EXPLORING THE ANTI INFLAMMATORY PROPERTIES OF *MangiferaIndica* USING MOLECULAR DOCKING APPROACH

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Abstract:

Mango fruit contains a number of phytochemicals having medicinal properties. These constituents are used to treat diseases of skin and throat since ancient times. Herein we have investigated the effect of different constituents of mango stem on NFκB, which is the protein uplifted in inflammation. Different constituents show high binding affinity with NFκB calculated in terms of binding energy and stability in the cavity of the protein.

Introduction:

MangiferaIndica, (mango tree) is one of the flowering plant species belonging to the Anacardiaceae family. This family include about 30 tropical fruiting trees with the genus Mangifera, such as *Mangifera altissima, Mangifera persiciformis, Mangifera caesia, Mangifera camptosperma, Mangifera casturi, Mangifera decandra, Mangifera foetida, Mangifera indica, Mangifera griffithii, Mangifera laurina, Mangifera kemanga, Mangifera macrocarpa, Mangifera longipes, Mangifera odorata, Mangifera mekongensis, Mangifera quadrifi da, Mangifera pajang, Mangifera similis, Mangifera siamensis, Mangifera sylvactia, Mangifera torquenda, Mangifera zeylanica, Mangifera applanata,Mangifera swintonioides[1]*. Major uses of various parts of the plant are in the form ofdentifrice, antiseptic, astringent, diaphoretic, stomachic, vermifuge, and tonic, laxative and diuretic and to treat diarrhoea, dysentery, anaemia, asthma, bronchitis, cough hypertension, insomnia, rheumatism, toothache, leucorrhoea, haemorrhage and piles[2-6]. These are also used treatment of abscesses, broken horn, rabid dog or jackal bite, tumour, snakebite, stings, datura poisoning, heat stroke, miscarriage, anthrax, blisters, wounds in the mouth, tympanitis, colic, diarrhoea, glossitis, indigestion, bacillosis, bloody dysentery, liver disorders, excessive urination, tetanus and asthma[4-5].

As mentioned above, the varied application of all parts of the plant is based on the phytochemicals playing vital role towards proper health promotion, acting as antioxidant, stimulate the human system, in the liver inducing protective enzymes or inhibiting any kind of damage to genetic materials [7]. The phytochemicals in the plant includepolyphenols, flavonoids, triterpenoids, Mangiferin(a xanthone glycoside), isomangiferin, tannins &gallic acid derivatives. protocatechic acid, catechin, mangiferinare

found in bark. Apart from the phytochemicals mentioned before alanine, glycine, γ-aminobutyric acid, kinic acid, shikimic acid and the tetracyclic triterpenoids cycloart-24-en-3β,26diol, 3-ketodammar-24 (*E*)-en-20S,26-diol, C-24 epimers of cycloart-25 en 3β,24, 27-triol and cycloartan-3β,24,27-triol are also present in the plant *MangiferaIndica*. Other components isolated from this species are Indicoside A and B, manghopanal, mangoleanone, friedelin, cycloartan-3β-30-diol and derivatives, mangsterol, manglupenone, mangocoumarin, n-tetacosane, n-heneicosane, n-triacontane and mangiferolic acid methyl ester Mangostin, 29-hydroxy mangiferonic acid, etc [8,9].

The scope towards biological functions of the phytochemicals is extensive because of its antioxidant properties. These include different types of polyphenols (phenolic acid, hydroly-sable tannins and flavonoids) exhibit anti-carcinogenic and anti-mutagenic effect

NFκB is a complex protein family which are involved in the inflammation and immune responses. NFκB with its five members constitute a complex protein family of inducible transcription factors. The members, NF-κB1 (also named p50), NF-κB2 (also named p52), RelA (also named p65), RelB and c-Relare related to each other structurally[10]. The process of inflammation is brought about as a protective response by the host against infections & tissue damages, however deregulated inflammatory responses has the ability to cause excessive or persistent tissue damages resulting into acute or chronic inflammatory diseases. NFκB plays a central role of pro-inflammatory gene induction but its deregulated NFκB activation results in pathogenic processes of various inflammatory diseases.

Nowadays, it has become a necessity for researchers to give more emphasis on the alternative and complementary medicines which will be used to treat the dreadful diseases like diabetes and cancer as the synthetic drugs lead to side effects during or after its treatment. The computational biology and bioinformatics have the ability to accelerate the process of drug discovery while reducing the cost in the form of Rational Drug Design (RDD) process. It includes different processes that help in the identification of the novel compounds resulting into the discovery of some of the potent drugs.Docking is one of the methods which requires drug molecule with the receptor (target). Docking is a tool used to predict the conformations of the receptor with ligand, when it is in a bound state, forming more stable complex by providing the information about the binding energy, hydrogen bonding and the amino acid residues to which the ligand binds. As the conformation changes the binding affinity of the two molecules changes along with the amino acid residues to which it is binding. Docking, therefore, aids to predict the binding orientations of drug molecules with their target proteins.

Materials and methods:

Docking procedure:

Structures of different pharmacophores present in MangiferinIndica stem were drawn using chem draw software. All the structures were cleaned for 2D and 3D corrections using Chemdraw. The chemical structures were converted into PDB files by using 3D corina online tool and saved in separate folders. The protein structure of NFκB was obtained from RCSPDB online depository for protein structures. The PDB file was cleaned in discovery studio in order to remove water, heteroatom and repetitive chains in the

structure. The cleaned PDB files of protein and ligand were converted into PDBQT file by using MGL tools. The Docking of protein and ligand was done using auto dock vina software by specifying the grid box wherein the ligand was given freedom to bind in the protein [12-15].

The docking results were procured in anout.pdbqt file along with a log file containing binding energies. The docking results were visualized using Pymol software. The hydrogen bonds which the ligand makes in the cavity of protein and their bond distance were obtained and tabulated.

Results and Discussion:

Protein shows different types of structures like primary, secondary and tertiary structure. The tertiary structure of protein has a 3D orientation in which the ligand molecule binds. On the binding with ligand molecule there are several changes observed in the protein cavity which might attribute to its pharmacokinetics and pharmacodynamics. Study of ligand-protein interactions explains a number of protein characteristics and ligand characteristics in presence of each other. The mere presence of ligand in the vicinity of the protein can cause changes in the protein conformation. Drug discovery mainly targets inhibition of proteins responsible for causing a particular disease for instance inhibition of certain protein may reduce its expression resulting into healing of a disease. Thus in order to inhibit a protein it is necessary to study the ligand-protein interactions. In drug delivery it is crucial to see whether a particular ligand binds in the protein cavity, site of ligand binding, binding energy and the various bonds stabilizing the ligand in its cavity.A drug designing is done based on the development and designing novel molecules based on protein cavity.

Molecular docking is an important tool to study drug-protein interactions. Using this technique we can predict the size of the protein cavity and protein characteristics using which we can elucidate the properties of ligand and design ligands accordingly. The ligand designing is majorly dependent on the protein and availability of the similar pharmacophores. Indian traditional medicine has collection of number of plants which show varied medicinal properties. Mango plant is one such plant containing a number of phytochemical structures. The formulation of mango leaves and stems has been used since ancient times to treat diseases of skin, throat and stomach. Mango stem contains varied chemical structures and their medicinal properties are least explored to treat diseases.

Inflammation is a cause of number of diseases like diabetes and cancer. Prolonged inflammation can result into harmful effects in the body. One of the proteins overexpressed during inflammation is NFκB. The crystal structure of NFκB is reported and using its PDBiD 1NFK we have tried to elucidate the effect of mango stem phytochemicals in the cavity of NFκB. The structures guanine, aromandrene, campesterol, elemen, eudesmpl, sitosterol, salinene, catechin, epicatechin, gallic acid methyl ester, gallic acid propyl ester, hinesol, hydroxyl chromone, mangiferin, methoxy chromone and quercetin are present in mango stem (Figure 1). The molecular docking results are tabulated (Table 1) and the results show variable bonding energy and number of hydrogen bonds in the cavity of NFκB. The structural variation of different molecules shows large difference in the binding affinity. The different structures show binding energy ranging from 6-8 Kcal/mole. The negative sign of the binding energy attributes to the bound state and release in energy when

the ligand binds in the cavity of the protein. Amongst the different structures quercetin shows the highest binding energy followed by hydroxyl chromone, mangiferin and epicatechin. The molecular docking images show clearly the nature of binding within different constituents of mango stem and NFκB (Figure 2). The stability of the ligand in the cavity is due to hydrogen bonds, weak electrostatic bonds and vander waal's forces. The presence of all these interactions stabilizes the ligand in the cavity. The structures showing higher binding energy may show better inhibition of the protein in the body causing decrease in its activity.

Conclusions:

The mango stem has a number of phytochemical structures showing high affinity towards NFκB. The binding energy of different structure varies from 6-8 Kcal/mole. Amongst the different structures quercetin, hydroxyl chromone, mangiferin and epicatechin show high binding energy in the cavity of NFκB. Mango fruit constituents act as better binding agents to NFκB.

Acknowledgement:

The authors would like to acknowledge Department of Chemistry, Abeda Inamdar Senior College for providing necessary facilities and resources.

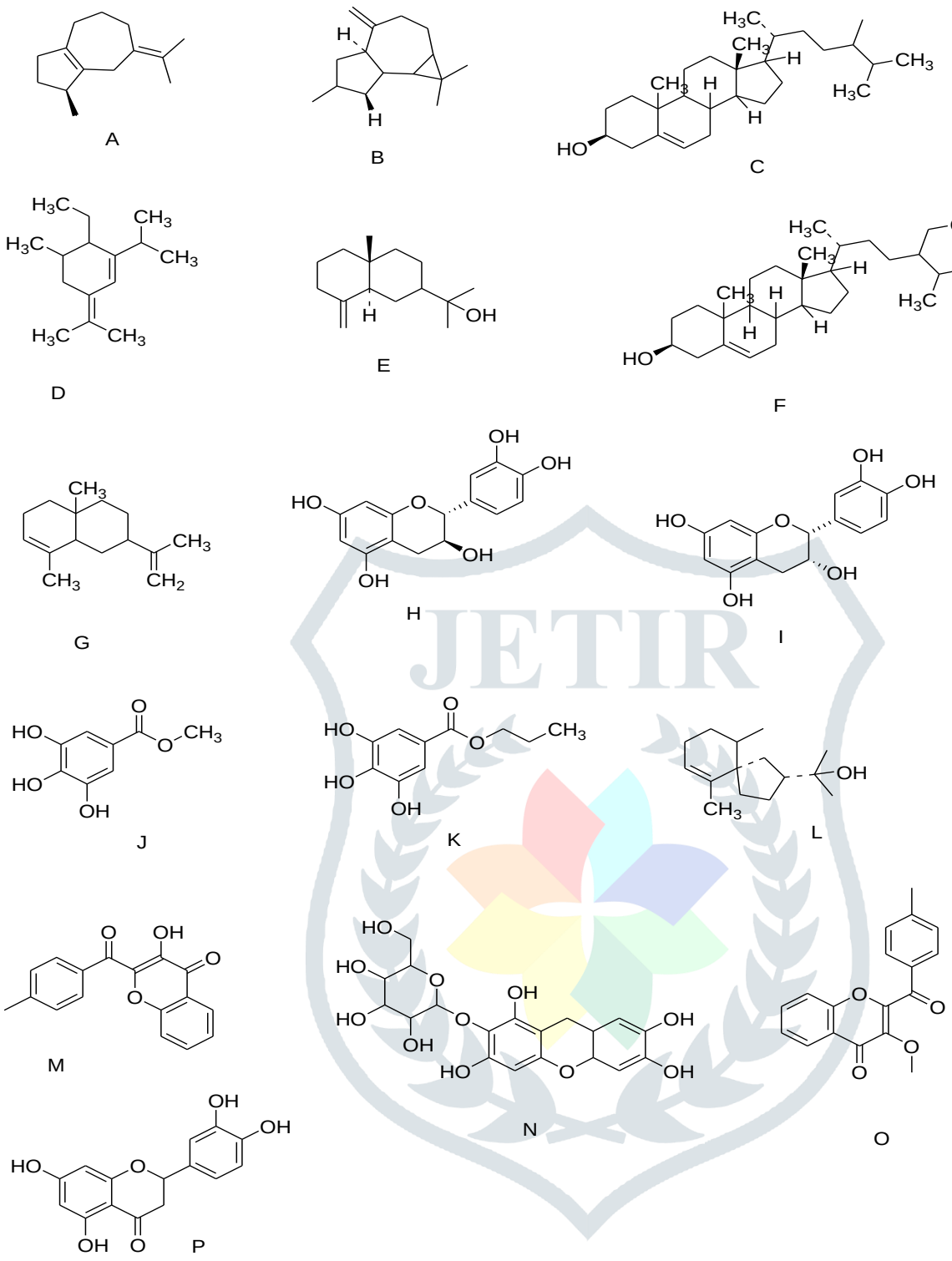


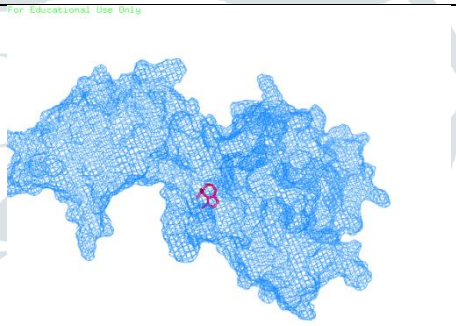
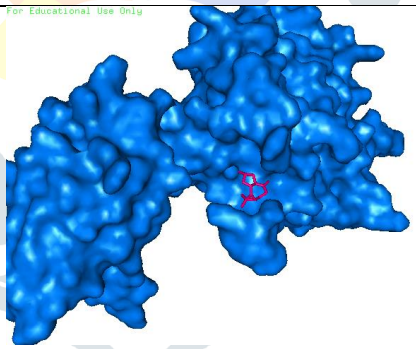
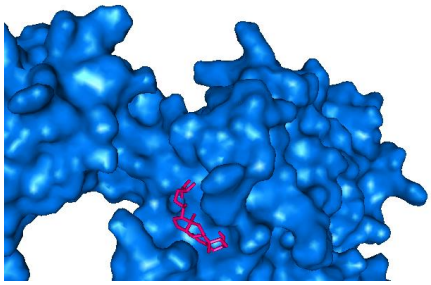
Figure 1: Structures of different constituents of mango stem

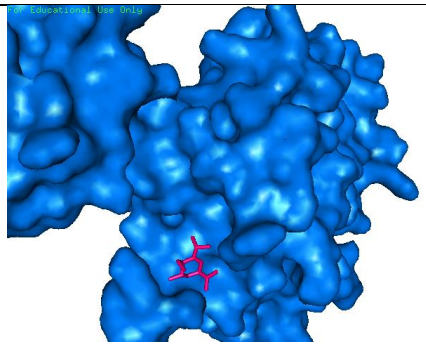
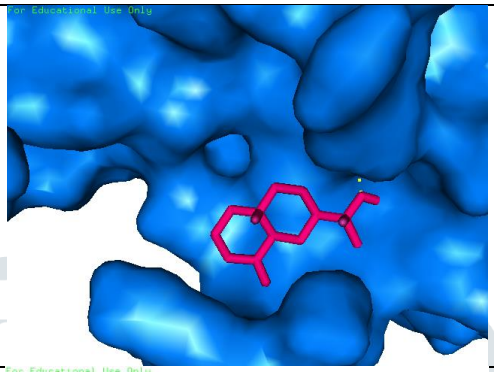
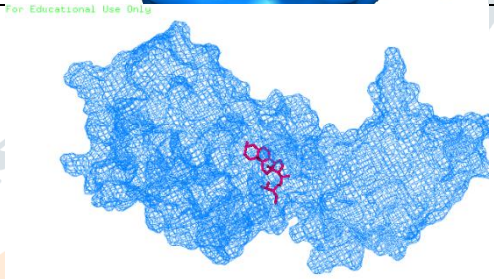
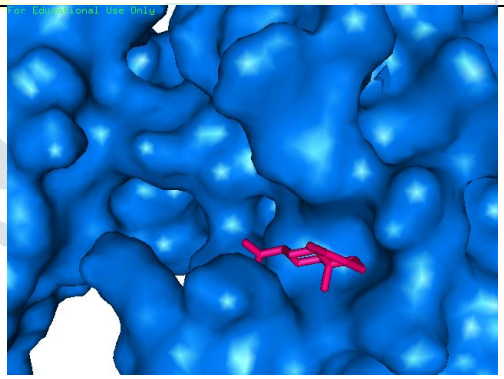
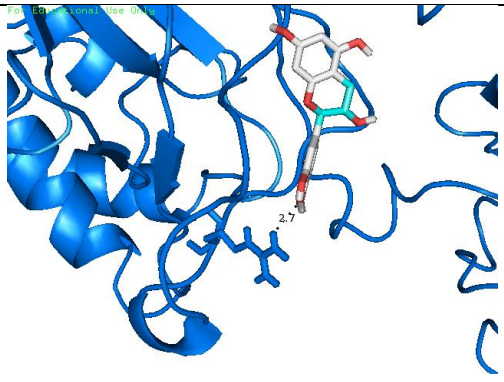
Table 1: Docking results of different constituents of mango stem in NFκB

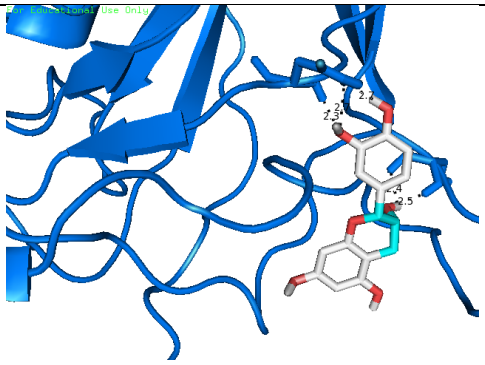
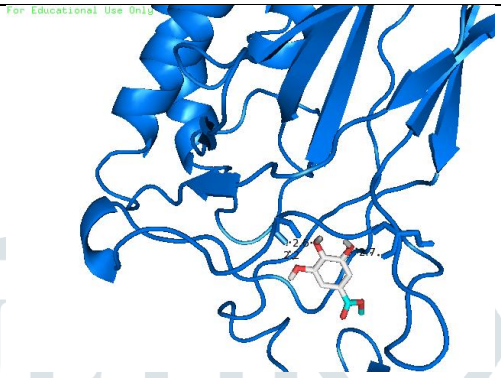
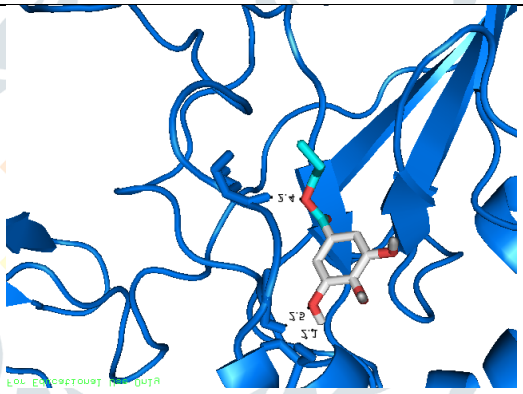
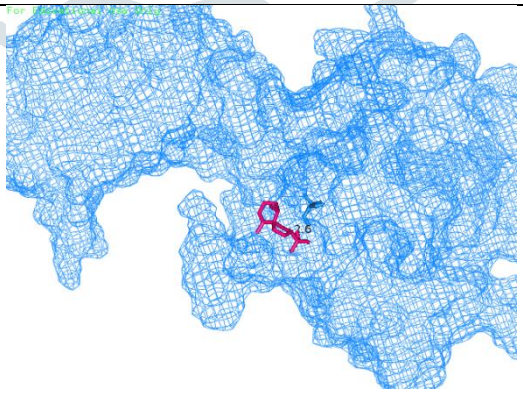
Sr no.	Name of compound	Binding energy in Kcal/mol
1.	A-guanine	-5.9
2.	Aromandrene	-6.1
3.	B-campesterol	-6.8
4.	B-Elemen	-5.9

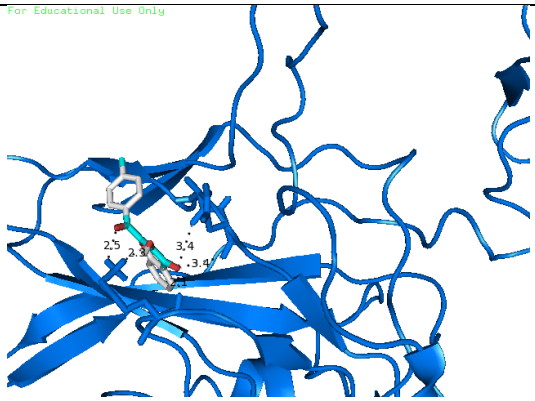
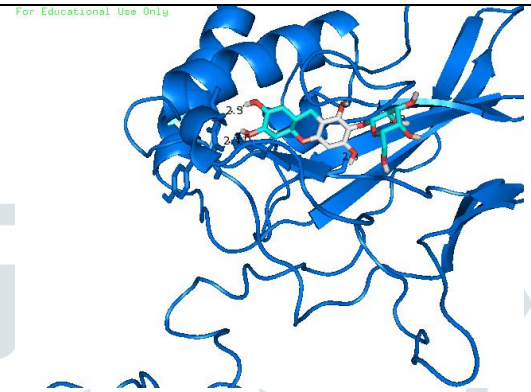
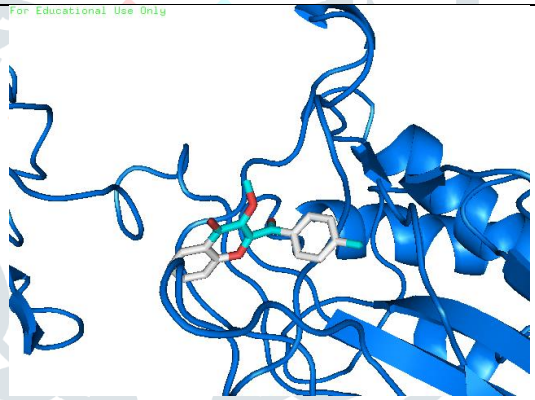
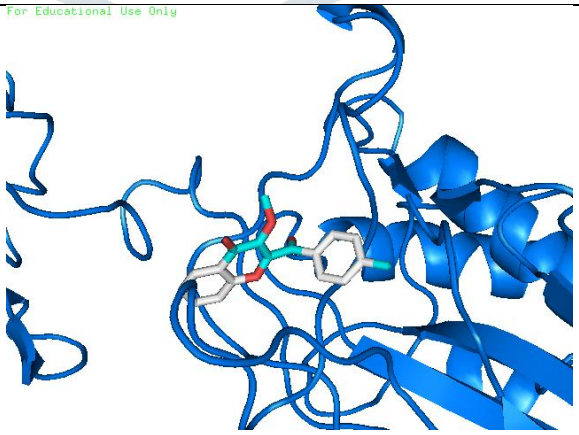
5.	B-Eudesmpl	-6.0
6.	B-Sitosterol	-7.0
7.	B-Salinene	-5.9
8.	Catechin	-6.3
9.	Epicatechin	-7.1
10.	Gallic acid methyl ester	-5.2
11.	Gallic acid propyl ester	-5.2
12.	Hinesol	-6.4
13.	Hydroxychromone	-7.2
14.	Mangiferin	-7.1
15.	MethoxyChromone	-6.8
16.	Quercetin	-7.3

Figure 2: Docking images of different constituents in NFkB

Sr No.	Name of compound	Docking image in NFκB
1.	A-guanine	
2.	Aromandrene	
3.	B-campesterol	

4.	B-Elemen	
5.	B-Eudesmpl	
6.	B-Sitosterol	
7.	B-Salinene	
8.	Catechin	

9.	Epicatechin	
10.	Gallic acidd methyl ester	
11.	Gallic acid propyl ester	
12.	Hinesol	

13.	Hydroxychromone	
14.	Mangiferin	
15.	MethoxyChromone	
16.	Quercetin	

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