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QUANTUM MODELING TO DETERMINE THE CARCINOGENIC POTENTIAL OF AFLATOXIN B2 PRODUCED BY ASPERGILLUS FLAVUS AND A. PARASITICUS

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ABSTRACT

Aflatoxin B2 (AFB2) is produced mainly by the mycotoxin Aspergillus flavus and, Aspergillus parasiticus. Aflatoxins are toxic substances produced by some types of fungi that can grow in food. People who eat foods that contain high levels of aflatoxins can get sick, as can individual animals. The primary objective of this study is to calculate the electron transfer coefficients (ETC) of aflatoxin B2 (AFB2), the metabolite M2 (AFM2) and the nitrogenous bases that form DNA and RNA to verify the mutagenic potential of this mycotoxin. We used the hyperchem quantum simulator for Windows specifically the SE-PM3 method. AFB2 is a potent human and animal hepatocarcinogen. The metabolite AFM2 has a sizeable mutagenic capacity. These statements are confirmed by the findings seen in the results of quantum modeling in which it is demonstrated that AFB2 is a carcinogenic substance of high potential that exists. AFB2 and AFM2 cause severe mutations in both DNA and RNA. Due to the demand of the production and consumption of dry grains and cereals in Mexico, the need arises for an investigation into the danger of this most potent carcinogen produced by nature.

KEYWORDS: Aflatoxin B2, Aflatoxin M2, Electron Transfer Coefficient, Mycotoxins, AFM2, AFB2.

INTRODUCTION

Overview of Aflatoxins

Nowadays the presence of molds in food is still considered as a problem of appearance, without stopping to think about the consequences that the presence of these fungi can have on the products. There are more than 200 types of toxigenic molds that under particular conditions are capable of producing toxins and are known as mycotoxins.

Acute exposure to aflatoxins (AF) can cause death and disease (aflatoxicosis) in humans. It has been documented that fatality rates due to aflatoxicosis are as high as 40% in Kenya.[1]

The presence of the aflatoxin issue has been recorded in many articles since the last century, indirectly mentioned the same symptoms, spoke of the fungus that caused it, mentioned animals and humans intoxicated by the same product consumed, but had not given the task of documenting the exact cause of the problem.

The species of the Aspergillus fungus can be found anywhere in the world, growing in a great variety of environmental conditions and on a significant amount of food.

In Mexico, research on AF has revealed a large part of its dangerousness and carcinogenic potential. In Mexico the issue of importance is based on corn, since being a producer and consumer of this grain, it is grown in highly active areas for the development of the fungus.

Although the best-known route of aflatoxin exposure for humans and animals is through the diet, there is evidence that aflatoxins can enter the respiratory tract, being inhaled as dust particles and causing acute and chronic cases of poisoning by this toxin.

Rapid and cheap methods are being used to detect their urinary biomarkers.[2]

Commonly contaminated products include cereals such as corn, rice, barley, and sorghum and oilseeds such as peanuts, cocoa, nuts, and pistachios, as well as dried fruits and spices, pepper and dried chilies, among others.

This fungus reproduced easily in poorly stored grains and conditioned unconsciously with favorable climates for its reproduction.

Aflatoxins, produced by molds of the genus Aspergillus flavus, cannot be seen, lack flavor and smell, are resistant to heat (they support between 260 and 320 degrees Celsius without decomposing) and to processes such as cooking, ultrapasteurization, nixtamalization and fermentation. They are insoluble in water and soluble in organic solvents.[3,4]

MATERIAL AND METHODS

General parameters of the quantum simulation

The Hyperchem quantum simulator for Windows was used. Serial number # 12-800-1501800080, manufactured by Hypercube and distributed in Mexico by MultiOn, S.A de C.V. Specifically the SE-PM3 method. The geometry of the molecules was optimized by the Polak Ribiere method.

The molecule and its compounds are schematized and represented with HYPERCHEM software.

The software must be configured in SEMIEMPIRICAL (SE-PM3) to perform the BG, EP, ETC calculation.

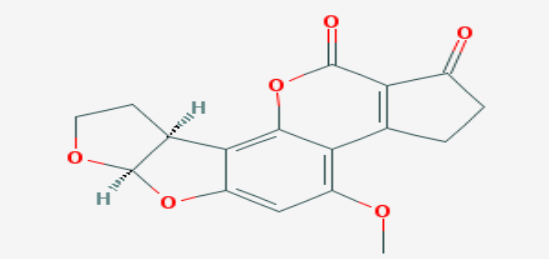
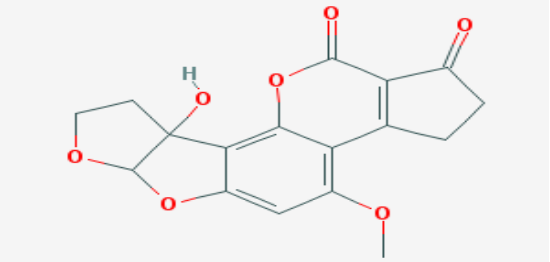
When plotting the molecule with all its compounds, the values of HOMO (-), LUMO (+), E- and E + are set to zero and with a density of 0.015.

The resulting values will be captured on an Excel sheet, and necessary mathematical procedures will be performed to obtain BG, EP, ETC.

The cross-band calculus of the compounds, it is done by taking the value HOMO and E- of the first compound and the value of LUMO and E + the second compound.

The results of lower ETC of the cross-band will be the value that will determine which compound will be more reactive and the information that be used for the graphing of the quantum well.

Table 1. Molecular structure and names.

Chemical substance	Molecular structure
Chemical Name: *AFLATOXIN B2.* *Dihydroaflatoxine B1.* *(6aR,9aS)-4-methoxy-2,3,6a,8,9,9a-hexahydrocyclopenta[c]furo[3',2':4,5]furo[2,3-h]chromene-1,11-dione.* PubChem CID:2724360	
ChemicalNames: *AFLATOXIN M2.* *4-Hydroxyaflatoxin B2.* *2,3,6a,8,9,9a-Hexahydro-9a-hydroxy-4-methoxycyclopenta(c) furo (3',2':4,5) furo (2,3-h) (1) benzopyran-1,11-dione.* PubChem CID:23318	

To establish the limits of the graphs, the highest ETC will be placed in the upper limit and the lower ETC as, the lower limit of the compounds to be compared.[5-8]

The molecules that were taken for the simulation are shown in Table 1.

Analytical Formulas

$$ETC = \left|\frac{BG}{EP}\right| \qquad Eq.\ 1$$

Where:

ETC = Electron Transfer Coefficient. It is considered dimensionless.

BG = Bandgap. ElectronVolt (eV).

EP = Electrostatic Potential. ElectronVolts / Bohr radius $\frac{eV}{a^0}$ (Bohr radius is handled dimensionless).

$$BG = |HOMO - LUMO| \qquad Eq\ 2$$

Where:

HOMO = Highest Occupied Molecular Orbital

LUMO = Lowest Unoccupied Molecular Orbital

$$EP = |E_- - E_+| \qquad Eq.3$$

Where:

E- = Negative pole of the electrostatic potential of the molecule.

E + = Positive pole of the electrostatic potential of the molecule.

The quantum well is defined as the area in which the value of the ETC may fall.[9] These zones are divided into 3 (Figure 1):

1. The hight probability area. It is the area below the inferior limit of the ETC of a compound (ZONE I) where a very high probability that a chemical reaction or simple molecular interaction occurs.
2. The basic probability area. It is the area between the inferior and superior limit of the ETCs of both compounds interacting (ZONE II).
3. The low probability area. It is the zone above the superior limit of the ETC of a compound (ZONE III). It is the zone where a very low probability molecular interaction occurs.

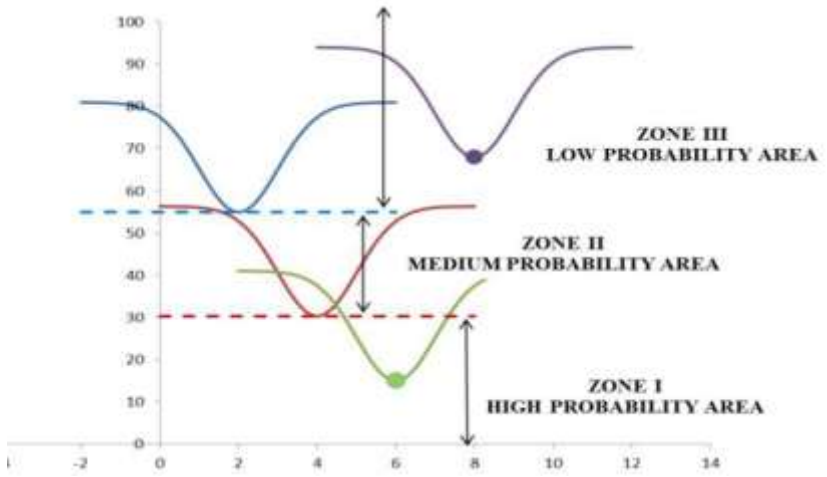


Figure 1: Probability zones for molecular interaction according to their quantum wells ETCs.

RESULTS AND DISCUSSION

In Table 2 it can see the calculated ETCs for each pair of bases allowed in the DNA and RNA. The highest ETCs in the table belong to AFB2 and its metabolite. Due to these high values, the two substances can attack any database allowed.

Table 2: ETCs for each pair of bases allowed in the DNA and RNA.

No	Reducing substance	Oxidizing substance	HOMO	LUMO	BG	E-	E+	EP	ETC
1	AFB2	AFB2	-9.264	-1.369	7.895	-0.128	0.142	0.270	29.241
2	AFM2	AFM2	-9.374	-1.443	7.931	-0.119	0.168	0.287	27.634
3	A:T	A:T	-8.654	-0.475	8.179	-0.14	0.169	0.309	26.469
4	A:U1	A:U1	-8.654	-0.511	8.143	-0.14	0.171	0.311	26.183
5	C:G	C:G	-9.142	-0.206	8.936	-0.174	0.172	0.346	25.827
6	A:U2	A:U2	-8.654	-0.415	8.239	-0.14	0.202	0.342	24.091

Solubility of AFB2 and AFM2

Figure 2 shows that AFB2 is a toxin of medium solubility in water. The deepest quantum well with ETC = 40,695 indicates that the interaction of water-AFB2 is the most likely and that AFB2 preferably acts as an oxidizing agent (The right-sided molecule is oxidant and the molecule placed on the left side is reductive or antioxidant).

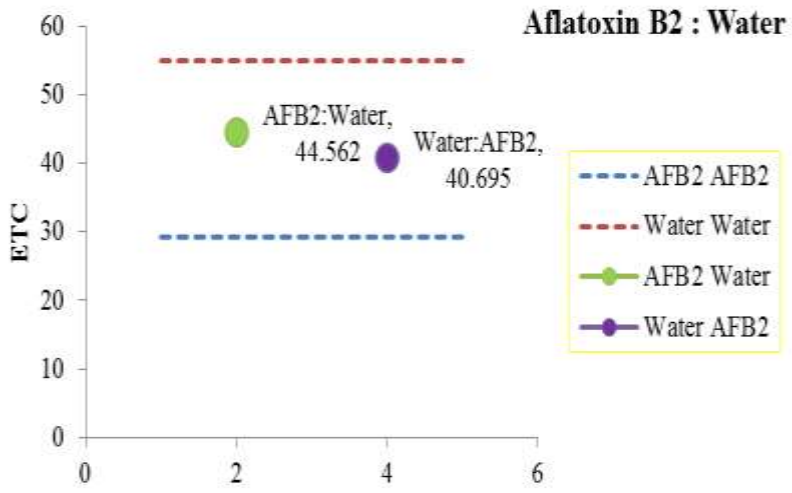


Figure 2: Quantum wells or ETCs of the interaction of the AFB2 vs Water in the medium probability zone.

Figure 3 shows the interaction of the metabolite AFM2 with water. It is observed that ETC = 36.858 (it went down a bit more concerning its toxin). This decrease indicates a more significant molecular interaction concerning water. Therefore, AFM2 is more soluble than AFB2.

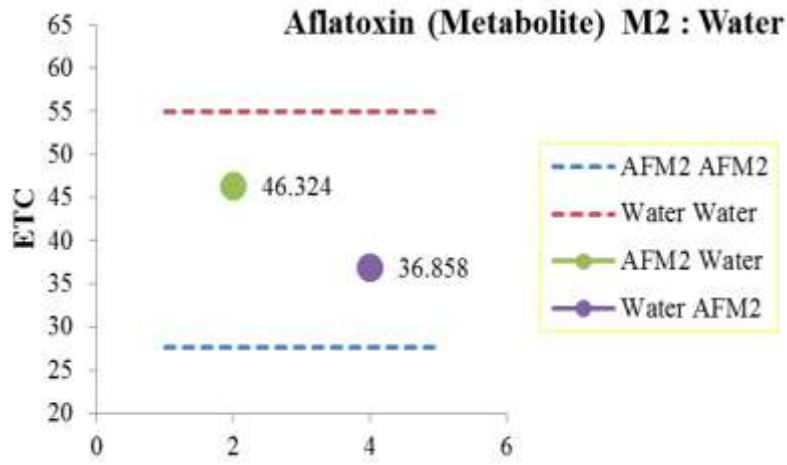


Figure 3. Quantum wells or ETCs of the interaction of the AFM2 vs Water in the medium probability zone.

The interactions of the allowed pairs of bases for both DNA and RNA vs. AFB2 and AFM2 are presented in table 3. We can see that the interactions of the bases allowed with AFM2 are the most likely to occur. This preference occurs due to better water solubility.

Table 3: Interactions crossed bands of the toxin AFB2 and its metabolite AFM2 vs. the allowed nitrogenous bases of DNA and RNA.

#	Reducing substance	Oxidizing substance	HOMO	LUMO	BG	E-	E+	EP	ETC
1	AFM2	C:G	-9.374	-0.206	9.168	-0.119	0.172	0.291	31.505
2	AFM2	A:T	-9.374	-0.475	8.899	-0.119	0.169	0.288	30.899
3	AFM2	AFB2	-9.374	-1.369	8.005	-0.119	0.142	0.261	30.670
4	AFM2	A:U1	-9.374	-0.511	8.863	-0.119	0.171	0.290	30.562
5	AFB2	C:G	-9.264	-0.206	9.058	-0.128	0.172	0.300	30.193
6	AFB2	A:T	-9.264	-0.475	8.789	-0.128	0.169	0.297	29.593
7	AFB2	A:U1	-9.264	-0.511	8.753	-0.128	0.171	0.299	29.274
8	AFB2	AFB2	-9.264	-1.369	7.895	-0.128	0.142	0.270	29.241
9	AFM2	A:U2	-9.374	-0.415	8.959	-0.119	0.202	0.321	27.910
10	AFM2	AFM2	-9.374	-1.443	7.931	-0.119	0.168	0.287	27.634
11	A:U2	C:G	-8.654	-0.206	8.448	-0.140	0.172	0.312	27.077
12	A:U1	C:G	-8.654	-0.206	8.448	-0.140	0.172	0.312	27.077
13	A:T	C:G	-8.654	-0.206	8.448	-0.140	0.172	0.312	27.077
14	AFB2	A:U2	-9.264	-0.415	8.849	-0.128	0.202	0.330	26.815
15	A:U2	A:T	-8.654	-0.475	8.179	-0.140	0.169	0.309	26.469
16	A:U1	A:T	-8.654	-0.475	8.179	-0.140	0.169	0.309	26.469
17	A:T	A:T	-8.654	-0.475	8.179	-0.140	0.169	0.309	26.469
18	AFB2	AFM2	-9.264	-1.443	7.821	-0.128	0.168	0.296	26.422
19	A:U2	A:U1	-8.654	-0.511	8.143	-0.140	0.171	0.311	26.183
20	A:U1	A:U1	-8.654	-0.511	8.143	-0.140	0.171	0.311	26.183
21	A:T	A:U1	-8.654	-0.511	8.143	-0.140	0.171	0.311	26.183
22	A:U2	AFB2	-8.654	-1.369	7.285	-0.140	0.142	0.282	25.833
23	A:U1	AFB2	-8.654	-1.369	7.285	-0.140	0.142	0.282	25.833
24	A:T	AFB2	-8.654	-1.369	7.285	-0.140	0.142	0.282	25.833
25	C:G	C:G	-9.142	-0.206	8.936	-0.174	0.172	0.346	25.827
26	C:G	A:T	-9.142	-0.475	8.667	-0.174	0.169	0.343	25.268
27	C:G	A:U1	-9.142	-0.511	8.631	-0.174	0.171	0.345	25.017
28	C:G	AFB2	-9.142	-1.369	7.773	-0.174	0.142	0.316	24.598
29	A:U2	A:U2	-8.654	-0.415	8.239	-0.140	0.202	0.342	24.091
30	A:U1	A:U2	-8.654	-0.415	8.239	-0.140	0.202	0.342	24.091
31	A:T	A:U2	-8.654	-0.415	8.239	-0.140	0.202	0.342	24.091
32	A:U2	AFM2	-8.654	-1.443	7.211	-0.140	0.168	0.308	23.412
33	A:U1	AFM2	-8.654	-1.443	7.211	-0.140	0.168	0.308	23.412
34	A:T	AFM2	-8.654	-1.443	7.211	-0.140	0.168	0.308	23.412
35	C:G	A:U2	-9.142	-0.415	8.727	-0.174	0.202	0.376	23.210
36	C:G	AFM2	-9.142	-1.443	7.699	-0.174	0.168	0.342	22.512

The most likely interactions are presented in Table 4. This table is an extract from Table 3. In the extract, we can see more clearly, which base pairs are most likely to be hit by each toxin.

Table 4. Extract from the general cross-band table 3. In this table, AFB2 and AFM2 are observed as agents of the permitted DNA and RNA pairs.

#	Reducing substance	Oxidizing substance	HOMO	LUMO	BG	E-	E+	EP	ETC
22	A:U2	AFB2	-8.654	-1.369	7.285	-0.14	0.142	0.282	25.833
23	A:U1	AFB2	-8.654	-1.369	7.285	-0.14	0.142	0.282	25.833
24	A:T	AFB2	-8.654	-1.369	7.285	-0.14	0.142	0.282	25.833
28	C:G	AFB2	-9.142	-1.369	7.773	-0.174	0.142	0.316	24.598
32	A:U2	AFM2	-8.654	-1.443	7.211	-0.14	0.168	0.308	23.412
33	A:U1	AFM2	-8.654	-1.443	7.211	-0.14	0.168	0.308	23.412
34	A:T	AFM2	-8.654	-1.443	7.211	-0.140	0.168	0.308	23.412
36	C:G	AFM2	-9.142	-1.443	7.699	-0.174	0.168	0.342	22.512

We can also observe that the bases most affected by the toxin AFM2 are the bases that make up the DNA; however, the difference in ETCs between the bases of the RNA and the metabolite AFM2 is not very large. Therefore, we conclude that the metabolite hits more strongly both DNA and RNA.

CONCLUSIONS

It was found a high mutagenic probability of AFB2 as well as AFM2.

It was found that the mycotoxin (AFB2) and its metabolite (AFM2) work as oxidizing agents because they are molecules that absorb electrons. These statements are deduced by the depth and changes presented by the quantum wells.

The mutation of one nitrogenous base by another in any of the nucleic acids results from the change of the altered "mutated" information, and therefore the amino acids are assembled in different order.

The mycotoxin AFB2 and its metabolite AFM2 have a very high mutagenic power, due to the demonstration of alteration in the DNA and RNA chains. In this way, chaos is provoked and generates massive productions of mutated and unwanted substances for the metabolic and vital functioning of the human and animal body.

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