International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Impact Factor (2012): 3.358

In Silico, Study of Flavonoids and their potential application as Anti-Cancer Agents

Shahnawaz Ahmad[1], Amit Chattree[2], Sikander Dar[3]

[1, 2, 3]Department of Chemistry, Sam Higginbottom Institute of Agriculture, Technology and Sciences (Formerly AAI-DU), Allahabad, U.P. India.

Abstract: ***Flavonoids represent an unlimited source of compounds with anti-tumor and immune-stimulating properties, and their intake has been shown to reduce the risk of breast cancer. Flavonoids are the important contributors to cancer prevention, due to their interaction with Cytochrome P450 family enzymes. The present study was concerned with docking of flavonoid derivatives and their application as anti cancer agents in order to get effective drug like molecule from selective six derivatives of flavonoid compounds through the chemo-informatics approach. The flavonoid ligands used in the present study got docked onto the predicted protein template, Crystal structure of human placental aromatase complexed with breast cancer drug exemestane (3S7S), With varying docking energy from -1.409863e+o1 to -9.391901e+01. Based on docking scores, the molecular property and bioactivity score of the compounds, it is possible to conclude that the flavonoid ligands, [3-(3,4-dihydroxyphenyl)-6,8-dihydroxy-2,3-dihydro-4H-chromen-4)-one] and [2-(2,4-dihydroxyphenyl)-5,7-dihydroxy-2,3-dihydro-4H-chromen-4-one] showed best docking scores, best molecular properties and bioactivity hence it can be considered to have best antitumor activity.***

Keywords: Flovonoids, tumor, homology modeling, ligand-receptor interaction, Docking energy

1. Introduction

Flavonoids are widely distributed in plants, fulfilling many functions. Flavonoids are the most important plant pigments for flower coloration, producing yellow or red/blue pigmentation in petals designed to attract pollinator animals. In higher plants, flavonoids are involved in UV filtration, symbiotic nitrogen fixation and floral pigmentation. They may also act as chemical messengers, physiological regulators, and cell cycle inhibitors. Flavonoids have been shown to have a wide range of biological and pharmacological activities in in-vitro studies. Examples include anti-allergic **[1]**, anti-inflammatory and antioxidant **[2]**, anti-microbial (antibacterial **[3],** antifungal and antiviral, anti-cancer **[4]** and anti-diarrheal activities **[5]**. Flavonoids have also been shown to inhibit topoisomerase enzymes **[6]** and to induce DNA mutations in the mixed-lineage leukemia (MLL) gene in in-vitro studies **[7]**.

Cancer chemoprevention by use of natural or synthetic substances and its prevention through dietary intervention has become an important issue. It may be controlled by various means, including suppression, prevent the formation of new cancers from blockage, and transformation. Suppressing agents procarcinogens, blocking agents prevent carcinogenic compounds from reaching critical initiation sites, and transformation agents facilitate the metabolism of carcinogenic components into less toxic materials or prevent their biological actions. Flavonoids can act in all the three ways **[8]**. Many other potential chemopreventive polyphenols may interrupt or reverse the carcinogenesis process **[9]**.

The different mechanisms underlying the potential anticancer action of plant flavonoids await further elucidation. Certain dietary flavonols and flavones targeting cell surface signal transduction enzymes, such as protein tyrosine and focal adhesion kinases, and the processes of angiogenesis appear to be promising candidates as anticancer agents. A further in vivo study of these bioactive constituents is deemed necessary in order to develop flavonoid-based anticancer strategies. In view of the increasing interest in the association between dietary flavonoids and cancer initiation and progression, this important field is likely to witness expanded effort and to attract and stimulate further vigorous investigations. So our work was, *in silico*, study of different flavonoids and their potential application as anti-cancer agents.

2. Materials and Methods

An investigation was carried out at Bioinformatics laboratory of Department of Computational Biology and Bioinformatics (SHIATS) to identify flavonoids compounds using chemoinformatics and to study the binding action of flavonoid compounds on molecular target.

2.1 Identification of flavonid Compounds

For identification of flavonoid compounds following procedures were undertaken:

2.2 Sketch the structures of various flavonoid compounds

Structure of various flavonoid compounds which are used as a ligand are drawn with the help of PUBCHEM project (The resources developed by the Structure Group of the NCBI Computational Biology Branch (CBB) are freely available to the public). 2-d as well as 3-d structure were generated using this software, which was further used in docking. The structures in this study were suggested with the help of various research papers.

2.3 Open Babel: The Open Source Chemistry Toolbox

OpenBabel is free software, a chemical expert system mainly used for converting chemical file formats **[10].** Due to the strong relationship to informatics this program

belongs more to the category cheminformatics than to molecular modeling.

2.4 Miscreen - Molinspiration Fragment-based Virtual Screening Engine v2013.02

Molinspiration miscreen engine allows fast prediction of biological activity - virtual screening of large collections of molecules and selection of molecules with the highest probability to show biological activity. The screening is based on identification of fragments or substructure features typical for the active molecules. No information about the 3D structure of receptor is necessary, the set of active molecules (encoded as SMILES or SDfile) is sufficient for training; therefore the procedure may be applied also in the early project stage when detailed information about the binding mode is not yet available.

2.5 Selection of Molecular Target

Selection of molecular target was done with the help of RCSB Protein Data Bank (www.rcsb.org) based on the information collected through various research papers and a book (flavonid Chemistry) written on flavonid compounds and their activity. The protein template selected was Crystal structure of human placental aromatase complexed with breast cancer drug exemestane (3S7S).

2.6 Hex Protein Docking

Hex is an interactive protein docking and molecular superposition program, written by Dave Ritchie. Hex understands protein and DNA structures in PDB format, and it can also read small-molecule SDF files.

3. Results and Discussion

Drug-likeness may be defined as a complex balance of various molecular properties and structure features which determine whether particular molecule is similar to the known drugs. These properties, mainly hydrophobicity, electronic distribution, hydrogen bonding characteristics, molecule size and flexibility and presence of various pharmacophores features influence the behavior of molecule in a living organism, including bioavailability, transport properties, affinity to proteins, reactivity, toxicity, metabolic stability and many others. Activity of all compounds and standard drugs were rigorously analyzed under four criteria of known successful drug activity in the areas of GPCR ligand activity, ion channel modulation, kinase inhibition activity, and nuclear receptor ligand activity. Results are shown for all compounds in Table 2, 3 and 4 by means of numerical assignment. Likewise all compounds have consistent negative values in all categories and numerical values conforming and comparable to that of standard drugs used for comparison. Therefore it is readily seen that all the compounds are expected to have near similar activity to standard drugs used based upon these four rigorous criteria (G protein coupled receptor ligand, ion channel modulator, kinase inhibitor, and nuclear receptor ligand).

In the fields of computational chemistry and molecular modeling, scoring functions are fast approximate mathematical methods used to predict the strength of the non-covalent interaction (also referred to as binding affinity) between two molecules after they have been docked (i.e. ligand which in this study is flavonoid compounds and protein), as lesser the docking energy means more binding affinity and hence better association between ligand and the target molecule.

According to the results obtained, flavoniod compounds show best molecular properties and have only zero violation to Lipinski's Rule of 5.This violation is due to molecular weight but there are many known drugs that are used these days also have this violation**.** For example- Actinomycin D (Molecular weight-1255).

4. Conclusion

There is an increase interest in interfacing the studies on drug cytotoxicity based on the NCI's tumor screening panels with gene expression databases and the mechanisms of drug action, cell sensitivity and resistance. These complimentary approaches should provide clues about the mechanism of some molecules, which ultimately can be developed as antitumor agents**.** Drug binding noncovalently to DNA have been in cancer treatment since the 60's, and a detailed structural and functional data on these molecules is available. Out of these 6 the compound, 3-(3,4-dihydroxyphenyl)-6,8-dihydroxy-2,3-dihydro-4*H*-chromen-4)-one and 2-(2,4-dihydroxyphenyl)-5,7-dihydroxy-2,3-dihydro-4*H*-chromen-4-one shows best drug-likeness (molecular property bioactivity score) and Docking energy as these shows best compatibility with the Lipinski's rule of five and has the most near values a drug should have as suggested by Lipinski rule. Hence according to present study it can be suggested that the study of these two flavonoid compounds can be the first step in the development of novel agent which can act as an anti-tumor drug.

5. Acknowledgement

The authors are grateful to the Sam Higginbottom Institute of Agriculture, Technology and Sciences (formely Allahabad Agricultural Institute-Deemed to be University) Allahabad for providing the necessary facalities and support for completing the present work.

References

[1] **Yamamoto, Yumi, Gaynor, Richard B. (2001)**. Therapeutic potential of inhibition of the NFκB pathway in the treatment of inflammation and cancer. *Journal of Clinical Investigation* **107(2):** 135–42.

[2] **Cazarolli L.H., Zanatta L., Alberton E.H., Figueiredo M.S., Folador P., Damazio R.G., Pizzolatti M.G., Silva F.R. (2008)**. Flavonoids: Prospective Drug Candidates. *Mini-Reviews in Medicinal Chemistry* **8(13):** 1429–1440.

[3] **Cushnie T.P.T., Lamb A.J. (2011)**. Recent advances in understanding the antibacterial properties of flavonoids. *International Journal of Antimicrobial Agents* **38(2):** 99–107.

[4] **De Sousa R.R., Queiroz K.C., Souza A.C., Gurgueira S.A., Augusto A.C., Miranda M.A., Peppelenbosch M.P., Ferreira C.V., Aoyama H. (2007)**. "Phosphoprotein levels, MAPK activities and NFkappaB expression are affected by fisetin". *J Enzyme Inhib Med Chem* **22(4):** 439–444.

[5] **Schuier M., Sies H., Illek B., Fischer H. (2005)**. "Cocoa-related flavonoids inhibit CFTR-mediated chloride transport across T84 human colon epithelia". *J. Nutr.* **135(10):** 2320–5.

[6] **Esselen Melanie, Fritz Jessica, Hutter Melanie, Marko Doris (2009)**. Delphinidin Modulates the DNA-Damaging Properties of Topoisomerase II Poisons. *Chemical Research in Toxicology* **22(3):** 554–64. **.***Nutrition and Food Research* **51(1):** 116–134.

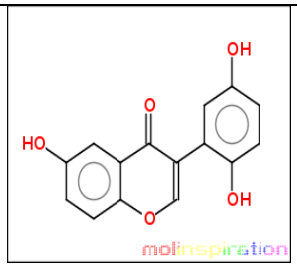
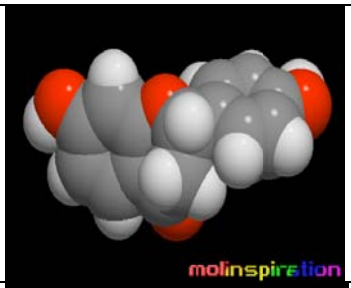
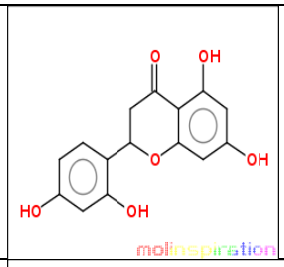
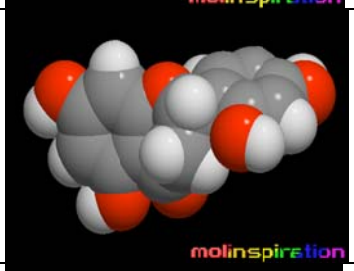
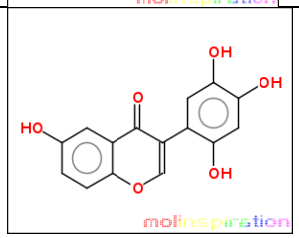
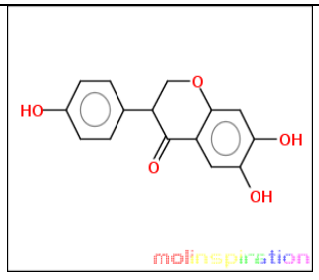
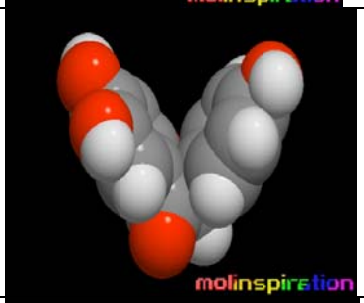
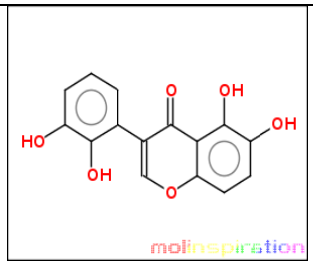
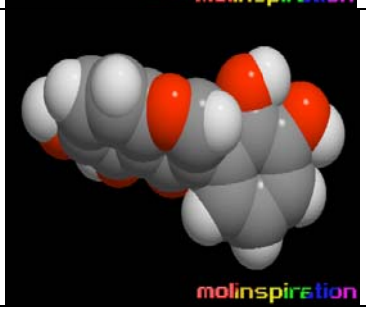
[7] **Barjesteh van Waalwijk van Doorn-Khosrovani S., Janssen J., Maas L.M., Godschalk R.W., Nijhuis J.G., van Schooten F.J. (2007)**. "Dietary flavonoids induce MLL translocations in primary human CD34+ cells". *Carcinogenesis* **28(8):** 1703–9.

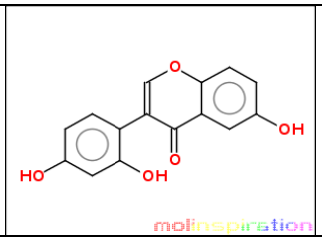
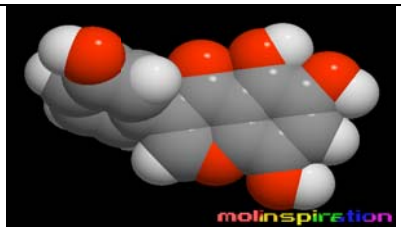
[8] **Manthey J.A., Guthrie N., Grohmann K. (2001)**. Biological properties of Citrus flavonoids Pertaining to cancer and inflammation. *Curr Med Chem*. **8:** 135–53.

[9] **Surh Y.J. (2003)**. Cancer chemoprevention with dietary phytochemicals. *Nat Rev Cancer*. **3:** 768–80.

[10] **O'Boyle N. M., Banck M., James C. A., Morley C., Vandermeersch T. and Hutchison, G. R. (2011).** "Open Babel: An open chemical toolbox, ". *Journal of Cheminformatics* **3:** 33.

Table 1: 2-D and 3-D structures of flavonoid compounds

Ligand	*2-D Structure*	*3-D Structure*
$C_{15}H_{12}O_5$		
$C_{15}H_{12}O_6$		
$C_{15}H_{10}O_6$		
$C_{15}H_{12}O_5$		
$C_{15}H_{10}O_6$		

$C_{15}H_{10}O_5$		

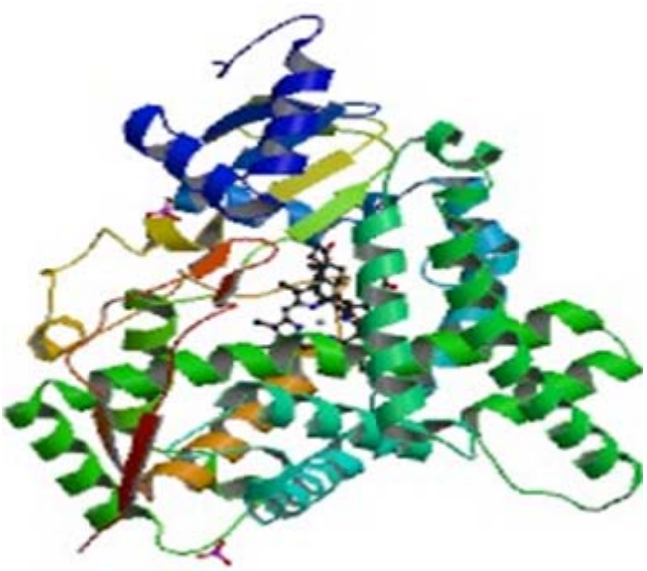


Figure 1: Crystal structure of human placental aromatase complexed with breast cancer drug exemestane(3S7S).

Table 2: Molecular properties of flavonoid compounds

Chemical formula	*mlogp*	*TPSA*	*No. or non H-atoms*	*Molecular weight*	*NO. OF VIOLATIONS*	*Volume*
$C_{15}H_{12}O_5$	2.439	90.895	20.0	270.24	0	224.049
$C_{15}H_{10}O_6$	2.033	107.217	21.0	288.255	0	238.279
$C_{15}H_{10}O_6$	1.286	127.445	22.0	304.254	0	246.297
$C_{15}H_{12}O_6$	1.628	107.217	21.0	288.255	0	238.279
$C_{15}H_{10}O_5$	2.236	111.123	21.0	286.239	0	232.067
$C_{15}H_{12}O_5$	1.778	111.123	21.0	286.239	0	232.067

Table 3: Calculation of Bioactivity Score

Chemical Formula	*GPCR Ligand*	*Ion Channel Modulator*	*Kinase Inhibitor*	*Nuclear receptor ligand*	*Protease inhibitor*	*Enzyme Inhibitor*
$C_{15}H_{12}O_5$	0.04	-0.17	-0.28	0.36	-0.13	0.21
$C_{15}H_{10}O_6$	0.27	-0.60	-0.16	0.05	-0.80	0.03
$C_{15}H_{10}O_6$	0.07	-0.18	-0.12	0.31	-0.34	0.26
$C_{15}H_{12}O_6$	0.07	-0.20	-0.22	0.46	-0.09	0.21
$C_{15}H_{10}O_5$	0.19	-0.53	-0.05	0.17	-0.62	0.21
$C_{15}H_{12}O_5$	0.09	-0.19	-0.03	0.41	-0.24	0.33

Table 4: Docking Energy of flavonoid compounds

S.No.	*Chemical formula of ligand*	*IUPAC Name of Flavonoids*	*DOCKING ENERGY*
1	$C_{15}H_{12}O_5$	3-(2,3-dihydroxyphenyl)-5,6-dihydroxy-4*H*-chromen-4-one	-9.451260kcal/mol
2	$C_{15}H_{12}O_6$	2-(2,4-dihydroxyphenyl)-5,7-dihydroxy-2,3-dihydro-4*H*-chromen-4-one	-9.470030kcal/mol
3	$C_{15}H_{10}O_6$	5,7-dihydroxy-2-(3-hydroxyphenyl)-2,3-dihydro-4*H*-chromen-4-one	-9.672671kcal/mol
4	$C_{15}H_{12}O_5$	6-hydroxy-3-(2,3,5-trihydroxyphenyl)-2,3-dihydro-4*H*-chromen-4-one	-9.275607kcal/mol
5	$C_{15}H_{10}O_6$	(6,7-dihydroxy-3-(4-hydroxyphenyl)-2,3-dihydro-4*H*-chromen-4-one	-9.391901kcal/mol
6	$C_{15}H_{10}O_5$	(6,7-dihydroxy-3-(2,4,6-trihydroxyphenyl)-4*H*-chromen-4-one)	-9.292828kcal/mol