Ciencia Latina Revista Científica Multidisciplinar
Julio-Agosto, 2023, Volumen 7, Número 4.
https://doi.org/10.37811/cl_rcm.v7i4.7439

Analysis of the Interactions of Capsaicin with DNA and RNA using Computational Chemistry

José Arturo Olguín Rojas[1]
j.a.olguin.rojas@personal.uttecam.edu.mx
https://orcid.org/0000-0001-5280-1043
Universidad Tecnológica de Tecamachalco, Tecamachalco, México

Manuel González Pérez
m.gonzalez.perez@personal.uttecam.edu.mx
https://orcid.org/0000-0001-8700-2866
Universidad Tecnológica de Tecamachalco, Tecamachalco, México

Paulina Aguirre Lara
paulina.agla@gmail.com
https://orcid.org/0009-0005-5170-9268
Universidad Tecnológica de Tecamachalco, Tecamachalco, México

Cecilia Vázquez González
c-v-g@hotmail.com
Universidad Tecnológica de Tecamachalco, Tecamachalco, México

Laura M. Aguilar Veloz
c.r.camarrillo@personal.uttecam.edu.mx
https://orcid.org/0000-0002-2059-8586
Universidad Tecnológica de Tecamachalco, Tecamachalco, México

Carlos Roberto Camarillo Rojas
c.r.camarrillo@personal.uttecam.edu.mx
https://orcid.org/0009-0008-3398-6386
Universidad Tecnológica de Tecamachalco, Tecamachalco, México

ABSTRACT

Fruits of the Capsicum family or chilies, native to Mexico and Central America, exhibit highly diverse biological effects, including antioxidant, anti-inflammatory, and anticarcinogenic properties. This research used computational chemistry to determine the interactions between Capsaicin (CAP) and nitrogenous bases (NB). Parameterized semi-empirical model number 3 (SE-PM3) drew the corresponding molecules in the Hyperchem simulator. The geometry was optimized with the Polak Ribiere method, and the variables of HOMO-LUMO, Band gap (BG), Electronic potential (EP), and other properties were calculated. We found a small HOMO-LUMO energy gap of CAP molecules. This overlap leads us to conclude that CAP can form spheres and micelles. As a general conclusion, we found that CAP is not a mutagenic agent. Among 49 interactions, CAP showed its first interaction with uracil (CAP: U2), and therefore, it evidenced 19 more related interactions with freely formed NB.

***Keywords*:** *capsaicin, electron transfer coefficient, DNA, ARN*

[1] Autor principal.
Correspondencia: j.a.olguin.rojas@personal.uttecam.edu.mx

Análisis de las Interacciones de la Capsaicina con el ADN y el ARN mediante Química Computacional

RESUMEN

Los frutos de la familia Capsicum o chiles, nativos de México y Centroamérica, exhiben efectos biológicos muy diversos, incluyendo propiedades antioxidantes, antiinflamatorias y anticancerígenas. Esta investigación utilizó química computacional para determinar las interacciones entre la capsaicina (CAP) y las bases nitrogenadas (NB). El modelo semiempírico parametrizado número 3 (SE-PM3) dibujó las moléculas correspondientes en el simulador Hyperchem. La geometría se optimizó con el método de Polak Ribiere y se calcularon las variables de HOMO-LUMO, Band gap (BG), Potencial electrónico (EP) y otras propiedades. Encontramos una pequeña brecha de energía HOMO-LUMO de moléculas CAP. Esta superposición nos lleva a concluir que CAP puede formar esferas y micelas. Como conclusión general, encontramos que CAP no es un agente mutagénico. Entre 49 interacciones, CAP mostró su primera interacción con uracilo (CAP: U2) y, por lo tanto, evidenció 19 interacciones más relacionadas con NB de formación libre.

Palabras clave: *Capsaicina; coeficiente de transferencia de electrones; ADN; ARN*

Artículo recibido 20 julio 2023

Aceptado para publicación: 20 agosto 2023

INTRODUCTION

Reactive oxygen species (ROS), such as superoxide radicals, singlet oxygen, peroxyl radical, H2O2, hydroxyl radicals, and peroxynitrite, can be formed from various sources and cellular processes, including mitochondria, peroxisomes, inflammatory cell activation, as well as exogenous sources like environmental agents, pharmaceuticals, and industrial chemicals. The increased production of ROS and defective DNA repair mechanisms can lead to cellular macromolecule damage, chromosomal instability, genetic mutations, and modulation of cell growth, ultimately resulting in cancer (Cijo George et al., 2015). Recently, there has been growing interest in phytochemicals due to their antioxidant effects, which can be applied in the treatment of various cancers (Ranjan et al., 2019). An antioxidant-rich diet helps regulate ROS production and prevent cellular and tissue damage (Cijo et al., 2015).

Capsicum plants are native to Mexico and Central America, but they are cultivated in many warm regions around the world. CAP, the principal bioactive substance in chilies, is a pungent vanilloid and hydrophobic compound present in varying concentrations depending on the fruit's maturity stage and tends to increase as the fruit grows and develops (Olguín-Rojas et al., 2019; Suzuki & Iwai, 1984). Several studies have shown that Capsicum fruits or chilies, exhibit high biological effects, including antioxidant, anti-inflammatory, and anticarcinogenic properties (De Lourdes Reyes-Escogido et al., 2011; Kogure et al., 2002; Rollyson et al., 2014). The investigations have revealed that CAP having anticarcinogenic effects, prevents DNA strand breaks and chromosomal aberrations (De et al., 1995; Surh et al., 1998). CAP has numerous therapeutic applications, including regulating body temperature, treating chronic pain, and treating obesity (Kaiser & Goycoolea, 2014). At a cellular level, mammals interact with the TRPV1 receptor, an ion channel responsible for heat sensing (Caterina, M.J. 1997). Besides, it is known that CAP causes the reversible opening of tight junctions, and the molecular basis of this phenomenon was investigated in MDCK (Madin-Darby canine kidney) cells (Shiobara et al., 2013). However, the administration of CAP is not always feasible due to its pungency, low bioaccessibility, sparing solubility in water, and proven cytotoxicity at high concentrations (Kiser et al., 2015). Several studies have incorporated this substance into nanoformulations to make it more compatible with aqueous physiological environments (Kiser et al., 2015; Wu et al., 2022; Liu et al.,

2023).

Regarding CAP cytotoxicity, some reports suggest that CAP may have tumor-promoting effects in gastric cancer (Agrawal et al., 1986; López-Carnllo et al., 1994). Zhang et al. (2020) present a review of CAP as a therapeutic drug in human cancers. An important conclusion is that in the tumorigenesis process, the CAP could act as a carcinogen or as a cancer preventive agent about concentration. In this sense, a study of interactions between CAP and NB can provide valuable insights into the impact of Capsaicin on DNA-related diseases.

Computational chemistry and quantum chemical methods offer alternative approaches to evaluating molecular interactions (Obot et al., 2015). The molecular orbital theory states that electrons are not assigned to specific atoms or bonds but move through the molecule in their orbitals. This theory predicts electrons' spatial and energetic properties, which are crucial in determining molecular properties. It forms the basis for most semi-empirical methods used in quantum chemistry (Živković, 1983). The difference between the highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO) energy has been used as a straightforward indicator of chemical reactivity. A small HOMO-LUMO gap implies a chemical reactivity because it is energetically favorable for electron transfer and forms the complex of any potential reaction (Aihara, 1999).

Gonzalez-Perez (2017) proposes a methodology to evaluate the molecular interaction by the determination of electron transfer coefficient (ETC) (eq. 1). ETC represents an opposition to the displacement of the electron; this opposition is equivalent to the impedance in the electronic theory. A lower ETC represents a lower obstacle to the electron in its trajectory (bond valence), according to the principle of Feynmann's most minor action (Gray, 2018).

$$\mathbf{ETC=BG/EP} \qquad \textbf{Eq. 1}$$

Where BG is defined as bandgap (eq. 2), and it is the absolute difference between HOMO and LUMO values; in other words, the BG is the value of the energy that an electron (electronic cloud) needs to move it from one molecule to another.

$$\mathbf{BG=|HOMO-LUMO|} \qquad \textbf{Eq. 2}$$

EP is defined as the electrostatic potential which is relative to the interaction between two molecules.

The EP is the absolute difference of the electrostatic potentials from each pole (eq. 3).

$$EP = \delta^- - \delta^+ \qquad \text{Eq. 3}$$

Recently the ETC theory was applied to determine the biodegradation pathway of the endocrine-disruptor di (2-ethyl hexyl) phthalate by Pleurotus ostreatus (Ahuactzin-Pérez et al., 2018) and determine the carcinogenic potential of mycotoxins such as aflatoxin B1 and M1(González-Pérez, 2017). Therefore, this work aims to characterize CAP using computational chemistry by quantum chemistry and its molecular interaction with NB using ETC values.

METODOLOGY

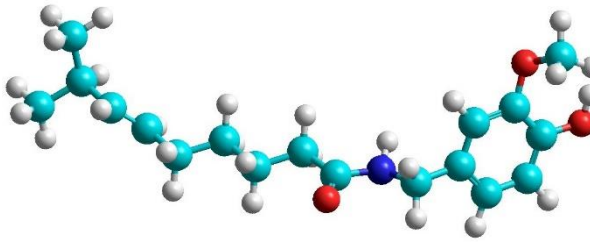
Quantum chemical variables (HOMO-LUMO, BG, EP) was determined by Hyper Chem simulator (MultiON for Windows. Serial #12-800-1501800080. MultiON). The specific parameters selected for each of the simulations were as follows: SET UP. Semi-empirical Method, PM3. Semi- Empirical Options: Charge and Spin, Total Charge 0. Spin Multiplicity, 1. SCF Control. Converge limit, 0.01. Interaction limit, 1000. Accelerate converge, Yes. Spin Pairing, Lowest. Overlap Weighting Factors, Sigma-Sigma 1, Pi-Pi, 1. Polarizabilities were not calculate. Hamiltonian technique in an array two at a time was used to calculate all possible interactions between CAP and the NB of the nucleic acids. Using the equations 1 to 3 the EP, BG and ETC were calculated.

RESULTS AND DISCUTIONS

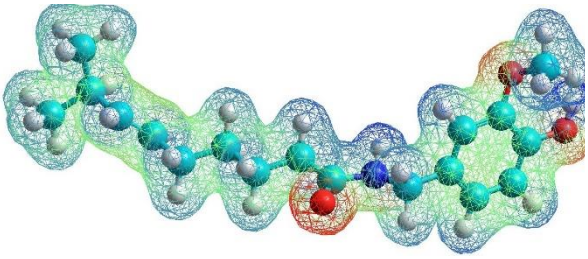
The HOMO energy is related to the ionization potential in molecules; however, LUMO energy is related to electron affinities. Figure 1 shows 3D structures and HOMO–LUMO energies projected on the van der Waals surface for CAP using the PM3 semi-empirical method. The figure shows that the HUMO and LUMO bands are in the same region. This property means that there is a small energy gap. This overlap leads us to the conclusion that the CAP can form spheres or micelles. Hence, CAP behaves like a fatty acid, which is congruent with CAP's physical properties (hydrophobicity) (De Lourdes Reyes-Escogido et al., 2011). Molecules with small HOMO–LUMO gaps are highly polarizable. That molecules require a small energy gap for their excitation, for they are more reactive (Pilli et al., 2015).

Figure 1.

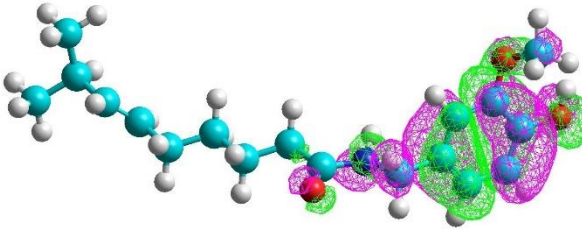
Quantum characterization of the CAP molecule. a) chemical structure, b) electronic configuration, c) HOMO, d) LUMO.



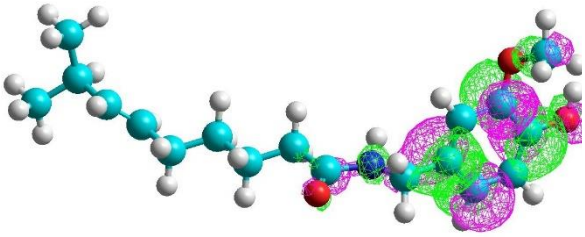
A) Capsaicin (CAP). C = cian, O = red, H = white, N = blue.



B) CSC □□ = - 0.116 eV/a°; □□ = + 0.176 eV/a°. Red-, Blue+, Green neuter.



C) CAP. HOMO = - 9.282 eV



D) CAP. LUMO = - 0.083 eV

Calculus:

Bg = |HOMO-LUMO| = |-9.047523-0.05923759| = 9.10676.59 eV.

EP = δ- δ += |0.018-0.140| = 0122 eV/a°.

ETC = Bg/EP = 74.645786 a°.

Figure 2 shows the box-and-whisker plot of the ETC of the interactions of CAP and NB. In agreement with the ETC value, the reactions where CAP acts as a reducer or antioxidant of NBs are more probable; but it is not clear in this diagram. The table 1 shows the interactions of the CAP and the interactions allowed by the nature of both DNA and RNA macromolecules. Column 8 pertains to the Electronic Transition Coefficient (ETC), which quantifies the extent of the electron's transition from the highest

occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO) state within each molecule of the pure substance. A smaller transition indicates a more pronounced chemical affinity and an increased likelihood of reactions. CAP exhibits diminished affinity among its constituent molecules due to its larger ETC value (31.503 a°). This results in CAP displaying lower stability when compared to the pure NBs molecules. Conversely, the A:U2 interaction stands out as the most stable due to its lowest ETC value (ETC = 24.91 a°).

Figure 2. *Box-and-whisker plot of the ETC of the interactions of Capsaicin and NB.*

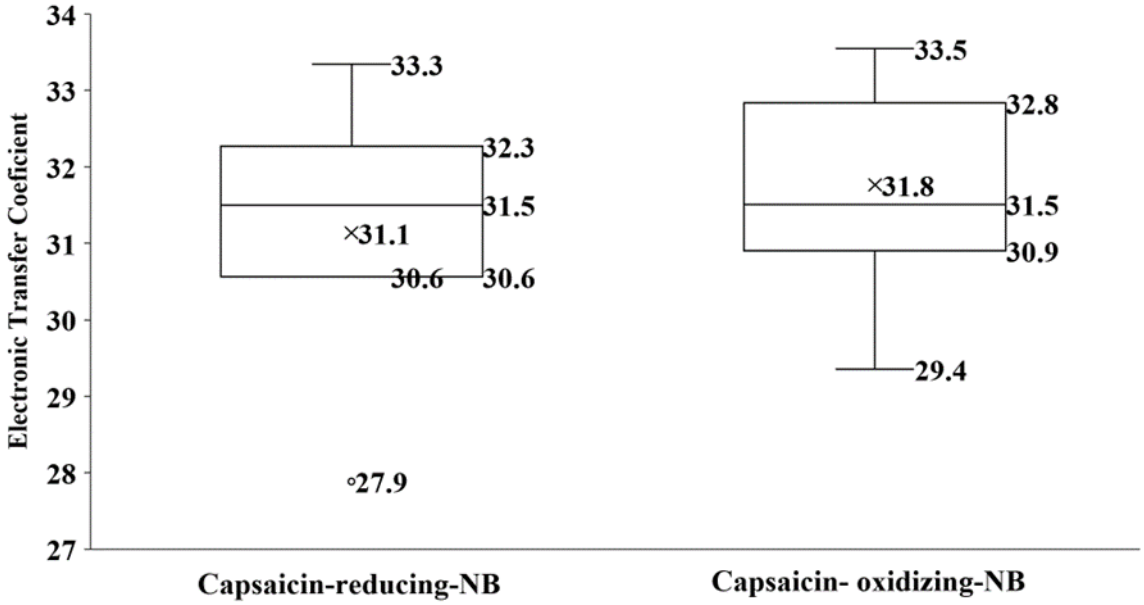


Table 1. *Molecular binary interaction between nucleobases and CAP*.

Interaction	HOMO [eV]	LUMO [eV]	Bg [eV]	δ- [eV/a°]	δ + [eV/a°]	EP [eV/a°]	ETC [a°]
CAP-CAP	-9.282	-0.083	9.199	-0.116	0.176	0.292	31.503
A:T	-8.654	-0.475	8.179	-0.14	0.169	0.309	26.469
C:G	-9.142	-0.206	8.936	-0.174	0.172	0.346	25.826
A:U1	-8.654	-0.511	8.143	-0.14	0.171	0.311	26.183
A:U2	-8.654	-0.415	8.239	-0.14	0.202	0.342	24.091

CAP: *Capsaicin, A: adenine, C: cytosine, G: guanine, T: thymine, U1: uracil tautomer amide or lactam, U2: uracil tautomer imide or lactim, HOMO: highest unoccupied molecular orbital, LUMO: lowest unoccupied molecular orbital, Bg: bandgap, δ-: electrostatic potentials of negative pole, δ-: electrostatic potentials of positive pole, EP: electrostatic potential, ETC: electronic transfer coefficient. units. eV: electron-volts, a°: Bohr radius*

The interaction of CAP as a reducing agent (antioxidant) of NB is shown in Table 2. The ETC values are 27.884 - 30.902 a°. This range leads us to the assertion that CAP is not an antioxidant for the NB binding of nucleic acids.

Table 2.

Analysis of reduction properties during molecular binary interaction between CAP and nucleobases pairs.

Interaction	HOMO [eV]	LUMO [eV]	Bg [eV]	δ- [eV/a°]	δ + [eV/a°]	EP [eV/a°]	ETC [a°]
CAP: (A:T)	-9.282	-0.475	8.807	-0.116	0.169	0.285	30.902
CAP: (C:G)	-9.282	-0.206	9.076	-0.116	0.172	0.288	31.514
CAP: (A:U1)	-9.282	-0.511	8.771	-0.116	0.171	0.287	30.561
CAP: (A:U2)	-9.282	-0.415	8.867	-0.116	0.202	0.318	27.884

CAP: Capsaicin, A: *adenine,* C*: cytosine,* G*: guanine,* T*: thymine,* U1*: uracil tautomer amide or lactam,* U2*: uracil tautomer imide or lactim,* HOMO*: highest unoccupied molecular orbital,* LUMO*: lowest unoccupied molecular orbital,* Bg*: bandgap, δ-: electrostatic potentials of negative pole, δ-: electrostatic potentials of positive pole,* EP*: electrostatic potential,* ETC*: electronic transfer coefficient. units. eV: electron-volts, a°: Bohr radius.*

Table 3 presents the interactions when CAP led electrons to natural NB´s. The ETC values are 25.883 – 27.123 a°. These values lead us to affirm that CAP acts less likely as an oxidant of nucleic acids.

Table 3. *Analysis of oxidation properties during molecular binary interaction between CAP and nucleobases pairs.*

Interaction	HOMO [eV]	LUMO [eV]	Bg [eV]	δ- [eV/a°]	δ + [eV/a°]	EP [eV/a°]	ETC [a°]
(A:T): CAP	-8.654	-0.083	8.571	-0.140	0.176	0.316	27.123
(C:G): CAP	-9.142	-0.083	9.059	-0.174	0.176	0.350	25.883
(A:U1): CAP	-8.654	-0.083	8.571	-0.140	0.176	0.316	27.123
(A:U2): CAP	-8.654	-0.083	8.571	-0.140	0.176	0.316	27.123

CAP: *Capsaicin, A: adenine, C: cytosine, G: guanine, T: thymine, U1: uracil tautomer amide or lactam, U2: uracil tautomer imide or lactim, HOMO: highest unoccupied molecular orbital, LUMO: lowest unoccupied molecular orbital, Bg: bandgap, δ-: electrostatic potentials of negative pole, δ-: electrostatic potentials of positive pole, EP: electrostatic potential, ETC: electronic transfer coefficient. units. eV: electron-volts, a°: Bohr radius*

According to Qais et al. (2017), the CAP has high binding potential with circulating tumor DNA, and the binding process is spontaneous, involving hydrogen bonds and Van der Waals interactions. Table 4 shows all the possible natural combinations of the NB, including the CAP.

Table 4. *Electronic transfer coefficient values of all possible interactions between CAP and* NB.

N	Reducing Agent	Oxidizing Agent	HOMO [eV]	LUMO [eV]	Bg [eV]	δ- [eV/a°]	δ + [eV/a°]	EP [eV/a°]	ETC [a°]
49**	U1	A	-9.71	-0.213	9.497	-0.126	0.156	0.282	33.679
48	U1	CAP	-9.71	-0.083	9.627	-0.116	0.171	0.287	33.543
47	CAP	A	-9.282	-0.213	9.069	-0.116	0.156	0.272	33.342
46**	T	A	-9.441	-0.213	9.228	-0.123	0.156	0.279	33.076
45	T	CAP	-9.441	-0.083	9.358	-0.116	0.169	0.285	32.835
44	C	CAP	-9.142	-0.083	9.059	-0.116	0.161	0.277	32.704
43	U1	C	-9.71	-0.344	9.366	-0.126	0.161	0.287	32.637
42	CAP	C	-9.282	-0.344	8.938	-0.116	0.161	0.277	32.267
41	T	C	-9.441	-0.344	9.097	-0.123	0.161	0.284	32.033
40**	U2	A	-9.91	-0.213	9.697	-0.147	0.156	0.303	32.004
39	U1	G	-9.71	-0.206	9.504	-0.126	0.172	0.298	31.894
38	CAP	G	-9.282	-0.206	9.076	-0.116	0.172	0.288	31.514
37	A	CAP	-8.654	-0.083	8.571	-0.116	0.156	0.272	31.511
36	CAP	CAP	-9.282	-0.083	9.199	-0.116	0.176	0.292	31.503
35	U1	T	-9.71	-0.475	9.235	-0.126	0.169	0.295	31.307
34	T	G	-9.441	-0.206	9.235	-0.123	0.172	0.295	31.305
33	U2	C	-9.91	-0.344	9.566	-0.147	0.161	0.308	31.061
32	U1	U1	-9.71	-0.511	9.199	-0.126	0.171	0.297	30.973
31	U2	CAP	-9.91	-0.083	9.827	-0.116	0.202	0.318	30.902
30	CAP	T	-9.282	-0.475	8.807	-0.116	0.169	0.285	30.902
29	T	T	-9.441	-0.475	8.966	-0.123	0.169	0.292	30.705
28	CAP	U1	-9.282	-0.511	8.771	-0.116	0.171	0.287	30.561
27	U2	G	-9.91	-0.206	9.704	-0.147	0.172	0.319	30.42
26	T	U1	-9.441	-0.511	8.93	-0.123	0.171	0.294	30.375
25	U2	T	-9.91	-0.475	9.435	-0.147	0.169	0.316	29.859
24	U2	U1	-9.91	-0.511	9.399	-0.147	0.171	0.318	29.558
23****	G	CAP	-8.537	-0.083	8.454	-0.116	0.172	0.288	29.354
22	A	A	-8.654	-0.213	8.441	-0.14	0.156	0.296	28.517

21	U1	U2	-9.71	-0.415	9.295	-0.126	0.202	0.328	28.34
20***	CAP	U2	-9.282	-0.415	8.867	-0.116	0.202	0.318	27.884
19	T	U2	-9.441	-0.415	9.026	-0.123	0.202	0.325	27.773
18	A	C	-8.654	-0.344	8.31	-0.14	0.161	0.301	27.61
17	U2	U2	-9.91	-0.415	9.495	-0.147	0.202	0.349	27.206
16	G	A	-8.537	-0.213	8.324	-0.15	0.156	0.306	27.202
15	A	G	-8.654	-0.206	8.448	-0.14	0.172	0.312	27.078
14	C	A	-9.142	-0.213	8.929	-0.174	0.156	0.33	27.058
13*	A	T	-8.654	-0.475	8.179	-0.14	0.169	0.309	26.471
12**	G	C	-8.537	-0.344	8.193	-0.15	0.161	0.311	26.345
11	C	C	-9.142	-0.344	8.798	-0.174	0.161	0.335	26.263
10*	A	U1	-8.654	-0.511	8.143	-0.14	0.171	0.311	26.185
9	G	G	-8.537	-0.206	8.331	-0.15	0.172	0.322	25.873
8*	C	G	-9.142	-0.206	8.936	-0.174	0.172	0.346	25.827
7	G	T	-8.537	-0.475	8.062	-0.15	0.169	0.319	25.273
6	C	T	-9.142	-0.475	8.667	-0.174	0.169	0.343	25.27
5	C	U1	-9.142	-0.511	8.631	-0.174	0.171	0.345	25.019
4	G	U1	-8.537	-0.511	8.026	-0.15	0.171	0.321	25.003
3*	A	U2	-8.654	-0.415	8.239	-0.14	0.202	0.342	24.092
2	C	U2	-9.142	-0.415	8.727	-0.174	0.202	0.376	23.212
1	G	U2	-8.537	-0.415	8.122	-0.15	0.202	0.352	23.074

*Interactions allowed by the nature of DNA and RNA. High affinity.

**Interactions allowed by the nature of DNA and RNA. Low affinity.

***First attack by the CAP on U2 as a reducing agent (antioxidant).

****Second attack of the CAP on the G as an oxidizing agent.

Interactions with smaller ETC values evidence higher affinity between compounds. Here it was observed that the first attack of the CAP occurs through interaction 20. Therefore there are 19 more related interactions. This phenomenon leads us to conclude that CAP has a moderate mutagenic effect or does not act as a mutagenic agent. It is possible that Qais's statement would show a higher dependence on interaction with amino acids and not with NB. This statement must be studied, considering the effect of CAP on cell permeability. According to Zhang et al. (2020), the mechanisms of CAP as anticancer are principally related to anti-angiogenesis and anti-metastasis, induction of apoptosis, antiproliferation,

and autophagy. Therefore, CAP could be used as a chemopreventive or therapeutic auxiliary in the diet to prevent cancer. However, its use is limited due to its low solubility in water (hydrophobicity). In this sense, some authors have considered a hydrophobic property of CAP to develop attractive emulsions. Wu et al. (2022) entrapped it in the water phase of water-in-oil (W/O) high internal phase emulsions (HIPEs) using a pH-driven method. A thick lipid shell formed around the water droplets, and a dense network in the aqueous core was demonstrated. The addition of CAP caused an increase in the viscoelasticity of the HIPEs. These particles exhibited good stability, and the CAP was shown to remain within the aqueous core (rather than moving to the oil phase) during storage. The encapsulation of CAP is an alternative for use as an anticancerogenic auxiliary (Olguín-Rojas et al., 2017; Zang et al., 2017; Lan et al., 2019).

CONCLUSIONS

Objective.

Study of CAP interaction with nitrogen bases (DNA and RNA) using quantum chemistry.

Thesis.

CAP is not a mutagenic agent. Among 49 interactions, the CAP attacks U2 in interaction 20. This attack indicates that CAP leaves free the natural and allows the assembly of all NBs in nucleic acids.

Corollary.

A small HOMO-LUMO energy gap in the CAP molecules was found. This overlap may indicate that the CAP forms spheres or micelles, which means it behaves similarly to fatty acids.

ACKNOWLEDGMENTS: The authors express their acknowledgments to Consejo Nacional de Ciencia y Tecnología (CONACyT) for the scholarship assigned to J.A. Olguín-Rojas.

REFERENCES

Agrawal, R. C., Wiessler, M., Hecker, E., & Bhide, S. V. (1986). Tumour-promoting effect of chilli extract in BALB/c mice. International Journal of Cancer, 38(5), 689–695. https://doi.org/10.1002/IJC.2910380512.

Ahuactzin-Pérez, M., Tlecuitl-Beristain, S., García-Dávila, J., Santacruz-Juárez, E., González-Pérez, M., Gutiérrez-Ruíz, M. C., & Sánchez, C. (2018). A novel biodegradation pathway of the endocrine-disruptor di (2-ethyl hexyl) phthalate by *Pleurotus ostreatus* based on quantum

chemical investigation. Ecotoxicology and Environmental Safety, 147, 494–499. https://doi.org/10.1016/J.ECOENV.2017.09.004

Caterina, M. J. Schumacher; M.A., Tominaga; M., Rosen, T.A., Levine, J.D.; Julius, D.J. (1997). The Capsaicin receptor: A heat-activated ion channel in the pain pathway. Nature 389, 816–824.

Cijo G., V., Naveen Kumar, D. R., Suresh, P. K., & Ashok Kumar, R. (2015). Antioxidant, DNA protective efficacy and HPLC analysis of *Annona muricata* (soursop) extracts. Journal of Food Science Technology, 52(3). https://doi.org/10.1007/s13197-014-1289-7.

De Lourdes Reyes-Escogido, M., Gonzalez-Mondragon, E. G., & Vazquez-Tzompantzi, E. (2011). Chemical and pharmacological aspects of Capsaicin. In Molecules (Vol. 16, Issue 2, pp. 1253–1270. https://doi.org/10.3390/molecules16021253.

De, A. K., Agarwal, K., Mukherjee, A., & Sengupta, D. (1995). Inhibition by Capsaicin against cyclophosphamide-induced clastogenicity and DNA damage in mice. Mutation Research/Environmental Mutagenesis and Related Subjects, 335 (3), 253–258. https://doi.org/10.1016/0165-1161(95)00028-3.

González-Pérez, M. (2017). Quantum modeling to determine the carcinogenic potential of aflatoxin B1 produced by *Aspegillus* sp and its metabolic derivate aflatoxin M1 Modelamiento cuántico para determinar el potencial cancerígeno de la aflatoxina B1 producida por *Aspegillus* sp y de su derivado metabólico aflatoxina M1 ORIGINAL RESEARCH. Mexican Journal of Biotechnology, 2(2), 255–270. https://doi.org/10.29267/mxjb.2017.2.2.255.

González-Pérez, M. (2017). Quantum Theory of the Electron Transfer Coefficient. International Journal of Advanced Engineering, Management and Science, 3(10), 1024–1028. https://doi.org/10.24001/ijaems.3.10.9.

Kaiser, M. & Goycoolea (2014) F. M. in Capsaicin: Food Sources, Medical Uses and Health Implications (ed Gilliam, B.) 53–74 Nova Science Publishers.

Kaiser, M., Pereira, S., Pohl, L. (2015). Chitosan encapsulation modulates the effect of Capsaicin on the tight junctions of MDCK cells .Science Reports, 5, 10048. https://doi.org/10.1038/srep10048.

Kogure, K., Goto, S., Nishimura, M., Yasumoto, M., Abe, K., Ohiwa, C., Sassa, H., Kusumi, T., & Terada, H. (2002). Mechanism of potent antiperoxidative effect of Capsaicin. Biochimica et

Biophysica Acta - General Subjects, 1573(1), 84–92. https://doi.org/10.1016/S0304-4165(02)00335-5.

Lan, Y., Sun, Y., Yang, T., Ma, X., Cao, M., Liu, L., Liu, Y. (2019). Co-delivery of paclitaxel by a capsaicin prodrug micelle facilitating for combination therapy on breast cancer. Molecular pharmaceutics, 16(8), 3430-3440.

Liu, X., Saleh ,A.S.M., Zhang, B., Liang, W., Zhao, W., Zheng, J., Ge, X., Shen, H., Li, W. (2023). Capsaicin microcapsules with high encapsulation efficiency and storage stability based on sodium caseinate–acetylated wheat starch: preparation and characterization International Journal of Food Science & Technology. V. 58, 2, pp. 741-754. https://doi.org/10.1111/ijfs.16225.

López-Carnllo, L., Avila, M. H., & Dubrow, R. (1994). Chili Pepper Consumption and Gastric Cancer in Mexico: A Case-Control Study. American Journal of Epidemiology, 139(3), 263–271. https://doi.org/10.1093/OXFORDJOURNALS.AJE.A116993

Lu, M., Chen, C., Lan, Y., Xiao, J., Li, R., Huang, J., Ho, C. T. (2020). Capsaicin—The major bioactive ingredient of chili peppers: Bio-efficacy and delivery systems. Food & function, 11(4), 2848-2860.

Obot, I. B., Macdonald, D. D., & Gasem, Z. M. (2015). Density functional theory (DFT) as a powerful tool for designing new organic corrosion inhibitors: Part 1: An overview. In Corrosion Science (Vol. 99, pp. 1–30). Elsevier Ltd. https://doi.org/10.1016/j.corsci.2015.01.037

Olguín-Rojas, J. A., Fayos, O., Abel Vázquez-León, L., Ferreiro-González, M., Del Carmen Rodríguez-Jimenes, G., Palma, M., Garcés-Claver, A., & Barbero, G. F. (2019). Progression of the total and individual Capsaicinoids content in the fruits of three different cultivars of Capsicum chinense Jacq. https://doi.org/10.3390/agronomy9030141

Olguín-Rojas, J. A., Morales-Guillermo, M., Escobar, J. C., Ramirez-Velazquez, M., Torres-Cadena, J., Garcia-Alvarado, M. A., Rodriguez-Jimenes G.C. (2017) Secado por aspersion de extractos de chile habanero empleando goma arabiga como material de soporte. Avance de la Ciencia en México. Ed. Centro de Investigaciones en Óptica A.C.

Qais, F. A., Abdullah, K. M., Alam, M. M., Naseem, I., & Ahmad, I. (2017). Interaction of Capsaicin with calf thymus DNA: A multi-spectroscopic and molecular modelling study. International

Journal of Biological Macromolecules, 97, 392–402. https://doi.org/10.1016/J.IJBIOMAC.2017.01.022

Ranjan, A., Ramachandran, S., Gupta, N., Kaushik, I., Wright, S., Srivastava, S., Das, H., Srivastava, S., Prasad, S., & Srivastava, S. K. (2019). Role of phytochemicals in cancer prevention. International Journal of Molecular Sciences 2019, Vol. 20, Page 4981, 20(20), 4981. https://doi.org/10.3390/IJMS20204981

Rollyson, W. D., Stover, C. A., Brown, K. C., Perry, H. E., Stevenson, C. D., McNees, C. A., Ball, J. G., Valentovic, M. A., & Dasgupta, P. (2014). Bioavailability of Capsaicin and its implications for drug delivery. In Journal of Controlled Release (Vol. 196, pp. 96–105). https://doi.org/10.1016/j.jconrel.2014.09.027

Shiobara, T., Usui, T., Han, J., Isoda, H. & Nagumo, Y. (2013). The reversible increase in tight junction permeability induced by Capsaicin is mediated via cofilin-actin cytoskeletal dynamics and decreased level of occludin. PLoS ONE 8).

Surh, Y. J., Lee, E., & Lee, J. M. (1998). Chemoprotective properties of some pungent ingredients present in red pepper and ginger. Mutation Research - Fundamental and Molecular Mechanisms of Mutagenesis, 402(1–2), 259–267. https://doi.org/10.1016/S0027-5107(97)00305-9

Susuki T., & Iwai K. (1984). Constituents of Red Pepper Species: Chemistry, Biochemistry, Pharmacology, and food science of the pungent principle of Capsicum species. In The Alkaloids: Chemistry and Pharmacology (pp. 227–299). https://sci-hub.se/10.1016/S0099-9598(08)60072-3

Wu, X., Xu, N., Cheng, C., McClements, D.M., Chen, X., Zou. L., Liu, W. (2022), Encapsulation of hydrophobic Capsaicin within the aqueous phase of water-in-oil high internal phase emulsions: Controlled release, reduced irritation, and enhanced bioaccessibility. Food Hydrocolloids, V. 123, February 2022, 107184.

Zhang S, Wang D, Huang J, Hu Y, Xu Y. (2020) Application of capsaicin as a potential new therapeutic drug in human cancers. J Clin Pharm Ther; 45:16–28. https://doi.org/10.1111/jcpt.13039

Zhang, W., Liu, M., Liu, A., Zhai, G. (2017). Advances in functionalized mesoporous silica nanoparticles for tumor targeted drug delivery and theranostics. Current Pharmaceutical Design, 23(23), 3367-3382.

Živković, T. P. (1983). Molecular orbital resonance theory: A new approach to the treatment of quantum chemical problems. Theoretica Chimica Acta. 62(4): 335-350.