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CHEMICAL-QUANTUM ANALYSIS OF THE BIOLOGICAL ACTIVITY OF BIOACTIVE DIPEPTIDS FOR THE POSSIBLE TREATMENT OF DIABETES

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ABSTRACT

Currently, public health problems in developed countries are focused on the aging of the population and the increase in the prevalence of certain chronic diseases. Chronic diseases have been overtaken by noncommunicable diseases "typical lifestyle diseases"; such as high blood pressure, obesity, or diabetes. The objective of this work was to analyze the chemical-quantum interactions of glucose with each of the amino acids (AA) that makeup insulin. The Hyperchem simulator was used to perform quantum calculations. These calculations are based on the theory of the electron transfer coefficient (ETC) published in other articles. We found that Arginine and Histidine adhere more easily to glucose. It is probable that these AAs and their dipeptides act positively in the treatment of diabetes as growth adjuvants for the maintenance of muscle tissue since they adhere to the active site of insulin, preventing glucose from increasing. We concluded that: A) Arginine and histidine have the lowest ETC of all interactions of the AAs that make up insulin. For this reason, these two AAs determine the active site of insulin for glucose. B) The dipeptides derived from arginine and histidine (approximately 40) are related to the active site of insulin. These dipeptides have the potential to help cells use glucose as an energy source and decrease hyperglycemia in diabetes.

KEYWORDS: Bioactive Dipeptides, Diabetes, Biological activity, Quantum chemistry, Arginine.

INTRODUCTION

Currently, public health problems in developed countries are focused on the aging of the population and the increase in the prevalence of certain chronic diseases.[1] Chronic diseases have been overtaken by noncommunicable diseases "typical lifestyle diseases"; such as high blood pressure, obesity, or diabetes mellitus type-2 (DM-2).[2]

Among the measures to be taken to deal with these diseases are functional foods that help reduce the risk of pathologies and maintain good health. In this sense, useful products with biologically active peptides are available in the market. The type and amount of administration of the peptides depend on the protein source used, as well as the degree and kind of hydrolysis used.[1]

Human beings consume certain daily foods that, to a greater or lesser extent, contain macronutrients (MNM) such as carbohydrates, lipids, proteins. Among these MNM are food proteins (PA), which consist of AA sequences and bioactive peptides. These PAs have beneficial effects with the potential to influence health and help reduce the risk of certain chronic diseases.[3]

Bioactive dipeptides

A bioactive component of food provides a physiological health benefit. The bioactive components are found in small amounts in products of vegetable origin and foods rich in lipids. When a bioactive part is ingested; This can provide physiological benefits, such as a) the reduction of the risk of cardiovascular diseases, b) the modulation of tumor growth, c) the decline of the level of sugar in the blood. Most of these bioactive compounds are found to be part of the native polypeptide sequence within food proteins. When these compounds are inserted in the protein chain, they do not present physiological activity. On the other hand, with the release by enzymatic or chemical hydrolysis, the free peptides become physiologically active (bioactive) and can be used as ingredients to formulate therapeutic foods.[4]

What is the diabetes?

Diabetes is a disease in which the body can not produce or respond adequately to the hormone insulin. The body needs insulin to convert glucose into energy, and due to this disease, the non-organism appropriately uses the power of the food consumed. When this energy transfer does not occur, the cells are damaged. Moreover, it can not assimilate glucose, which causes hyperglycemia.[5]

There are mainly two types of diabetes that are the best known:

Type 1 diabetes, which is characterized by the presence of high concentrations of blood glucose (hyperglycemia). There is an alteration or absence of insulin. Within diabetes mellitus type 1, two basic types are distinguished: diabetes mellitus type 1a of autoimmune origin and diabetes mellitus type 1b of idiopathic character. In autoimmune diabetes (1a), the insulin-producing cells (beta cells of the pancreas) are attacked and destroyed, because the lack of insulin means that the metabolism of carbohydrates, fats and proteins cannot be correctly carried out. On the other hand, idiopathic diabetes (1b) refers to the disease with no known cause.[6]

Type 2 Diabetes: This is the most common type of diabetes; it is diagnosed mostly in people over 20 years. Insulin is produced in type 2 diabetes, but it is not enough, or the body does not use it properly.[5] There is a pancreatic failure in which non-functional insulin is produced, and this causes the cells to absorb less glucose and glucose to accumulate in the blood. The concentration of sugar in the blood can be controlled with diet and exercise. When type 2 diabetes is mild, it can go unnoticed for many years, but if the disease is not treated for a long time, it can lead to serious medical problems such as diseases of the heart and blood vessels.[7-9]

MATERIALS AND METHODS

The Hyperchem simulator was used to perform quantum calculations. These calculations are based on the theory of the electron transfer coefficient (ETC) published in other articles. The same author has already announced the database. In this database, it shows the ETC of twenty AA.[10-17]

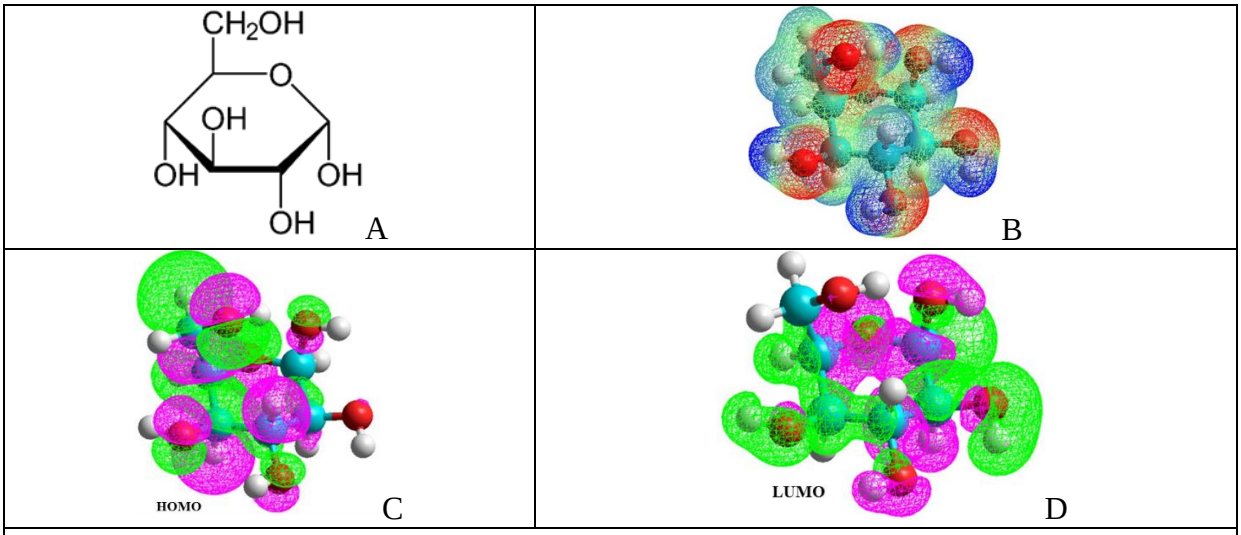

Figure 1: Glucose molecule. A) Haworth shape, B) Simulated shape: Electrostatic potential, C) Simulated molecular: HOMO, D) Simulated molecular: LUMO.

RESULTS AND DISCUSSION

This table shows the calculations of the ETCs (electronic impedances) ordered from highest to lowest. Each ETC represents a level in a general quantum well.

Observation 1. Interactions 40 and 41 are the strongest because they have the smallest ETCs, that is, they have less impedance to interact. Therefore, Arginine and Histidine adhere more easily to glucose. It is probable that these AAs and their dipeptides act positively in the treatment of Diabetes as growth adjuvants for the maintenance of muscle tissue since they adhere to the active site of insulin, preventing glucose from increasing. If there is no insulin or does not work correctly, the epithelial tissues also have histidine and arginine; these will stick and will cause muscle tissue damage.

Table 1: Interactions of the GLU vs. AA measures of ETCs crossbands.

No.	Reducing Agent	Oxidicing Agent	HOMO	LUMO	BG	E-	E+	EP	ETC
1	GLU	Val	-11.020	0.931	11.951	-0.116	0.109	0.225	53.117
2	GLU	Leu	-11.020	0.922	11.942	-0.116	0.130	0.246	48.545
3	GLU	Ala	-11.020	0.749	11.769	-0.116	0.132	0.248	47.456
4	GLU	Phe	-11.020	0.283	11.303	-0.116	0.127	0.243	46.516
5	**GLU**	**GLU**	**-11.020**	**2.128**	**13.148**	**-0.116**	**0.169**	**0.285**	**46.135**
6	Glu	GLU	-10.374	2.128	12.503	-0.111	0.169	0.280	44.652
7	Ser	GLU	-10.156	2.128	12.285	-0.108	0.169	0.277	44.350
8	Asp	GLU	-10.370	2.128	12.498	-0.118	0.169	0.287	43.548
9	GLU	Gly	-11.020	0.902	11.922	-0.116	0.159	0.275	43.351
10	GLU	Cys	-11.020	-0.236	10.784	-0.116	0.140	0.256	42.127
11	Gln	GLU	-10.023	2.128	12.152	-0.124	0.169	0.293	41.473

12	Thr	GLU	-9.896	2.128	12.025	-0.123	0.169	0.292	41.181
13	GLU	Trp	-11.020	0.133	11.153	-0.116	0.155	0.271	41.154
14	Asn	GLU	-9.929	2.128	12.058	-0.125	0.169	0.294	41.012
15	Ala	GLU	-9.879	2.128	12.007	-0.124	0.169	0.293	40.980
16	Ile	GLU	-9.872	2.128	12.001	-0.128	0.169	0.297	40.406
17	GLU	His	-11.020	0.503	11.523	-0.116	0.171	0.287	40.150
18	Val	GLU	-9.914	2.128	12.042	-0.131	0.169	0.300	40.141
19	Leu	GLU	-9.645	2.128	11.774	-0.126	0.169	0.295	39.911
20	Phe	GLU	-9.553	2.128	11.681	-0.126	0.169	0.295	39.598
21	Cys	GLU	-9.639	2.128	11.767	-0.129	0.169	0.298	39.487
22	GLU	Ile	-11.020	0.972	11.992	-0.116	0.188	0.304	39.446
23	Lys	GLU	-9.521	2.128	11.649	-0.127	0.169	0.296	39.355
24	Gly	GLU	-9.902	2.128	12.031	-0.137	0.169	0.306	39.317
25	Pro	GLU	-9.447	2.128	11.575	-0.128	0.169	0.297	38.973
26	GLU	Thr	-11.020	0.832	11.852	-0.116	0.191	0.307	38.606
27	GLU	Pro	-11.020	0.792	11.812	-0.116	0.191	0.307	38.476
28	GLU	Lys	-11.020	0.943	11.963	-0.116	0.195	0.311	38.465
29	Tyr	GLU	-9.056	2.128	11.184	-0.123	0.169	0.292	38.303
30	GLU	Gln	-11.020	0.755	11.775	-0.116	0.192	0.308	38.230
31	GLU	Asn	-11.020	0.644	11.664	-0.116	0.193	0.309	37.748
32	Trp	GLU	-8.299	2.128	10.427	-0.112	0.169	0.281	37.107
33	Met	GLU	-9.062	2.128	11.190	-0.134	0.169	0.303	36.932
34	GLU	Ser	-11.020	0.565	11.585	-0.116	0.198	0.314	36.894
35	GLU	Arg	-11.020	0.558	11.578	-0.116	0.199	0.315	36.755
36	GLU	Tyr	-11.020	0.293	11.313	-0.116	0.193	0.309	36.610
37	GLU	Met	-11.020	0.145	11.165	-0.116	0.192	0.308	36.250
38	GLU	Glu	-11.020	0.438	11.458	-0.116	0.201	0.317	36.146
39	GLU	Asp	-11.020	0.420	11.440	-0.116	0.204	0.320	35.750
40	Arg	GLU	-9.176	2.128	11.305	-0.165	0.169	0.334	33.846
41	His	GLU	-9.307	2.128	11.436	-0.169	0.169	0.338	33.834

Glucose oxidizes both histidine and arginine and blocks them.

According to doctors, antioxidation has beneficial effects on the body. The interactions between glucose and AAs from 35 to 40 are antioxidants, which nature prefers is number 40 (arginine) as it can be blocked or not blocked, in other words, antioxidant or oxidant.

Glucose is an energy molecule that can act on any AA. According to the order of the AAs presented in the table, they determine the interaction between them, the higher an AA is located, the lower the probability of interaction and vice versa.

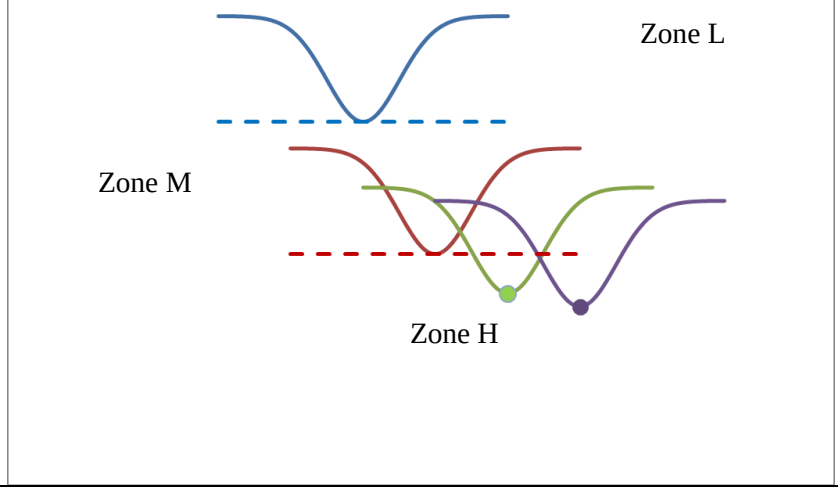

Figure 2: Graphical representation of the quantum wells of two substances in crossed bands HOMO-LUMO.

Observation 2. The dotted lines represent the pure substances because they are the ones that weaken the interactions. The purple dots represent the oxidized agent; the glucose is oxidizing. If red is below the green, the substance is behaving like an oxidant. Below the dotted red line is the most likely area. From the red wire to the blue dotted line is of medium probability. Above the blue is a low probability of interaction. If both are below the red line, it means that both have a high likelihood of oxidizing or reducing (oxidizing agent or antioxidant).

The green curve represents reduction; glucose is reducing the function of arginine; what happens is that glucose is blocking.

With quantum calculations, we find that glucose blocks arginine, one of its primary functions is to be an energy molecule of the body through different mechanisms that trigger in the body. Arginine is an AA that, when it comes into contact with the oxide-synthetase enzyme that it secretes in the body, becomes nitric oxide inside our body. It is, therefore, a direct generator of body nitric oxide that has various vasodilator functions, thus improving blood circulation and increasing the risk of all parts of our biological system. However, it is remarkable the importance of the secretion of several essential hormones for body and muscle growth, such as glucagon, insulin, and growth hormone.

It can be proven that a person with diabetes cannot be cut because he has an arginine block. Also, that does not allow proper healing, since arginine has other beneficial functions for the

body as a healing function, since with the improvement of blood flow also helps to heal wounds and injuries.

Histidine is found in a dipeptide called carnosine, which is contained in veal, pork, and chicken, and is sold extracted; it is worth mentioning that it is not sold in the Mexican Republic.

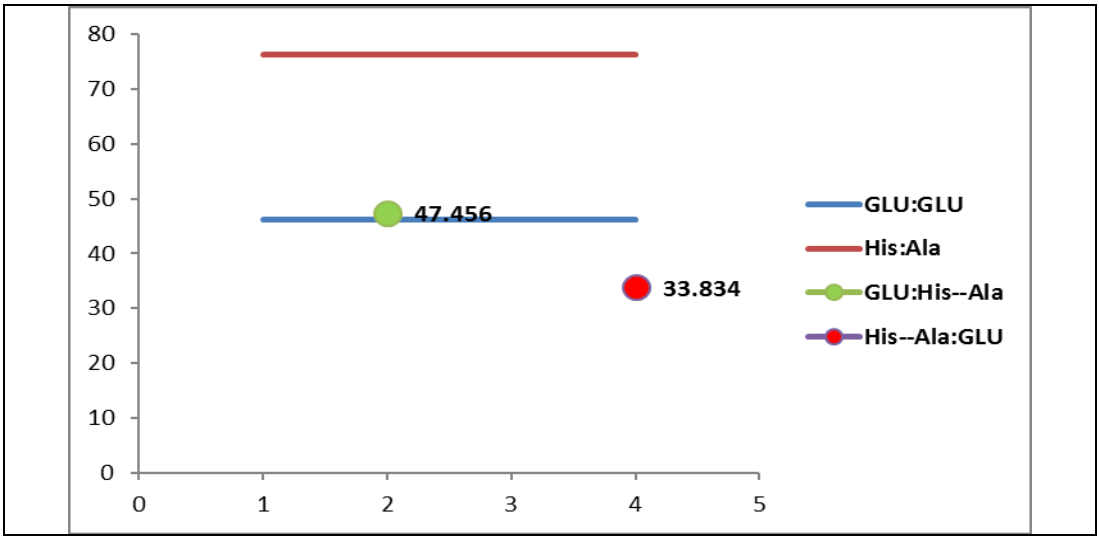

Figure 3: Quantum well representing the interaction of the dipeptide Carnosine (Histidine-Alanine) vs. glucose.

Observation 3. Figure 3 determines the interaction of AA (400 amino acids) with glucose.

The lower the red dot of the green indicates the greater oxidation. As a particular case, the quantum well of the interaction of carnosine vs. glucose.

Of the 400 dipeptides interactions with glucose, 169 are oxidized by it, giving a percentage of 42.25%.

This thing means that glucose will react with the AAs affecting the tissues that make them up. A clear example is diabetics, they have high glucose, and the muscles that make up your body are affected.

For these glucose levels to remain stable, functional dipeptides can be administered to avoid hyperglycemia.

In general, all dipeptides formed with histidine and with arginine have a substantial potential for the treatment of diabetes.

Observation 4. This table determines the percentage of components that insulin has. Insulin has 18 leucines that represent 12.33% of its parts. Isoleucine is the AA most frequently in insulin. Only 33% of insulin does not have isoleucine. The AAs of lesser presence are tryptophan and cysteine.

Diabetes is constituted by a group of metabolic disorders that is characterized mainly by a high level of glucose in the blood, known as hyperglycemia; the causes are a deficiency in the secretion of insulin or a failure in the cells, which is known as Insulin resistance. This alteration causes an alteration in the metabolism of nutrients (carbohydrates, proteins, and lipids). Studies have concluded that the complications of diabetes such as retinopathies, kidney, bone diseases, among others, are caused by the excessive production of free radicals. Free Radicals cause oxidative damage to biomolecules, and this cannot be counteracted with the defense's antioxidants. However, exogenous antioxidants are intended to reduce the consequences caused by RL.

Table 2: Determination of insulin components. Data were taken from NCBI.

				Units	Percentage
1	a	A	Ala	15	10.27%
2	r	R	Arg	4	2.74%
3	n	N	Asn	8	5.48%
4	d	D	Asp	7	4.79%
5	c	C	Cys	2	1.37%
6	q	Q	Gln	5	3.42%
7	e	E	Glu	7	4.79%
8	g	G	Gly	13	8.90%
9	h	H	His	7	4.79%
10	i	I	Ile	0	0.00%
11	l	L	Leu	18	12.33%
12	k	K	Lys	11	7.53%
13	m	M	Met	2	1.37%
14	f	F	Phe	8	5.48%
15	p	P	Pro	6	4.11%
16	s	S	Ser	6	4.11%
17	t	T	Thr	5	3.42%
18	w	W	Trp	2	1.37%
19	y	Y	Tyr	3	2.05%
20	v	V	Val	17	11.64%
			Total	146	100.00%

LOCUS AAA59172 110 aa linear PRI 10-JUN-2016
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KEYWORDS .
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ORGANISM Homo sapiens

It has been shown that arginine can have beneficial effects on insulin resistance in patients with type 2 diabetes mellitus. The beneficial effect of arginine on insulin resistance could be related to the increase in adiponectin, which is a hormone that It is synthesized by adipose tissue, which participates in the metabolism of Glucose, which is why it is thought that arginine helps contribute to the regulation of Insulin sensitivity. Because of this, arginine is beneficial both for insulin resistance and for leveling adiponectin levels.

CONCLUSIONS

We found that

1. Arginine and histidine have the lowest ETC of all interactions of the AAs that make up insulin. For this reason, it is concluded that these two AAs determine the active site of insulin for glucose.
2. The dipeptides derived from arginine and histidine (approximately 40) are related to the active site of insulin. These dipeptides have the potential to help cells use glucose as an energy source and decrease hyperglycemia in Diabetes Mellitus (Table 2).

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