International Journal of Scientific Research in Biological Sciences
Vol.9, Issue.1, pp.48-52, February (2022)
Research Paper
E-ISSN: 2347-7520

# Comparison and Prediction of toxicity parameters of principal Aflatoxins, antimicrobial compounds and Antifungal Drugs by pKCSM server

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**Available online at: www.isroset.org**

Received: 05/Jan/2022, Accepted: 10/Feb/2022, Online: 28/Feb/2022

***Abstract*—** The purpose of this short study is to estimate the main toxicity properties of main Aflatoxins, Antimicrobial bio- compounds and Antifungal Drugs by pKCSM server. Several tests are performed, for instance AMES toxicity; Max. tolerated dose (human) (log mg/kg/day in units); Oral Rat Acute Toxicity (LD50) (mol/kg in units) Oral Rat Chronic Toxicity (LOAEL); Log mg/kg_bw/day in units);Hepatotoxicity; Skin Sensitisation; Pyriformis toxicity (log µg/L)and Minnow toxicity (log mM in units).

***Keywords*—** *pKCSM server, Aflatoxins, Antifungal Drugs*

## I. INTRODUCTION

Nowadays, Pharmacology plays a key role, in studying drugs and their interactions that take place, to discover new active biological compounds for human beings. Many online servers are freely available, in which it is possible to predict the several chemical-physical and pharmacological characteristics of drugs with excellent reliability, intending to lower production costs and focus in a targeted way in therapy research. It is important aspect reaffirm the importance to know the mechanism of action, toxicity, dosage, effectiveness, selectivity, and potency of drugs are only some key characteristics to find out new medications. Fortunately several tools can predict the main chemical-physical and pharmacokinetic characteristics of thousands of compounds and drugs, for instance, ADMET Lab ( https://admet.scbdd.com/calcpre/index/), ADME ( https://preadmet.qsarhub.com/adme/) and pKCSM server ( http://biosig.unimelb.edu.au/pkcsm/).

All provide analysis similarly and reliable comparable results. Generally speaking, Aflatoxins are secondary metabolites produced by some fungi (fungi) and they can cause serious problems to human health, especially in the food field, where many cases of food poisoning have occurred at present.

Generally, they are the ability to induce hepatocellular carcinoma when they are ingested in large quantities and for long periods [2, 3]. Indeed, Mycotoxins are various poisonous carcinogens and mutagens that are manufactured by certain molds, particularly Aspergillus species. They are bifuranocoumarine with low molecular weight (c.a. 300 d), high melting points, and high alcohol-extractable thermostability of fungal origin and represent one of the main groups of carcinogens. They can be found in food products such as peanuts, tree nuts, corn, rice, etc. [2-4]. The most known is Aflatoxin B1 which is considered the most toxic and is produced by both Aspergillus flavus and Aspergillus parasiticus [5]. Other toxins reported in Literature are Aflatoxin G1 and G2 (AFG) [6], produced by some Group II Aflavus and Aspergillus parasiticus, Aflatoxin M1 (as known "milk toxin ", AFM1) [7], a metabolite of aflatoxin B1 in humans and animals (exposure in ng levels may come from a mother's milk), Aflatoxin M2 [8], a metabolite of aflatoxin B2 in the milk of cattle fed on contaminated foods. [18] Regarding Aflatoxicol (AFL) is a metabolite produced by breaking down the lactone ring [9], Aflatoxin Q1 (AFQ1), a major metabolite of AFB1 in vitro liver preparations of other higher vertebrates [10]. Nowadays human beings there are important weapons at their disposal in the fight against aflatoxins, ranging from the optimization of controls and the phases of cultivation, collection, and storage. Currently, in scientific research, there are several interesting works to identify these toxins, for example through the use of Biosensors based on cholinesterase inhibition or enzymatic sensor reported by Arduini et al, 2007 and 2010 respectively. [11, 12].

Elizalde-Gonzalez et al.,1998 [13] and Holcomb et al.,1992 [14] have determinated aflatoxins by high-performance liquid chromatography with amperometric detection.

 

The complexity of this type of analysis has carried out research towards the development of alternative systems based on immunological methods, even though at times they have proved to be not very reliable, presenting problems of antibody cross-reactivity and not always adequate affinity towards the antigen[ 15].

## II. RELATED WORK

This work is focused on identifying what is the most estimated harmful toxin for humans and what is the best drug that has antimicrobial properties to be able to counteract it.

## III. METHODOLOGY

*drug likeness evaluation by Lipinski's rules*
MW (Molecular weight g/mol ) <=500; LogP ( Partition Coefficient) <=5; Hacc ( (hydrogen bond acceptor)<=10; Hdon ( (hydrogen bond donor)<=5 [16]

*pkCSM server for toxicity evaluation*
Herein, several toxicity parameters are performed by pkCSM platform ( http://biosig.unimelb.edu.au/pkcsm/ ), for instance: AMES toxicity; Max. tolerated dose (human) (log mg/kg/day in units); Oral Rat Acute Toxicity (LD50) (mol/kg in units) Oral Rat Chronic Toxicity (LOAEL); Log mg/kg_bw/day in units);Hepatotoxicity; Skin Sensitisation; Pyriformis toxicity (log µg/L)and Minnow toxicity (log mM in units) [17].

## IV. RESULTS AND DISCUSSION

By and large, to evaluate the therapeutic efficacy of a Drug,it must be selective, potent, soluble, low toxicity with an excellent therapeutic index, a quantitative measurement of the relative safety of a drug and to be not harmful to the organism, and also to Bioavailable, (an indicator of the efficiency of the drug delivery to the systemic circulation) on the human being.

This paper aims to carry out a Drug –Likeness evaluation and investigated several indexes of principal Aflatoxins, antimicrobial compounds and Antifungal Drugs, through Lipinski's rules estimated by pKCSM server ( See below Table 1-6). Some tests evaluated are: AMES toxicity; Max. tolerated dose (human) (log mg/kg/day in units); Oral Rat Acute Toxicity (LD50) (mol/kg in units) Oral Rat Chronic Toxicity (LOAEL); Log mg/kg_bw/day in units);Hepatotoxicity; Skin Sensitisation; Pyriformis toxicity (log µg/L) and Minnow toxicity (log mM in units). To short to summarize , the Ames test is a adaptable method for evaluating whether the target compound is mutagenic or not. It can give a positive or negative (mutagenic action) and negative (no mutagenic function) result. Oral rat Chronic Toxicity are calculated by LOAEL value (Lowest Observed Adverse Effect) in log(mg/kg_bw/day), Minnow toxicity ( the lethal concentration values, LC50 below 0.5 mM, log LC50<-0.3). and T. pyriformis toxicity (pIGC50, negative logarithm of the concentration required to inhibit 50% growth in log ug/L, with a value >-0.5 log ug/L is considered toxic).

Moreover, one of the most important parameters considered is Max. tolerated dose (human) (log mg/kg/day in units), which describes the highest dose of a radiological or pharmacological treatment that will produce the desired effect without unacceptable toxicity. This parameter is commonly estimated as the maximum dose that can be given for the duration of a specific study. As we see, in Table 1, Aflatoxin B1, Aflatoxin B2, Aflatoxin P1, Aflatoxin G2, Aflatoxin G1, Aflatoxin M1, Aflatoxin M2, Aflatoxicol, Aflatoxin Q1 and Aflatoxicol H1 reported a very low tolerated dose, indicating their high toxicity effectively. In addiction also others toxicological tests such as, Oral Rat Acute Toxicity (LD50) (mol/kg in units, Oral Rat Chronic Toxicity (LOAEL), Log mg/kg_bw/day), HepatotoxicitySkin Sensitisation, T. Pyriformis toxicity (log ug/L), Minnow toxicity (log mM) and AMES toxicity confirmed their negative roles. However, according to these estimates, calculated by pkCSM server there are some exceptions for example regarding AMES toxicity Aflatoxin M2 is tested negative values for Ames test. Regaring Druglikeness estimation , (see Table 2) , all of them obtained values understood according to the rules of Lipinski's rules (See Table 2). Regarding detected antimicrobial compounds [18] to toxicity tests are performed 10 main molecules such as : Eugenol, Ferulic acid, Isoeugenol, Dehydrozingerone, Zingerone, Methylisoeugenol, Vanillin, vanillin acetate, vanillic acid, Acetovanillone. From our results, only three of them are considered the best ones, if they are compared to others substances. They are : Isoeugenol, Dehydrozingerone and Vanillin respectively.

*Predicted values of Vanillin* : AMES toxicity ( No), Max. Tolerated dose (1.285 log mg/kg/day), Oral Rat Acute Toxicity (LD50) (1.937 mol/kg) Oral Rat Chronic Toxicity (LOAEL) 2.007 Log mg/kg_bw/day), Hepatotoxicity ( No), Skin Sensitisation ( No) T. Pyriformis toxicity ( -0.014 log ug/L), Minnow toxicity (1.899 log mM) . From these tests an excellent result is certainly to have a high value of Max. tolerated dose of about 1.285 log mg/kg/day Instead, as regards the downsides aspects of this compound are Pyriformis toxicity ( -0.014 log ug/L), Minnow toxicity (1.899 log mM). ( See Table 3) . In Table 4 are reported their Druglikeness evaluation.

*Predicted values of Isoeugenol*: AMES toxicity ( No), Max. Tolerated dose (0.578 log mg/kg/day), Oral Rat Acute Toxicity (LD50) (2.128 mol/kg), Oral Rat Chronic Toxicity (LOAEL) 2.316 Log mg/kg_bw/day), Hepatotoxicity (Yes), Skin Sensitisation ( Yes) T. Pyriformis toxicity ( 0.772 log ug/L), Minnow toxicity (1.311 log mM) . In this case Its advantages are Pyriformis toxicity ( 0.772 log ug/L), Minnow toxicity (1.311 log mM) if they are compared to the previous molecule investigated, whereas its disadvantages are manly bad

 

score in terms of Max. Tolerated dose (0.578 log mg/kg/day) against Max. Tolerated dose (1.285 log mg/kg/day) reported by Vanillin. In addition is sensible to Hepatotoxicity and Skin Sensitisation tests.

*Predicted values of Dehydrozingerone* : AMES toxicity ( No), Max. Tolerated dose (0.513 log mg/kg/day), Oral Rat Acute Toxicity (LD50) (2.137 mol/kg) Oral Rat Chronic Toxicity (LOAEL) 1.931 Log mg/kg_bw/day), Hepatotoxicity ( No), Skin Sensitisation ( No) T. Pyriformis toxicity ( 0.716 log ug/L), Minnow toxicity (1.696 log mM) . As we see there are many results scores in common with Isoeugenol, even though on the whole it can be said that this substance seems to report a lower toxicity. In addition also in this case Max. tolerated dose of about 0.513 log mg/kg/day). Finally we investigated Antifungal drugs shown in Table 6-7. They are : Ketoconazole, Clotrimazole, Miconazole, Fluconazole, Itraconazole, Posaconazole, Voriconazole, Isavuconazole, Amphotericin B, Nystatin, Flucytosine, Micafungin, Caspofungin, respectively. As highlighted in From Table 6, Itraconazole and Posaconazole they have proven to be the best although like other drugs they have a high molecular weight, which makes them off-scale according to by Lipinski's rules.

Predicted values of Itraconazole: AMES toxicity ( No), Max. Tolerated dose (0.91 log mg/kg/day), Oral Rat Acute Toxicity (LD50) (2.938 mol/kg), Oral Rat Chronic Toxicity (LOAEL) 0.068 Log mg/kg_bw/day), Hepatotoxicity ( Yes), Skin Sensitisation ( No) T. Pyriformis toxicity ( 0.285 log ug/L), Minnow toxicity (-4.446 log mM). Its significant advantages in terms of toxicity prediction are Max. Tolerated dose with score 0.91 log mg/kg/day and Minnow toxicity with score -4.446 log mM. Its drawbacks posite values of Hepatotoxicity test, low score of Pyriformis toxicity ( 0.285 log ug/L).

Predicted values of Posaconazole: AMES toxicity ( No), Max. Tolerated dose (0.875 log mg/kg/day), Oral Rat Acute Toxicity (LD50) (4.156 mol/kg) Oral Rat Chronic Toxicity (LOAEL) 1.931 Log mg/kg_bw/day), Hepatotoxicity ( Yes), Skin Sensitisation ( No) T. Pyriformis toxicity ( 0.285 log ug/L), Minnow toxicity (-2.621 log mM).

Table 1. toxicity evaluation of Aflatoxins , evaluated by pkCSM server.

| **Aflatoxins** | **AMES toxicity** | **Max. tolerated dose (human) (log mg/kg/day)** | **Oral Rat Acute Toxicity (LD50) (mol/kg)** | **Oral Rat Chronic Toxicity (LOAEL) Log mg/kg_bw/day)** | **Hepatotoxicity** | **Skin Sensitisation** | **T. Pyriformis toxicity (log ug/L)** | **Minnow toxicity (log mM)** |
|---|---|---|---|---|---|---|---|---|
| Aflatoxin B1 | Yes | -0.215 | 4.478 | 0.906 | No | No | 0.379 | 1.229 |
| Aflatoxin B2 | Yes | -0.221 | 3.042 | 0.912 | No | No | 0.379 | 1.237 |
| Aflatoxin P1 | Yes | -0.633 | 3.833 | 1.944 | No | No | 0.48 | 1.623 |
| Aflatoxin G2 | Yes | -0.005 | 3.069 | 1.017 | No | No | 0.32 | 1.312 |
| Aflatoxin G1 | Yes | -0.001 | 4.494 | 1.012 | No | No | 0.32 | 1.304 |
| Aflatoxin M1 | Yes | -0.173 | 4.156 | 1.072 | yes | No | 0.361 | 2.201 |
| Aflatoxin M2 | **No** | -0.175 | 2.544 | 1.077 | yes | No | 0.36 | 2.209 |
| Aflatoxicol | Yes | -0.444 | 4.331 | 0.924 | No | No | 0.398 | 1.957 |
| Aflatoxin Q1 | Yes | -0.227 | 4.235 | 0.951 | No | No | 0.316 | 1.956 |
| Aflatoxicol H1 | Yes | -0.264 | 3.919 | 1.895 | No | No | 0.321 | 2.488 |

Table 2. Drug-likeness evaluation of Aflatoxins through Lipinski's rules by pkCSM server.

| **Aflatoxins** | **Molecular Weight (g/mol)** | **LogP** | **Rotatable Bonds** | **Acceptors** | **Donors** | **Surface Area** |
|---|---|---|---|---|---|---|
| Aflatoxin B1 | 312.277 | 2.2765 | 1 | 6 | 0 | 129.794 |
| Aflatoxin B2 | 314.293 | 2.1529 | 1 | 6 | 0 | 130.484 |
| Aflatoxin P1 | 298.25 | 1.9735 | 0 | 6 | 1 | 123.110 |
| Aflatoxin G2 | 330.292 | 1.7369 | 1 | 7 | 0 | 135.597 |
| Aflatoxin G1 | 328.276 | 1.8605 | 1 | 7 | 0 | 134.908 |
| Aflatoxin M1 | 328.276 | 1.3805 | 1 | 7 | 1 | 134.588 |
| Aflatoxin M2 | 330.292 | 1.2569 | 1 | 7 | 1 | 135.278 |
| Aflatoxicol | 314.293 | 2.1272 | 1 | 6 | 1 | 130.427 |

 

| | | | | | | |
|---|---|---|---|---|---|---|
| Aflatoxin Q1 | 328.276 | 1.7674 | 1 | 7 | 1 | 134.588 |
| Aflatoxicol H1 | 330.292 | 1.6181 | 1 | 7 | 2 | 135.221 |

Table 3. toxicity evaluation of antimicrobial compounds , evaluated by pkCSM server.

| **antimicrobial compounds** | **AMES toxicity** | **Max. tolerated dose (human) (log mg/kg/day)** | **Oral Rat Acute Toxicity (LD50) (mol/kg)** | **Oral Rat Chronic Toxicity (LOAEL) Log mg/kg_bw/day)** | **Hepatotoxicity** | **Skin Sensitisation** | **T. Pyriformis toxicity (log ug/L)** | **Minnow toxicity (log mM)** |
|---|---|---|---|---|---|---|---|---|
| Eugenol | Yes | 1.024 | 2.118 | 2.049 | No | yes | 0.3 | 1.702 |
| Ferulic acid | No | 1.082 | 2.282 | 2.065 | No | No | 0.271 | 1.825 |
| **Isoeugenol** | **No** | **0.578** | **2.128** | **2.316** | **Yes** | **Yes** | **0.772** | **1.311** |
| **Dehydrozingerone** | **No** | **0.513** | **2.137** | **1.931** | **No** | **No** | **0.716** | **1.696** |
| Zingerone | No | 0.544 | 2.129 | 1.953 | Yes | No | 0.634 | 1.645 |
| Methylisoeugenol | Yes | 0.776 | 1.836 | 2.242 | No | yes | 1.192 | 0.92 |
| **Vanillin** | **No** | **1.285** | **1.937** | **2.007** | **No** | **No** | **-0.014** | **1.899** |
| vanillin acetate | **No** | 1.238 | 2.385 | 2.634 | No | No | 0.492 | 1.628 |
| vanillic acid | **No** | 0.719 | 2.454 | 2.032 | No | No | 0.265 | 1.926 |
| Acetovanillone | **No** | 0.647 | 1.823 | 2.291 | No | No | 0.351 | 1.834 |

Table 4. Drug-likeness evaluation of antimicrobial compounds through Lipinski's rules by pkCSM server.

| **antimicrobial compounds** | **Molecular Weight (g/mol)** | **LogP** | **Rotatable Bonds** | **Acceptors** | **Donors** | **Surface Area** |
|---|---|---|---|---|---|---|
| Eugenol | 164.204 | 2.1293 | 3 | 2 | 1 | 72.109 |
| Ferulic acid | 194.186 | 1.4986 | 3 | 3 | 2 | 81.065 |
| Isoeugenol | 164.204 | 2.4339 | 2 | 2 | 1 | 72.109 |
| Dehydrozingerone | 192.214 | 2.003 | 3 | 3 | 1 | 82.636 |
| Zingerone | 194.23 | 1.9224 | 4 | 3 | 1 | 83.325 |
| Methylisoeugenol | 178.231 | 1.3805 | 3 | 2 | 0 | 78.794 |
| Vanillin | 152.149 | 1.2133 | 2 | 3 | 1 | 64.231 |
| vanillin acetate | 194.186 | 1.433 | 3 | 4 | 0 | 81.441 |
| vanillic acid | 168.148 | 1.099 | 2 | 3 | 2 | 69.025 |
| Acetovanillone | 166.176 | 1.6034 | 2 | 3 | 1 | 70.596 |

Table 5. toxicity evaluation of Antifungal drugs, evaluated by pkCSM server.

| **Antifungal drugs** | **AMES toxicity** | **Max. tolerated dose (human) (log mg/kg/day)** | **Oral Rat Acute Toxicity (LD50) (mol/kg)** | **Oral Rat Chronic Toxicity (LOAEL) Log mg/kg_bw/day)** | **Hepatotoxicity** | **Skin Sensitisation** | **T.Pyriformis toxicity (log ug/L)** | **Minnow toxicity (log mM)** |
|---|---|---|---|---|---|---|---|---|
| Ketoconazole | **No** | 0.957 | 2.84 | 0.935 | Yes | No | 0.285 | -0.434 |
| Clotrimazole | Yes | 0.353 | 2.565 | -0.005 | No | No | 0.285 | 2.255 |
| **Miconazole** | **No** | 1.104 | 2.696 | 0.935 | No | No | 0.285 | -0.189 |
| Fluconazole | **No** | 0.114 | 2.328 | 2.328 | Yes | No | 0.312 | 3.872 |
| Itraconazole | **No** | **0.91** | **2.938** | **0.068** | **Yes** | **No** | **0.285** | **-4.446** |
| **Posaconazole** | **No** | **0.875** | **4.156** | **1.072** | **Yes** | **No** | **0.285** | **-2.621** |
| Voriconazole | **No** | 0.556 | 2.574 | 0.743 | Yes | No | 0.287 | 2.934 |
| Isavuconazole | **No** | 0.627 | 2.762 | 0.364 | Yes | No | 0.286 | 1.727 |
| Amphotericin B | **No** | 0.292 | 2.518 | 2.049 | No | No | 0.285 | 11.261 |
| Nystatin | **No** | 0.281 | 2.518 | 2.035 | No | No | 0.285 | 11.182 |
| Flucytosine | **No** | 1.512 | 1.776 | 1.767 | No | No | 0.092 | 3.144 |
| Micafungin | **No** | 0.437 | 2.482 | 6.673 | Yes | No | 0.285 | 19.286 |
| Caspofungin | **No** | 0.502 | 2.492 | 2.492 | Yes | No | 0.285 | 15.691 |

 

Table 6. Drug-likeness evaluation of Antifungal drugs through Lipinski's rules by pkCSM server.

| Antifungal drugs | Molecular Weight (g/mol) | LogP | Rotatable Bonds | Acceptors | Donors | Surface Area |
|---|---|---|---|---|---|---|
| Ketoconazole | 531.44 | 4.2058 | 7 | 7 | 0 | 219.815 |
| Clotrimazole | 344.845 | 5.3767 | 4 | 2 | 0 | 151.910 |
| Miconazole | 416.135 | 6.4548 | 6 | 3 | 0 | 165.606 |
| Fluconazole | 306.276 | 0.7358 | 5 | 7 | 1 | 123.419 |
| Itraconazole | 705.647 | 5.5773 | 11 | 12 | **0** | 293.884 |
| Posaconazole | 700.791 | 4.5732 | 12 | 12 | **1** | 294.020 |
| Voriconazole | 349.316 | 2.1769 | 5 | 6 | **1** | 140.562 |
| Isavuconazole | 437.475 | 4.24298 | 6 | 7 | **1** | 180.632 |
| Amphotericin B | 924.091 | 0.7117 | 3 | 17 | **12** | 380.536 |
| Nystatin | 926.107 | 0.9357 | 3 | 17 | **12** | 381.225 |
| Flucytosine | 129.094 | -0.5088 | 0 | 3 | **2** | 49.538 |
| Micafungin | 1270.291 | -3.902 | 18 | 23 | **16** | 507.437 |
| Caspofungin | 1093.331 | -3.3119 | 23 | 18 | **16** | 450.184 |

## V. CONCLUSION AND FUTURE SCOPE

This study aims to make a comparison of the main principal Aflatoxins, antimicrobial compounds, and Antifungal Drugs by the pKCSM server in terms of toxicity aspects. Although these theoretical analyses are presented as preliminary data, we are confident that they will be useful to the scientific community in the drug design field and discover similar biological compounds. According to our results, Isoeugenol, Dehydrozingerone, and Vanillin and also Miconazole and Posaconazole have shown excellent scores against most predictive toxicity tests.

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Ivan Vito Ferrari has published more than 10 research papers in reputed international journals and His main research work focuses on Bioinformatic Tools, Electrochemistry field and Polymer Science. He obtained Ph..D in Industrial Engineering, co-tutele PhD in materials sciences and Master Degree in Industrial Biotechnology at the University of Rome Tor Vergata. He obtained double master of which 1 in "Management of organizations and Social Doctrine of the Church" at Tor Vergata and 1 in Master in Bioeconomy of Organic Waste and Biomass / National Research Council / Institute of Agricultural Biology and Biotechnology.

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