes simplex virus type 1 (HSV 1) thymidine kinase (TK) is a multifunctional enzyme that possesses kinase activities normally performed by three separate cellular enzymes. It transforms thymidine and deoxyuridine (dU) into the triphosphorylated DNA block via cell kinases; both reactions can be compared to the work of human cell TK. Until now, no effective treatment is available for such infections. The treatments of the day include the use of antiviral medicines in order to reduce the physical severity of the outbreak of associated lesions and viral shedding. [20]

This work was aimed to describe the antiviral activity of compounds from *Cinnamomum zeylanicum* bark by using *in silico* molecular docking analysis to find out the novel compound having the inhibitory activity against Thymidine Kinase enzyme.

2. MATERIALS AND METHOD

2.1 Preparation of Ligand

The five isolated phytocompounds from *Cinnamomum zeylanicum* such as Rutin, Quercetin, Kaempferol, Isorhamentine and Catechin have been investigated as promising therapeutic compounds for their pharmacological potential and biological activity. 2D and 3D structures of the chemical compound were collected from the online server, Pubchem (http:/pubchem.nnlm.nih.gov/) and ChemSpider (http:/www.chemspider.com/), and every chemical compound was designed using ACD / chemsketch bioinformatics software and saved as a '.mol' in the format of a '.mol'.

2.2 Preparation of Protein

The protein was prepared by retrieving the three-dimensional crystal structure of the Thymidine Kinase (TK) (ID - 4OQL) from the Protein Data Bank and this was used as the receptor for molecular docking.

2.3 Molecular Docking Using AutoDock Vina

AutoDock Vina input files have been optimized using AutoDock Tools versus 1.5.6. Using AutoDock Vina at 1.00A to identify the binding site, the protein was put in a grid box measuring 26.85Å / 28.17Å = 24.53Å along the x, y and z axes respectively after the minimizing process. Along with the addition of hydrogen bonds and the Gasteiger charge, the configuration file used for the docking process was also prepared. The docking procedure was done using the prompts provided for the command. The docking results included the binding energy value in kcal / mol, hydrogen bond positions, pi-pi interactions and strongly interactive residue. [22]

2.4 Analyzing and Output Visualization using Discovery Studio.

The docking poses were ranked according to the docking scores. In AutoDock, scoring function was used to predict one ligand's binding affinity to the receptor molecule. After the docking phase, the conformation with the lowest binding affinity was selected for further study. The Ki equation was determined by the equation: $Ki = \exp[(\Delta G*1000)/(R*T)]$, where ΔG is docking energy, R (gas constant) is 1.98719 cal K^{-1} mol^{-1} and T (temperature) is 298.15K. For each ligand only the best pose was considered (the one with the lowest binding energy). The docked complexes were molecularly visualized using the Accelrys Discovery Studio software package.

3. RESULT

Using default scoring function in AutoDock Vina, the ligand conformations were ranked according to their expected binding affinities. Thymidine Kinase enzyme residues that formed close contacts with compounds are listed in Table 1 and shown in Fig. 1. Isorhamentin showed a binding affinity of – 7.5 kcal mol^{-1}, while Rutin showed the most active antiviral activity with a binding affinity of –9.2 kcal mol^{-1} among the five compounds studied. All compounds exhibit the highest binding affinity Compared to Acyclovir, which is widely used as an antiviral agent. The binding affinities, interaction energy and intermolecular hydrogen bonds formed along with their distances between each compound and Thymidine Kinase are presented in Table 1.This shows that most hydrogen bond donors came from protein residues and that the corresponding acceptors came from ligand. It is evident that there were interactions of the ligand with 9 residues in the active site of Thymidine Kinase (Catechin: ASP313; Isorhamentin: ASP313; Kaemperol: ALA 137, SER 254, ARG 256, ARG 320, LYS 317; Quercetin: TRP 310; Rutin: TRP 310, VAL 314;). There was also one pi-pi interaction between Isorhamentin with Thymidine Kinase residue Trp 255 (Table 2). The best docking pose for each ligand and its interaction was shown in Figure 1-4.

Table 1: Binding affinity, Interaction residue and Intermolecular H bond between each compound against TK

S.No	Compound	Docking score (Kcal/mol)	No of Bond	Interacting Residues	Bond Length (Å)
1.	Catechin	-7.2	1	ASP 313	2.94 (O-H)
2.	Isorhamentin	-7.5	1	ASP 313	3.79 C-H
3.	Kaemperol	-7.4	5	ALA 137	2.38(O-H)
				SER 254	1.99(O-H)
				ARG 256	2.10(O-H)
				ARG 320	2.43(O-H)
				LYS 317	1.99(O-H)
4.	Quercetin	-7.3	1	TRP 310	2.53(O-H)
5.	Rutin	-9.2	1	TRP 310 VAL 314	2.53(O-H) 3.52 (C-H)
6.	Acyclovir	-5.6	2	ARG 320 HIS 142	2.29 (O-H) 2.62 (O-H)

Table 2: Pi-pi interaction between Isorhamentin and TK, TRP 255.

S.No	Compound	Docking score	No of Bond	Interacting Residues	Bond Length (Å)
1.	Isorhamentin	-7.5 Kcal/mol	1	TRP 255	4.90 Pi-pi

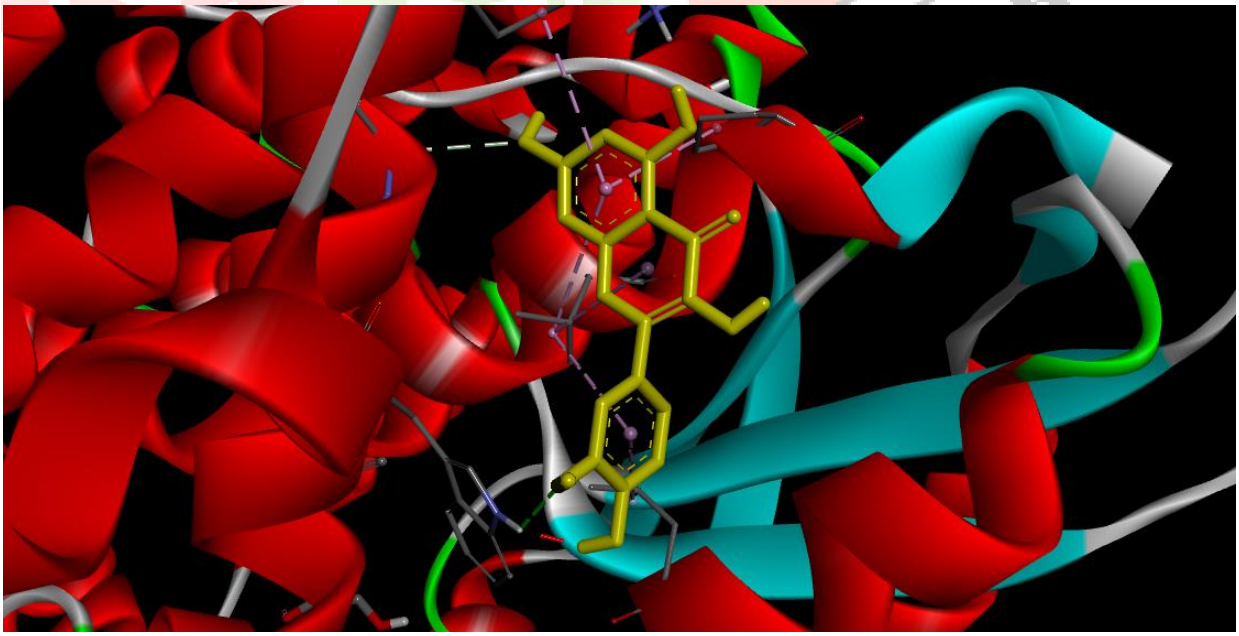

Figure 1: Rutin Docked to the active site of Thymidine Kinase (TK)

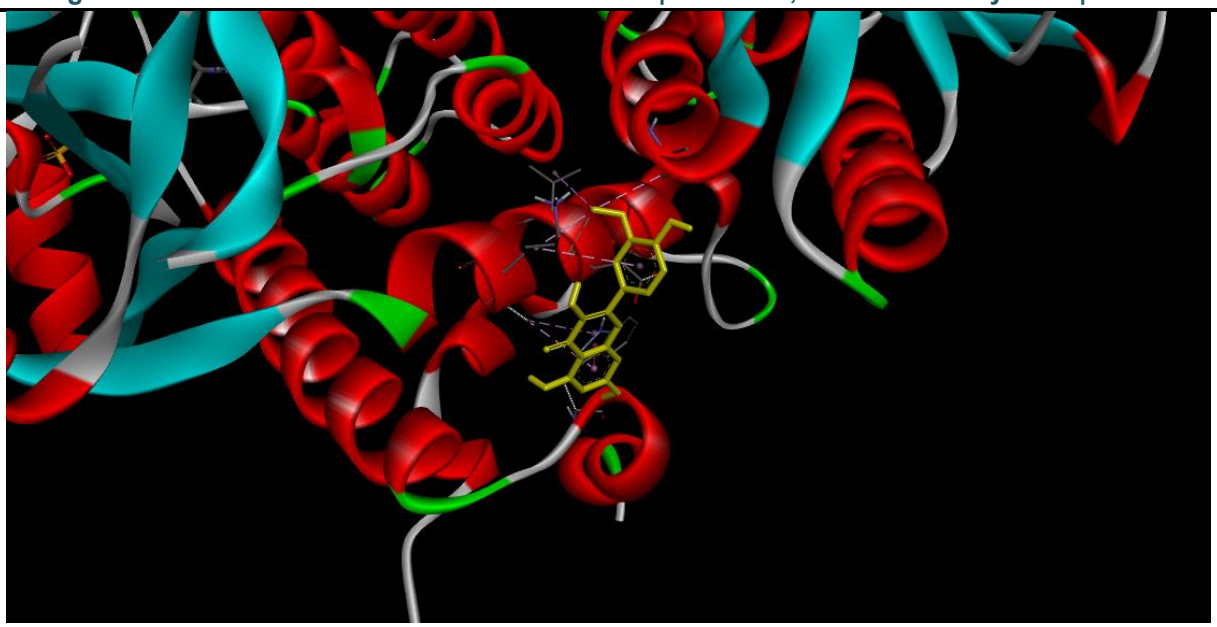

Figure 2: Isorhamentin docked to the active site of Thymidine Kinase (TK)

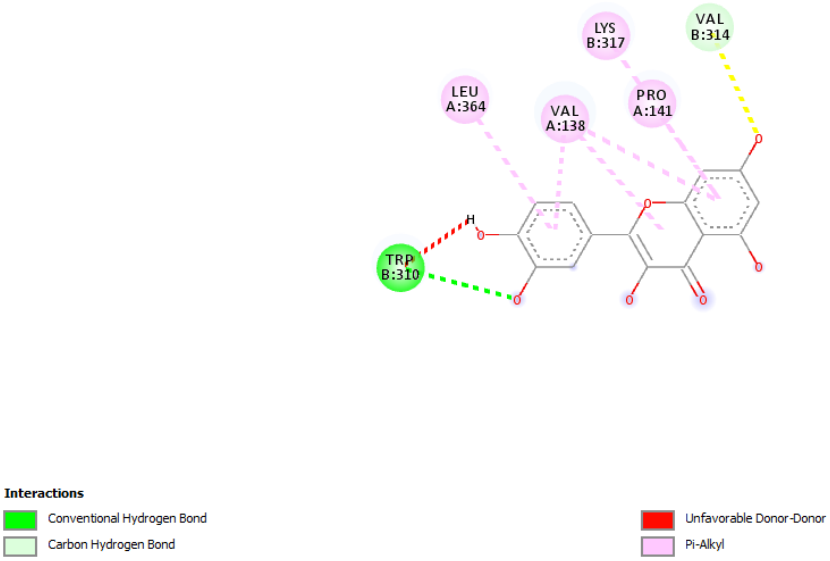

Figure 3: Ligand Interaction Map of Rutin

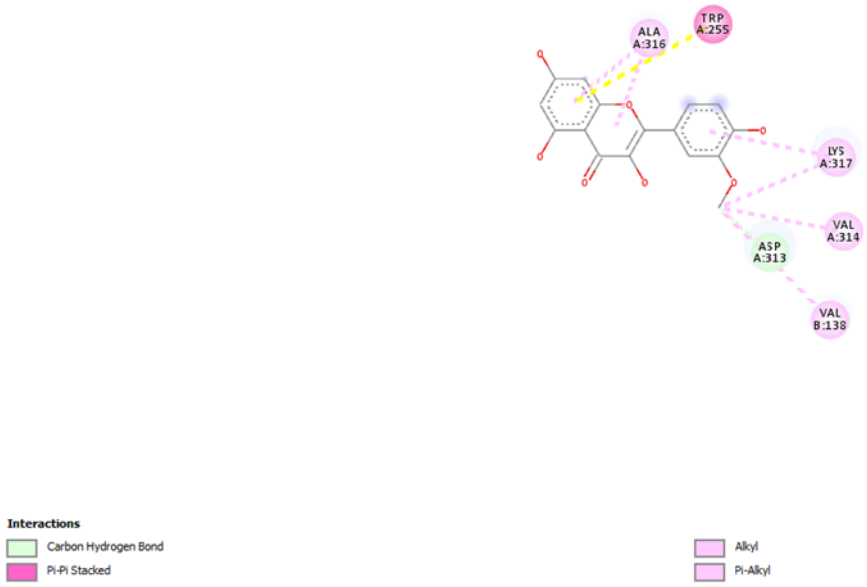

Figure 4: Ligand Interaction Map of Isorhamentin

4. DISCUSSION

In this research, we carried out molecular docking of the Rutin, Catechin, Kaempferol, Isorhamentin and Quercetin by AutoDock Vina. All the compounds exhibit strong inhibitory action against HSV Type -1 Virus by acting against Thymidine Kinase, enzyme necessary for viral replication. Rutin showed the stronger interaction with Thymidine Kinase and has shown the most potent anti-HSV (Type-1) activity with a binding affinity of −9.2 kcal / mol, preceded by Isorhamentin and Kaempferol with binding affinities of −7.5 and −7.4 kcal / mol respectively.

Rutin showed interaction with two residues of active site (TRP 310, VAL 314) with distance ranges from 2.53 and 3.52 A. Similarly, the hydrogen bonds formed when Isorhamentin (THR111) and Kaempferol (CYS34, LEU108, ARG144) were docked to the active site were also observed.All intermolecular hydrogen bonds between Rutin and active site in this study fell under the moderate bond group with one exception, interaction with the VAL 314 residue, which was categorised as a carbon Hydrogen bond.

New therapeutic molecules can be developed using computerized drug design. A promising target for the selected compounds of *Cinnamomum zeylanicum* for the Herpes Simples Virus (HSV-1) compounds with the Thymidine Kinase was achieved during the current study. The interactions between receptor and inhibitor were studied with AutodockVina along with Discovery Studio and the ideal interacting inhibitor tested. The Thymidine Kinase receptor, which participates in replication of HSV1, is interactive for Rutin, Catechin, Kaempferol, Isorhamentin and Quercetin with optimal fitness ratings. This work is also important in the pharmaceutical industry as computer screens minimize the difficulty of identifying new lead molecules and manufacturing them.

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