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STUDY OF CHEMICAL-QUANTUM INTERACTIONS OF STRUCTURAL AMINO ACIDS OF HER-2 AND QUERCETIN

***Manuel González-Pérez, Michelle Isasmendi-Cortés, José Sergio Buendía-Córdova, Aaron Caamal-Mota, Horacio Castro-Jara, Edgar Alfonzo Zúñiga-Márquez and Víctor Hugo de Román-Mello**

Tecnológico Nacional De México (TecNM), Campus Tepeaca. División De Gastronomía Y División De Ingeniería De Alimentos.

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***Corresponding Author**
Manuel González-Pérez
Tecnológico Nacional De México (TecNM), Campus Tepeaca. División De Gastronomía Y División De Ingeniería De Alimentos.

ABSTRACT

Quercetin (QT) is an anticancer agent used in cancer models due to its antioxidant and antitumor properties. The objective of this study was to investigate the chemical-quantum interactions of QT vs. the structural amino acids (AAs) of HER-2. It used the Hamiltonian combinatorial possibilities to perform all the valence electron's hops between each substance. It used (HC) Semi-Empirical Parameterized Model number 3 (SE-PM3) to draw the corresponding molecules. Then it selected SE-PM3. 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 do not calculate. As a general result, it is observed that both the AAs in the highest quantity (Leu) and the AAs in the smallest quantity (Trp) are the same in the two characterization tables of the HER2. Another important observation is that QT oxidizes all the AAs in HER2. On the other hand, it is observed that QT attacks arginine with greater probability and strength, although the ETC value of histidine is very close to the value of arginine. As a general conclusion. QT can oxidize all AAs of HER2.

KEYWORD: Chemical quantum, Amino acids, HER2, Quercetin, Hyperchem.

INTRODUCTION

QT is an anticancer agent used in cancer models due to its antioxidant and antitumor properties. Researchers synthesized QT-loaded honeycomb-structured nickel oxide (NiO) nanoparticles. QT treatment significantly inhibited the cytoplasmic HuR gene in both Triple-Negative Breast Cancer (TNBC) cell lines. For this reason, it is considered that QT's ability to inhibit the cytoplasmic HuR protein provides a rationale for its use as an anticancer agent for the treatment of aggressive TNBC. In other investigations, the anticancer activity of breast cancer, the biocompatibility, and the toxicity of QT nanoparticles encapsulated in polylactic acid was studied. The study established these nanoparticles' preliminary in vitro efficacy and in vivo safety as a possible formulation against breast cancer.[1-3]

Other researchers showed recent evidence that the maximum energy in metastatic breast cancer progression is supplied by fatty acid oxidation (FAO) governed by a rate-limiting enzyme, carnitine palmitoyltransferase 1 (CPT1). The functional limitation of FAO could be an emerging aspect to inhibit the progression of breast cancer. Furthermore, it was further confirmed by the successful prediction of in-silico molecular coupling for the active binding potential of QT to CPT1.[4]

In epidemiological and clinical studies, the most common nutritional tool to assess the dietary intake of flavonol is the food frequency questionnaire (FFQ), which must contain a detailed list of foods of plant origin and be previously validated. This study aimed to evaluate the precision of the dietary intake of flavonol (QT, kaempferol, and isorhamnetin) from a food frequency questionnaire (FFQ) compared to fasting plasma flavonol concentrations, as exposure biomarkers, in patients with breast cancer. Correlations and diagnostic performance with plasma concentrations could present a significant precision (validity) rate, which seems acceptable for a nutritional questionnaire (FFQ) to assess intakes and levels of intake of QT and kaempferol. An improvement in the accuracy of flavonol exposure can provide a more accurate relationship to health outcomes, which may increase its clinical significance.[5]

Research on the HER-2 target protein with natural compounds known to have antioxidant activity using computer simulations assisted by molecular modeling and docking. In this preliminary study, it can be concluded that anthocyanidin compounds (free binding energy -9.88 to -10.73 kcal/mol) have a sufficiently large potential as a breast cancer drug seen by the energy stability it produces and the number of interactions with HER-2 cancer cells.[6]

Another study was designed to examine the interaction of neratinib (NRB anticancer drug tyrosine kinase inhibitor used to treat breast cancer) with human serum albumin (HSA) in the presence of flavonoids QT and rutin. Both QT and rutin can compete with NRB to bind HSA and displace NRB from its binding site. The interaction mechanism was studied with various spectroscopic and molecular coupling techniques. According to the results of the thermodynamic parameters, the van der Waals force and the hydrogen bond were involved in the HSA-NRB interaction. Furthermore, conformational changes were observed in HSA in its interaction with NRB. NRB with HSA in the presence of QT and rutin resulted in changes in the binding constants of HSA-NRB, suggesting some impact on the binding of NRB in the presence of flavonoids.[7]

On the other hand, an approach was designed to explore the influence of QT on different molecular pathways involved in the evolution of breast cancer. The cytotoxic impact of QT on two breast cancer cell lines, MCF-7 and MDA-MB-231, was quantified by an MTT assay. The expression levels of the selected genes involved in apoptosis, proliferation, progression, invasion, and metastasis of breast cancer were analyzed by RT-PCR. Furthermore, molecular genetic analysis revealed that QT caused a significant down-regulation in the expression level of the survivin, STAT3, IL-6, VEGF, Slug, and MMP7 genes in both cell lines after hours. Meanwhile, MCF-7 exhibited negligible downregulation in the expression level of the Snail and Notch-4 genes after QT treatment. In MDA-MB-231 cells, QT caused negligible down-regulation at the level of expression of the Snail gene but significant down-regulation at the level of expression of the Notch-4 gene. In conclusion, this work provides a scientific clue that QT may fight breast cancer by modulating the consequent signal transduction pathways involved in the development of breast cancer.[8]

A systematic review was conducted focusing on the effects of QT in the human breast cancer cell lines MCF-7 and MDA-MB-231. Of 15 studies that examined the effects of QT on MDA-MB-231 cells, 14 reports showed successful apoptosis. It is concluded that QT could be beneficial in the elimination of breast cancer cells.[9]

The objective of this study was to investigate the chemical-quantum interactions of QT vs. the structural amino acids of HER-2.

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 and 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 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 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.[10-19]

The characterization of the HER2 proteins was carried out with the Model6000 designed and published by the principal author. The sequencing was taken from the NCBI website.[20]

RESULTS AND DISCUTIONS

In table 1, two sub-tables of this HER2 are presented; these differ very little. In both tables, the first column presents the AA numbers. In the second column, we can see the international abbreviations of AAs. In the third column, the abbreviations of the AAs are presented in a single letter. The fourth column shows us the three-letter abbreviation of AAs. The fifth column represents the number of AAs in HER2. The sixth column shows us the percentage of each AA. It is observed that both the AA in the highest quantity (Leu) and the AA in the smallest quantity (Trp) are the same in the two characterization tables.

Table 1: Characterization of two versions of HER2.

N	AA	AA	AA	Units	Percentage
1	a	A	Ala	81	6.61%
2	r	R	Arg	68	5.55%
3	n	N	Asn	41	3.34%
4	d	D	Asp	64	5.22%
5	c	C	Cys	58	4.73%
6	q	Q	Gln	60	4.89%
7	e	E	Glu	77	6.28%
8	g	G	Gly	97	7.91%
9	h	H	His	32	2.61%
10	i	I	Ile	44	3.59%
11	l	L	Leu	138	11.26%
12	k	K	Lys	39	3.18%
13	m	M	Met	22	1.79%
14	f	F	Phe	33	2.69%
15	p	P	Pro	105	8.56%
16	s	S	Ser	70	5.71%
17	t	T	Thr	66	5.38%
18	w	W	Trp	15	1.22%
19	y	Y	Tyr	35	2.85%
20	v	V	Val	81	6.61%
			Total	1226	100.00%

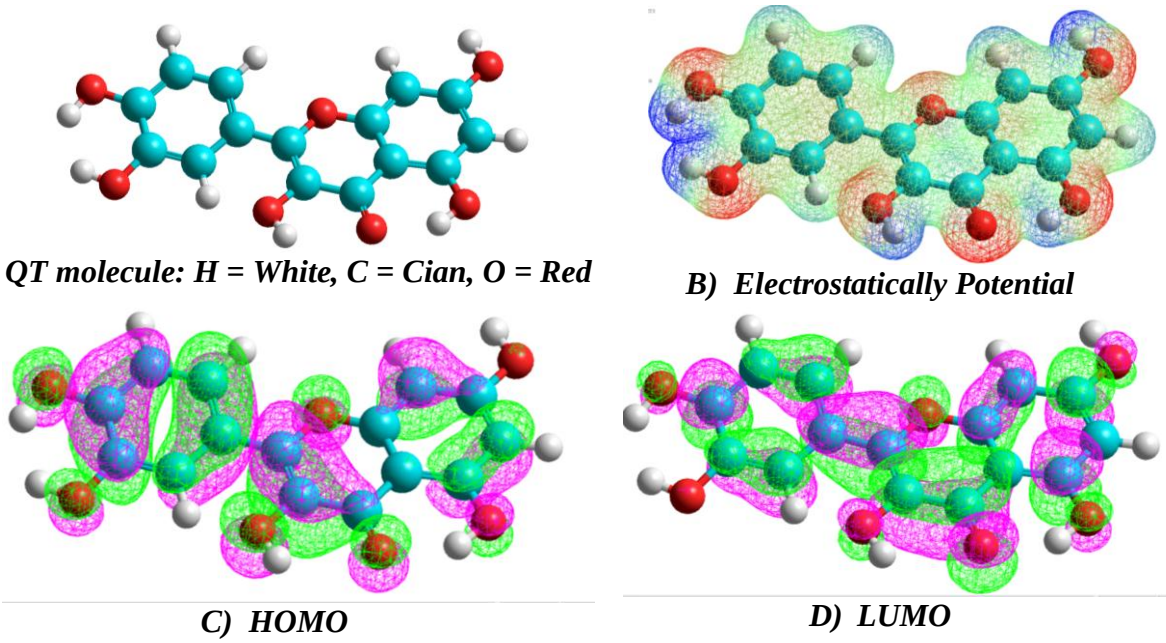
ORGANISM: Homo sapiens

N	AA	AA	AA	Units	Percentaje
1	a	A	Ala	83	6.62%
2	r	R	Arg	71	5.66%
3	n	N	Asn	41	3.27%
4	d	D	Asp	65	5.18%
5	c	C	Cys	59	4.70%
6	q	Q	Gln	62	4.94%
7	e	E	Glu	76	6.06%
8	g	G	Gly	101	8.05%
9	h	H	His	35	2.79%
10	i	I	Ile	44	3.51%
11	l	L	Leu	138	11.00%
12	k	K	Lys	39	3.11%
13	m	M	Met	23	1.83%
14	f	F	Phe	35	2.79%
15	p	P	Pro	109	8.69%
16	s	S	Ser	73	5.82%
17	t	T	Thr	67	5.34%
18	w	W	Trp	15	1.20%
19	y	Y	Tyr	35	2.79%
20	v	V	Val	83	6.62%
			Total	1254	100.00%

ORGANISM: Homo sapiens

Molecules and orbitals calculated with quantum chemistry are shown in Figure 1.

It is observed that both the HOMO and the LUMO occupy the same space. This observation means that the QT is grouped like grape bunches.



QT molecule: H = White, C = Cian, O = Red

B) Electrostatically Potential

C) HOMO

D) LUMO

Figure 1. QT molecules. Representation of quantum calculations.

Table 2 shows the molecular interactions of oxide-reduction of the substances in their pure state. Column one shows the ascending order of the quantum well. In column two, reducing agents are shown. In column three, oxidizing agents are shown. Columns four to six are shown the quantum calculations of the energies of HOMO and LUMO and their result, the forbidden band. Columns seven through nine-show electrostatic field calculations. Column ten shows the electron transfer coefficient between molecules (ETC).

A relevant observation is that QT is in the second place of the quantum well; on the other hand, arginine is in the first place of the quantum well. The difference means that arginine is more stable than QT but with a minimal difference. As published before, valine is the AA with minor stability.

Table 2: Of ordered AAs and substance. Quantum Well.

N	Reduzing agent	Oxidizing agent	HOMO	LUMO	BG	E-	E+	EP	ETC
21	Val	Val	-9.914	0.931	10.845	-0.131	0.109	0.240	45.188
20	Ala	Ala	-9.879	0.749	10.628	-0.124	0.132	0.256	41.515
19	Leu	Leu	-9.645	0.922	10.567	-0.126	0.130	0.256	41.279
18	Phe	Phe	-9.553	0.283	9.836	-0.126	0.127	0.253	38.879
17	Gly	Gly	-9.902	0.902	10.804	-0.137	0.159	0.296	36.500
16	Ser	Ser	-10.156	0.565	10.721	-0.108	0.198	0.306	35.037
15	Cys	Cys	-9.639	-0.236	9.403	-0.129	0.140	0.269	34.956
14	Glu	Glu	-10.374	0.438	10.812	-0.111	0.201	0.312	34.655
13	Ile	Ile	-9.872	0.972	10.844	-0.128	0.188	0.316	34.316
12	Thr	Thr	-9.896	0.832	10.728	-0.123	0.191	0.314	34.167

11	Gln	Gln	-10.023	0.755	10.778	-0.124	0.192	0.316	34.108
10	Asp	Asp	-10.370	0.420	10.790	-0.118	0.204	0.322	33.509
9	Asn	Asn	-9.929	0.644	10.573	-0.125	0.193	0.318	33.249
8	Lys	Lys	-9.521	0.943	10.463	-0.127	0.195	0.322	32.495
7	Pro	Pro	-9.447	0.792	10.238	-0.128	0.191	0.319	32.095
6	Trp	Trp	-8.299	0.133	8.431	-0.112	0.155	0.267	31.577
5	Tyr	Tyr	-9.056	0.293	9.349	-0.123	0.193	0.316	29.584
4	His	His	-9.307	0.503	9.811	-0.169	0.171	0.340	28.855
3	Met	Met	-9.062	0.145	9.207	-0.134	0.192	0.326	28.243
2	QT	QT	-8.573	-0.752	7.821	-0.084	0.206	0.290	26.968
1	Arg	Arg	-9.176	0.558	9.734	-0.165	0.199	0.364	26.742

Table 3 has an ordering equal to table 2. This table shows the oxide-reduction interactions of QT vs. the AA of HER2 proteins (61).

An important observation is that QT oxidizes all the AAs in HER2. Another observation is that QT attacks arginine with greater probability and strength, although the ETC value of histidine is very close to the value of arginine.

Table 3: Oxide-reduction interactions of HER2 AAs vs. QT.

N	Reduzing agent	Oxidizing agent	HOMO	LUMO	BG	E-	E+	EP	ETC
61	QT	Val	-8.573	0.931	9.504	-0.084	0.109	0.193	49.245
These interactions are skipped for space									
21	His	His	-9.307	0.503	9.811	-0.169	0.171	0.340	28.855
20	Met	Met	-9.062	0.145	9.207	-0.134	0.192	0.326	28.243
19	Gln	QT	-10.023	-0.752	9.271	-0.124	0.206	0.330	28.093
18	Thr	QT	-9.896	-0.752	9.144	-0.123	0.206	0.329	27.794
17	Asn	QT	-9.929	-0.752	9.177	-0.125	0.206	0.331	27.724
16	Ala	QT	-9.879	-0.752	9.126	-0.124	0.206	0.330	27.656
15	Ile	QT	-9.872	-0.752	9.120	-0.128	0.206	0.334	27.305
14	Val	QT	-9.914	-0.752	9.161	-0.131	0.206	0.337	27.185
13	QT	QT	-8.573	-0.752	7.821	-0.084	0.206	0.290	26.968
12	Leu	QT	-9.645	-0.752	8.893	-0.126	0.206	0.332	26.786
11	Arg	Arg	-9.176	0.558	9.734	-0.165	0.199	0.364	26.742
10	Gly	QT	-9.902	-0.752	9.150	-0.137	0.206	0.343	26.677
9	Cys	QT	-9.639	-0.752	8.886	-0.129	0.206	0.335	26.527
8	Phe	QT	-9.553	-0.752	8.801	-0.126	0.206	0.332	26.508
7	Lys	QT	-9.521	-0.752	8.768	-0.127	0.206	0.333	26.331
6	Pro	QT	-9.447	-0.752	8.694	-0.128	0.206	0.334	26.030
5	Tyr	QT	-9.056	-0.752	8.304	-0.123	0.206	0.329	25.239
4	Met	QT	-9.062	-0.752	8.310	-0.134	0.206	0.340	24.440
3	Trp	QT	-8.299	-0.752	7.546	-0.112	0.206	0.318	23.730
2	His	QT	-9.307	-0.752	8.555	-0.169	0.206	0.375	22.814
1	Arg	QT	-9.176	-0.752	8.424	-0.165	0.206	0.371	22.706
				First	*Quartile:*	*27.656*		*Average:*	*32.296*

All the possible interactions (461) that the QT will have with the AA that make up HER2 were analyzed. The results are shown in Table 4. It is observed that the oxidative character of the QT is maintained, despite the increase in interactions.

Table 4: Interactions of HER2 AAs vs. QT (all vs. all).

No.	Reduzing agent	Oxidizing agent	HOMO	LUMO	BG	E-	E+	EP	ETC
461	Glu	Val	-10.374	0.931	11.305	-0.111	0.109	0.220	51.388
These interactions are skipped for space									
27	Ile	QT	-9.872	-0.752	9.120	-0.128	0.206	0.334	27.305
26	Val	QT	-9.914	-0.752	9.161	-0.131	0.206	0.337	27.185
25	QT	QT	-8.573	-0.752	7.821	-0.084	0.206	0.290	26.968
24	His	Ser	-9.307	0.565	9.872	-0.169	0.198	0.367	26.900
23	Arg	Ser	-9.176	0.565	9.741	-0.165	0.198	0.363	26.835
22	His	Arg	-9.307	0.558	9.865	-0.169	0.199	0.368	26.808
21	Leu	QT	-9.645	-0.752	8.893	-0.126	0.206	0.332	26.786
20	Arg	Arg	-9.176	0.558	9.734	-0.165	0.199	0.364	26.742
19	Arg	Arg	-9.176	0.558	9.734	-0.165	0.199	0.364	26.742
18	Gly	QT	-9.902	-0.752	9.150	-0.137	0.206	0.343	26.677
17	Cys	QT	-9.639	-0.752	8.886	-0.129	0.206	0.335	26.527
16	His	Tyr	-9.307	0.293	9.600	-0.169	0.193	0.362	26.519
15	Phe	QT	-9.553	-0.752	8.801	-0.126	0.206	0.332	26.508
14	Arg	Tyr	-9.176	0.293	9.469	-0.165	0.193	0.358	26.449
13	His	Glu	-9.307	0.438	9.746	-0.169	0.201	0.370	26.340
12	Lys	QT	-9.521	-0.752	8.768	-0.127	0.206	0.333	26.331
11	Arg	Glu	-9.176	0.438	9.615	-0.165	0.201	0.366	26.269
10	His	Met	-9.307	0.145	9.453	-0.169	0.192	0.361	26.184
9	Arg	Met	-9.176	0.145	9.321	-0.165	0.192	0.357	26.110
8	His	Asp	-9.307	0.420	9.728	-0.169	0.204	0.373	26.079
7	Pro	QT	-9.447	-0.752	8.694	-0.128	0.206	0.334	26.030
6	Arg	Asp	-9.176	0.420	9.596	-0.165	0.204	0.369	26.006
5	Tyr	QT	-9.056	-0.752	8.304	-0.123	0.206	0.329	25.239
4	Met	QT	-9.062	-0.752	8.310	-0.134	0.206	0.340	24.440
3	Trp	QT	-8.299	-0.752	7.546	-0.112	0.206	0.318	23.730
2	His	QT	-9.307	-0.752	8.555	-0.169	0.206	0.375	22.814
1	Arg	QT	-9.176	-0.752	8.424	-0.165	0.206	0.371	22.706
				First	*Cuartile:*	*31.101*		*Average:*	*34.117*

CONCLUSIONS

We did

- The characterization of HER2.
- Three calculations of the ETCs: a) pure substances (21), 20 AA of the structure HER2 and QT, b) oxidation-reduction interactions (61) of the same substances, and c) all possible interactions of AA and QT (461).

- Table 5 shows 400 of the possible interactions of the 20 AAs that make up the HER2 structure of this in silico experiment. These 400 interactions were carried out in the presence of the QT.
- 97% of the interactions of the AAs that make up the HER2 proteins are unstable in the presence of QT.

Table 5. Summary.

	QT		AAs
Interactions	**Amount**	**%**	**Interacciones**
Stables	388	97.00%	Unstables
Unstables	12	3.00%	Stables
Total	400	100.00%	

We found

- The Leu is in greater abundance in the two HER2 AA sequences.
- The Trp is minor AA in HER2 AA sequencing.
- A relevant observation is that QT is in the second place of the quantum well as a pure substance.
- Arginine is in the first place of the quantum well.
- The difference means that arginine is more stable than QT but with a tiny difference.
- Valine is the AA with minor stability.
- An important observation is that QT oxidizes all the AAs in HER2.
- Another observation is that QT attacks arginine with greater probability and strength.
- The ETC value of histidine is very close to the value of arginine.
- It is observed that the oxidative character of the QT is maintained, despite the increase in interactions all against all AA and QT.

As a general conclusion, QT can oxidize all AAs of HER2. We will prepare some anticancer dishes and drinks, such as salads, stews.

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