# In-Silico studies on the Interaction of Flavones with DNA

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## *Abstract*

*DNA is the basic building block of all organisms. It is in charge of all kinds of genetic information. DNA is regarded as the molecule of life that governs all the necessary chemical changes inside the cell. Information inside DNA is stored in form of chemical compounds known as bases which are: adenine (A), cytosine (C), guanine (G), and thymine (T).The detail of interaction of drugs with DNA is of main significance for drug-designing of chemotherapeutic agents and anticancer drugs. Current work deals with theoretical computational interaction of a few flavones with DNA sequences. Flavones are a type of Flavonoids. Flavonoids are present in many parts of plants. They are natural antioxidants. From literature survey, it is found that flavonoids show a lot of biological actions like anticancer, antibiotic, antitumor, antiviral, anti-inflammatory, antiallergicetc. Molecular Docking was performed with three flavones (Apigenin, Diosmin and Luteolin) and DNA sequence segments with PDB ID 195D, 1BNA, 1CP8, 1RMX, 1D66 and 2ROU. To do molecular docking process AUTODOCK4 software was used. This research could be supportive in the synthesis and designing of new less toxic drugs and enhance their applications in the field of pharmacology.*

**Keywords:** Flavonoids, flavones, binding energy, molecular docking, binding constant, stability.

## 1. Introduction

DNA is regarded as the molecule of life that governs all the necessary chemical changes inside the cell. Information inside DNA is stored in form of chemical compounds known as bases which are: adenine (A), cytosine (C), guanine (G), and thymine (T)[1,2]. The sequence of these DNA bases controls the information that is necessary for the organism to look like its actual self, similar to the manner in which alphabets are arranged to form particular word or sentence. Adenine pairs up with thymine (A-T) and guanine pairs up with cytosine (G-C) via hydrogen binding which are called as base pairs. The DNA comprises of bases pairs, phosphates, and sugar groups; together they are called nucleotide. The nucleotides form two long stands that spiral together two give DNA a double helix structure[3].

DNA is major target for anticancer drug interaction, due to the inhibition of processes of transcription and DNA replication which are necessary for the growth and survival of cell inside living being[4]. Three possible ways are known by which DNA as a drug target can block cancerous cell growth. In polymerases where DNA is directly binded to protein the anti-cancer drug can bind to this protein, secondly it can bind to exposed single stranded DNA region where DNA –RNA hybrid will be forming, this will intervene in the transcriptional process[2]. Lastly, it could bind with double helical DNA itself trough non-covalent interaction by intercalation or groove binding.

Here interaction of DNA with drug as intercalation or groove binding has been tried to studied for flavonoids. On the grounds of the binding mode and binding energy between specific drug and DNA, their effectiveness as a potent medicine for any particular disease can be predicted[5].

## FLAVONOIDS

Diverse group of phytoneutrients are present in plants, fruits and vegetables, these classes of polyphenolic chemicals are known as flavonoids. These bioactive compounds are responsible for medicinal and antioxidant properties of plants. Hence, they are considered as good source of disease preventing dietary supplements that promote health[6-7]. Their biological activities such as antibacterial/viral, anti-ageing, anti-cancer, anti-inflammatory, cardioprotective, anti-diabetic are well known through various researches carried out so far[8]. Flavonoids thus are indispensible component in

pharmaceutical, nutraceutical, cosmetics and may other applications. Flavonoids occur in nature as glycosides, aglycones (*i.e.*, flavonoids without attached sugar), and methylated derivatives. The basic chemical structure of flavonoid is a skeleton of diphenyl propane, which comprises fifteen carbon atoms in their primary nucleus: two six-membered rings linked with a three carbon unit which may or may not be a part of a third ring[9]. Mainly two benzene rings (ring A and B) are linked together through third heterocyclic oxygen-containing pyrene ring. So, this structure is also referred to as C6-C3-C6.Broadly flavonoids are classified by three ways (i) by oxidation degree, (ii) annularity of ring C and (iii) connection position of ring B[10].

Flavones are a type of Flavonoids. As they are natural products, flavonescan prove to be better anticancer drugs due to their low toxicity[11]. The flavones used for docking were Apigenin, Diosmin and Luteolin. These were docked with DNA sequences with PDB ID 195D, 1BNA, 1CP8, 1RMX, 1D66 and 2ROU. Docking studies yield details of the biological complexes formed between each one of the drugs and DNA sequence.

## 2. Computational Details

### Dataset

DNA: The pdb format file of DNA sequences with PDB ID 195D, 1BNA, 1CP8, 1RMX, 1D66 and 2ROU were taken from Protein Data Bank RCSB [12]. To delete previously attached ligands and water molecules CHIMERA was used[13]. PDB ID and their sequence DNA are shown in **Table 1**.

Drugs: The chemical structures of Apigenin, Diosmin and Luteolin were gathered from the literature[14-17]. **Figure 1** represents the structures of selected flavones. Ligands were submitted to geometrical optimization using Gaussian 09 software at B3LYP level using 631G basis set[18].

### Molecular Docking

AutoDock4 software was set up for molecular docking computational process implementing Lamarckian Genetic Algorithm (LGA)[19]. Docking was done by taking DNA segment as macromolecule, whereas flavones were taken as ligands. The bio

molecule DNA and ligand files were obtained for docking procedure using the AutoDockTools (ADT) [20]. Grid boxes of appropriate dimensions were prepared and grid maps by Auto-Grid for every DNA sequence. Proper charges were added and docking files were also prepared.Lamarckian genetic algorithms, as administered in AutoDock, were setup to do blind docking calculations. For eachcase, the docked conformation of lowest energy, according to scoring function, was regarded as the binding mode.

## 3.Results

Nearly all of the flavones bind with the DNA sequences in the minor groove concluding that all these flavones are minor groove binders. But interaction with 2ROU is little different. The complexes of Apigenin and Diosmin showed intercalation. They stack between the base pairs of DNA. This analysis gives direction to the conclusion that the mode of bindinglinking DNA and drug not only depend on the shape and size of drug but also on the helical structure of DNA sequence. Since 2ROU sequence has intercalative gap so apigenin and diosmin gave intercalative mode of binding. The computationally calculated binding energies are listed in **Table 2**.

The complex Diosmin with 1RMX have lowest binding energy -9.30 kcal/Mol. This represent that the interplay between DNA sequence 5'-CGACTAGTCG-3' and diosmin have better stablility as compare to other complexes. So it can be a potent drug against cancer and other diseases. For each of the DNA sequences, non-covalent interaction for most stable complex is shown in **Figure 2**.

## 4.Conclusion

Flavones fall in a category of flavonoids having potential application in the field of medicine and pharmacology. Preset study gives description about the interaction of flavones Apigenin, Diosmin and Luteolin with DNA . It also gives binding energies and binding modes of the complexes. Many complexes displayed minor-groove binding including hydrogen bonds and pi-pi non-covalent interactions as prime interaction. But the DNA sequence having intercalation gap shows intercalative mode of binding with Apigenin and Diosmin. This proposes that binding mode between DNA and drug depends also on the DNA sequence structure. This study gives help to get deeper perception about the DNA binding technique and binding chemistry ofantioxidant flavones.

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**Table captions**

Table 1. List of PDB IDs taken for the study with their DNA sequence

Table 2. Binding energies(kcal/mol) of flavones with different DNA sequences.

**Table 1**

| S.no. | PDB ID | DNA Sequence |
|---|---|---|
| 1 | 1BNA | 5'-CGCGAATTCGCG-3' |
| 2 | 1CP8 | 5'-TTGGCCAA-3' |
| 3 | 1D66 | 5'-CCGGAGGACAGTCCTCCGG-3' |
| 4 | 1RMX | 5'-CGACTAGTCG-3' |
| 5 | 195D | 5'-DCGCGTTAACGCG-3' |
| 6 | 2ROU | 5'-ATCGCGCGGCATG-3' |

| Drug | 1BNA | 1CP8 | 1D66 | 1RMX | 195D | 2ROU |
|---|---|---|---|---|---|---|
| Apigenin | -8.43 | **-7.17** | -8.99 | -7.25 | **-8.62** | -6.34 |
| Diosmin | -5.13 | -5.95 | -5.18 | **-9.30** | -8.43 | -6.89 |
| Lutelin | **-8.60** | -6.86 | **-9.00** | -7.03 | -8.49 | **-7.59** |

**Table 2**

**Figure Captions**

Figure 1. Chemical structures of used flavones.

Figure 2. Non-covalent interaction between DNA and drug having lowest binding energy for each DNA sequence.

(a) 1BNA and Luteolin

(b) 1CP8 and Apigenin

(c) 1D66 and Luteolin

(d) 1RMX and Diosmin

(e) 195D and Apigenin

(f) 2ROU and Luteolin

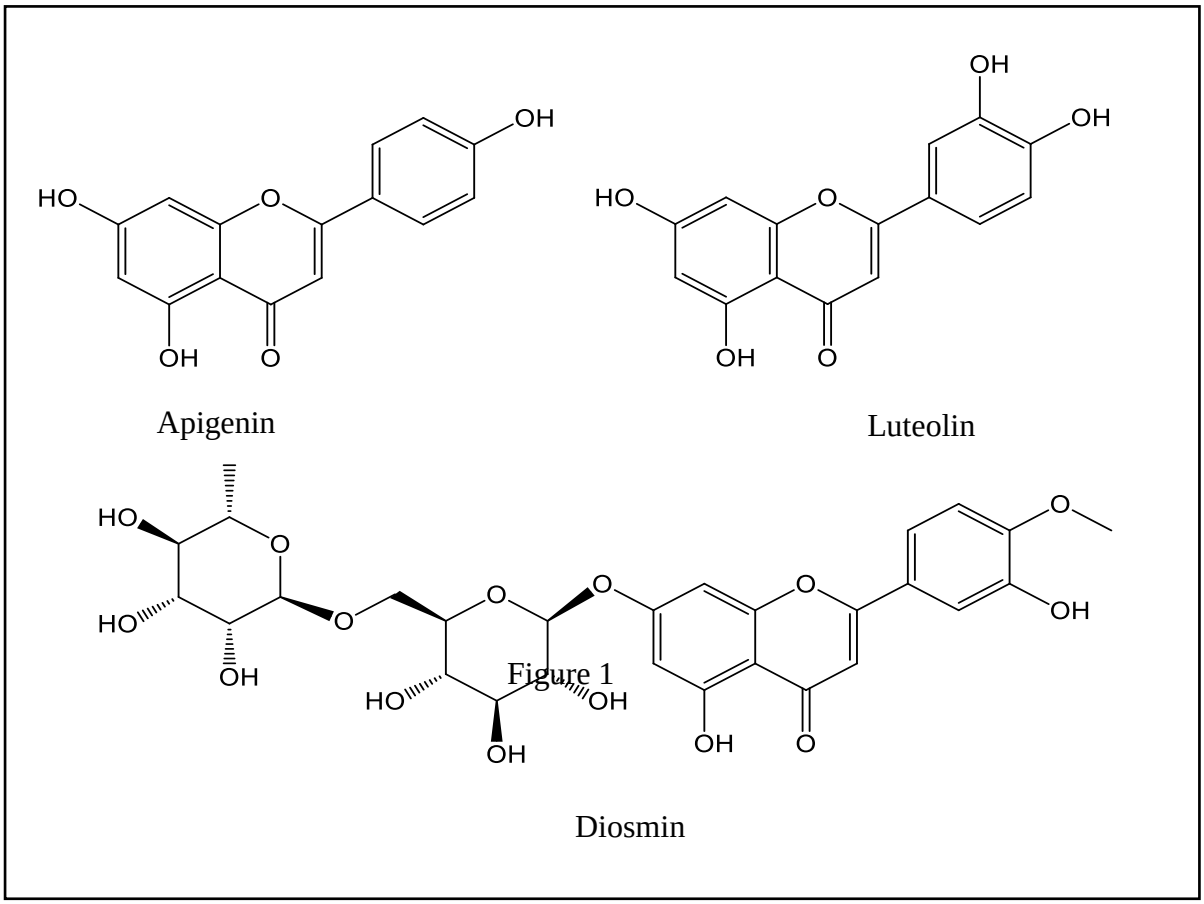
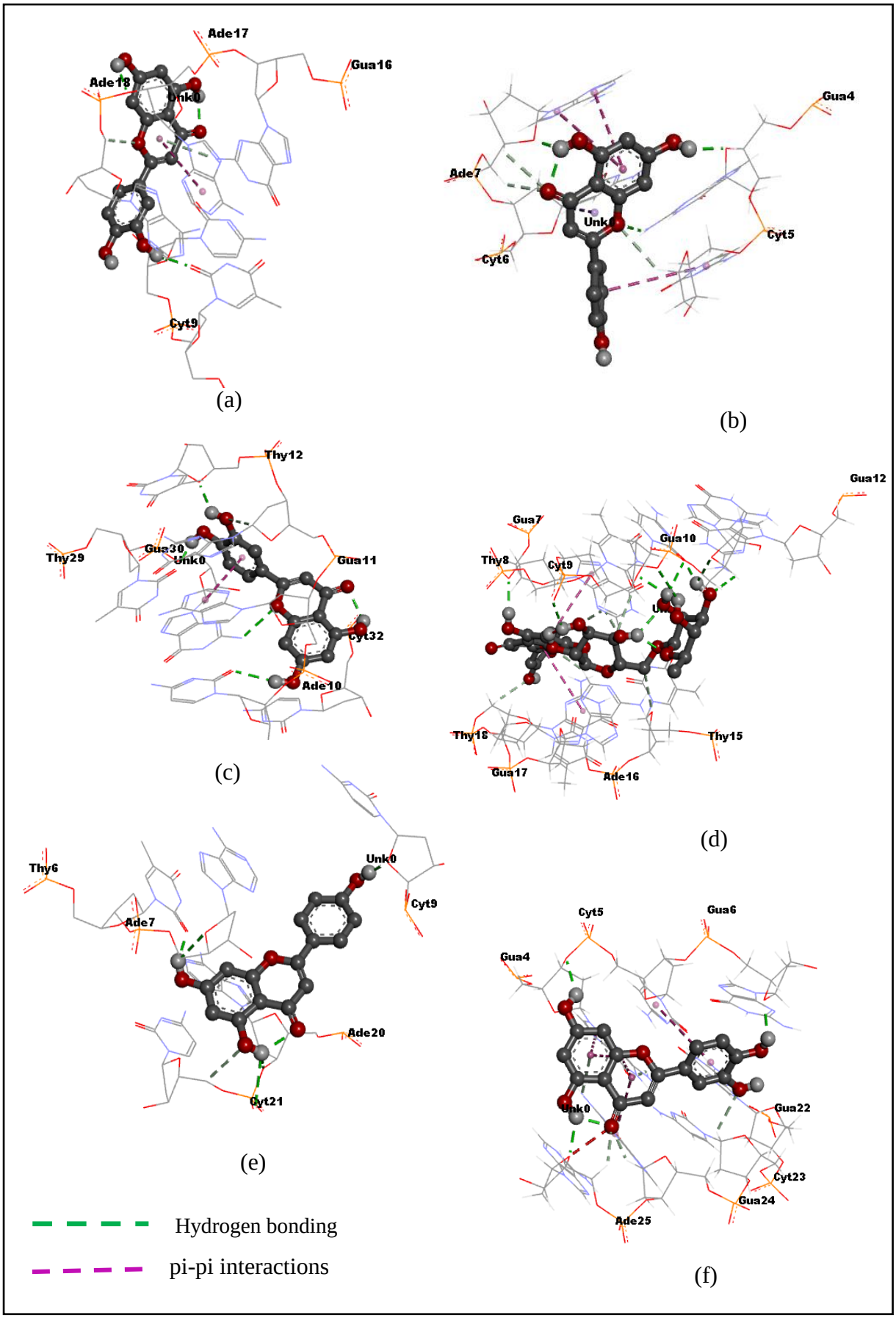



Figure 1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Gua16
Ade18
Unk0
Cyt9
(a)
Gua4
Ade7
Unk0
Cyt5
Cyt6
(b)
Thy12
Thy29
Gua30
Unk0
Gua11
Cyt32
Ade10
(c)
Gua12
Gua7
Gua10
Thy8
Cyt9
Thy18
Thy15
Gua17
Ade16
(d)
Thy6
Unk0
Cyt9
Ade7
Ade20
Cyt21
(e)
Cyt5
Gua6
Gua4
Unk0
Gua22
Cyt23
Gua24
Ade25
(f)
Hydrogen bonding
pi-pi interactions

Figure 2