https://doi.org/10.46344/JBINO.2022.v11i03.30

QUANTUM-CHEMICAL ANALYSIS OF THE INTERACTIONS OF EUGENOL VS. NITROGENOUS BASES OF THE NUCLEIC ACIDS RNA AND DNA.

[1,2]Manuel González-Pérez, [1]Cecilia Vázquez-González, [1]Alex Ortiz-Ruiz, [1]Carlos Roberto Camarillo-Rojas, [1]Alfredo Salvador Castro-Díaz, [1]Diana Gómez Flores, [1]Dolores del Carmen Lora Sánchez.

[1]UNIVERSIDAD TECNOLÓGICA DE TECAMACHALCO (UTTECAM). Ingeniería en Procesos Bioalimentarios, Ingeniería en Agricultura Sustentable y Protegida.
[2]TECNOLÓGICO SUPERIOR DE TEPEACA, (TecNM campus Tepeaca). Subdirección de investigación y desarrollo.

ABSTRACT

Eugenol is a cheap, readily available phenylpropene that has been known to humankind since ancient times and is used as a medicinal agent. This essence is the main component of clove oil. We use the possible Hamiltonian combinatorics to perform all the valence electron jumps between each substance. We use the parameterized semi-empirical model number 3 (SE-PM3) from Hyperchem to draw the corresponding molecules. Then we select the SE-PM3 method. To optimize the geometry, we use the Polak Ribiere method and calculate the variables of HOMO-LUMO, BG, EP, and other properties, resulting in a tab-delimited table for BG and EP. Eugenol, as a pure substance, is very unstable. Eugenol functions as a reducing agent (antioxidant) for the U2 tautomer. Eugenol goes from the first quartile in oxidation-reduction interactions to the second quartile in the quantum soup (all against all). Eugenol interactions with nitrogenous bases do not have the appropriate probability or affinity to cause mutations in DNA or RNA. In the case of random mutagenic interaction, the most likely (probability almost 0). Eugenol functions as a reducing agent (antioxidant) for RNA in this interaction.

KEYWORDS
Eugenol, nitrogenous bases, DNA, RNA, quantum chemistry.

INTRODUCTION

Kaufman (2015) states that eugenol is an inexpensive and readily available phenylpropene that has been known to humanity since ancient times and is used as a medicinal agent. This essence is the main component of clove oil. Blowman et al. (2018), in a literature review, demonstrate that essential oils possess cancer cell-targeting activity and can increase the efficacy of commonly used chemotherapy drugs, including paclitaxel and docetaxel. They further mention that many essential oils, such as eugenol, have shown pro-immune functions when administered to cancer patients.

In other investigations, Bezerra et al. (2022) evaluated the antibacterial activity of eugenol by inhibition of TetK Efflux Pump in strains of Staphylococcus aureus resistant to Tetracycline, in addition to evaluating its toxicity in Drosophila melanogaster. They concluded that eugenol did not have a relevant direct effect against S. aureus; however, it potentiated the action of the antibiotic. Adhikari et al. (2022) carried out larvicidal bioassays in thirty successive generations. They determined the median lethal concentration in each generation and measured the esterase (alpha and beta), cytochrome P450, and GST activities of surviving larvae exposed to that concentration. In addition, they applied synergists (TPP, DEM, and PBO) together with eugenol at concentrations F30 and LC50, and these enzymatic activities were recorded. Overall, the results inferred that eugenol would function effectively as a larvicide for a more extended period in successive generations without initiating rapid resistance and thus could be recommended to control A. aegypti.

Ni et al. (2022) evaluated the antimicrobial and antibiofilm potential of the Ocimum tenuiflorum plant extract. The extract showed the maximum inhibition of biofilms, proteins, and carbohydrates present with the extracellular polymeric substance. Eugenol and linalool reduced the maximum inhibition of genomic RNA and DNA content. Jannuzzi (2022) investigated eugenol's cytotoxic and genotoxic effects on UVA-induced damage using human keratinocyte cells. The trial results showed that eugenol causes DNA single strand breaks and that increasing doses of UVA radiation aggravate the genotoxic potential of eugenol.

Zhan et al. (2022) studied the underlying molecular mechanisms of eugenol acting on T. castaneum. They concluded that a nerve conduction carboxylesterase and a detoxifying glutathione S-transferase were significantly inhibited after eugenol exposure, leading to paralysis or death of the beetles. In addition, several differentially expressed genes (DEGs) could be involved in respiratory metabolism in beetles exposed to eugenol. Some DEGs encoding CYP, UGT, GST, OBP, CSP, and ABC transporters were involved in the xenobiotic or drug metabolism pathway, suggesting that these T. castaneum genes were involved in response to eugenol exposure. Furthermore, TcOBPC11/TcGSTs7, detected by qRT-PCR and RNA-interference against these genes,

significantly increased the mortality of T. castaneum treated with eugenol.

Jiang et al. (2022) evaluated the relationship between eugenol in producing the mycotoxin ochratoxin A (OTA). The minimum inhibitory concentration (MIC) for eugenol treatment was 0.8 µL/mL. They found that transcription of clustered genes for OTA biosynthesis was significantly reduced under eugenol stress and further confirmed by RT-qPCR. Eugenol damaged cell structure by altering DEG expression. This damage was shown by monitoring chitinase activity, malondialdehyde (MDA), and ergosterol content. Eugenol causes oxidative stress and changes in superoxide dismutase, catalase, and glutathione. This activity was consistent with changes in gene expression. On the other hand, they tell us that these findings provide valuable information on the antifungal mechanisms of eugenol on A. carbonarius.

Regarding statistics and computational chemistry, Gerber et al. (2022) used bioinformatics (in silico laboratory) as a tool to analyze the dynamics of GTP binding (triphos guanosine fat) of the KRAS protein when it mutates. According to them, KRAS undergoes significant conformational changes, affecting the GTP-binding confirmation within the KRAS active site due to high torsional stresses, hydrophobicity, and altered regions. This study provides insight into the details of GTP-KRAS protein binding that are important in defining the parameters that need to be explored to design the appropriate inhibitor for each type of mutant KRAS protein.

Regarding the benefit for humans, El-Far et al. (2022) investigated the antioxidant activity of eugenol (EU) or carvacrol (CAR) on D-gal-induced aging in rats for 42 days. They concluded that EU and CAR supplements are considered anti-aging compounds.

Due to this accumulation of research, we propose an objective to analyze the chemical-quantum interactions of the nitrogenase bases that make up the nucleic acids and eugenol to obtain quantitative information on these affinities.

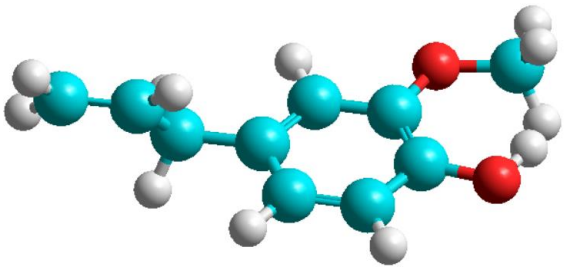
MATERIALS AND METHODS

Hamiltonian technic: It used the Hamiltonian combinatorial possibilities to perform all the valence electron's hops between each substance. Quantum methodology: It bought the molecular simulator Hyper Chem (HC). (Hyper Chem. Hypercube, MultiON for Windows. Serial #12-800-1501800080. MultiON. Insurgentes Sur 1236 - 301 Tlacoquemecatl Col. del Valle, Delegación Benito Juárez, D. F., México CP. 03200).

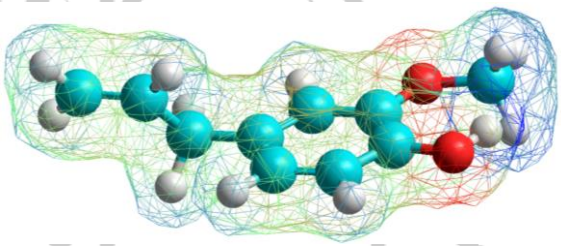
It used HC Semi-Empirical Parameterized Model number 3 (SE-PM3) to draw the corresponding molecules. Then it selected SE-PM3. It optimized the geometry with the Polak Ribiere method. It calculated the variables of HOMO-LUMO, BG, EP, and other properties, resulting in a Tab-delimited table for BG and EP.

The specific parameters selected for each simulation were as follows: SET UP. Semiempirical Method: PM3. Semiempirical 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-Pi1. Polarizabilities
do not calculate.
COMPUTE 1. Geometry Optimization. Algorithm Polak Ribiere (conjugate gradient). Options Termination conditions. RMS gradient of:0.1 kcal/mol or 1000 maximun cycles. In vacuo, yes. Screen refresh period one cyclos.
COMPUTE 2. Orbitals. Plot Orbital Options Isosurface Rendering. Orbital Contur Value 0.05. Rendering Wire mesh Isosurface Grid. Grid meshes size Coarse. Grid layout Default. Gird contour Default. Transparency level Default.
COMPUTE 3. Plot Molecular Graphs. Plot Molecular Options. Molecular Properties. Properties. Electrostatic Potential Yes. Representations. 3D Mapped Isosurface. Grid Mesh Size Coarse. Grid layout Default. Contour gird Default. Isosurface Rereading. Total Charge Density Contour Value (TCDCV) 0.015. Rendering Wire mesh. Transparency level Default. Mapped Options Functions Default. González-Pérez et al. (2022).

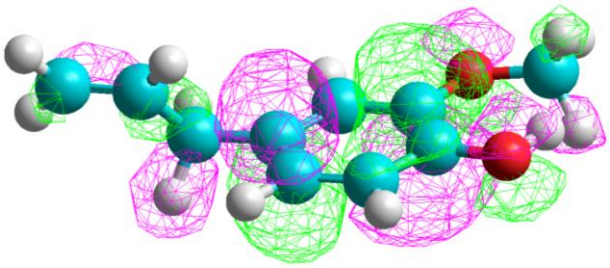
RESULTS AND DISCUSSION



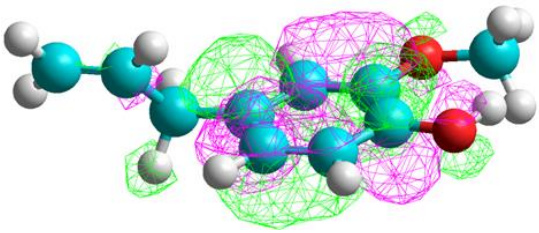
A) Eugenol hyperchem simulator molecule.
C = Cyan, H = White, O = Red.



Eugenol. Electrostatic potential.
E- = -0.094 eV/au (Red), E+ = +0.184 eV/au (Blue).
Apolar = green.



C) Eugenol. HOMO = -8.857753 eV



D) Eugenol. LUMO = +0.2994357 eV

Figure 1. Representative images of each of the calculations of the eugenol molecule.

HOMO AND LUMO are almost in the same atoms; they likely form threads, like hair less than 20 nanometers thick.

Latest calculations.

$EP = |(E-)-(E+)| = |(-0.094) -(0.184)| = 0.278$ eV/au — Eq. 1

$BG = |HOMO - LUMO| = |-8.857753-0.2994357| = 9.1571887$ eV — Eq. 2

$ETC = 32.939527697841$ au (this is considered dimensionless) — Eq. 3

Where:
EP = Electrostatic Potential.
BG = Bandgap.
ETC = Electron transfer coefficient.
And, au = atomic unit. González-Pérez M. (2017).

In Table 1, we can see that eugenol has the highest ETC of all competing substances; therefore, it is the most unstable substance of all. On the other hand, Guanine is observed as the most stable substance of all due to its lower ETC (bottom of the quantum well).

Table 1. Individual calculations of ETC of pure substances.

N	Reducing agent	Oxidizing agent	HOMO	LUMO	BG	E-	E+	EP	ETC
7	Eugenol	Eugenol	-8.858	0.299	9.157	-0.094	0.184	0.278	32.940
6	U1	U1	-9.710	-0.511	9.199	-0.126	0.171	0.297	30.973
5	T	T	-9.441	-0.475	8.966	-0.123	0.169	0.292	30.705
4	A	A	-8.654	-0.213	8.441	-0.140	0.156	0.296	28.517
3	U2	U2	-9.910	-0.415	9.495	-0.147	0.202	0.349	27.206
2	C	C	-9.142	-0.344	8.798	-0.174	0.161	0.335	26.263
1	G	G	-8.537	-0.206	8.331	-0.150	0.172	0.322	25.873

The smallest ETC is the bottom of the quantum well.

Table 2 summarizes the oxidation-reduction interactions of eugenol vs. the nitrogenous bases.
The most important observation from this table (quantum well) is that eugenol reduces to the hydroxylated tautomer (U2). According to the antioxidant theory, eugenol is an antioxidant agent of U2 and therefore antioxidizes RNA. This interaction 5 in the table is in the first quartile of all oxidation-reduction interactions.

As shown in Table 2, the antioxidant character continues in the second quartile (interactions 8, 9, and 10). Quartiles 3 and 4 are of low probability and low chemical affinity.

Table 2. Oxidation-reduction interactions between eugenol vs. nitrogenous bases.

N	Reducing agent	Oxidizing agent	HOMO	LUMO	BG	E-	E+	EP	ETC
19	U1	Eugenol	-9.710	0.299	10.009	-0.094	0.171	0.265	37.771
18	T	Eugenol	-9.441	0.299	9.740	-0.094	0.169	0.263	37.036
17	C	Eugenol	-9.142	0.299	9.441	-0.094	0.161	0.255	37.025
16	A	Eugenol	-8.654	0.299	8.953	-0.094	0.156	0.250	35.814
15	Eugenol	A	-8.858	-0.213	8.645	-0.094	0.156	0.250	34.579
14	U2	Eugenol	-9.910	0.299	10.209	-0.094	0.202	0.296	34.491
13	Eugenol	C	-8.858	-0.344	8.514	-0.094	0.161	0.255	33.387
12	G	Eugenol	-8.537	0.299	8.836	-0.094	0.172	0.266	33.220
11	Eugenol	Eugenol	-8.858	0.299	9.157	-0.094	0.184	0.278	32.940
10	Eugenol	G	-8.858	-0.206	8.652	-0.094	0.172	0.266	32.525
9	Eugenol	T	-8.858	-0.475	8.383	-0.094	0.169	0.263	31.874
8	Eugenol	U1	-8.858	-0.511	8.347	-0.094	0.171	0.265	31.497
7	U1	U1	-9.710	-0.511	9.199	-0.126	0.171	0.297	30.973

6	T	T	-9.441	-0.475	8.966	-0.123	0.169	0.292	30.705
5	Eugenol	U2	-8.858	-0.415	8.443	-0.094	0.202	0.296	28.523
4	A	A	-8.654	-0.213	8.441	-0.140	0.156	0.296	28.517
3	U2	U2	-9.910	-0.415	9.495	-0.147	0.202	0.349	27.206
2	C	C	-9.142	-0.344	8.798	-0.174	0.161	0.335	26.263
1	G	G	-8.537	-0.206	8.331	-0.150	0.172	0.322	25.873
								Second quartile	32.117
								First quartile	29.614

Table 3 shows the interactions of all the combined bases with themselves and with eugenol.
Interaction 26 is the first of eugenol. In this interaction, eugenol acts as an antioxidant agent of U2 in the second quartile. The other interactions have a very low probability and power to occur.

Table 3. ETCs quantum soup. All against all interactions.

N	Reducing agent	Oxidizing agent	HOMO	LUMO	BG	E-	E+	EP	ETC
55	U1	Eugenol	-9.710	0.299	10.009	-0.094	0.171	0.265	37.771
28 interactions are omitted due to lack of space.									
27	U2	U1	-9.910	-0.511	9.399	-0.147	0.171	0.318	29.558
26	Eugenol	U2	-8.858	-0.415	8.443	-0.094	0.202	0.296	28.523
25	A	A	-8.654	-0.213	8.441	-0.140	0.156	0.296	28.518
24	A	A	-8.654	-0.213	8.441	-0.140	0.156	0.296	28.517
23	U1	U2	-9.710	-0.415	9.295	-0.126	0.202	0.328	28.340
22	T	U2	-9.441	-0.415	9.026	-0.123	0.202	0.325	27.773
21	A	C	-8.654	-0.344	8.310	-0.140	0.161	0.301	27.610
20	U2	U2	-9.910	-0.415	9.495	-0.147	0.202	0.349	27.208
19	U2	U2	-9.910	-0.415	9.495	-0.147	0.202	0.349	27.206
18	G	A	-8.537	-0.213	8.324	-0.150	0.156	0.306	27.202
17	A	G	-8.654	-0.206	8.448	-0.140	0.172	0.312	27.078
16	C	A	-9.142	-0.213	8.929	-0.174	0.156	0.330	27.058
15	A	T	-8.654	-0.475	8.179	-0.140	0.169	0.309	26.471
14	G	C	-8.537	-0.344	8.193	-0.150	0.161	0.311	26.345
13	C	C	-9.142	-0.344	8.798	-0.174	0.161	0.335	26.265
12	C	C	-9.142	-0.344	8.798	-0.174	0.161	0.335	26.263
11	A	U1	-8.654	-0.511	8.143	-0.140	0.171	0.311	26.185
10	G	G	-8.537	-0.206	8.331	-0.150	0.172	0.322	25.873
9	G	G	-8.537	-0.206	8.331	-0.150	0.172	0.322	25.872
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	-0.150	0.169	0.319	25.273
6	C	T	-9.142	-0.475	8.667	-0.174	0.169	0.343	25.270
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	-0.150	0.171	0.321	25.003
3	A	U2	-8.654	-0.415	8.239	-0.140	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	-0.150	0.202	0.352	23.074
								Second quartile	29.633
								First quartile	26.408

Table 4 shows the ETCs of the nitrogenous base interactions allowed by nature. These interactions form both DNA and RNA.
Interaction number 26, eugenol-U2 in Table 3 shows an ETC = 28.523. It is observed outside the range (above) of the natural interactions (Table 4). This observation follows that eugenol is not mutagenic since it does not compete with natural interactions. If it were to compete, its behavior would be RNA antioxidant.
The U1 tautomer does not compete since its lowest ETC is 37.771 (totally outside the range of the ETCs in Table 4).

Table 4. ETCs allowed by nature. Includes the tautomers of uracil.

N	Reducing agent	Oxidizing agent	HOMO	LUMO	BG	E-	E+	EP	ETC	Nucleic acid
4	A	T	-8.654	-0.475	8.180	-0.14	0.169	0.309	26.471	DNA
3	A	U1	-8.654	-0.511	8.144	-0.14	0.171	0.311	26.185	RNA
2	C	G	-9.142	-0.206	8.936	-0.174	0.172	0.346	25.827	DNA, RNA
1	A	U2	-8.654	-0.415	8.239	-0.140	0.202	0.342	24.092	RNA

CONCLUSIONS

Objective.
Analyze the quantum chemical interactions of Eugenol vs. Nitrogenous bases of the nucleic acids RNA and DNA.

Hypothesis.
In this investigation, we wanted to demonstrate that "Eugenol is not mutagenic."

Thesis.
Eugenol's interactions with nitrogenous bases do not have the appropriate probability or affinity to cause mutation in either DNA or RNA.
In the event of random mutagenic interaction, the most probable (probability almost 0) would be number 26, Table 3—eugenol functions as a reducing agent (antioxidant) for RNA in this interaction.

Corollary or arguments of the thesis.
To arrive at this thesis, we find that:

1. As a pure substance, Eugenol is very unstable (Table 1. Interaction 7).
2. Eugenol works as a reducing agent (antioxidant) of U2 (Table 2, interaction 5, first quartile, and Table 3, interaction 26, second quartile).
3. Eugenol goes from the first quartile in oxidation-reduction interactions to the second quartile in the quantum soup (all against all).
4. Quantum soup refers to the combination of nitrogenous bases in nucleic acids.
5. It is work we interpreted as probability almost 0 of the interaction of Eugenol with U2 as a reducing agent (antioxidant).
6. This probability (point 5) refers to the ETC value outside the range of ETCs allowed by nature (Table 4).

REFERENCES

Adhikari, K., Khanikor, B., & Sarma, R. (2022). Persistent susceptibility of Aedes aegypti to eugenol. Scientific reports, 12(1):1-11.

Bezerra, S. R., Bezerra, A. H., de Sousa Silveira, Z., Macedo, N. S., dos Santos Barbosa, C. R., Muniz, D. F., ... & da Cunha, F. A. B. (2022). Antibacterial activity of eugenol on the IS-58 strains of Staphylococcus aureus resistant to tetracycline and toxicity in Drosophila melanogaster. Microbial Pathogenesis, 164, 105456.

Blowman, K., Magalhães, M., Lemos, M. F. L., Cabral, C., & Pires, I. M. (2018). Anticancer properties of essential oils and other natural products. Evidence-Based Complementary and Alternative Medicine, 1-12.

El-Far, A. H., Mohamed, H. H., Elsabagh, D. A., Mohamed, S. A., Noreldin, A. E., Al Jaouni, S. K., & Alsenosy, A. A. (2022). Eugenol and carvacrol attenuate brain d-galactose-induced aging-related oxidative alterations in rats. Environmental Science and Pollution Research, 1-12.

Gerber, M., Goel, S., & Maitra, R. (2022). In silico comparative analysis of KRAS mutations at codons 12 and 13: Structural modifications of P-loop, switch I&II regions preventing GTP hydrolysis. Computers in biology and medicine, 141(C):105110.

González-Pérez M, Barroeta-Gómez D, Pérez-Sánchez D, Rodríguez-Asenjo AS. (2022). Study of quantum chemical interactions of theobromine and some neurotransmitters. World Journal of Pharmaceutical Research, 11(2):40-47.

González-Pérez. M. (2017). Quantum Theory of the Electron Transfer Coefficient. International Journal of Advanced Engineering, Management and Science, 3(10).

Jannuzzi, AT. (2022). Eugenol aggravates UVA-induced cytotoxic and genotoxic responses in HaCaT human keratinocytes. Journal of Research in Pharmacy, 26(2):354-361.

Kaufman, T. S. (2015). The multiple faces of eugenol. A versatile starting material and building block for organic and bio-organic synthesis and a convenient precursor for bio-based fine chemicals. Journal of the Brazilian Chemical Society, 26(6):1055-1085.

Ni, K., Cai, D., Lu, J., & Tian, J. (2022). Eugenol-Mediated Inhibition of Biofilm Formed by S. aureus: a Potent Organism for Pediatric Digestive System Diseases. Applied Biochemistry and Biotechnology, 194(3):1340-1358.

Zhang, Y., Gao, S., Zhang, P., Sun, H., Lu, R., Yu, R., ... & Li, B. (2022). Response of xenobiotic biodegradation and metabolic genes in Tribolium castaneum following eugenol exposure. Molecular Genetics and Genomics, 1-15.