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Research Article

Pharmacological and Toxicological Analysis of Flavonoid 5,7,4'-Trimethoxyflavone: An *In Silico* Approach

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ABSTRACT
Flavonoids are known to exhibit a variety of effects in different biological systems. In the study, the flavonoid 5,7,4'-trimethoxyflavone was evaluated for its pharmacological and toxicological effect. Approximately 50% of the reasons that lead to failure in development of a drug are associated with the pharmacokinetic profile and toxicology. Thus, determination of the pharmacokinetic profile (ADME) together with toxicity (ADMET) are important parameters in the definition of bioavailability and toxic effects of a molecule. The Osiris program and PASS online program were used in the study for activities *in silico*. *In silico* models are being applied for the evaluation of toxicity of compound in metabolic environment of mammals. The obtained results showed the molecule was drug-like with 58 possible activities at Pa>70% and this flavonoid present low toxicity theoretical risk.

Keywords: Flavonoid, Toxicological, Pharmacological, *In silico*

INTRODUCTION

Flavonoids can be divided into different classes depending on their oxidative status and substituents. They are biosynthesised via the acetate- and shikimic acid pathways, resulting in a C6-C3-C6 skeleton consisting of two aromatic rings and an oxygen-containing heterocyclic benzopyran[1].

Flavonoids are known to exhibit a variety of effects in different biological systems. They modulate the activities of enzymes involved in the biotransformation of precarcinogens, altering their biological activity, while under certain conditions flavonoids may exhibit genotoxic activity by yielding reactive intermediates, such as free radicals[2].

Carcinogenicity and mutagenicity are among the toxicological effects that cause the highest concern for human health; thus, they are the object of intense research activity, as well as of recognized regulatory testing methods. Generally, flavonoids have been characterized as antioxidants capable of providing beneficial health effects. However, many flavonoids have also been reported to be mutagenic in diverse strains of Salmonella typhimurium in the Ames test as well as in several mammalian cell systems used to assess different toxic end points[3].

Approximately 50% of the reasons that lead to failure in development of a drug are associated with the pharmacokinetic profile and toxicology. Thus, determination of the pharmacokinetic profile (ADME) together with toxicity (ADMET) are important parameters in the definition of bioavailability and toxic effects of a molecule, aiding in reducing the time and cost of process research and development of new drugs[4].

Considering the few studies on the toxic effects of the flavonoid 5,7,4´-trimethoxyflavone, the aim of the present study was to evaluate toxicological effects of this compost, using the *in silico* approach.

MATERIALS AND METHODS

PASS online

Prediction of Activity Spectra for Substances (PASS) online is designed to evaluate the general biological potential of an organic drug-like molecule. It provides simultaneous predictions of many types of biological activities based on the structure of organic compounds. The biological activity spectrum of a chemical compound is the set of different types of biological activity that reflect the results of the compound's interaction with various biological entities. PASS online gives various facets of the biological action of a compound. Pa (probability "to be active") and Pi (probability "to be inactive") estimates the categorization of potential compound is belonging to the sub-class of active or inactive compounds respectively[5].

PASS gives hits based on the probability of new effects and mechanism of action with required activity spectra among the compounds from in-house, old and commercial databases. PASS online predicts the

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Table 1: Predicted activities of the flavonoid at Pa> 70% depicted through Pass online tool.

Pa	Pi	Activity
0,956	0,002	Chlordecone reductase inhibitor
0,949	0,004	Membrane integrity agonist
0,942	0,004	HIF1A expression inhibitor
0,925	0,002	Kinase inhibitor
0,910	0,004	Anaphylatoxin receptor antagonist
0,903	0,002	4-Nitrophenol 2-monooxygenase inhibitor
0,910	0,010	CYP2C12 substrate
0,902	0,008	Aspulvinone dimethylallyltransferase inhibitor
0,891	0,004	Membrane permeability inhibitor
0,878	0,009	Ubiquinol-cytochrome-c reductase inhibitor
0,874	0,005	Aldehyde oxidase inhibitor
0,863	0,002	CYP1A inducer
0,855	0,002	CYP1A1 inducer
0,852	0,004	27-Hydroxycholesterol 7alpha-monooxygenase inhibitor
0,850	0,003	CYP2B5 substrate
0,836	0,004	Vasoprotector
0,834	0,003	Antimutagenic
0,836	0,009	Gluconate 2-dehydrogenase (acceptor) inhibitor
0,823	0,003	MAP kinase stimulant
0,827	0,009	TP53 expression enhancer
0,821	0,007	Apoptosis agonist
0,814	0,003	Beta-carotene 15,15'-monooxygenase inhibitor
0,812	0,004	Histidine kinase inhibitor
0,811	0,006	CYP1A substrate
0,807	0,007	2-Dehydropantoate 2-reductase inhibitor
0,794	0,005	Peroxidase inhibitor
0,781	0,004	CYP1A inhibitor
0,796	0,020	Antiseborrheic
0,774	0,005	UGT1A9 substrate
0,758	0,004	CYP1A2 inhibitor
0,757	0,005	NADPH-ferrihemoprotein reductase inhibitor
0,745	0,003	CYP2C9 inducer
0,741	0,004	5 Hydroxytryptamine release inhibitor
0,739	0,002	CYP1A1 inhibitor
0,737	0,004	AR expression inhibitor
0,737	0,005	Pin1 inhibitor
0,739	0,009	Caspase 3 stimulant
0,733	0,004	Aryl-alcohol dehydrogenase (NADP+) inhibitor
0,747	0,019	Antineoplastic
0,733	0,005	CYP2A11 substrate
0,742	0,013	JAK2 expression inhibitor
0,732	0,005	P-benzoquinone reductase (NADPH) inhibitor
0,735	0,010	CYP3A4 inducer
0,728	0,005	Carminative
0,726	0,006	Insulysin inhibitor
0,724	0,004	Histamine release inhibitor
0,725	0,006	HMOX1 expression enhancer
0,717	0,005	MMP9 expression inhibitor
0,716	0,005	CYP2A4 substrate
0,712	0,005	UGT1A6 substrate
0,706	0,004	Beta glucuronidase inhibitor
0,707	0,007	CYP1A1 substrate
0,706	0,012	CYP3A inducer
0,726	0,038	Acrocylindropepsin inhibitor
0,726	0,038	Chymosin inhibitor
0,726	0,038	Saccharopepsin inhibitor
0,703	0,018	Complement factor D inhibitor
0,716	0,050	Mucomembranous protector

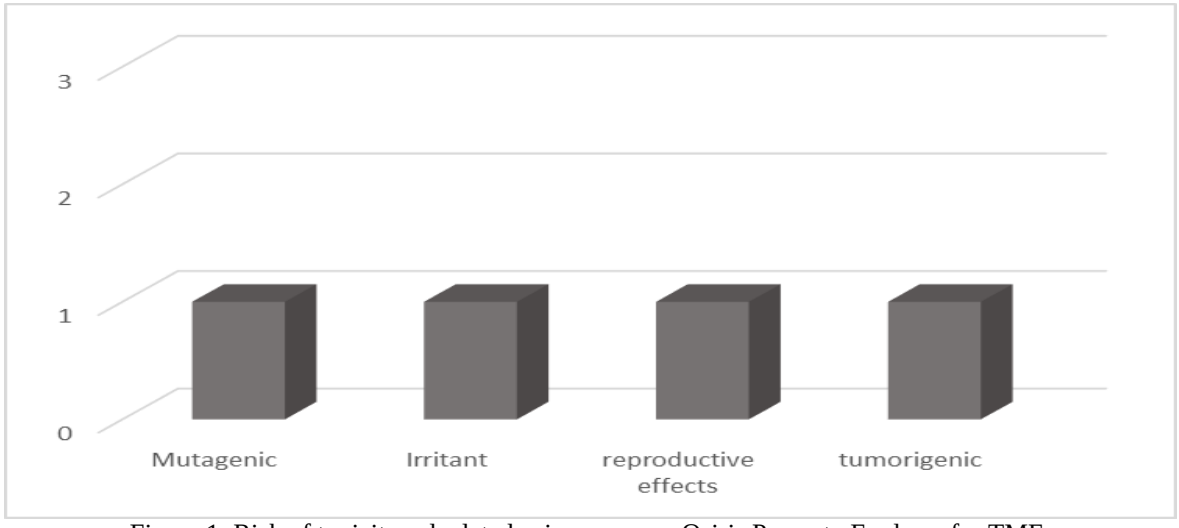

Figure 1: Risk of toxicity calculated using program Osiris Property Explorer for TMF.

biological activity spectrum for the modified imprints on the basis of its structural formula, along with different descriptors like antineoplastic, hematotoxic etc., so it is possible to estimate if new compounds have a particular effect[5].

OSIRIS

Toxicity risk assessment (http://www.organic-chemistry.org/prog/peo/): while drawing a structure, the toxicity risk predictor will start looking for potential toxicity risks as long as the currently drawn structure is a valid chemical entity. Toxicity risk alerts are an indication that the drawn structure may be harmful concerning the risk category specified. Risk alerts are by no means meant to be a fully reliable toxicity prediction nor should it be concluded from the absence of risk alerts that a particular substance is completely free of any toxic effect[5].

The prediction process relies on a precomputed set of structural fragments that gives rise to toxicity alerts, in case they are encountered in the structure currently being drawn. The OSIRIS toxicity predictions resulted for mutagenicity, tumorigenicity, irritability, reproductive effectiveness, cLogP value, druglikeness and drug-score of flavonoid molecule[5].

As the flavonoid was planned to be administered orally and hence must be capable of being absorbed into the tract gastrointestinal, he was evaluated according to the "Rule of Five" Lipinski, which states that at least three of four requirements must be provided so that the compound has a good oral bioavailability theoretical. Thus, compounds to be absorbed must possess molecular weight 500 daltons (Da), octanol / water calculated (ClogP) 5, the number of acceptors partition hydrogen bonding (nALH) 10 and the number of hydrogen bond donor groups (nDLH) 5[6].

RESULTS AND DISCUSSION

In silico models are being applied for the evaluation of toxicity of compound in metabolic environment of mammals. Their usage within a regulatory environment has also been encouraged by recent legislation. However, the major limitation with the toxicity evaluation in animal models is that they are efficient in evaluating the low to medium molecular weight organic molecules. Hence, several efficient statistical machine learning methods have been used to develop *in silico* tools for the prediction of toxicological hazards of molecular structure[7].

Computer-assisted prediction models, so-called predictive tools, play an essential role in the proposed repertoire of alternative methods besides *in vitro* models. Hence, these tools are used to study both existing and hypothetical compounds, which are fast, reproducible and are typically based on human bio- regulators[5,8].

The analysis of the possibilities of flavonoid TMF activity revealed that the molecule was drug-like with 58 possible activities at Pa>70% (Table 1) and numerous druglike properties at Pa>30%, for example: antifungal activity (Pa:0.411 and Pi:0.048), antiviral activity (Hepatitis B) (Pa:0.375 and Pi:0.019), antineoplastic (lung cancer) (Pa: 0.403 e Pi: 0.023) and antioxidant activity (Pa:0.553 and Pi: 0,005) through PASS online tool.

This variety of possible effects to the TMF are according to class of flavonoids, secondary metabolites that have been proposed to exert beneficial effects in the prevention of a large number of diseases, including cancer, cardiovascular disease and neurodegenerative disorders[9].

In addition, the results show that the flavonoid followed the "Rule of Five" Lipinski which requires that the compound must possess at least three of four requisites (nDLH 5, nALH 10, Da 500 e cLogP 5), thus the TMF may be active drug in humans by the oral route of administration[6] (Table 2).

The TMF was analyzed through OSIRIS tool for the determination of drug-relevant properties like mutagenic, irritant, reproductive effects, cLogP value, drug-score, druglikeness and their toxicity risks assessment. OSIRIS employed to predict the toxicity and carcinogenicity for antifungal agent was reported[10]. The results showed this flavonoid presents low theoretical risk of toxicity (Figure 1) and has considerable values druglikeness (-1,29) and

Table 2: Theoretical analysis of the physico-chemical properties of TMF involved in oral bioavailability of drugs following the "Rule of Five" Lipinski.

Substance	nDLH	nALH	Da	cLogP
TMF	0	5	312	3,28
Standard of "Rule of Five" Lipinski	= 5	= 10	< 500	< 5

drug-score (0,47). "Drug score" (combining "druglikeness", ClogP, logs, mass molecular and risk of toxicity) that generates a value infers that the potential of a compound become a future drug[11].

CONCLUSION

In silico study of flavonoid TMF demonstrated that this compound has several possible biological effects on the human body as well as good oral bioavailability and low toxicity theoretical risk.

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