Volume 9, Issue 4, April – 2024 International Journal of Innovative Science and Research Technology
ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24APR2622

A Review on Analysis of Flavonoid and Isoflavonoids Derivatives as Anticancer Agent using Swiss ADME

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Abstract:- Cancer, generally characterized by uncontrollable growth of abnormal cells that metastasize to other parts of the body. It is a one of the leading concerned disease that affects the worldwide population. It can originate from almost any organ or tissue and are of various types; leukemia, lung cancer, lymphoma, stomach cancer, cervical cancer.

Flavonoids and Isoflavonoids are naturally occurring polyphenolic secondary metabolites that possess numerous medicinal benefits including antioxidant, anti-inflammatory, anticancer and antiviral properties. Potential agents derived from flavonoids and isoflavonoids for its anticancer activity have been studied. Due to recent technological advancement, the detailed study of any moiety and molecules is possible. A virtual screening of flavonoids was carried out using molecular docking, drug similarity, ADMET prediction, drug likeness, chemical and physicochemical properties to determine its potential anticancer activity with the use of Swiss ADME and Chem Draw software.

In this review, analysis of drug likeness properties of flavonoids and isoflavonoids was thoroughly performed. Additionally, structures were examined and observed for better interaction of flavonoids scaffold with receptors. Due to their great stability, flavonoids are strongly recommended as anticancer medicines for various cancer stages.

I. INTRODUCTION

➢ *Cancer*

Cancer is a broad family of illnesses arising from uncontrolled division of abnormal cells that metastasize to other parts of the body. These problems can originate in almost any organ ortissue within the human system. The latter is known as metastasizing and has a significantrole in cancer-related deaths. Malignant tumour and neoplasm are other names for cancer[1,2]. Furthermore, a mutation in the p53 gene results in the production of a unique protein that modifies the molecular mechanisms associated with p53. There is a complicated relationship between the p53 gene and cancer; studies have demonstrated thatp53 aberration accounts for 60% of cancer cases. Cancer cells are produced as a result of these genetic and biological processes going away. Under normal circumstances, P53 is essential for angiogenesis, differentiation, senescence, cell death, cell division, and DNA metabolism. Furthermore, the DNA-binding area is impacted by most p53 gene mutations,and p53 controls the capacity of genes to replicate. Cancer cells associate with CDK1-P2 and CDC2. through p53, which keep them in the first and second growth phases of the cell cycle. (3,4)

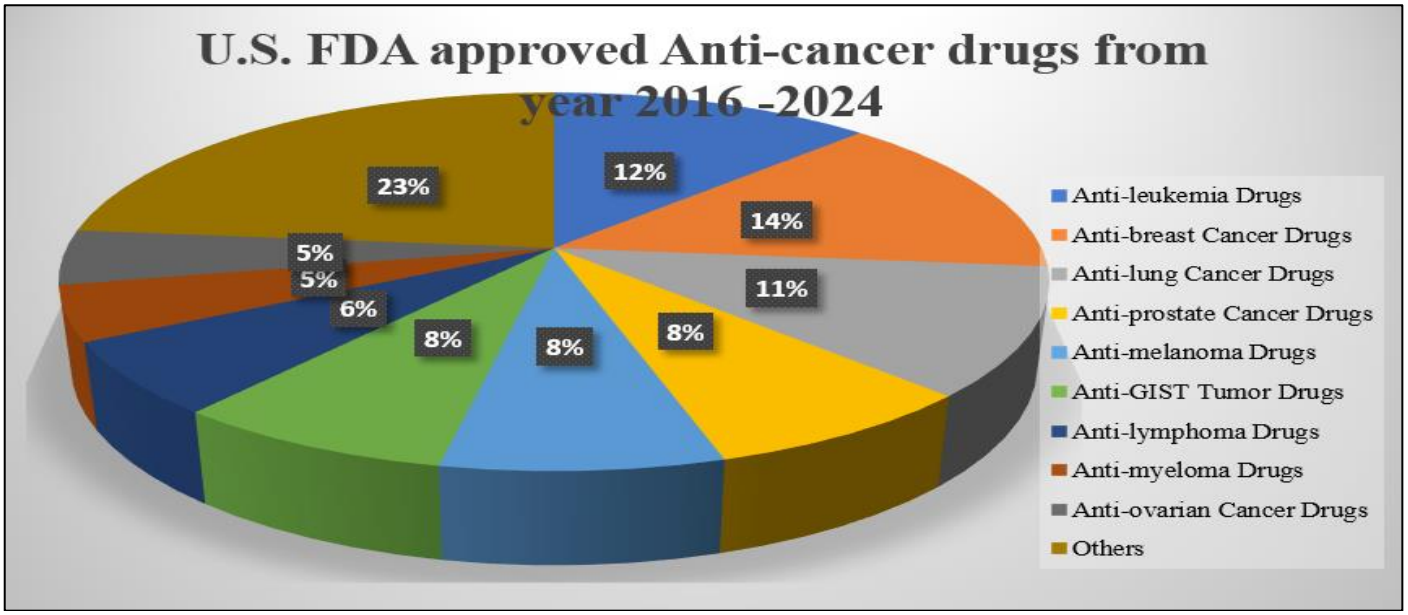

Fig 1: U.S. FDA Approved Anti-Cancer Drugs from Year 2016 -2024

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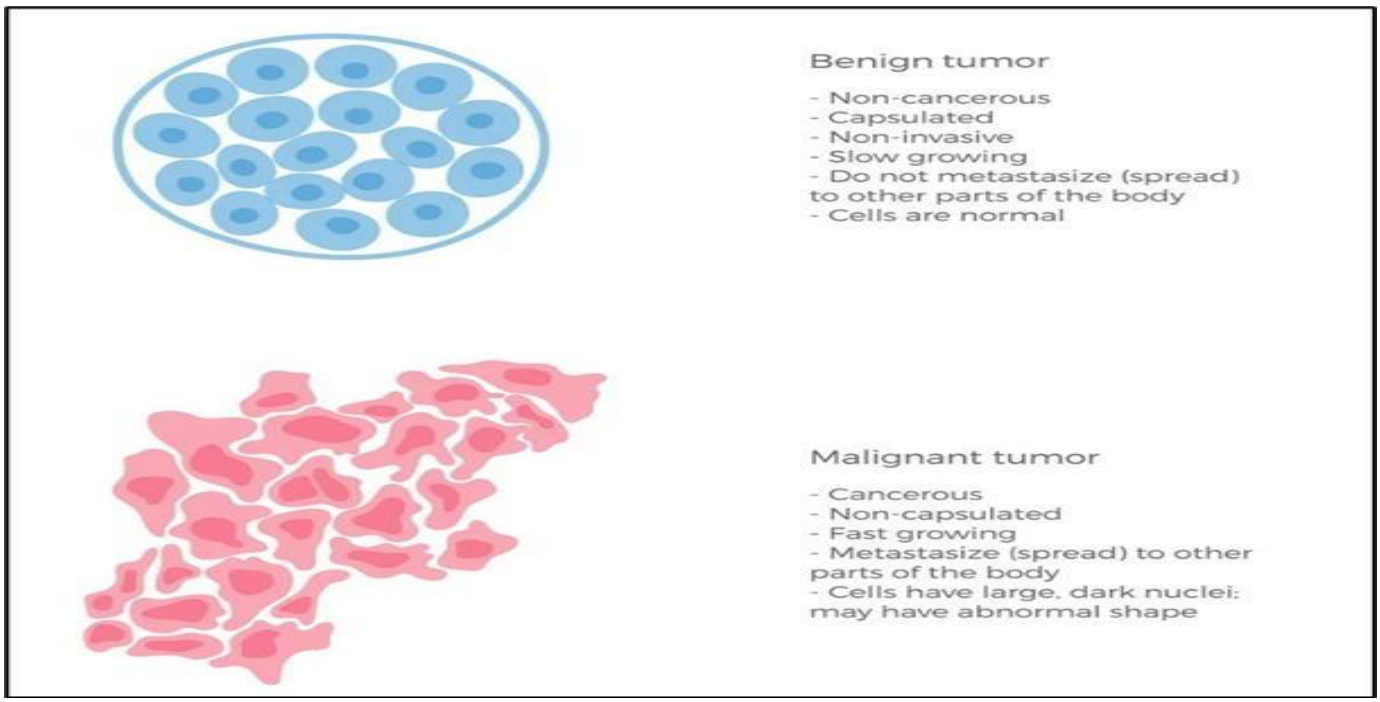

Fig 2: Types of Cancer

II. FLAVONES AS ANTICANCER AGENTS

Plants and 26 different foods include a class of secondary polyphenol metabolites called flavonoids. Numerous bioactive qualities are believed to be present in them, such as anti-cancer, antiviral, anti-inflammatory, anti-diabetic, cardioprotective, and anti-aging effects. Their fundamental structures of C6-C3-C6 rings(6).

A. SAR of Flavonoids for Anti-Cancer Activity

One family of flavonoids consists of the two main types: isoflavonoids, the first having a C6-C3-C6 structure, and flavonoids (in the strict sense). The significance of flavonoids in cancer therapy has been shown by a number of processes, such as the induction of programmed cell death, nuclear factor signalling inhibition, proteasome inhibition, differentiation induction, and initiation of cell cycle arrest. Many studies have been conducted on flavonoid-based cytostatic anti-cancer medicines because they may exhibit selective cytotoxicity on cancer cells. Double bonds between C2 and C3 are essential for planarity and molecular conjugation. Certain hydroxylated flavonoids between rings C and A/B have more inhibitory effects on cancer cells for effective carcinoma inhibition. Ring B's additional hydroxyl group alteration has no effect on the activity. It has been proposed to substitute ring B with a catechol moiety, which has significant ramification. In ring C, Figure 3 illustrates that 3-hydroxylation has been identified as a highly significant moiety for increasing biological action. Biological activity is enhanced by derivatives having ortho methylation substitution on flavanoids, which are generally associated with ring A polymethoxylation.(7)

B. Scaffold-hopping of Bioactive Flavones

Scaffold-hopping of bioactive template/drug is an important strategy in drug design to produce distinct molecules with desired properties. Lead hopping, often known as scaffold hopping, is a strategy for discovering structurally novel molecules. The finding of iso-functional molecular structures that, critically, contain several molecular backbones is referred to as "scaffold-hopping". By emphasising the degree of alteration relative to the original parent molecules, the classification of scaffold hopping techniques helps to rationalize the idea of scaffold hopping. A 1° hop is a little modification in which heteroatoms and carbon in a backbone ring are switched or replaced more extensive ring openings and closures are indicative of a 2° hop. A 3° hop occurs when the peptide backbone is replaced with non-peptic molecules. Finally, a completely new chemical structure that just maintains connections is referred to as a 4° hop. a technique that finds potent anticancer medications by jumping from one scaffold to another utilising bioactive natural chemicals like isoflavones and flavones(8)

III. IMPORTANCE OF FLAVANOID AND ISOFLAVANOID DERIVATIVES

Within the plant kingdom, flavonoids are a group of naturally occurring 2° plant polyphenolic metabolites that are extensively dispersed and, as a result, often found in diets. Typically, they are identified as compounds whose principal structure is the 15-carbon having C6-C3-C6 carbon nucleus. A heterocyclic ring, two phenyl rings (A and B), and two phenyl rings make up these oen. Biological studies on natural and synthetic flavonoid analogues have revealed a variety of bioactivities exhibited by these species, including anxiolytic, anti-microbial, anti-cancer, anti-inflammatory, anti-ulcer, and anti-thrombosis properties(9)

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IV. CHEMICAL PROPERTIES OF FLAVONOIDS

The phenylpropanoid chain containing 15-carbon (C_6-C_3C_6) which is made up of two aromatic rings (A and B) joined by a heterocyclic pyran ring (C) is the fundamental flavan skeleton shared by all flavonoids (Figure 3). Flavonoids might be further classsified into six main classes based on their chemical structure, degree of oxidation, and unsaturation in connecting chain, which are: isoflavonoids, flavanones, flavanols, flavones, and anthocyanidins.

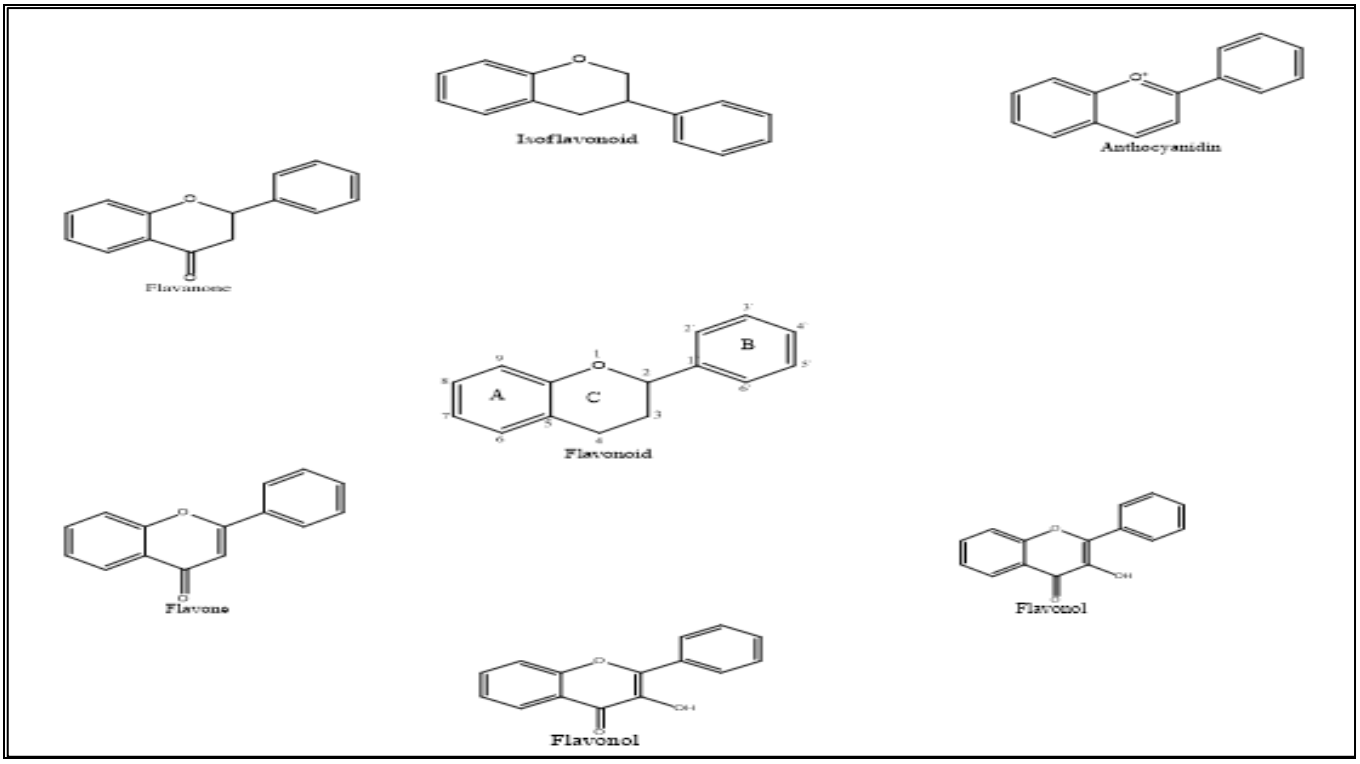

Fig 3: Different Structural Examples of Flavonoids

- *In Flavonoids or Isoflavonoids, a Chromane Ring (A and C) is Joined to a B Ring (Figure 3) at C2 or C3.*

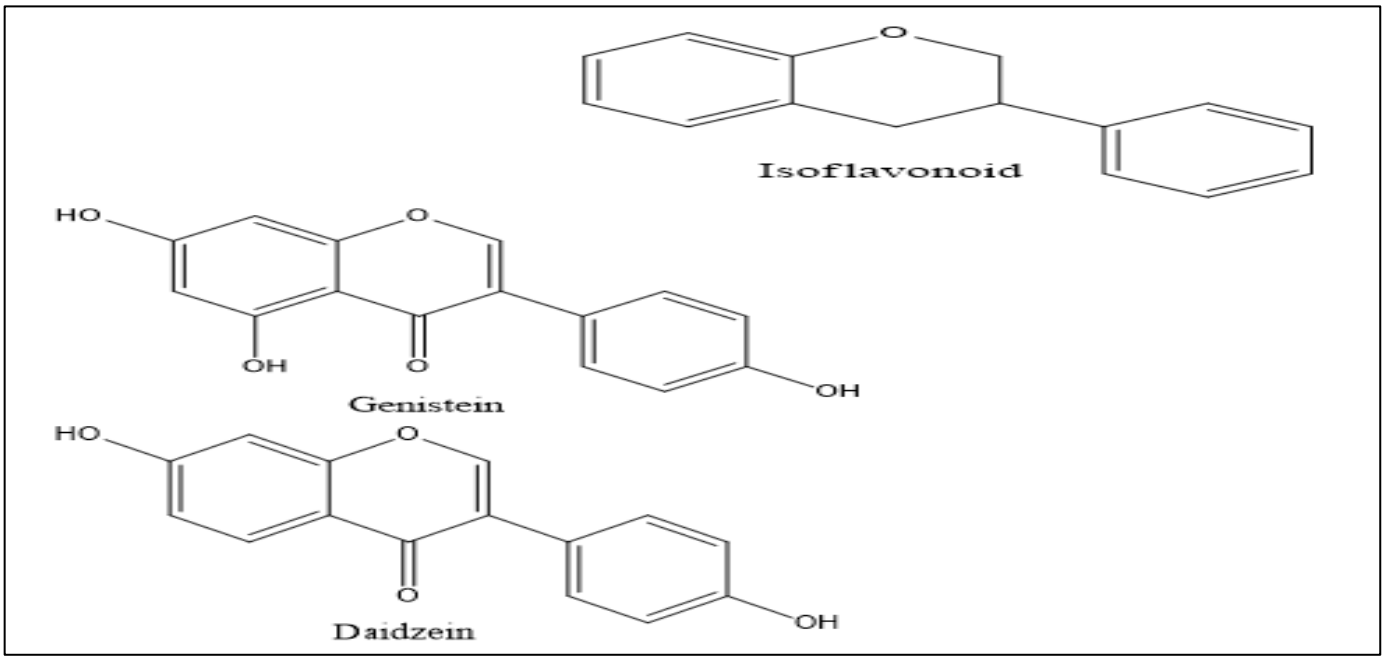

Fig 4: Structural Examples of the Main Isoflavonoids

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➢ *Flavanones, also Known as di-Hydroflavones, have Oxidised and Saturated, C Ring.*

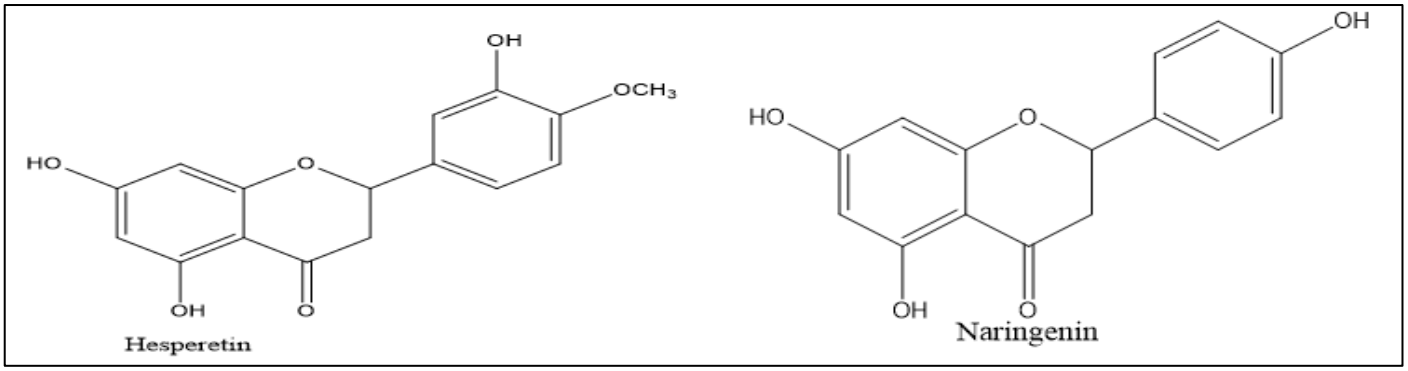

Fig 5: Chemical Structures of Main Flavanones

The C ring of flavanols is saturated, unoxidized, and has a hydroxyl group at position C_3. The most common stereoisomers of catechins are trans ((+) catechin or cis ((-)-epicatechin), depending on where C_2 and C_3 are located in the molecule. Epicatechin gallate, epigallocatechin, and epigallocatechin gallate are gallic acid conjugates that flavanols can produce during esterification with gallate groups.

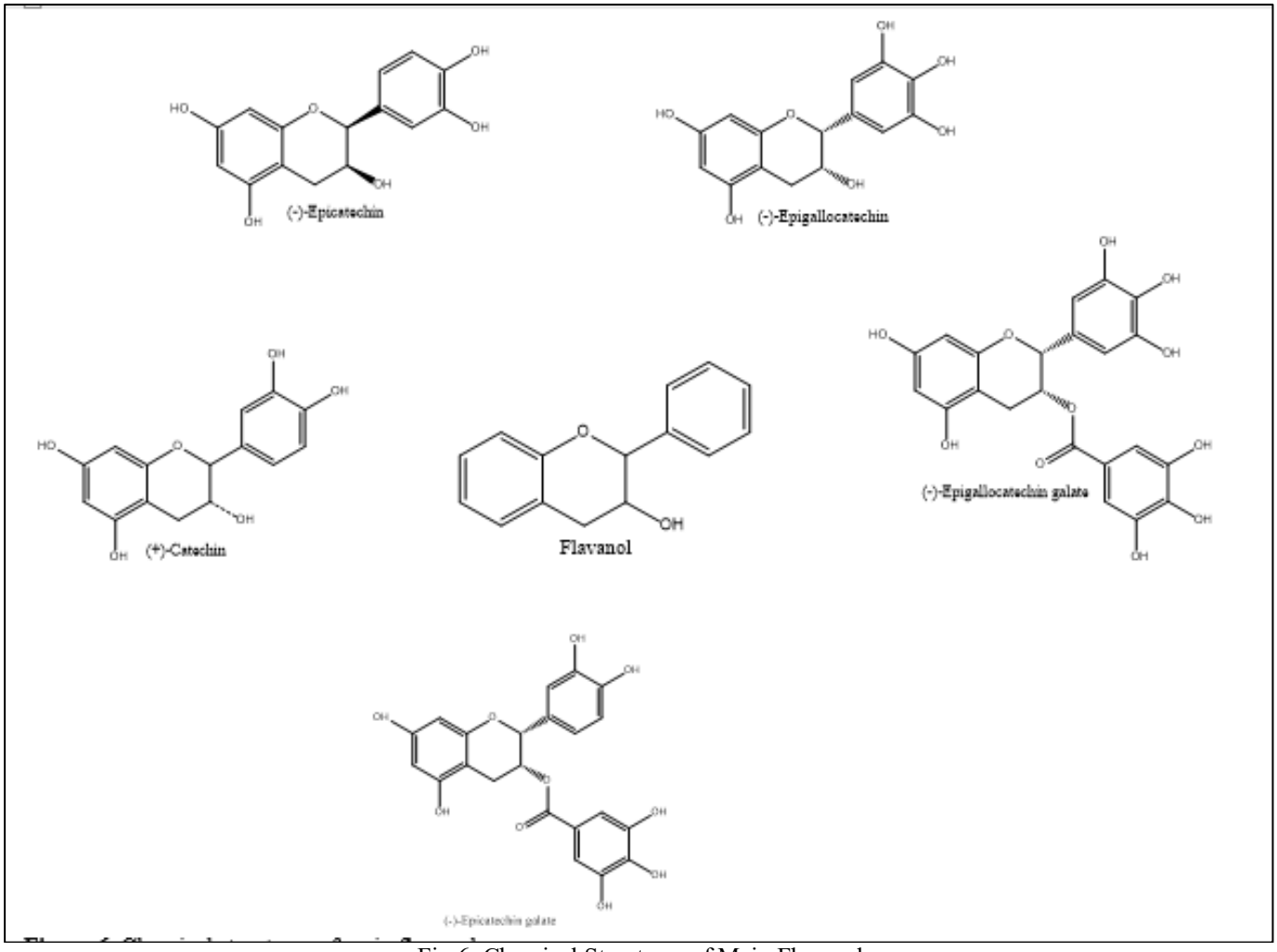

Fig 6: Chemical Structures of Main Flavanols

Flavonols have an unsaturated C ring at position C_2-C_3, which is usually oxidized at C_4 and hydroxylated at C_3. Kaempferol and quercetin are the main flavonols; myricetin, isorhamnetin, fisetin, and galangin are present in lesser amounts (Figure 7). The –OH moieties of flavonols are responsible for their biological effects.

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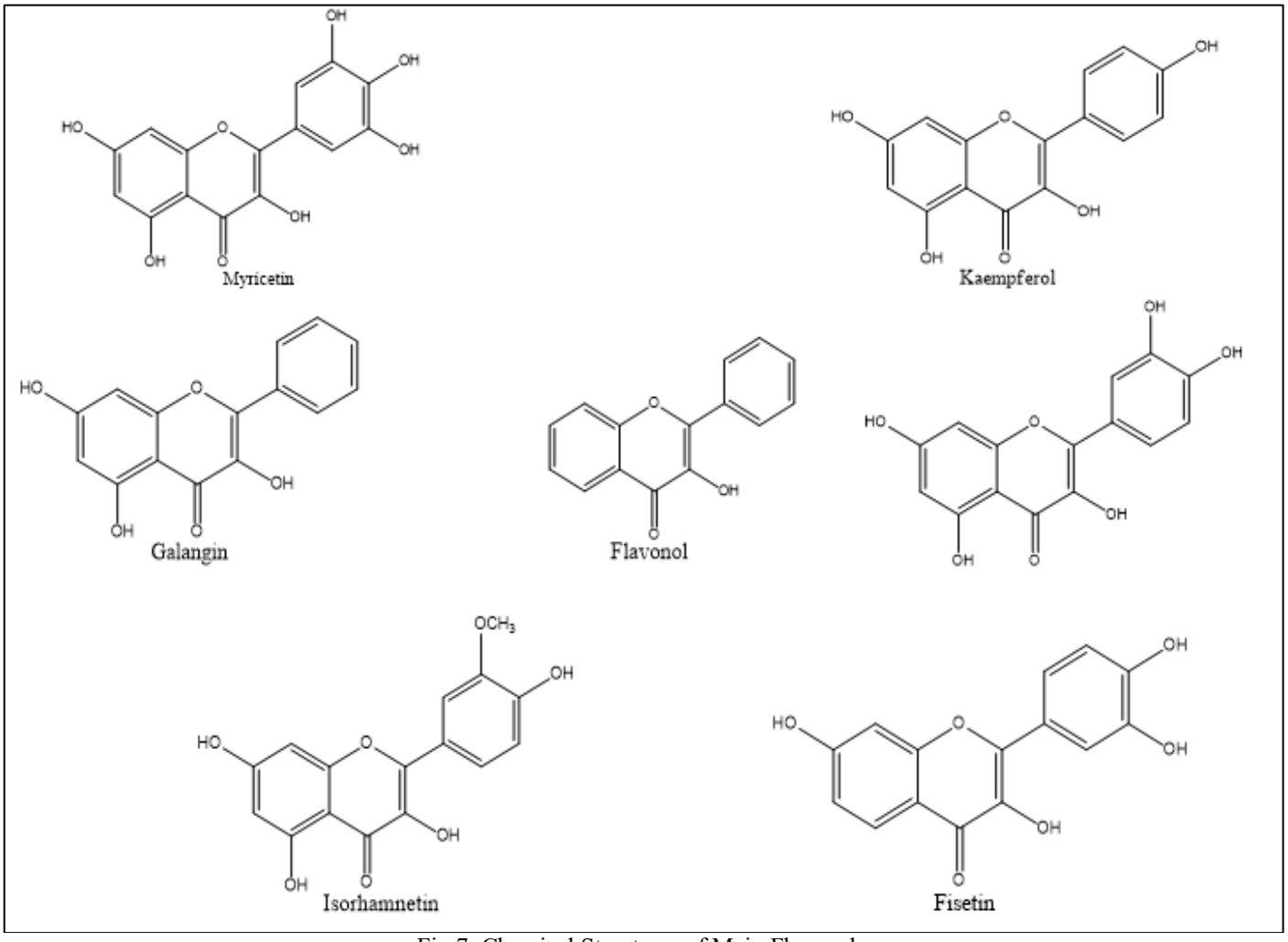

Fig 7: Chemical Structures of Main Flavonols

Flavones have no hydroxy group at C_3, and ring C is unsaturated at positions C_2–C_3, with ketonic group at position C_4(10). Apigenin, luteolin, chrysin, and tangeritin are the primary flavones (Figure 8).

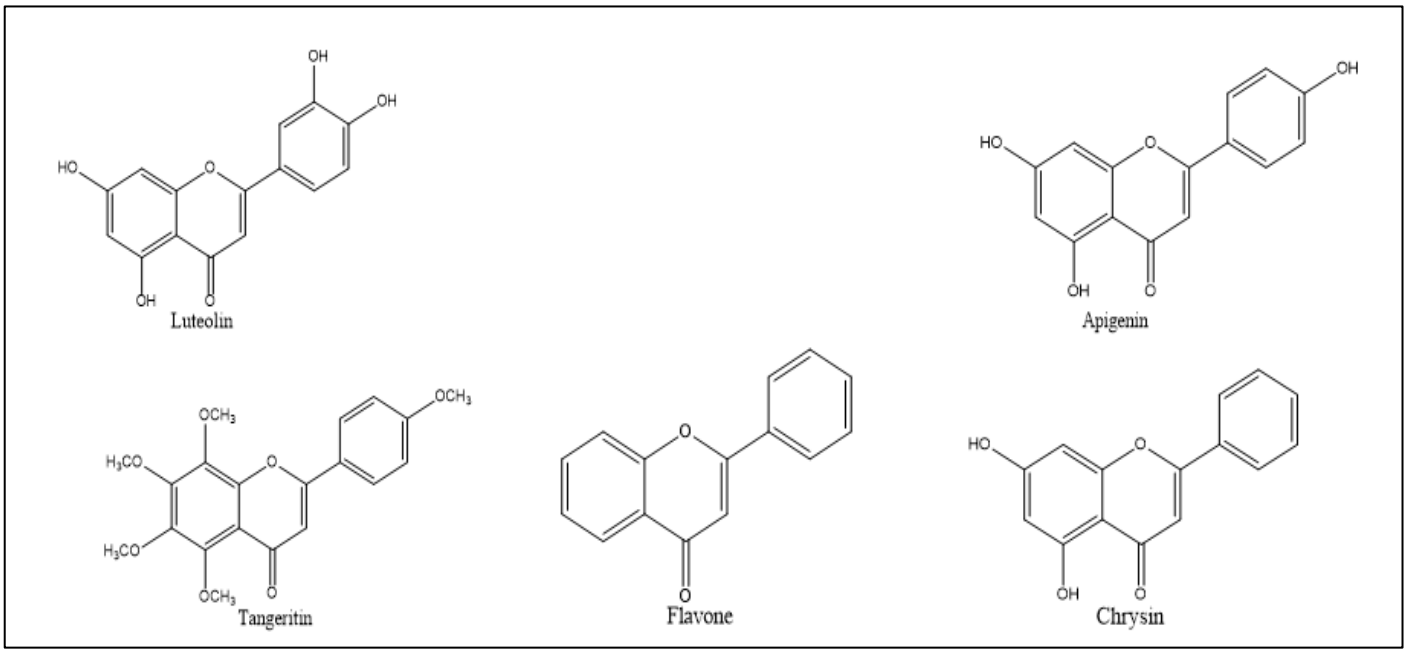

Fig 8: Chemical Structures of Main Flavones

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Anthocyanidins are pH-dependent pigments obtained from plant which are water-soluble, unsaturated, and unoxidized flavonoids. The fundamental structure of the phenylbenzopyrylium chromophore–flavylium ion serves as the basis for anthocyanidins. In anthocyanidins the ring B is hydroxylated at the C_3 position (11). (Figure 9) The principal anthocyanidins include cyanidin, pelargonidin, peonidin, petunidin, delphinidin and malvidin.

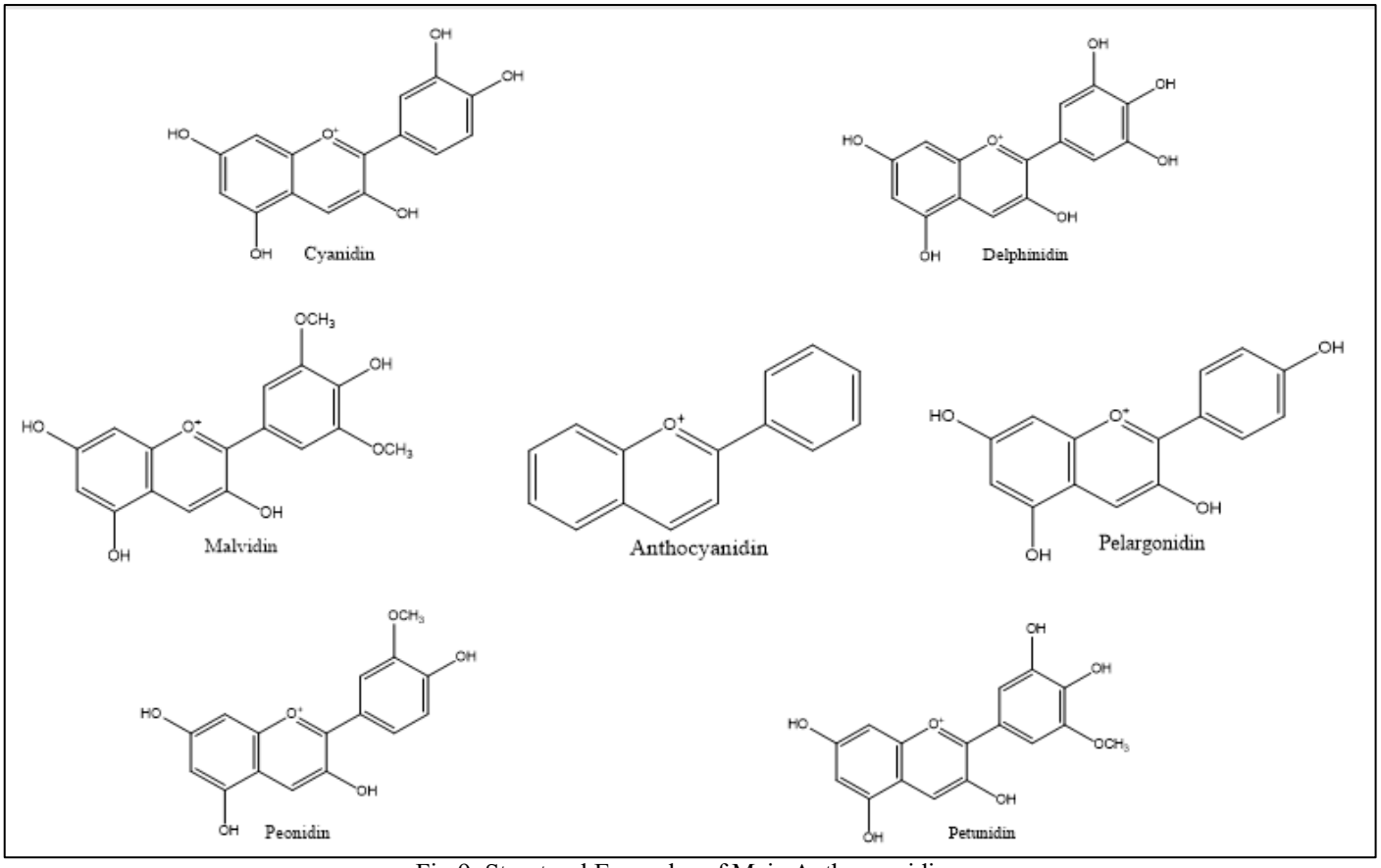

Fig 9: Structural Examples of Main Anthocyanidins

There are two forms of flavonoids: aglycones without connected sugars and glycosides with linked sugars(11, 12). Flavonoids combine to create phenolate anions and neutral phenols in the cytosol (pH 7.4). The pKa of every phenolic group determines their relative amounts. Given that flavonoids are weak hydrophobic acids, their ability to traverse cellular and mitochondrial membranes will depend on how lipophilic they are.

V. ANTICANCER EFFECTS OF FLAVONOIDS

Flavonoids may clean the free radicals, regulate cellular metabolism, and prevent diseases linked to oxidative stress, according to a number of studies. Many flavonoids have been shown to have anticancer activities by an increasing amount of research; however, the precise molecular processes underlying these actions are yet understood. Cancer is a multifaceted disease characterised by the growth of abberant cells that invade and spread to different areas of the body as a result of uncontrolled proliferation and a disturbed cell cycle. The main internal causes of cancer are Oxidative stress, hypoxia, genetic modifications, and loss of apoptotic function. The main external causes are elevated stress, pollution, smoking, radiation, and UV radiation exposure.(2)

Changes in metabolism, disturbed cell cycles, immunological response resistance, recurrent mutations, chronic inflammation, metastasis formation, and angiogenesis stimulation are the main features of cancer cells. A increasing body of research suggests that cancer is a metabolic disease caused by varied degrees of mitochondrial malfunction and metabolic abnormalities. The main metabolic changes in the cancer cells include increased aerobic glycolysis, acidosis, decreased lipid metabolism , increased ROS generation , and decreased enzyme activity(13)

This directly causes hyperpolarized mitochondria, decreased membrane cardiolipin levels that impair enzyme activities , increased glutamine-driven lipid biosynthesis that upregulates the pathways involved in the initiation and metastasis of tumours , an acidic extracellular environment that is more conducive to inflammation , and an effect that is correlated with the invasiveness and malignancy of cancer cells. Flavonoids have different types of anticancer properties, such as regulating the activities of enzymes that clean the reactive oxygen species, arresting the cell cycle, trigger the programmed cell death, autophagy, and reducing the growth and invasiveness of cancer cells.(2, 14)

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VI. ANALYSIS OF DRUG LIKENESS PROPERTIES FOR FLAVANOIDS AND ISOFLAVANOIDS USING SWISSADME SOFTWARE

We looked at the drug-like properties of several flavones and isoflavones derivatives in the study to ascertain the superior physiochemical properties of the basic moiety with a wide range of substitution on the flavones and isoflavones scaffold. To identify the possible flavanoids structure against CDK8, a virtual screening of flavanoids was performed utilising molecular docking, drug similarity, ADMET prediction, and a molecular dynamics MD simulation technique. Since flavonoids are naturally occurring substances that have been a part of human diet and drink since ancient times, they do not have the same aftereffects as manmade anticancer medications.

Several studies have shown their significant beneficial effects on the response of the immune system, the reduction of inflammation, and the maintenance and restoration of normal cellular functions. Because of their broad variety of anticancer actions, flavanoids may provide useful resources for future studies into the creation of novel cancer chemopreventive drugs and the subtleties of their modes of action.

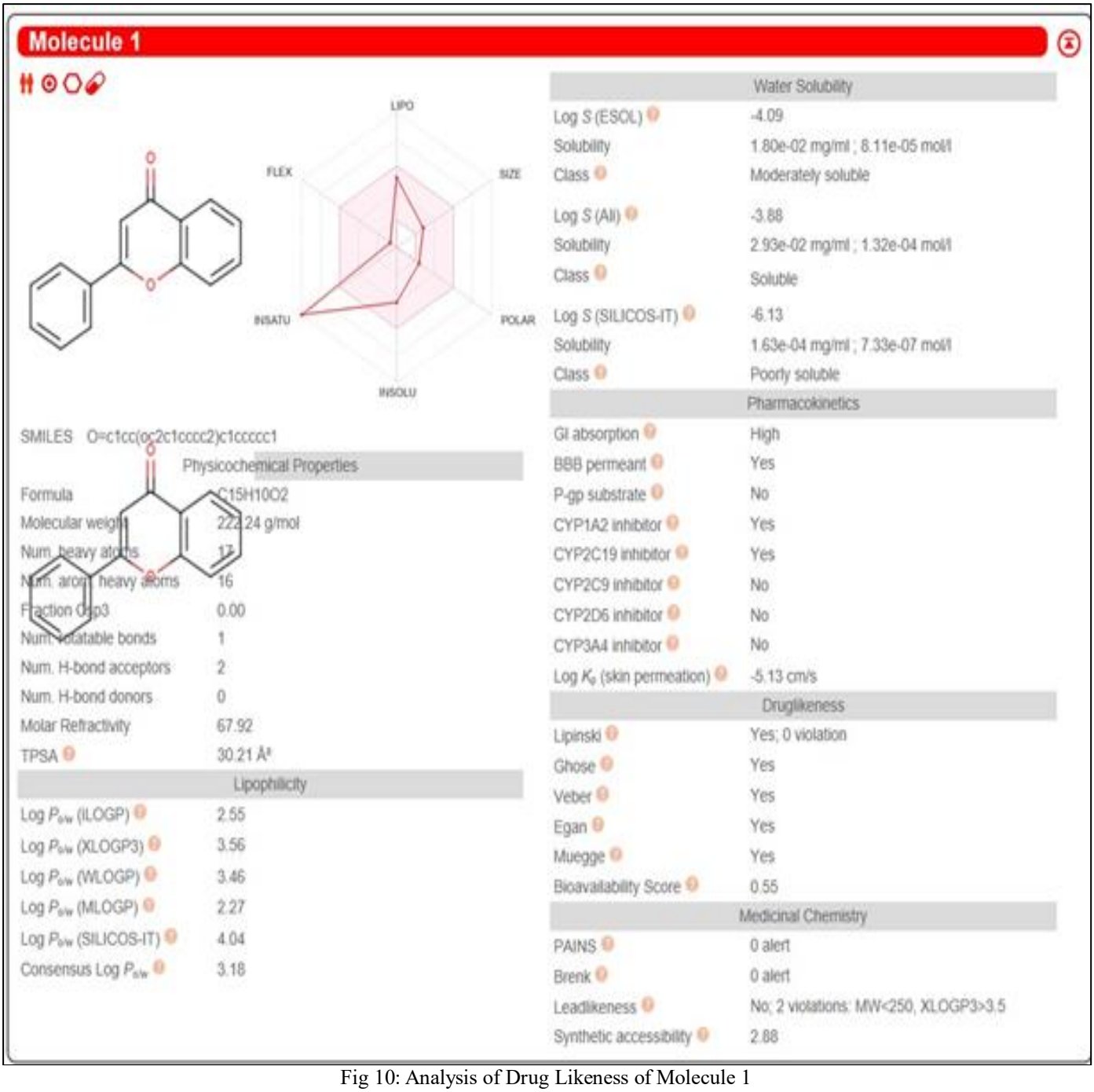

Fig 10: Analysis of Drug Likeness of Molecule 1

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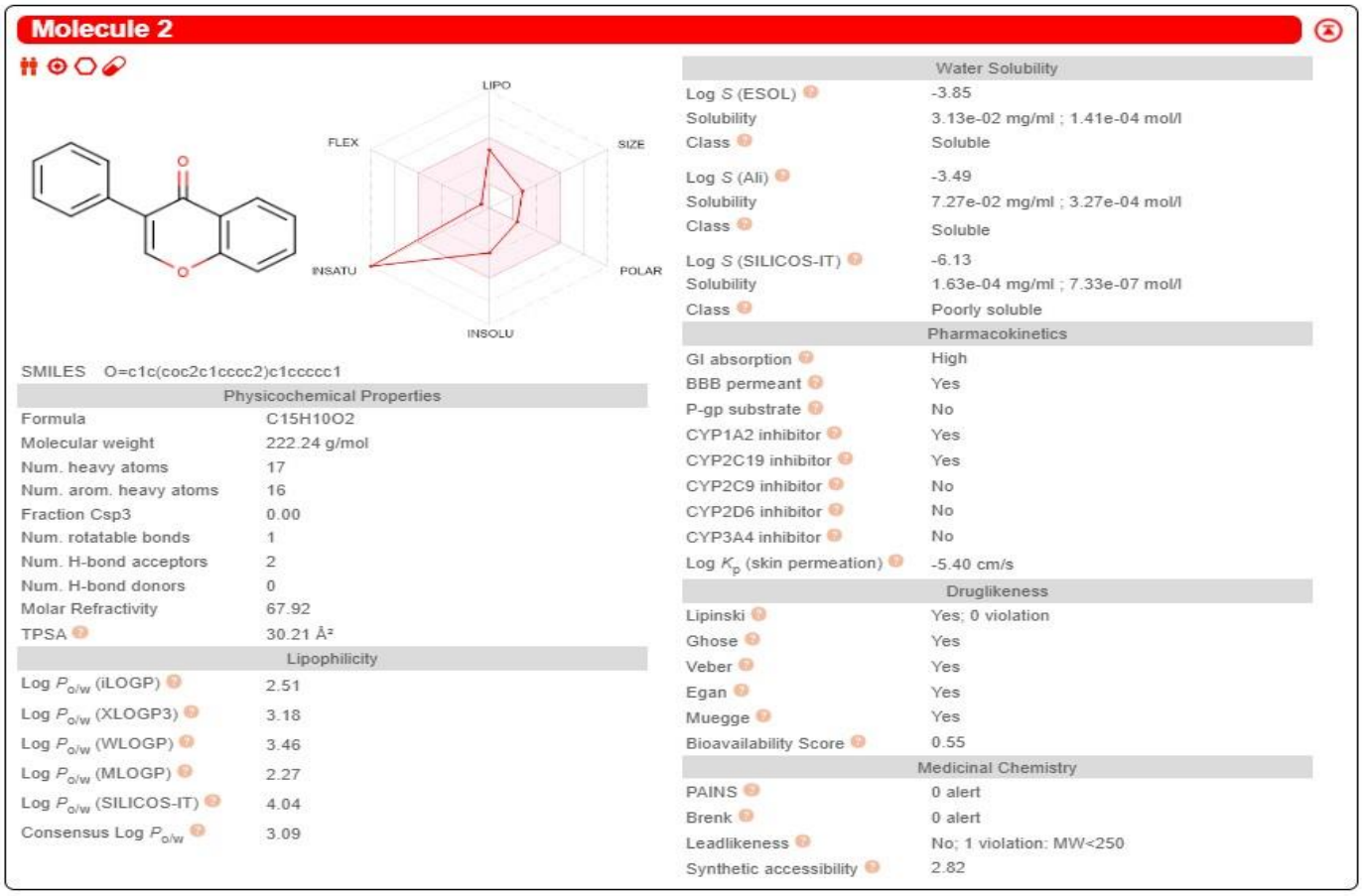

Fig 11: Analysis of Drug Likeness Property of Molecule 2

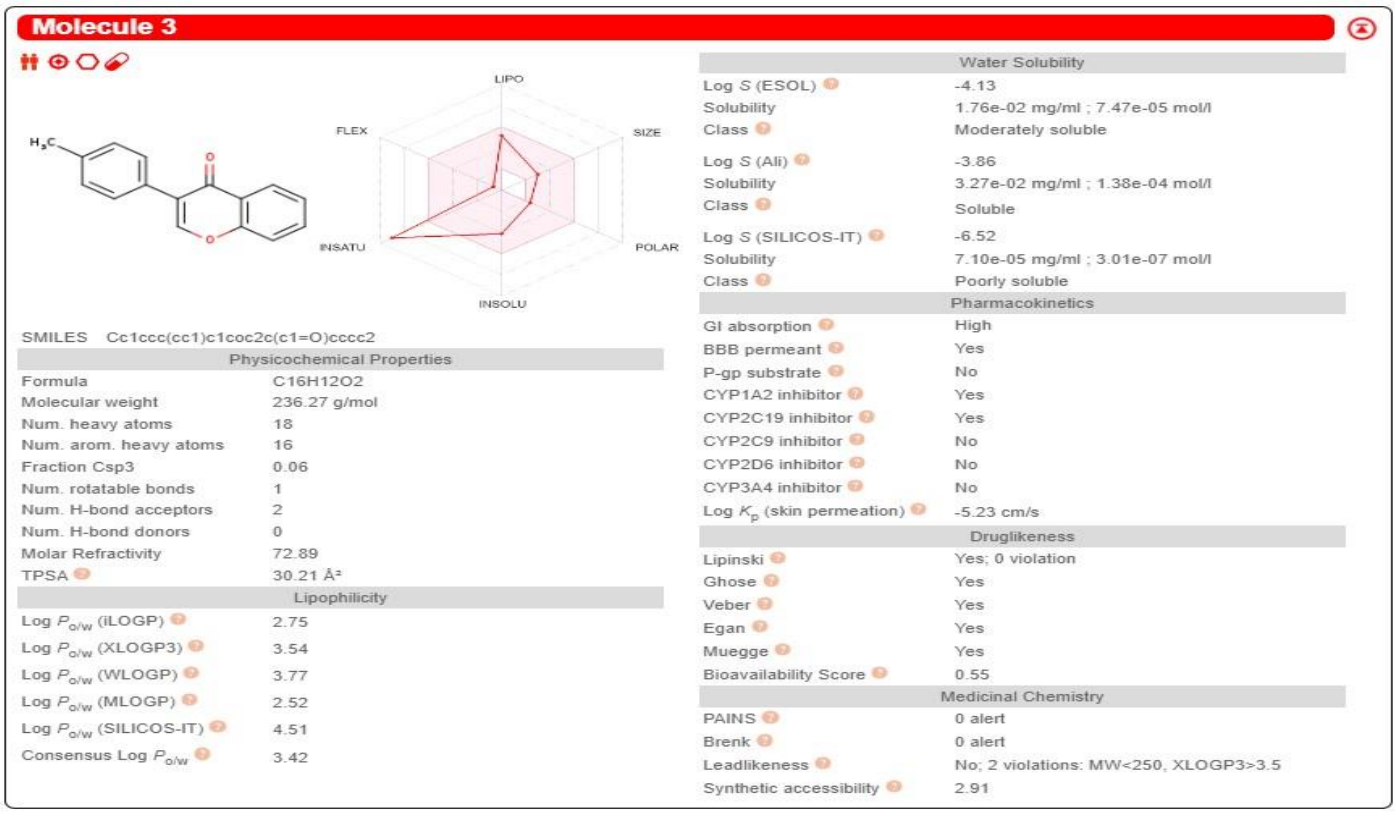

Fig 12: Analysis of Drug Likeness of Substituted Molecule 3

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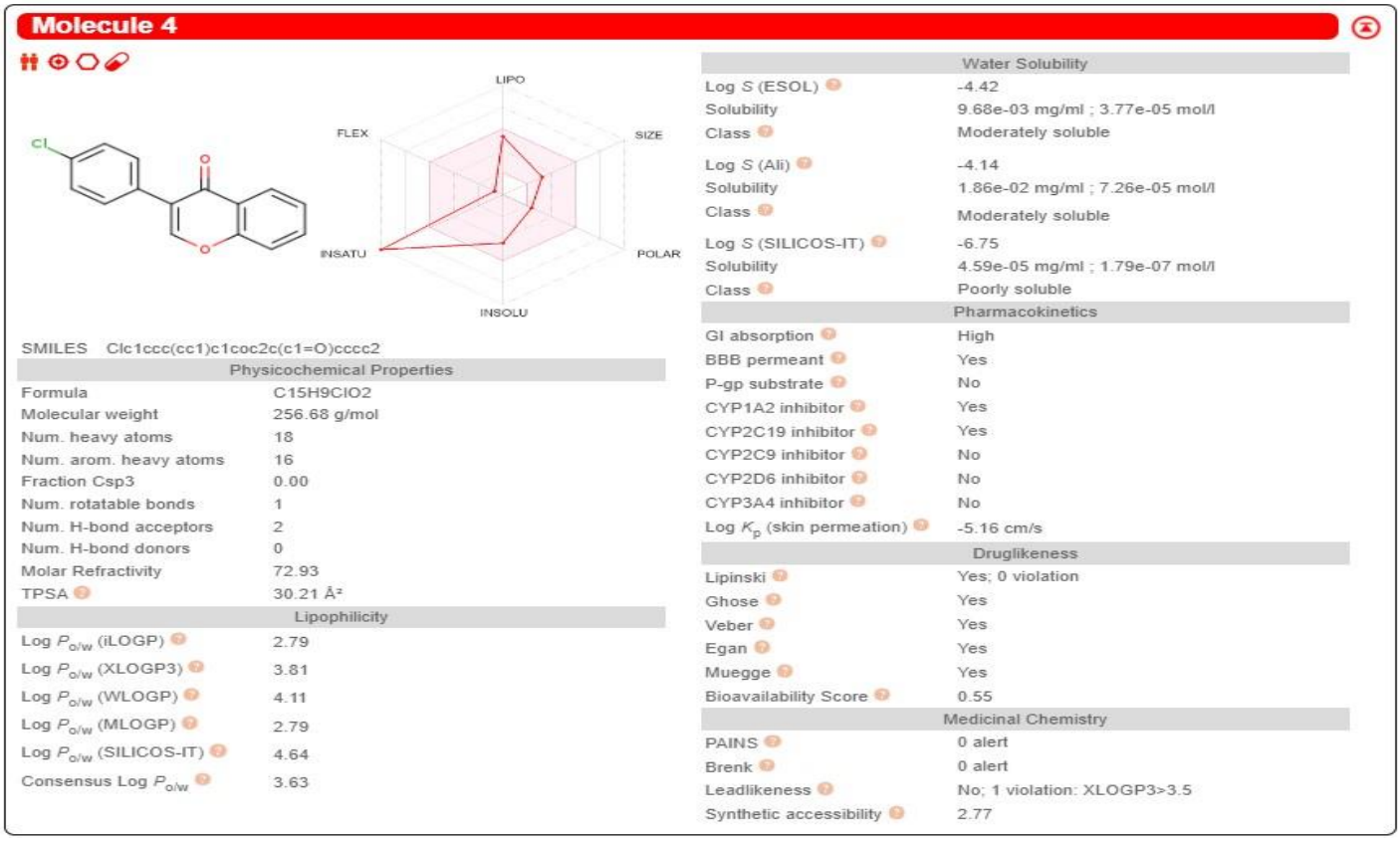

Fig 13: Analysis of Drug Likeness of Molecule 4

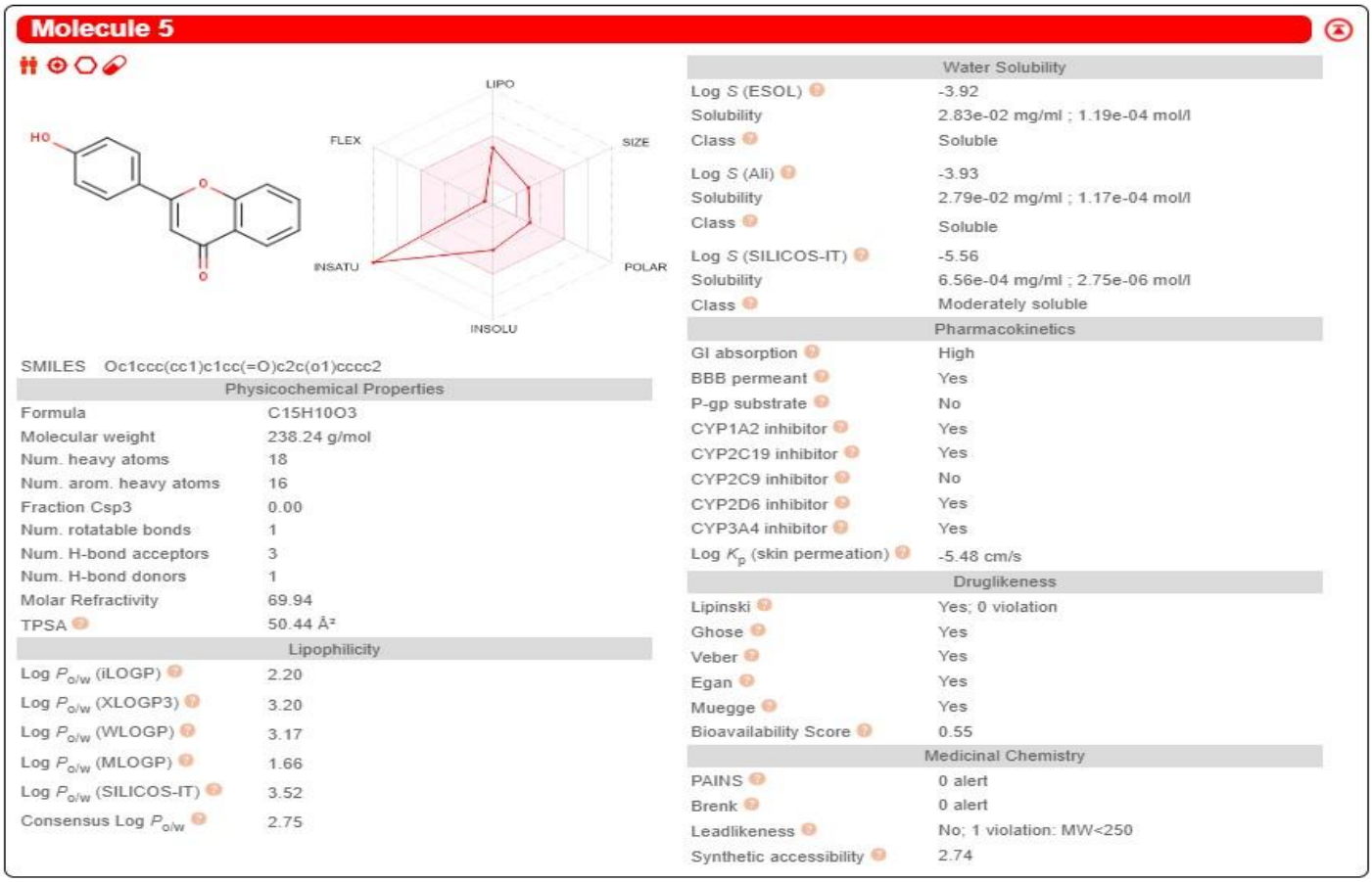

Fig 14. Analysis of drug likeness property 5

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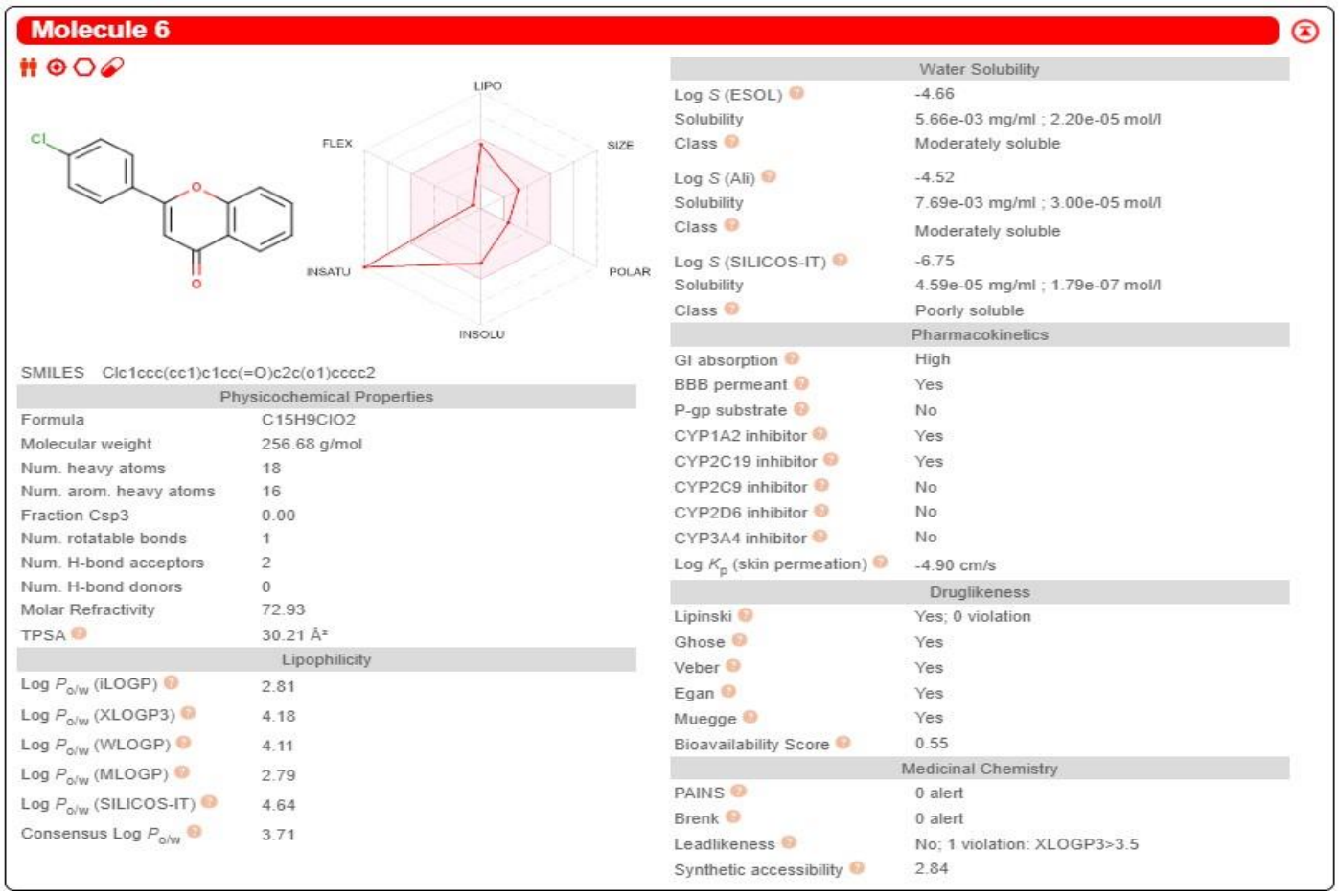

Fig 15: Analysis of Drug Likeness Property of Molecule 6

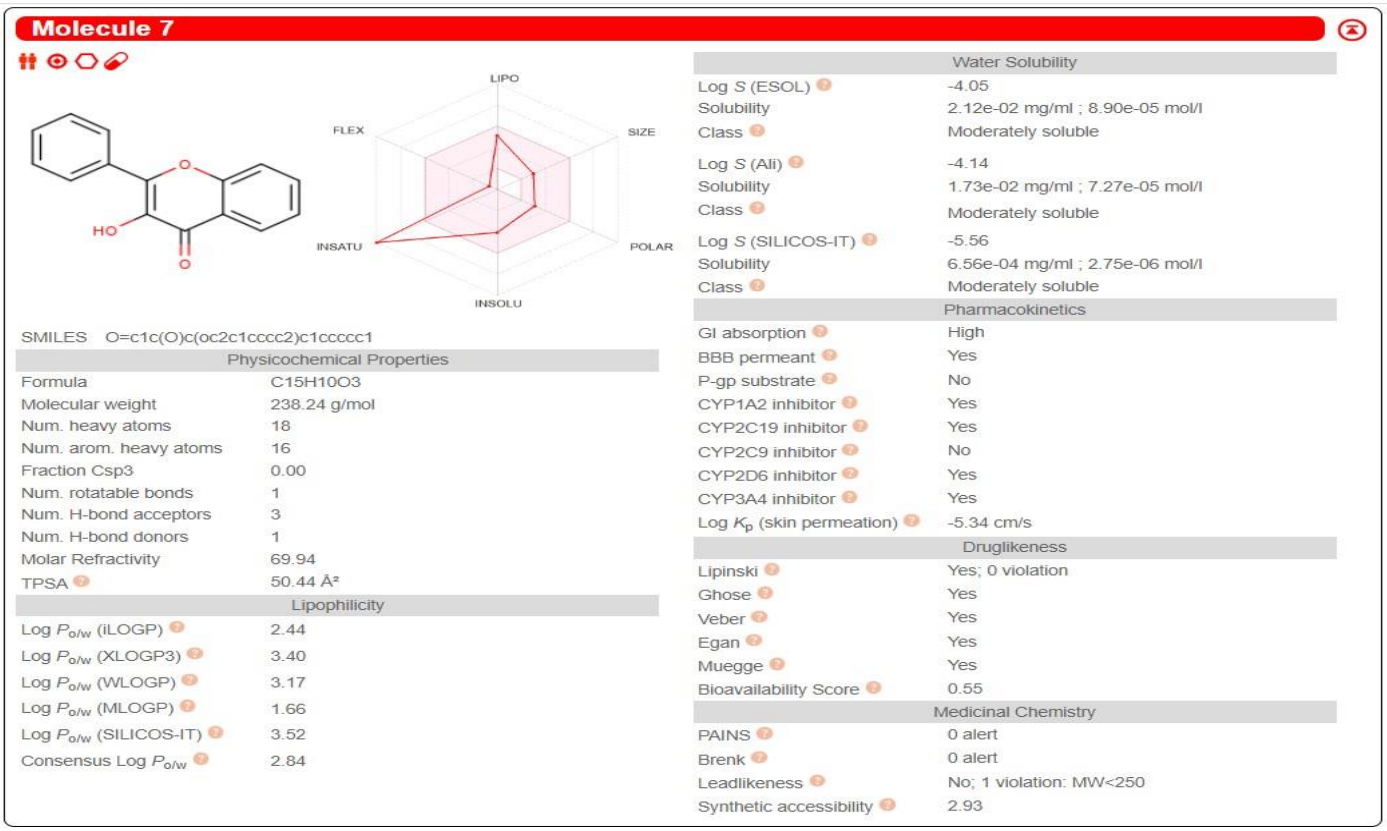

Fig 16: Analysis of Drug Likeness Property of Molecule 7

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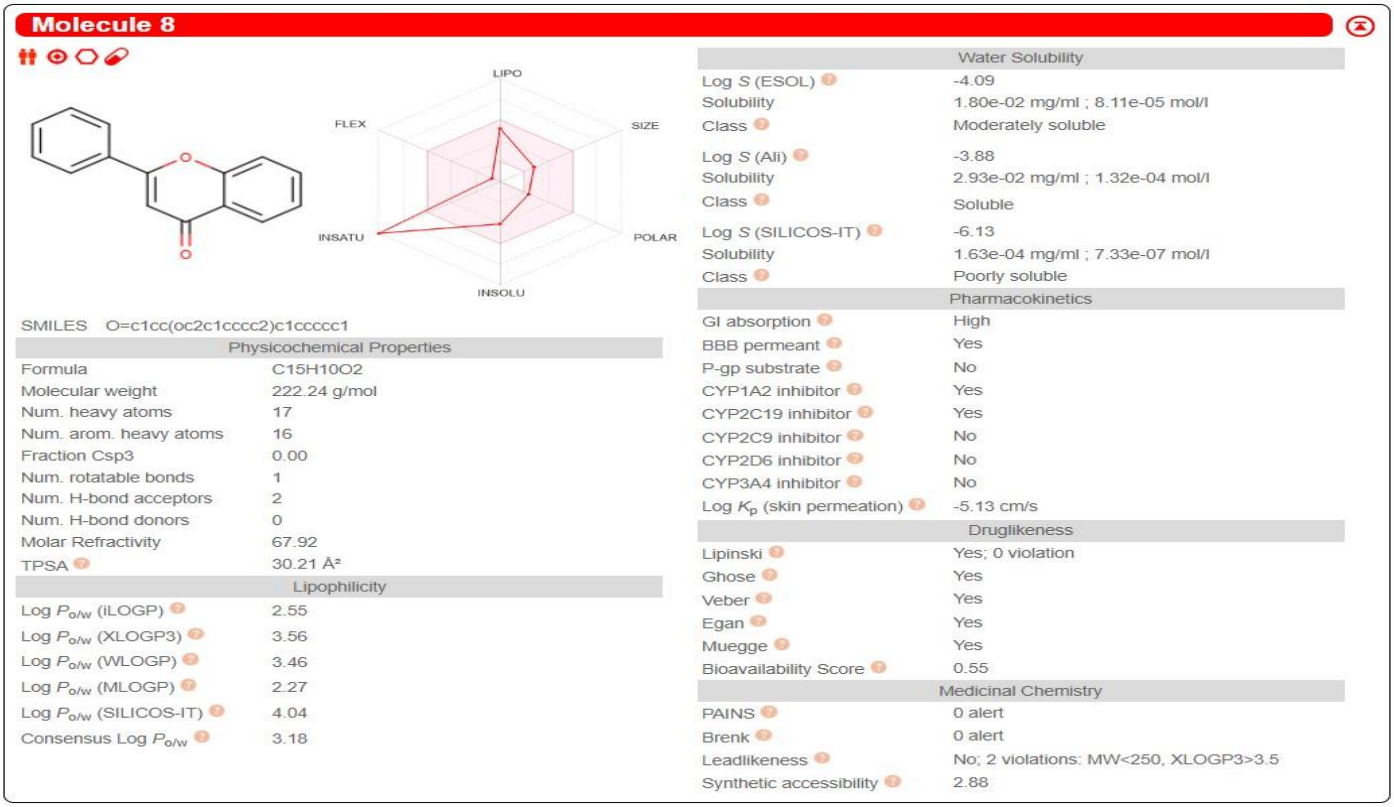

Fig 17: Analysis of Drug Likeness Property of Molecule 8

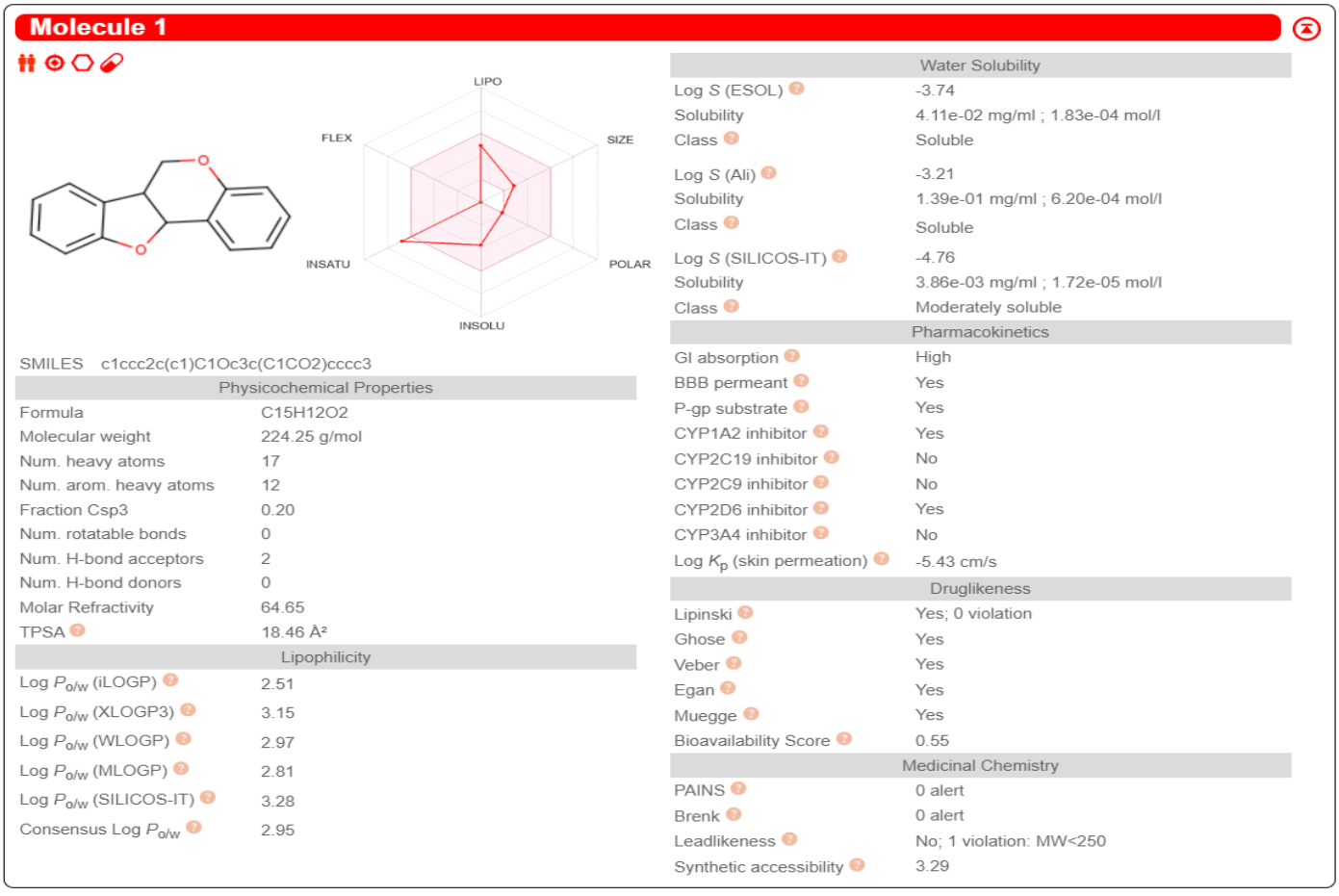

Fig 18. Analysis of Drug Likeness Property of Molecule 9

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A. Apigenin

Several studies have demonstrated their very positive benefits on the immune system's response, the reduction of inflammation, and the maintenance and restoration of normal cellular functions. Because flavanoids have a broad spectrum of anticancer characteristics, they can provide important information for future research on the subtleties of the mechanisms of action of novel cancer chemopreventive drugs.(15)

Apigenin is a small molecular weight compound that structurally produces pure yellow needles (mw = 270.24). With a melting point of 347.5, apigenin is soluble in DMSO and diluted KOH but insoluble in water. It also dissolves somewhat in heated alcohol. Using it with strong oxidising chemicals is not recommended. It is recommended to store pure apigenin at -20°C due to its high instability.(16) According to the single-pass intestinal perfusion method, it has a good intestinal permeability but a poor solubility in the aqueous phase.This flavone inhibit the growth of cancer cells by causing autophagy, initiating cell apoptosis, and altering the cell cycle. Moreover, apigenin prevents the migration and invasion of cancer cells as well as their motility. Apigenin has been shown to exhibit anti-cancer properties via inducing an immunological response.(17) In its chemical structure, apigenin has three H-bond donors and five H-bond acceptors. Its log P value of 1.91 indicates that it is suitable for oral formulations and does not break any Lipinski restrictions. It was discovered to have no BBB penetration and strong G.I. absorption. Through inducing cell cycle arrest at the G2/M phase, it has been found to possess antiproliferative action against human colon carcinoma and breast cancer cell lines.3. Hesperidin and apigenin exhibit minimal toxicity and strong cytotoxic effects on the MCF7 cell line, with an IC50 of 10 μg/ml..(18)

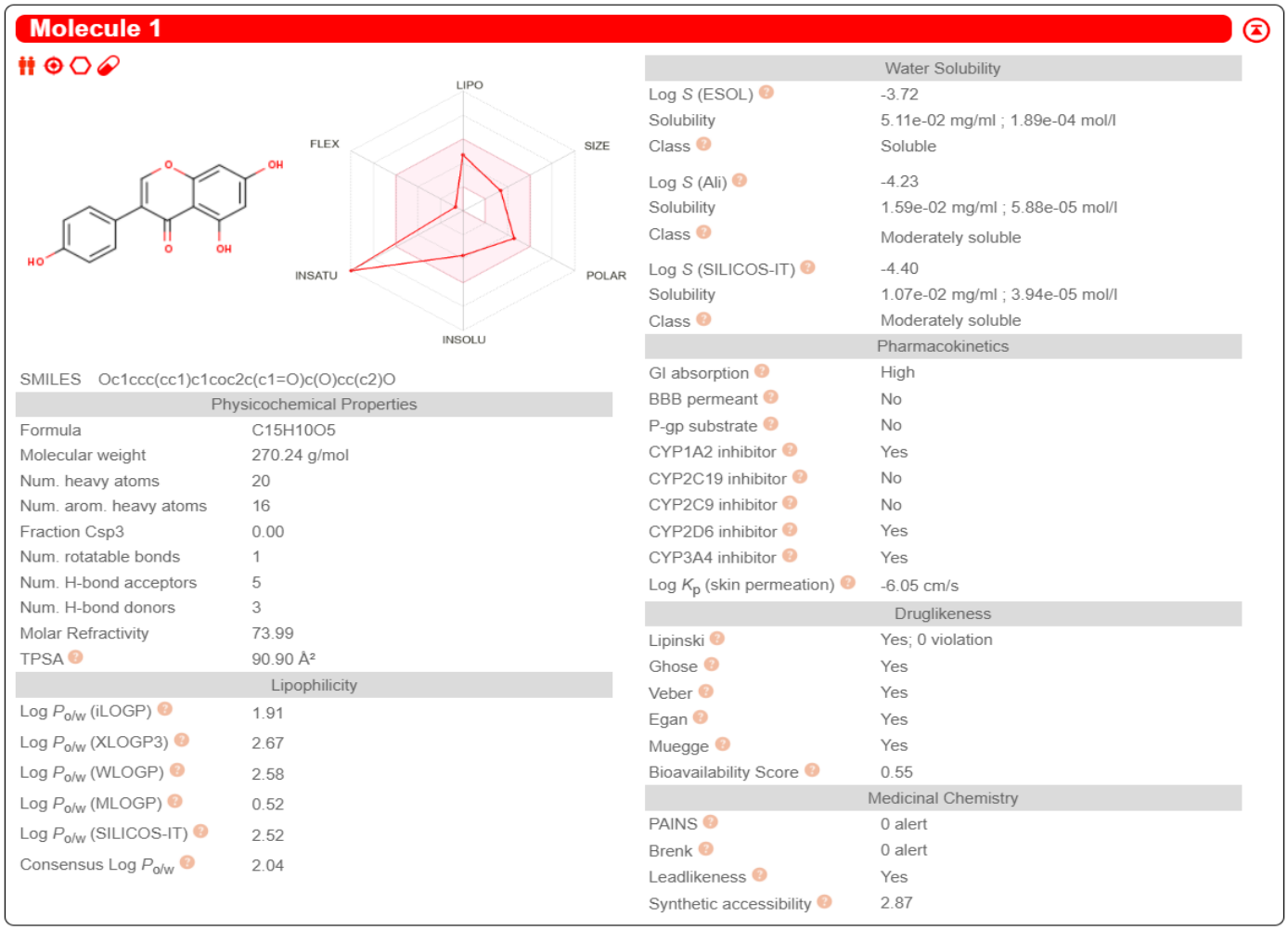

Fig 19: Analysis of Drug Likeness Property of Molecule 10

B. Genistein

People in Asian nations commonly consume soy and soy-based food items, which include genistein [5,7-dihyroxy-3-(-4-hydroxyphenyl)-4H-1-benzopyran-4-one]. Numerous epidemiological studies have revealed that Asian nations had lower rates of some cancer kinds than Western nations, including prostate and breast cancer. As a result, there has been a growing focus on the potential role that a rich isoflavone diet may have in both preventing and suppressing the development of tumours.(19) Genistein and oestrogen share a very similar structural makeup. Isoflavones have so been referred to as phytoestrogens.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24APR2622

Due to structural resemblance, genistein may attach itself to oestrogen receptors. By doing so, it influences the cell signal transduction system and controls the components involved in cell signalling. As a result, it has a broad range of biological functions, but its capacity to stop the spread of cancer is what makes it most famous.(20) Soybeans contain genistein, a naturally occurring isoflavone phytochemical. People having high intake of soy in their diet also excrete urine which contains free genistein and other linked isoflavones that are available in circulating blood, accumulate in tissue, and are converted by the natural gut microflora from the glucoside conjugates of soy in the gastrointestinal tract. Genistein's antiproliferative action has also been linked to the induction of apoptosis(21) and the direct inhibition of topoisomerase-II 34. The control of cytokine generation inhibits the growth of ovarian cancer cells. It has been found that genistein prevents the growth of ovarian cancer cells by influencing the cytokine IL-6, which impacts immunological homeostasis and inflammatory responses (22). An isoflavonoid called genistein controls the course of the cell cycle, programmed cell death, and metastasis. Genistein was shown to be a particular inhibitor of receptor tyrosine kinase (RTK), which includes EGFR(23), in 1987. Genistein is just as successful as its mother cell line in inducing differentiation in a multi-drug resistant K562 (human myelogenous leukaemia) cell line. It claims that soy contains the potent anti-cancer chemicals genistein and daidzein, which are isoflavones. With a molecular weight of only 270.24 g/mol, genistein is a lipophilic molecule containing 20 heavy atoms and 16 aromatic heavy atoms, respectively. It lacks BBB penetrating properties and has a high G.I. absorption rate. It has three H-bond donors and five H-bond acceptors. In cold water, genistein is insoluble; in hot water and other solvents, it is somewhat soluble.

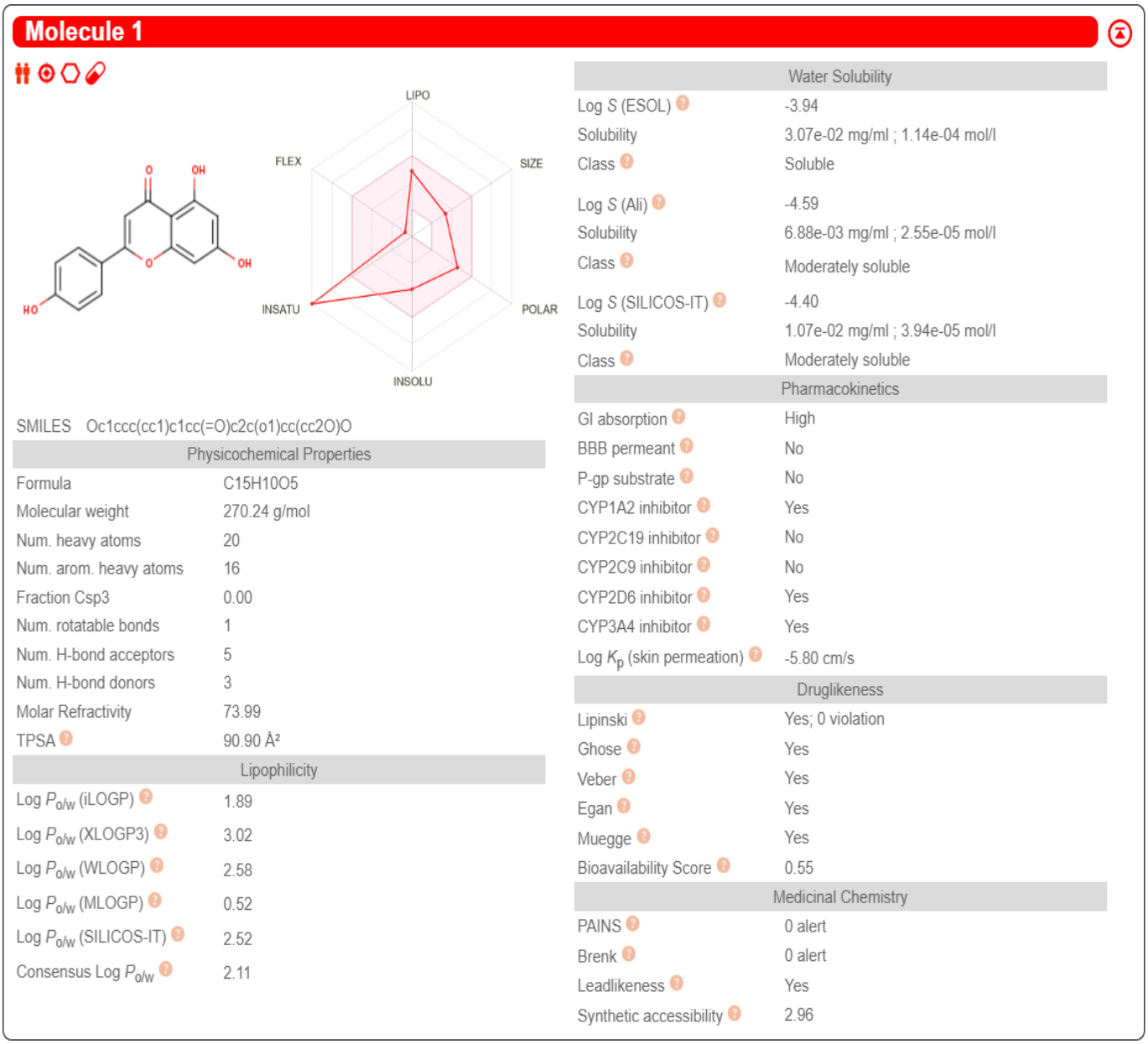

Fig 20: Analysis of Drug Likeness Property of Molecule 11

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24APR2622

C. Hesperetin

Hesperetin, or 3,5,7-trihydroxy-4-methoxyflavonone, is a flavonoid that is frequently present in citrus fruits, such as tangerines, oranges, and grapefruits. Citrus aurantinum, Citrus sinensis, and Citrus limon are the principal sources of it. Fruit juices come in a variety of forms, and orange and grapefruit drinks are particularly high in HSP. It is a naturally occurring bioactive substance that is a member of the flavanone class of flavonoids.(24)The 40-methoxy derivative of the flavanone eriodictyol is known as HSP. HSP has the chemical formula $C_{16}H_{14}O_6$. It has a topological polar surface area of 96.2 × 2, one covalently bound unit quantity, 22 heavy atom counts, and no formal charge. HSP has a precise mass of 302.079, while its molecular weight is 302.28 g/mol. Methyl eriodyctiol, or HSP, is an aglycone derived from hesperidin that is bound to rutinose in hesperidin. Phloroglucinol and HSP acid can be hydrolyzed alkaline together to generate HSP. The heterocyclic and aromatic ring contains three hydroxyl groups that are accessible and involved in a number of biological processes.(25) Through the stimulation of apoptosis, hesperetin demonstrated anticancer effectiveness against A431 skin carcinoma cancer cell lines, according to the current study. It was discovered that hesperetin caused Notch1 expression in carcinoid cells, which stops the growth of tumour cells, and triggered cell cycle arrest in the G1-phase in human breast cancer (MCF-7) cells. Hesperetin used death receptors, mitochondrial pathways, and cell cycle arrest to cause human cervical cancer cells to undergo apoptosis.(26) Hesperetin increases intracellular ROS levels, which further activates the mitochondrial pathway, inhibiting the growth of stomach cancer cells and inducing cell death.8 With an IC50 of 10 μg/ml, apigenin and hesperidin have strong cytotoxic effects in the MCF7 cell line while exhibiting modest toxicity. There are few scientific reports of hesperidin's negative effects, especially in pregnant women, making it a safe bioflavonoid.(27)

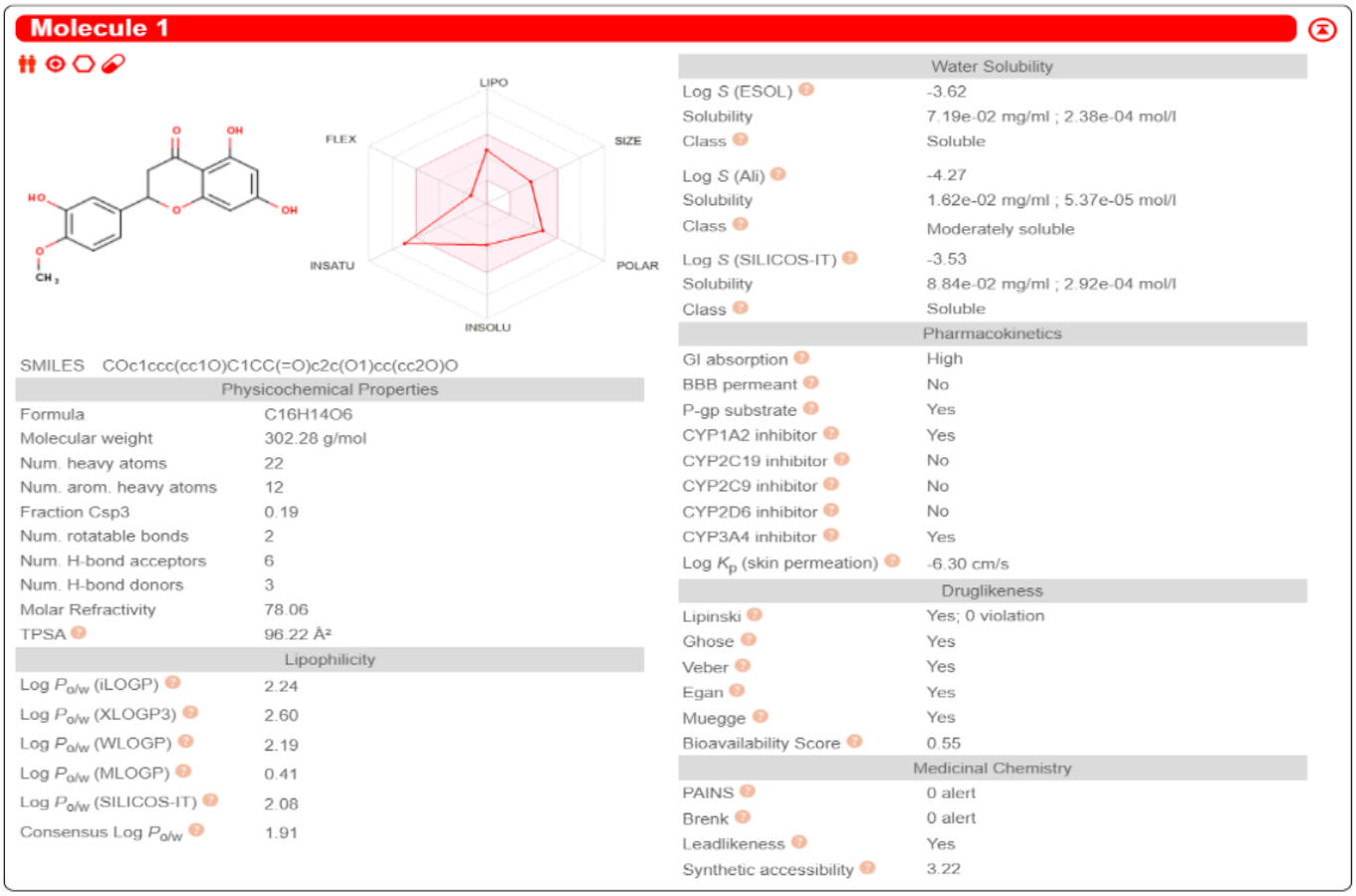

Fig 21: Analysis of Drug Likeness Property of Molecule 12

D. Quercetin

Quercetin (3,3′,4′,5,7-pentahydroxyflavone) is a naturally occurring flavonoid found in various plants, fruits, and vegetables, including broccoli, buckwheat, and onions, as well as in large amounts as glycoside. As a commercial dietary supplement, it has been added to functional meals and may help prevent or treat a number of illnesses, including cancer.10 With an IC_{50} value of 40 g/ml, the flavonoids quercetin and rutin found in Cissus quadrangularis Linn. fractions have strong anticancer properties against breast cancer cells (MCF7).(28)

In alcohol, quercetin is somewhat soluble, but it is insoluble in water. Because there is very little absorption of quercetin glycosides in the small intestine, the microflora in the lower intestines hydrolyzes the glycosides to produce quercetin and sugar, which is then absorbed into the enterohepatic system. When quercetin is used in conjunction with other forms of treatment for esophageal cancer, it seems

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24APR2622

to work better.(29) Because quercetin is lipophilic, it easily crosses cell membranes and has a variety of pleiotropic effects on intracellular pathways that are involved in chemoprevention (such as apoptosis, the cell cycle arrest, detoxification, cell invasion, and angiogenesis). Though, quercetin's limited solubility in water, quick metabolism, rapid bodily clearance, and enzymatic degradation significantly impede its practical applicability as an anticancer medication. The usage of quercetin has been limited since it has been demonstrated to have harmful effects on normal human cell lines in vitro.(30)

According to recent research, quercetin can both prevent and treat cancer by preventing cancer cells from growing. In order to lessen the negative effects of therapy, quercetin at lower doses might be used in conjunction with other therapeutic drugs. Therefore, in cases of oestrogen receptor-positive breast cancer, quercetin functions as a possible anti-breast cancer agent.(31). A nontoxic dosage of quercetin may somewhat mitigate the toxic side effects of doxorubicin while enhancing its chemotherapeutic activity against human breast cancer cells. Thus, quercetin may be utilised in combination with Dox as new moiety for treating breast cancer.(32) Its molecular weight was determined to be 302.24 g/mol, with 22 heavy atoms and 16 aromatic heavy atoms, in that order. It lacks BBB penetrating properties and has a high G.I. absorption rate. It has five H-bond donors and seven H-bond acceptors. Given that it complies with all Lipinski criteria, its drug resemblance is high. Thus, it is a formulation that may be taken orally. Because quercetin is a lipophilic substance, eating fat increases its bioavailability.

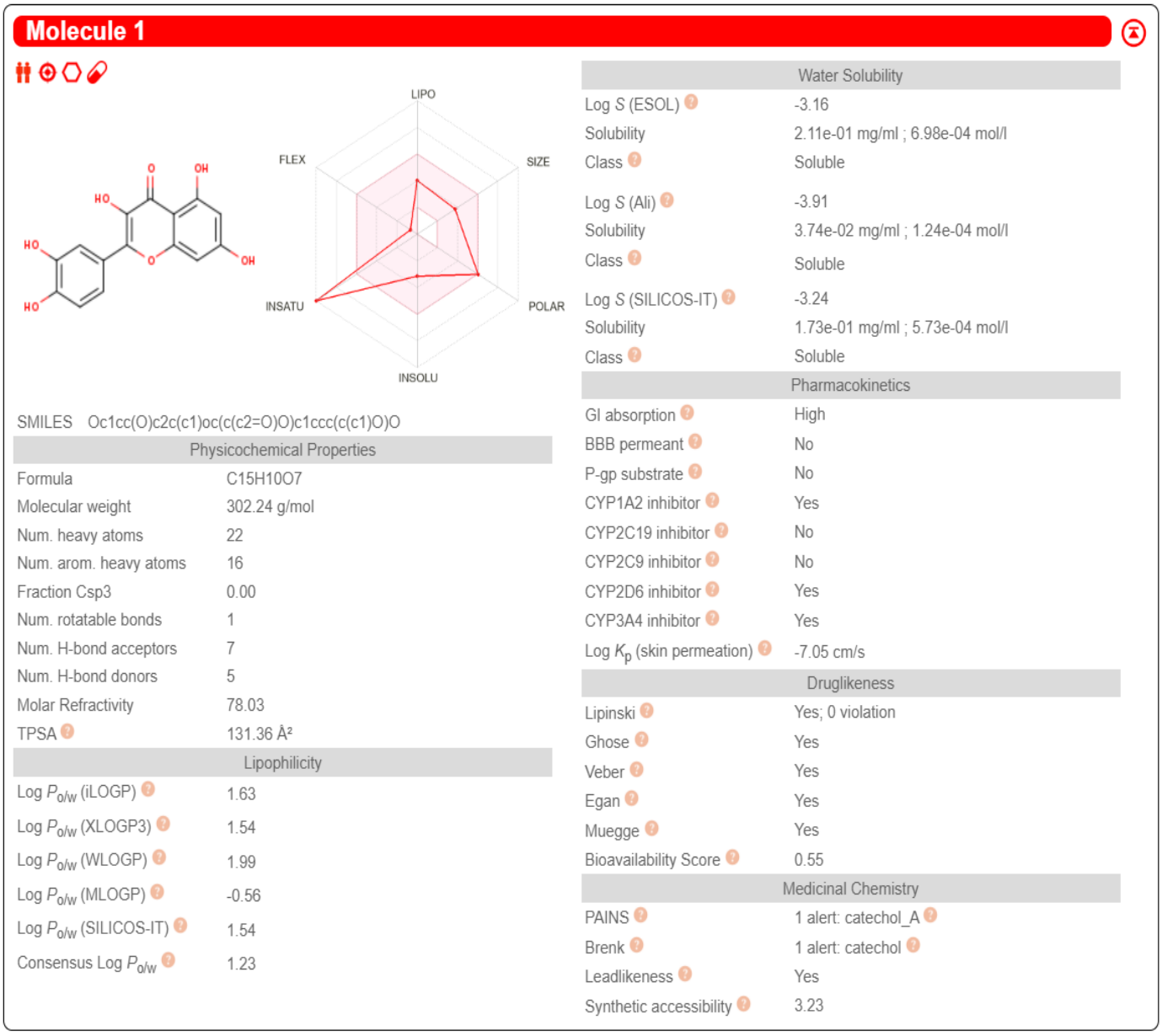

Fig 22: Analysis of Drug Likeness Property of Molecule 13

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24APR2622

E. Pterocarpans

Pterocarpans are naturally occurring substances with an ether bond and a tetracyclic ring structure formed from the fundamental isoflavonoid skeleton. The most effective of these compounds, 2,3,9-trimethoxypterocarpan, was shown to exhibit cytotoxic action against a panel of five tumour cell lines. Platymiscium floribundum, a Brazilian tree, is the source of these chemicals. Compared to the antineoplastic drugs doxorubicin and etoposide, it has 1000 times more activity. In three different breast cancer cell lines, 2,3,9-trimethoxypterocarpan at 8 mM demonstrated effectiveness regardless of the cells' aggressive characteristics.(33) It has been demonstrated that Lespedeza bicolor inhibits the growth of cancer cells. Pterocarpans isolated from the roots of L. bicolar showed strong cytotoxic effects, such as inducing apoptosis in Jurkat cells, and shown an antiproliferative activity against cancer cell lines.(34) It has been claimed that tokinensine A and B include cystisine-type alkaloids, which have been investigated for cytotoxicity against human breast cancer cells and feature a skeleton linked to the pterocarpan. They came from an extract of the traditional Chinese medicinal Sophora tonkinensis.(35) Indigocarpan's strong antioxidant activity suggests that it may have a function in preventing the development of cancer by shielding cells from oxidative stress(36). The current work highlights the significance of pterocarpans as a newly discovered family of potentially effective anticancer compounds. Pterocarpans block DNA synthesis and induce death in HL-60, hence showing an antiproliferative action(37).

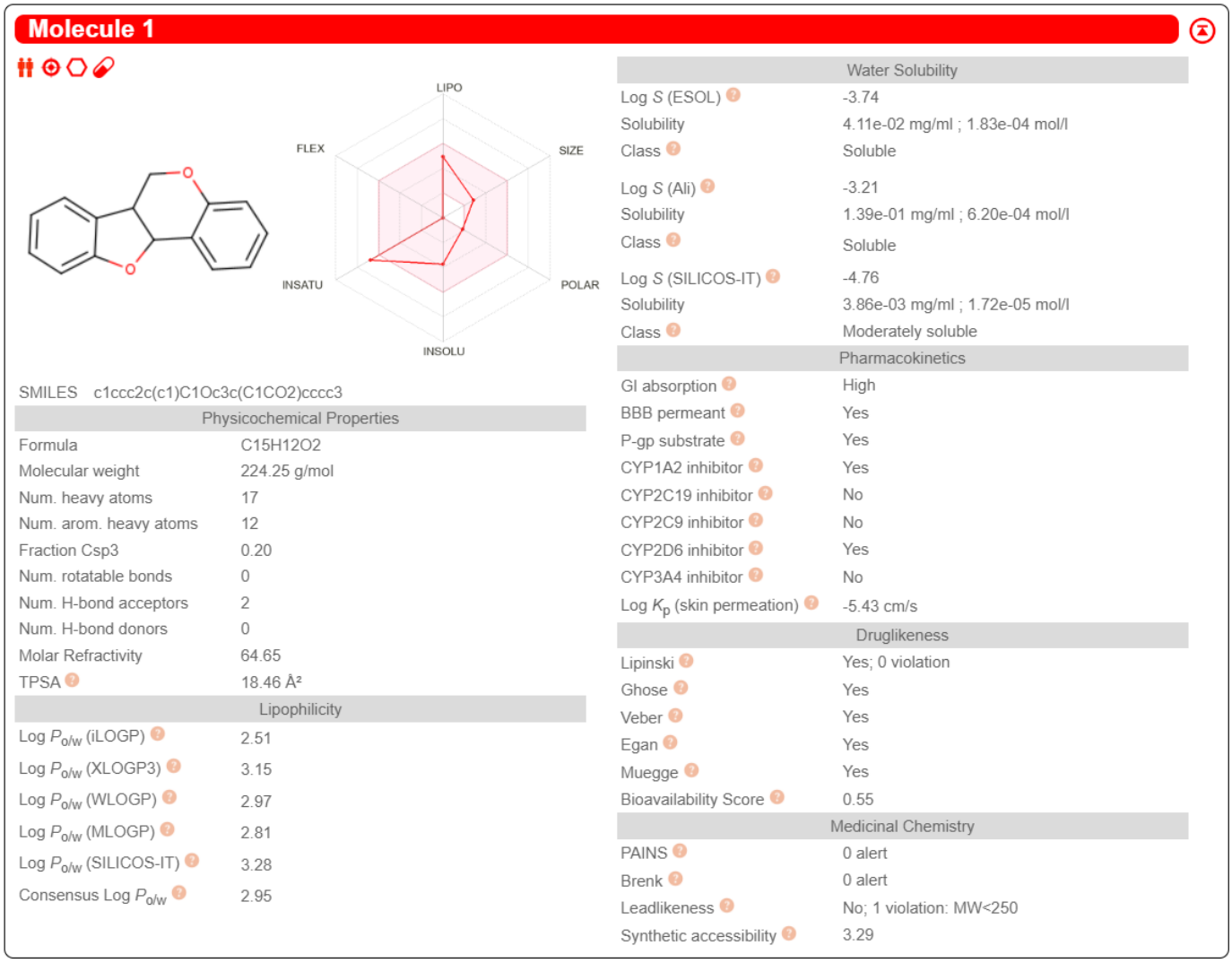

Fig 23. Analysis of Drug Likeness of Molecule 14

VII. CONCLUSION

In this review, we analysed the drug-like qualities of flavonoids and isoflavonoids as possible anticancer agents, and we chose various molecules with superior physiochemical characteristics. Additionally, by reading through various literature, we saw improved interactions between the flavonoid scaffold and receptors. The structures of all derivatives were analysed using SwissADME and Chemdraw tools, respectively. Furthermore, we have studied the structures of flavonoids and flavanols and calculated the total energy, or stability, using energy minimization. Flavonoids are highly suggested as anticancer medications for different stages of cancer because of their exceptional stability.

ISSN No:-2456-2165 https://doi.org/10.38124/ijisrt/IJISRT24APR2622

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