Virtual screening and docking assessment of catechin from Psidium guajava leaves as a natural therapeutic agent against breast cancer

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Abstract

Catechin is a strong bioactive substance that exhibits anticancer properties. This study investigates the anticancer efficacy of catechin from the leaves of Psidium guajava on breast cancer targets through in-silico analyses. The objectives of the current study were to predict the Lipinski rule of 5, examine its ADMET profile, and analyze protein-ligand interactions relevant to breast cancer progression and apoptosis regulation. The results from the in-silico analyses supported that the Catechin follows the Lipinski rule of 5 and has favourable ADMET properties. Catechin showed higher binding affinity towards Catalase, CDK4, and CDK6, as (-9.4, -8.3, and – 8.0) respectively. Catechin showed more hydrogen bond interactions with Bak, Caspase 9 and Superoxide dismutase. The findings provide compelling in-silico evidence for the anticancer potential of catechin, supporting its role as a therapeutic lead compound. Further in vitro and in vivo studies are warranted to validate these interactions and establish its clinical applicability. This study highlights catechin as a powerful herbal bioactive candidate with potential for the development of novel breast cancer therapeutics.

INTRODUCTION

Psidium guajava (L.), a fruit that is significant in tropical regions such as Bangladesh, Pakistan, Indonesia, India, and South America, is a member of the Myrtaceae family.[1] All the parts of guava have various pharmacological activities. Numerous phytochemicals, including quercetin, avicularin, apigenin, guaijaverin, kaempferol, hyperin, myricetin, gallic acid, catechin, epicatechin, chlorogenic acid, epigallocatechin gallate, and caffeic acid, have been linked to the health benefits of guava plant leaves.[2] It has also been used to treat dental conditions, coughs, and acne. The biological properties of guava leaf (GL) extracts, such as their antimalarial, anticancer, antidiabetic, antioxidant, antidiarrheal, antibacterial, lipid-lowering, and hepatoprotective properties, have been investigated.[3] Guava's anticancer properties have been tested on prostate cancer cells, cervical cancer cells, colon cancer cells, blood cell cancer and stomach cancer.[4]

Catechin is a flavonoid commonly found in berries, tea, fruits and medicinal plants. Catechin exhibits pharmacological activities including anti-bacterial activity, antifungal, anti-cataract, anti-viral, anti-hypercholesterolemic, anti-allergic effect, anti-oxidant, anti-diabetic, anti-allodynic properties, anti-inflammatory and anti-cancer activities. It works by scavenging reactive oxygen species and blocking pro-oxidant enzymes and transcription factors. By acting on the nuclear factor kappa B (NFκB), which possesses a redox-sensitive transcription factor, catechin is known to reduce oxidative stress.[5] Catechin has been reported to possess anti-cancer activities against breast cancer [6], lung cancer [7], stomach cancer cells, Colorectal cancer and liver cancer. [8]

Several variables contribute to breast cancer, one of the most fatal illnesses that affect women. The patient needs treatment during the healing phase, including chemotherapy, surgery, and radiation therapy. However, these methods harm healthy cells due to preventable flaws. Natural sources can still be used in the medical sector today. According to its phytochemical characteristics, Psidium guajava

produces chemicals that stop cancer cells from growing.[9] Therefore, the current study aimed to document the target-ligand interactions of catechin derived from the leaves of *Psidium guajava* with cell cycle, apoptotic, ROS and NF-κB proteins using an *in-silico* technique.

METHODOLOGY

LIGAND PREPARATION:

PubChem is a publicly accessible chemical information database maintained by the National Institutes of Health (NIH), United States. PubChem aggregates biological activity descriptions for a chemical from hundreds of sources and makes them available to all. The canonical SMILES of catechin were taken from PubChem. ACD/ChemSketch was employed to illustrate the 2D structure of the ligand catechin.[10, 11]

DRUG-LIKELINESS PROPERTIES:

The pharmacokinetic properties, including the Lipinski's Rule of 5 and ADMET characteristics were analysed using the pkCSM tool.[12]

PROTEIN PREPARATION:

The 3D structure of Cell cycle proteins, Cyclin-D1 (PDB ID:2W99_A), Cyclin-D3 (PDB ID:3G33_B), Cyclin-Dependent Kinase 4 (CDK4) (PDB ID:3G33_A), Cyclin-Dependent Kinase 6 (CDK6) (PDB ID:1G3N_A), Cyclin Dependent kinase inhibitor 4c (p18 INK4c) (PDB ID:1G3N_B), Cyclin Dependent kinase inhibitor 1 (p21WAF1 /CIP1) (PDB ID:1AXC_B), Cyclin-dependent kinase inhibitor 1B (p27 KIP1) (PDB ID:1JSU_C), Apoptotic proteins, B-cell lymphoma-extra-large (Bcl-xL) (PDB ID:1G5J_A), B-cell leukemia/lymphoma 2 protein (BCL-2) (PDB ID: 1G5M_A), Caspase 3- apoptosis-executing protease (Caspase 3) (PDB ID:1GFW_A), Caspase 9-apoptosis-initiating protease (Caspase 9) (PDB ID:1NW9_B), Caspase 6-apoptosis-executing protease (Caspase 6) (PDB ID: 2WDP_A), Caspase 8-apoptosis-initiating protease (Caspase 8) (PDB ID: 5JQE_A), BCL-2-associated X protein (Bax) (PDB ID: 2K7W_B), BCL-2 antagonist/killer (Bak) (PDB ID:2YV6_A), ROS (Reactive Oxygen Species) proteins, Catalase (CAT) (PDB ID:1QQW_A), Superoxide dismutase (SOD) (PDB ID:1SPD_A), Glutathione peroxidase-2 (GPx-2) (PDB ID:2HE3_A), Peroxiredoxin (PDB ID:1OC3_A), NF-κB Subunit proteins, Nuclear factor NF-kappa-B p52 subunit (NF-κB/p52) (PDB ID: 1A3Q_A), Nuclear factor NF-kappa-B p65 subunit (NF-κB/p65) (PDB ID: 1NFI_A) and Nuclear factor NF-kappa-B p100 subunit (NF-κB/p100) (PDB ID: 3DO7_B) were obtained from Protein Data Bank (PDB). The receptors were prepared by removing water molecules, nucleic acid groups, native ligand groups and heteroatoms, followed by the addition of polar hydrogen atoms to optimize receptor-ligand interactions using BIOVIA Discovery Studio Visualizer 2021 Client software.[13]

GRID BOX GENERATION

Grid box generation is a crucial step in molecular docking, as it defines the spatial boundaries within which the ligand explores potential binding conformations on the target protein. The grid box in this investigation was meticulously positioned to cover the target protein's whole active region. The centre coordinates were manually modified according to the location of important active site residues, and the grid dimensions were normally set at 25 × 25 × 25 Å. Either the co-crystallized ligand found in the protein structure or projected binding pocket studies were used to determine these coordinates. As a result, the most pertinent area of the protein for ligand interaction was sufficiently covered by the grid. Grid parameters were chosen to maximise docking result accuracy while preserving computational performance.

MOLECULAR DOCKING

PyRx version 0.8, which uses AutoDock Vina as its default docking engine, was used to run molecular docking simulations. The Open Babel module built into PyRx was used to minimise the energy of ligand molecules in order to optimise their shapes before docking. In order to balance computing efficiency and sampling thoroughness, the exhaustiveness value was set at 8 in the docking protocol, which used AutoDock Vina's default parameters. Binding affinity scores, which are represented as Vina scores (kcal/mol), were used to evaluate the docking data; lower values suggest more advantageous interactions. The native co-crystallized ligand was re-docked into the target protein's active site to confirm the docking protocol's accuracy. The predicted binding pose was then compared to the experimentally observed position using Root Mean Square Deviation (RMSD) analysis. An RMSD value of ≤ 2.0 Å was considered indicative of reliable and reproducible docking performance.[14, 15, 16, 17]

VISUALIZATION OF TARGET-LIGAND INTERACTION:

The docking poses were further analyzed to identify key molecular interactions, including hydrogen bonds, hydrophobic contacts, and π–π stacking, using the BIOVIA Discovery Studio Visualizer 2021 Client software. By bringing the result into the BIOVIA Discovery Studio Visualizer 2021 Client program, which showed the 3D and 2D interactions of the docking output with the bond length, we were able to find an important interaction between the ligands and the receptor binding site. [13]

RESULTS

Table 1
Catechin-LIPINSKI rule of 5

Ligand	Mol. Weight	LogP	# Rotatble bonds	# Acceptors	# Donors	Surface area
Catechin	290.271	1.5461	1	6	5	119.662

Table 2
ADMET properties of Catechin.

ADMET Properties	Catechin
Internal absorption (Human) (% Absorbed)	71.562
BBB permeability (log BB)	-0.905
CYP2D6 substrate	No
CYP2D6 inhibitior	No
Total clearance (log ml/min/kg)	0.215
AMES toxicity	Yes
Oral Rat Acute Toxicity (LD50) (mol/kg)	2.101
Oral Rat Chronic Toxicity (LOAEL) (log mg/kg-bw/day)	2.076
Hepatotoxicity	No

Table 3
Binding affinity and hydrogen bond interactions of catechin.

Target types	Targets	Binding affinity (kcal/mol)	H bond interaction with bond length	Other interactions with bond length
		Catechin		
Cell cycle proteins	**Cyclin D1**	-6.9	CYS A:73 (2.34Å) HIS A:158 (1.87Å)	Pi-Alkyl interaction: ALA A:187 (4.56Å) Carbon Hydrogen bond interaction: PRO A:79 (3.49Å)
	Cyclin D3	-6.9	ARG B:87 (2.64Å) ARG B:37 (2.30Å, 2.54Å)	Pi-Alkyl interactions: ARG B:41 (3.82Å) CYS B:91 (4.73Å) LYS B:149 (4.75Å) Pi-Anion interaction: ASP B:151 (4.22Å)
	CDK4	-8.3	GLU A:149 (2.04Å)	Pi-Alkyl interaction: ALA A:38 (4.50Å) ALA A:162 (5.21Å) ILE A:17 (4.79Å) Pi-Sigma interaction: LEU A:152 (3.49Å) Pi-Anion interaction: ASP A:104 (3.81Å)
	CDK6	-8.0	THR A:58 (1.97Å)	Pi-Alkyl interaction: VAL A:45 (4.45Å) LEU A:65 (4.79Å) Pi-Pi Stacked interaction: TYR A:24 (4.05Å) Pi-Anion interaction:

				GLU A:61 (3.63Å)
	P18 INK4c	-6.2	HIS B:125(2.52Å)	Pi-Alkyl interaction: VAL B:96 (5.37Å) Pi-Pi Stacked interaction: PHE B:121 (5.18Å) Pi-Sigma interaction: LEU B:90(3.85Å,3.96Å)
	P21 CIP1	-4.7	ARG B:156(2.27 Å) LYS B:154(1.77Å)	-
	P27 KIP1	-5.9	GLU C:75(2.83Å) GLN C:77(2.41Å)	Pi-Pi Stacked interactions: TRP C:60(3.69Å, 4.63Å) Carbon Hydrogen bond interaction: TRP C:76 (3.35Å)
Apoptotic proteins	**Bcl-xL**	-7.0	-	Carbon Hydrogen bond interaction: TRP A:173 (2.55Å, 3.05Å) Pi-Donor Hydrogen bond interaction: TYR A:124 (2.45Å)
	Bcl-2	-7.5	TYR A:9(2.29Å) ASP A:196(2.85Å)	Pi-Alkyl interaction: ILE A:189 (4.55Å) Pi-Pi Stacked interaction: HIS A:186 (4.69Å) Unfavorable Donor-Donor interaction: ASN A:182 (2.97 Å)
	Caspase 3	-5.9	THR A:140(2.49Å) ASN A:141 (2.03Å) GLY A:145(2.94Å)	Carbon Hydrogen bond interaction: ARG A:144 (3.35Å) Pi-Cation interaction: LYS A:156 (3.62Å, 4.71Å)

	Caspase 9	-6.9	SER B:339 (0.84Å, 2.89Å) GLY B:277 (2.39Å) LEU B:275 (2.76Å) GLY B:269 (2.45Å)	Unfavorable Donor-Donor interaction: ASP B:340 (2.95Å)
	Bax	-4.9	ARG B:153(2.71Å) GLN B:150(3.00Å) GLU B:151(2.28Å)	Pi-Sigma interaction: ARG B:154 (3.55Å)
	Caspase 6	-7.1	-	Pi-Sigma interaction: ALA A:162 (3.61Å) LYS A:133 (3.51Å) Pi-Alkyl interaction: LEU A:200 (4.88Å) Pi-Anion interaction: GLU A:214 (4.85Å)
	Bak	-7.1	ARG A:87 (3.01Å) ASP A:83 (2.24Å) ASN A:86 (2.96Å) ALA A:79 (2.85Å) GLN A:45 (2.25Å) ARG A:42 (2.14Å) SER A:91 (3.02Å)	Pi-Anion interaction: GLU A:46 (4.00Å)
	Caspase 8	-7.3	ALA A:372 (2.53Å) THR A:357 (2.59Å)	Pi-Alkyl interaction: ALA A:375 (4.28Å) Carbon Hydrogen bond interaction: HIS A:379 (3.56Å) GLU A:1056 (3.65Å) Pi-Pi T-Shaped interaction: TYR A:353 (5.75Å)
ROS proteins	**Superoxide dismutase**	-6.6	SER A:98 (1.96Å)	Pi-Alkyl interaction:

			ASN A:86(2.71Å, 2.75Å) SER A:102 (2.15Å, 2.40Å) PRO A:74 (3.00Å)	ILE A:99 (4.33 Å)
	Catalase	-9.4	HIS A:362 (2.24Å)	Unfavorable Donor-Donor interaction: ARG A:72 (1.20Å) PI-Alkyl interactions: ALA A:357 (5.38Å) ALA A:133 (5.10Å) VAL A:74 (5.31Å) Pi-Pi Stacked interaction: TYR A:358 (3.66Å) HIS A:75 (4.92Å) PI-Cation interaction: ARG A:112 (4.94Å)
	Glutathione peroxidase	-6.5	LYS A:87 (2.77Å) LEU A:101(1.82Å)	Unfavorable Acceptor - Acceptor interaction: PRO A:97 (2.91Å) Pi-Sigma interaction: LEU A:83 (3.96Å)
	Peroxiredoxin	-6.5	GLU A:16 (2.28Å) VAL A:94 (2.97Å) GLY A:85 (2.92Å)	Pi-Alkyl interaction: ALA A:90 (5.40Å) ARG A:86 (5.04Å) Pi-Anion interaction: GLU A:91 (4.92Å)
NF-κB Subunit proteins	**NF-κB/p52**	-6.9	GLU A:92 (2.84 Å)	Pi-Sigma interaction: ILE A:119 (3.71 Å)
	NF-κB/p65	-6.8	VAL A:244 (2.66Å) LYS A:221 (2.85Å, 4.35Å, 4.64Å)	Unfavorable Donor-Donor interaction: GLN A:247 (1.15Å)

		GLN A:29 (2.00Å,2.74Å)	Carbon Hydrogen bond interaction: ARG A:246 (3.47Å) GLN A:220 (3.01Å) Pi-Donor Hydrogen bond interaction: HIS A:181 (3.17Å)
NF-κB/p100	-7.3	HIS B:105 (2.55Å, 2.81Å)	Unfavorable Donor-Donor interaction: LYS B:153 (1.61Å) Carbon Hydrogen bond interaction: GLY B:118 (3.60Å) Pi-Alkyl interaction: ALA B:104 (4.47Å) ARG B:156 (5.45Å)

DISCUSSION

Lipinski's rule of five and ADME/T Properties

The molecular weight of catechin is 290.271Da, LogP is 1.5461, Hydrogen bond acceptors are 6 and Hydrogen bond donors are 5. It has 1 rotatable bond, with a surface area of 119.662 Å². The results show that catechin obeys Lipinski's rule of 5 (Table 1). Catechin has 71.562% of intestinal absorption. Catechin is not a substrate or inhibitior for CYP2D6. Catechin has − 0.905 (log BB) BBB permeability, 0.215 (log ml/min/kg) total clearance, 2.101 (LD50) (mol/kg) Oral Rat Acute Toxicity and 2.076 (log mg/kg-bw/day) Oral Rat Chronic Toxicity. Catechin shows no hepatotoxicity but exhibits AMES toxicity (Table 2).

Molecular Docking

Molecular interaction analyses were done for the cell cycle, apoptotic, ROS (Reactive Oxygen Species) proteins and NF-KB proteins. Catechin interacted with 22 targets (Cyclin D1, Cyclin D3, CDK4, CDK6, P18 INK4c, P21 CIP1, P27 KIP1, Bcl-xL, Bcl-2, Caspase 3, Caspase 9, Bax, Caspase 6, Bak, Caspase 8, Superoxide dismutase, peroxiredoxin, Catalase, Glutathione peroxidase, NF-κB/p52, NF-κB/p65, NF-κB/p100). Among them, catechin showed higher binding affinities towards catalase, CDK4 and CDK6 with docking scores of − 9.4, − 8.3, and − 8.0 kcal/mol, respectively.

Catechin showed seven hydrogen bond interactions with Bak (ARG A:87 (3.01Å), ASP A:83 (2.24Å), ASN A:86 (2.96Å), ALA A:79 (2.85Å), GLN A:45 (2.25Å), ARG A:42 (2.14Å), SER A:91 (3.02Å). Catechin showed

four hydrogen bond interactions with Caspase 9 (SER B:339 (0.84Å, 2.89Å), GLY B:277 (2.39Å), LEU B:275 (2.76Å), GLY B:269 (2.45Å) and Superoxide dismutase SER A:98 (1.96Å),ASN A:86(2.71Å, 2.75Å), SER A:102 (2.15Å, 2.40Å), PRO A:74 (3.00Å). There are no hydrogen bond interactions with Bcl-xL and Caspase 6 (Fig. 2, 3, 4, 5 and Table 3).

Molecular Insights into Breast Cancer Progression

Studies using shortened Bak molecules have shown that although they lack the membrane anchoring region, the truncated molecule can still attach to Bcl-xL. Gene transfer-induced increases in BAK protein levels hasten the apoptosis that growth factor deprivation induces in breast cancer cells.[18]

Apoptosis is triggered by two main pathways: the intrinsic (or mitochondrial) pathway is triggered by mitochondrial release of cytochrome c, which results in the formation of the Apaf-1 and cytochrome c complex with the aid of ATP, which in turn activates caspase-9 and caspase-3; the extrinsic [or death receptor (DR)] pathway is triggered by ligand binding of DRs superfamily members, which activates caspase-8 and caspase-3.[19] Two subgroups of the common apoptotic caspases are the starter caspases (caspase-2, -8, -9, and − 10), and the effector caspases (caspase-3, -6, and − 7). [20]

During G1, cyclin D may bind to CDK4 or CDK6 in response to a range of growth signals. This phosphorylates Rb, releases E2F, and advances the cell cycle. [21] Cyclin D3, one of the three cyclin D proteins, is overexpressed in breast cancer and other human cancers. The suppression of cyclin D3 expression in mammary tumour cells, which reduced the tumour burden in vivo and suppressed cancer cell proliferation in vitro, revealed the oncogenic relevance of cyclin D3 in cancer. It has been shown that the amounts of cyclin D3 within cells are controlled by the phosphorylation of cyclin D3 by proteasomes.[22] The cell cycle regulator p21 was initially discovered to be a CDK inhibitor that can induce growth arrest by blocking CDKs, which are essential for the G1 to S transition. The CDKN1A gene, commonly referred to as the CDKN1A gene, encodes the protein known as cell cycle regulator p21. The involvement of p21 in the development of carcinomas has garnered a lot of attention due to the intimate relationship between cell cycle control and carcinogenesis. Clinical research has shown that high p21 expression is associated with a bad prognosis, and other studies have proposed that CDKN1A/p21 stimulates the growth of cancer and may contribute to medication resistance.[23]

For cancer to form, spread, and metastasise, NF-B signalling is essential. In breast cancer, RANKL stimulates NF-B by targeting the cyclin D1 gene, which results in cellular proliferation. NF-B also mediates survival through increased amounts of Bcl-xL and inhibitors of apoptosis (IAPs).[24]

Because ROS harm proteins, DNA, and the integrity of the plasma membrane, they can result in programmed cell death.[25]

Catechin’s Therapeutic Potential

Catechin has the potential to be a useful tool in the prevention of cancer since it impedes cell growth and induces cell death. The anticancer properties of catechin are consistent with several characteristics of

cancer, such as regulating oxidative stress, cell cycle arrest, apoptosis, prevention of angiogenesis, manipulation of signal transduction pathways, epigenetic modifications, and suppression of metastases. These complex processes highlight catechin's potential as an anticancer drug. [26]

CONCLUSION

The molecular interactions between the markers and the catechin is documented. This study suggests that catechin follows Lipinski's rule of 5 and has favourable ADMET properties. Catechin showed higher binding affinity towards Catalase, CDK4, and CDK6, as (-9.4, -8.3, and − 8.0) respectively. Catechin showed more hydrogen bond interactions with Bak, Caspase 9 and Superoxide dismutase. Future confirmation through molecular dynamics, in vitro bioassays, and translational research is still crucial, even though computational predictions offer compelling mechanistic justification and support for their pharmacological promise. Thus, catechin is a unique candidate that fits in with current precision oncology initiatives and the continuous hunt for safe, efficient, and multitarget anticancer treatments.

Declarations

Author Contribution

Murugesan Viji-The conception or design of the work, analysis, interpretation of data.Periyasamy Vijayalakshmi-Drafted the work or revised it critically for important intellectual content.Manikkam Rajalakshmi-Approved the version to be published

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Figures

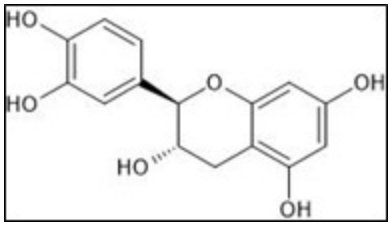

Figure 1

2D Structure of catechin.

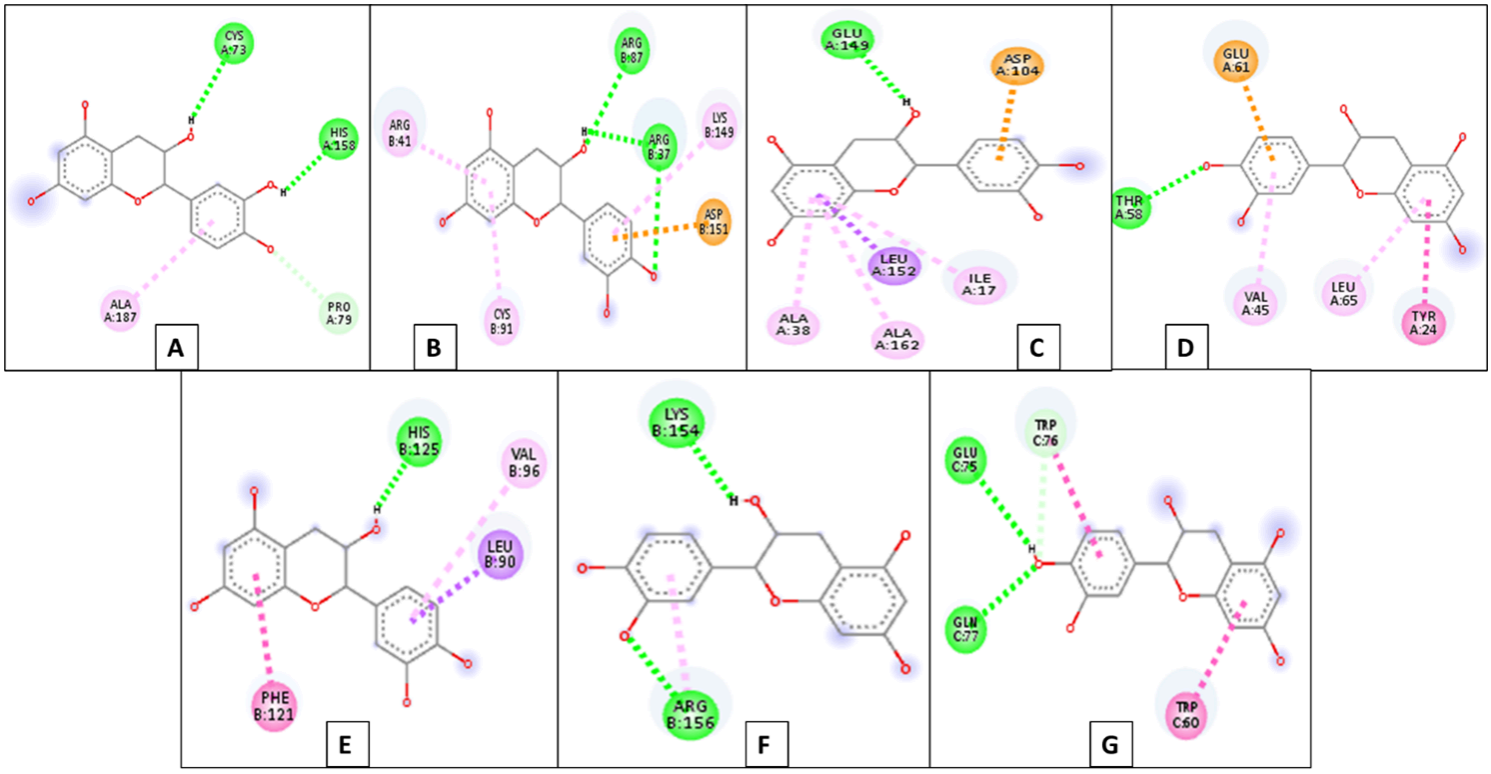

Figure 2

Molecular interaction between catechin and cell cycle proteins such as Cyclin D1, Cyclin D3, CDK4, CDK6, p18 INK4c, p21 CIP1 and p27 KIP1.

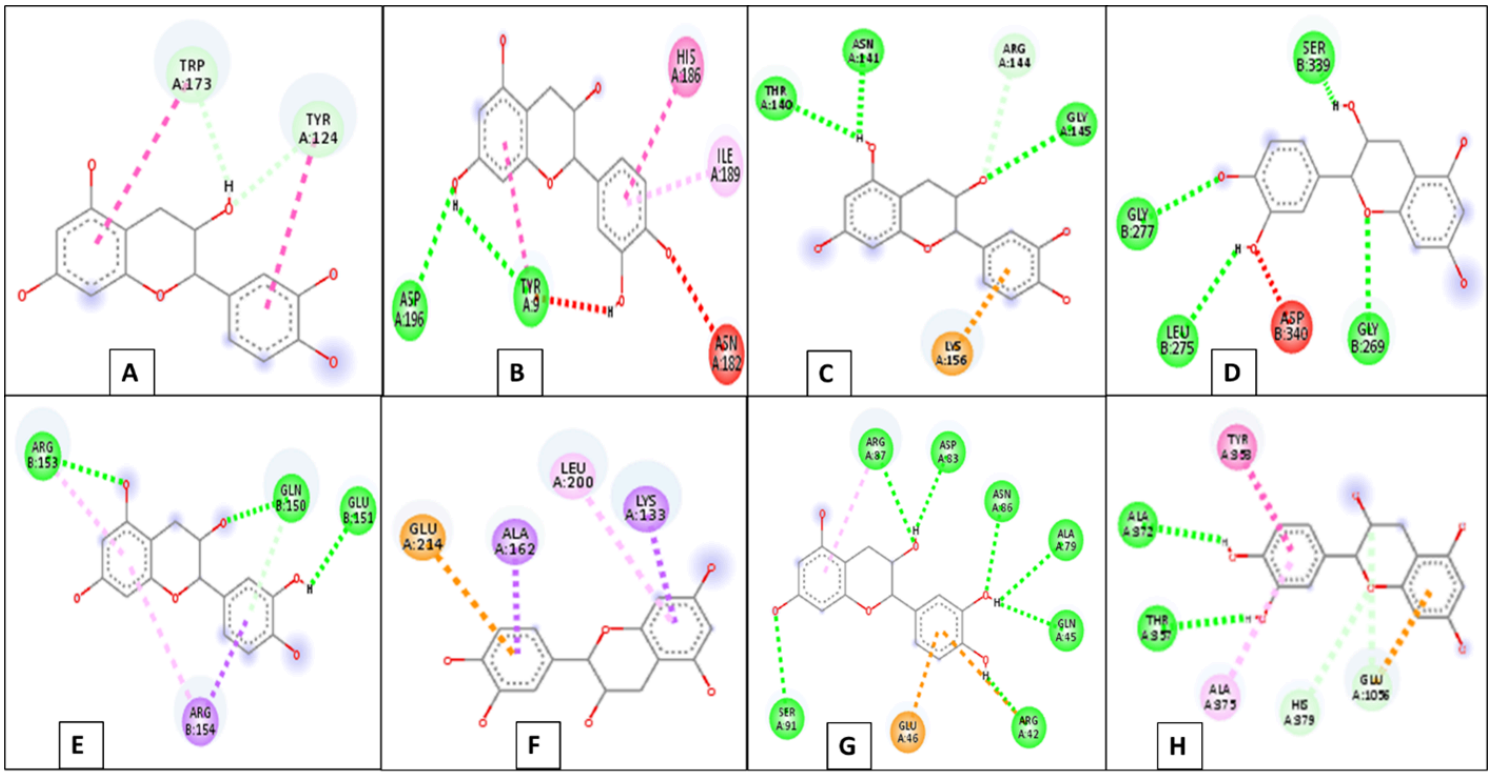

Figure 3

Molecular interaction between catechin and apoptotic proteins such as Bcl-xL, BCL-2, Caspase 3, Caspase 9, Bax, Caspase 6, Bak and Caspase 8.

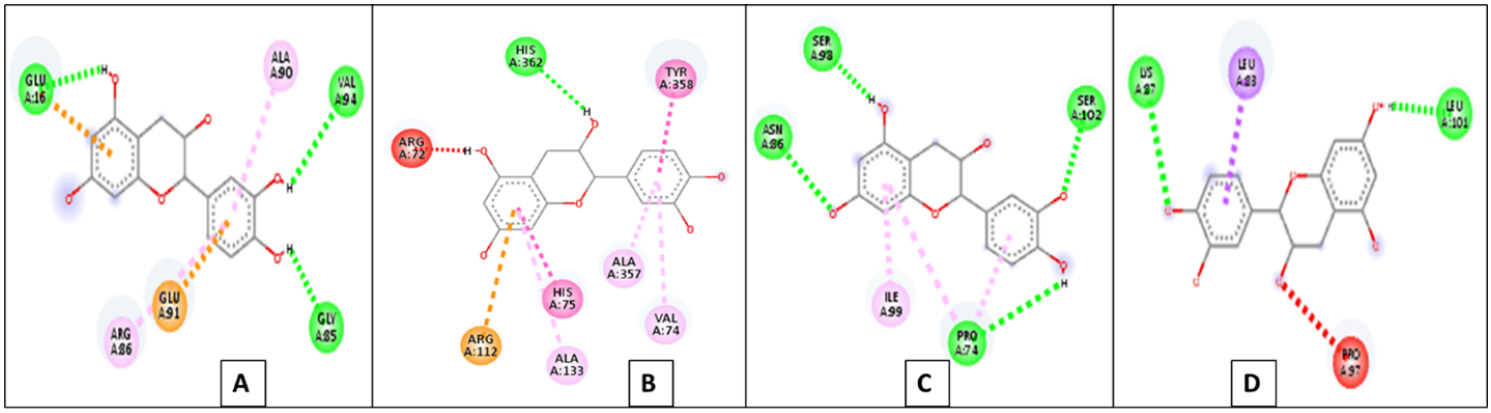

Figure 4

Molecular interaction between catechin and ROS proteins such as Peroxiredoxin, Catalase, Superoxide dismutase and Glutathione peroxidase.

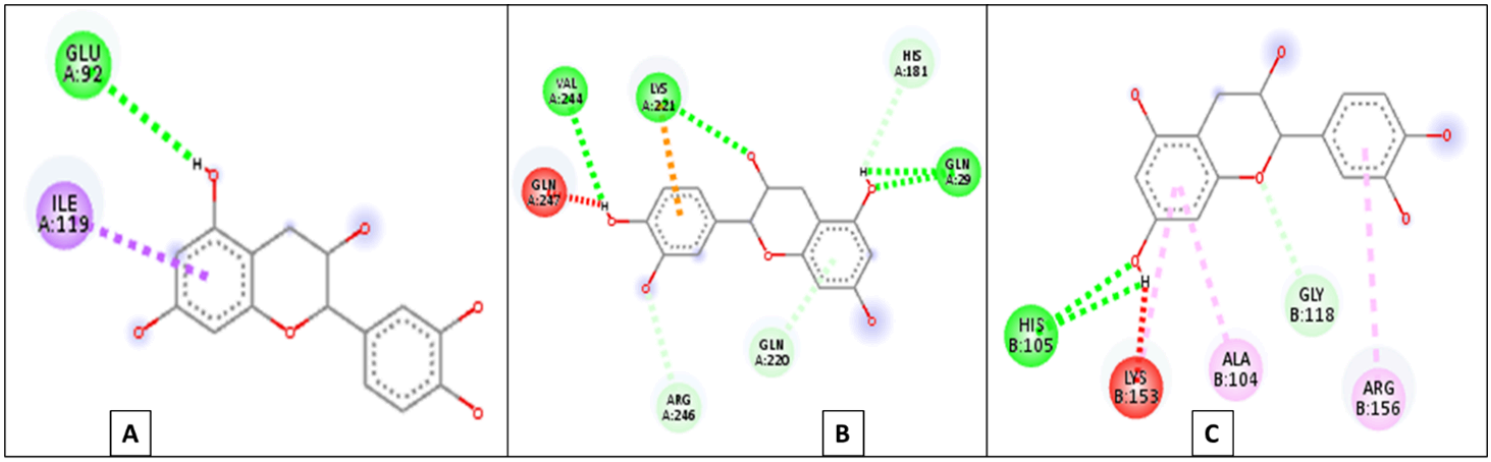

Figure 5

Molecular interaction between catechin and NF-κB proteins such as NF-κB/p52, NF-κB/p65 and NF-κB/p100.