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ANALYSIS OF CAFFEINE AND ITS INTERACTION WITH THE SLEEP HORMONE (MELATONIN), APPLYING QUANTUM CHEMISTRY

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ABSTRACT

Caffeine (CFI) is an alkaloid from the xanthine group that acts as a stimulant and psychoactive substance. This substance is found naturally in various species of plants. The primary sources of CFI are coffee, tea, guarana, yerba mate, and cocoa. Our objective in this research was to analyze caffeine and its interaction with the sleep hormone Melatonin (MLT), applying quantum chemistry. Hyperchem software was used as a quantum chemistry simulator. The fundamental basis of quantum calculations was the Electron Transfer Coefficient (ETC) theory. We calculated the Electrostatic Potential (EP) and used the Plot Molecular Graph method in three dimensions. Finally, the ETC was calculated by dividing the Bandgap (Bg) by the EP. The result of the HOMO and LUMO data for CFI and MLT, the ETC is slightly lower when CFI acts as an oxidant. With this, we can confirm that CFI oxidizes MLT as it competes with it. This fact confirms that CFI blocks MLT production. Another significant result is that the ETC is lower when CFI acts as an antioxidant or reducer; with this, we confirm that CFI is an excellent antioxidant of adrenaline. In conclusion, we can say that CFI oxidizes MLT, while it is an excellent antioxidant for adrenaline. Our results coincide with the behavior of patients who ingest CFI daily.

KEYWORD: Caffeine, melatonin, adrenaline, neurotransmitters, quantum chemistry.

INTRODUCTION

Caffeine

CFI is an alkaloid from the xanthine group that acts as a stimulant and psychoactive substance. This substance is found naturally in various plant species. The IFC's primary sources are coffee, tea, guarana, mate, and cocoa. The cytochrome P450 (CYP) 1A2 enzyme primarily metabolizes CFI in the liver. This metabolism explains interindividual variations in the effects of CFI and is affected by genetic and environmental factors.[1]

CFI is a competitive antagonist of adenosine receptors in the central nervous system. This substance produces psychostimulant, respiratory, musculoskeletal, and cardiovascular effects. Although the therapeutic use of this substance has been studied, the results have yet to be conclusive.[2,3]

Acute or chronic consumption of this substance can lead to a wide variety of adverse effects, poisoning, and even death. Furthermore, CFI can be considered a drug of abuse and has favorable reinforcing properties; when its consumption is stopped, a specific withdrawal syndrome appears.[3]

CFI is a complex substance that can be considered a drug, a nutrient, and a drug of abuse, depending on its use and individual circumstances. It is essential to understand this substance's mechanisms of action and effects for responsible and safe consumption.[3]

Regarding tolerance, it is said that the central nervous system does not seem to develop an excellent tolerance to the effects of CFI; However, dependence and withdrawal symptoms associated with chronic consumption of this substance have been reported.[4]

Some scientists have examined the literature for evidence on the effects of CFI and coffee on energy intake, gastric emptying, appetite-related hormones, and appetite perceptions. However, the results have been equivocal, and the influence of factors such as the genetics of this substance's metabolism and the bitter taste phenotype is unknown. Longer controlled studies are needed to clarify these effects.[5] The main motivations for increasing CFI consumption are improving concentration, memory, and physical performance.

Other scientists have analyzed the mechanisms of action of CFI, focusing on adenosine antagonism, intracellular calcium mobilization, and inhibition of phosphodiesterases. On the other hand, some researchers have studied the use, abuse, dependence, intoxication, and lethal effects of CFI. These concepts of toxic and lethal doses are relative. Doses of this substance below the toxic and lethal range may play a causal role in poisoning or death.[6]

CFI and the effect it has on the MLT

MLT is the primary hormone responsible for regulating the sleep-wake cycle. The secretion of this hormone is controlled by neurotransmitters that can be affected by CFI. One study showed that drinking coffee with CFI, compared to decaffeinated coffee, caused.

• A decrease in the total quantity and quality of sleep
• An increase in the time needed to fall asleep
• A decrease in nocturnal excretion of 6-sulfatoxymelatonin (6-SMT), the major metabolite of MLT.

These results confirm that coffee consumption with CFI interferes with the quantity and quality of sleep. The consumption of CFI decreases MLT levels. Therefore, it is crucial for individuals, especially those who suffer from sleep disorders, to be informed and empowered to avoid consuming this substance, especially close to bedtime.[7]

Some animal studies have investigated the effects of the interaction between MLT and CFI. CFI and cyclic nucleotides block MLT signaling to mitochondria through mechanisms independent of adenosine receptor antagonism.

The interaction of the MLT and the CFI can.

• Improve protein synthesis
• Stimulate the release of gonadotropins, which could be used as an oral contraceptive for women
• Be beneficial for the treatment of erectile dysfunction
• Stimulate tryptophan metabolism, preventing vitamin B6 deficiencies, anemia, etc.
• Be beneficial for the treatment of hypercholesterolemia and postmenopausal osteoporosis.[8]

CFI and its use for the treatment of Alzheimer's disease

Alzheimer's disease (AD) is the most common type of dementia, with approximately 135 million cases expected worldwide by 2050. Current medications for the treatment of AD can

only relieve symptoms but do not act as disease-modifying agents. the disease that can stop the course of AD. Several clinical studies suggest that drinking coffee can benefit health, especially in the fight against neurodegenerative diseases such as AD.[9, 10]

Based on in vivo and in vitro studies, there is strong evidence that CFI has neuroprotective properties in animal models of AD (21 of 22 studies support this).[11]

According to Merighi, S. et al. (2023), this review provides a summary of the scientific data supporting the critical role that A2A adenosine receptors (A2AR) play in memory loss and cognitive decline, as well as the evidence that supports the protective benefits against neurodegeneration that can be achieved through the antagonistic action of CFI on these receptors.[10]

CFI elicits most of its biological effects by antagonizing all types of adenosine receptors, including A2ARs.

Interaction of CFI with neurotransmitters

CFI plays a crucial role in modulating various neurotransmitter systems in the brain, thereby contributing significantly to the observed neurobehavioral effects.

Interaction with the dopaminergic system

CFI interacts with the dopaminergic system in several ways:

CFI blocks adenosine receptors, leading to increased dopaminergic activity.[12, 13]

CFI induces beneficial effects in animal models of disorders such as depression and attention-deficit/hyperactivity disorder (ADHD), in part by modulating the dopaminergic system.[14]

Studies have found that CFI exhibits neuroprotective effects in animal models by protecting dopaminergic neurons.[14]

Interaction with the glutamatergic system

Glutamatergic receptors are involved in the neurobiological effects of CFI.[14]

Interaction with the GABAergic system.

CFI has been shown to suppress inhibitory (GABAergic) activity and modulate GABA receptors.[15, 16]

Modulation of these neurotransmitter systems by CFI leads to neurobehavioral effects.[17]

CFI and its relationship with quantum chemistry

In a study by Jeliński T. et al. (2022), it is noted that the solubility of CFI in aqueous binary mixtures was measured in five aprotic proton acceptor solvents (APAS), including dimethyl sulfoxide, dimethylformamide, 1,4-dioxane, acetonitrile, and acetone. The results were

interpreted based on the values of CFI's affinities toward the formation of homo- and heteromolecular pairs, determined at an advanced level of quantum chemistry that includes electronic correlation and zero-point vibrational energy correction. It was found that CFI can act as a donor in pair formation with all considered aprotic solvents using the hydrogen atom attached to the carbon in the imidazole ring.[18]

MLT

The sleep hormone is an indoleamine known mainly for synchronizing the circadian rhythm. However, it has other essential actions, such as antioxidants and anti-inflammatory agents, which give it great potential in treating and preventing numerous diseases, especially chronic diseases. Neurodegenerative diseases such as AD.[19]

MLT is the primary hormone involved in regulating the sleep-wake cycle. It is easily synthesized and administered orally, which has led to interest in using it in the treatment of insomnia, one of the most prevalent human pathologies. MLT is produced in numerous organs and tissues in addition to the pineal gland and regulates not only the sleep/wake cycle but also other circadian and seasonal rhythms, also acting as an immunostimulant and cytoprotective agent.[20, 21]

The characterization of MLT in 1958 and the identification of its synthesis made it possible to describe its photoperiodic regulation and its relationship with biological rhythms, among others, the sleep/wake rhythm.[21]

This hormone is an effective chronobiotic in the treatment of chronobiological alterations in the sleep/wake cycle.

Synthetic drugs derived from MLT represent an attractive therapeutic tool from a pharmacokinetic point of view for treating these alterations.[21]

The decrease in daily MLT levels that occurs with age and in neuropsychiatric disorders is associated with alterations in the sleep-wake cycle, indicating its role as a chronobiotic.[22]

Effects of the MLT-CFI interaction

CFI can increase or decrease MLT levels in the body. When taken along with MLT supplements, CFI appears to block MLT signaling.[23]

Several studies have shown that consumption of coffee with CFI, compared to decaffeinated coffee, causes a decrease in the total quantity and quality of sleep, an increase in the time needed to fall asleep, and a decrease in nocturnal excretion of 6-sulfatoxymelatonin (6-SMT), the primary metabolite of MLT. This study is because CFI blocks adenosine receptors, a neurochemical that helps regulate sleep, and affects the production of MLT, the hormone that controls the sleep-wake cycle.[24, 25]

CFI and cyclic nucleotides block MLT signaling to mitochondria through mechanisms independent of adenosine receptor antagonism.[26]

The interaction of MLT and CFI can improve protein synthesis, stimulate the release of gonadotropins, be beneficial for the treatment of erectile dysfunction, stimulate tryptophan metabolism, and be beneficial for the treatment of hypercholesterolemia and postmenopausal osteoporosis. However, these effects have primarily been observed in animal studies, and more research is needed to understand the interactions between MLT and CFI in humans fully.[27, 28]

The sleep hormone and its relationship with quantum chemistry

The sleep hormone has an exciting relationship with quantum chemistry, although it is not fully understood.

The pineal gland, which produces MLT, contains calcite crystals that may have piezoelectric and quantum properties.[29]

Some researchers speculate that activation of the pineal gland through MLT could lead to transcendent experiences and maximize creative potential.[30]

According to quantum physics theories, MLT could affect consciousness and perception, such as making colors heard and music seen. However, scientific evidence on these quantum effects of MLT is minimal. Most studies are speculative or have been done on animals.[30, 31]

MLT does have proven biological effects, such as regulating the sleep-wake cycle, having antioxidant properties, and modulating the immune system. These effects are better explained by classical biochemistry than by quantum mechanics.[31]

Quantum chemistry

The area of computational quantum chemistry, which applies the principles of quantum mechanics to molecular and condensate systems, has developed dramatically in recent decades, largely due to the significant increase in computing power. This, coupled with the

efficient implementation of quantum chemical methods in programs, has brought this field within the reach of readily available computer systems.

This mechanism has allowed precise computational techniques to be applied to much larger systems than before, placing the area of biochemistry within the reach of quantum chemical methods of electronic structure.[32]

MATERIAL AND METHODS

Hyperchem software was used as a quantum chemistry simulator. The fundamental basis of quantum calculations was the ETC theory. In tables 1-2. The parameters used in this simulation are specified.

To calculate the electrostatic potential (EP), the Plot Molecular Graph method in three dimensions was used.

Finally, the ETC was calculated by dividing the bandgap by the EP.

Because there are too many calculations, only the tables, reduction-oxidation plots are presented in this article. If you would like more information, please contact Dr. Manuel González Pérez.

Table 1. Parameters used for quantum computing molecular orbitals-HOMO and LUMO

Parameter	Value	Parameter	Value
Total charge	0	Polarizability	Not
Spin Multiplicity	1	Geometry Optimization algorithm	Polak-Ribiere (Conjugate Gradient)
Spin Pairing	RHF	Termination condition RMS gradeint of	0.1 Kcal/Amol
State Lowest Convergent Limit	0.01	Termination condition or	1000 maximum cycles
Interaction Limit	50	Termination condition or	In vacuo
Accelerate Convergence	Yes	Screen refresh period	1 cycle

Table 2. Parameters used for visualizing the map of the electrostatic potential of the molecules

Parameter	Value	Parameter	Value
Molecular Property	Property Electrostatic Potential	Contour Grid increment	0.05
Representation	3D Mapped Isosurface	Mapped Function Options	Default
Isosurface Grid: Grid Mesh Size	Coarse	Transparency level	A criteria
Isosurface Grid: Grid Layout	Default	Isosurface Rendering: Total charge density contour value.	0.015
Contour Grid: Starting Value	Default	Rendering Wire Mesh	

Interpretation of the quantum well

Fig. 1 presents the quantum well of interactions through its ETC. On the left side are shown the antioxidant or reducing interactions, and on the right side are the oxidative interactions.

This well is divided into four quadrants, ordered from lowest to highest, from bottom to top. Interactions deeper in the well have a greater chemical affinity and probability of occurring.

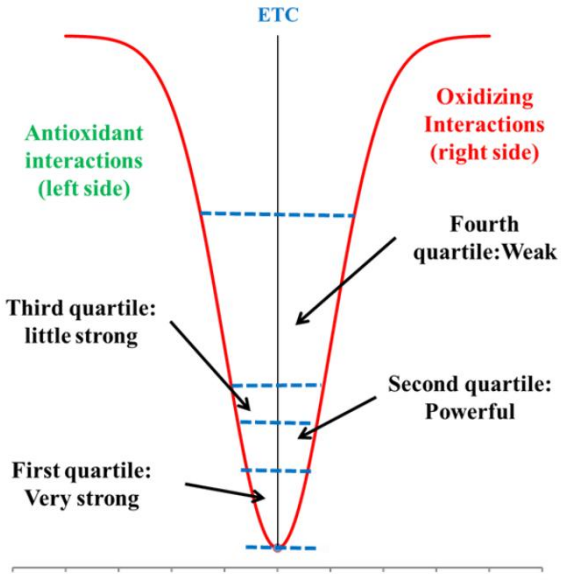
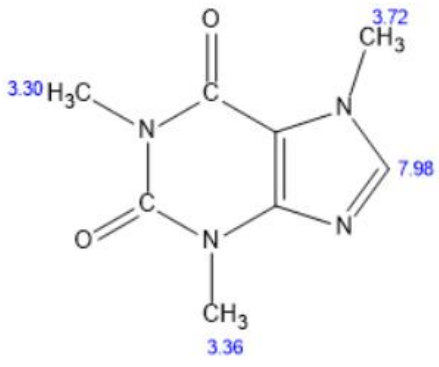


Fig. 1: Quantum well. Interpretation of interactions in the four statistical quadrants.

RESULTS AND DISCUSSIONS

Classic characterization

Fig. 2 and 3 show the results of the simulated characterization of Nuclear Magnetic Resonance H and the scientific name according to the UIPAC of CFI.



1,3,7-trimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione

Fig. 2: IUPAC scientific name and Nuclear Magnetic Resonance of H^1, with its quantized protons.

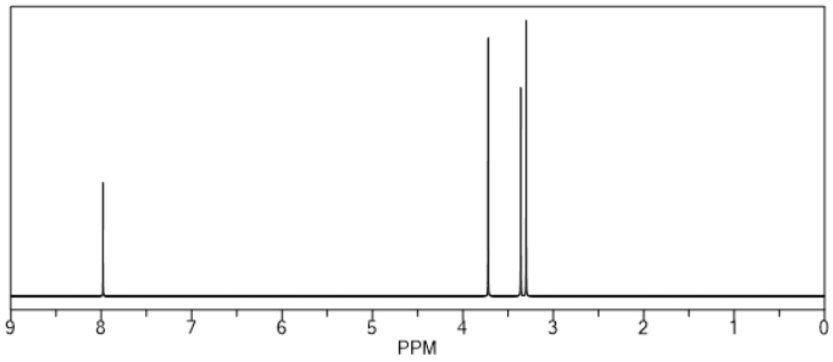
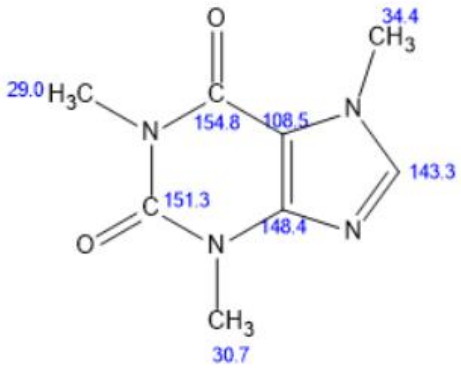


Fig. 3: Proton H^1 multiplicity diagram.

Fig. 4 and 5 show the results of the simulated characterization of C13 Nuclear Magnetic Resonance and the scientific name according to the UIPAC of CFI.



1,3,7-trimethyl-1*H*-purine-2,6(3*H*,7*H*)-dione

Fig. 4: C13 nuclear magnetic resonance. The molecule is shown with its quantification.

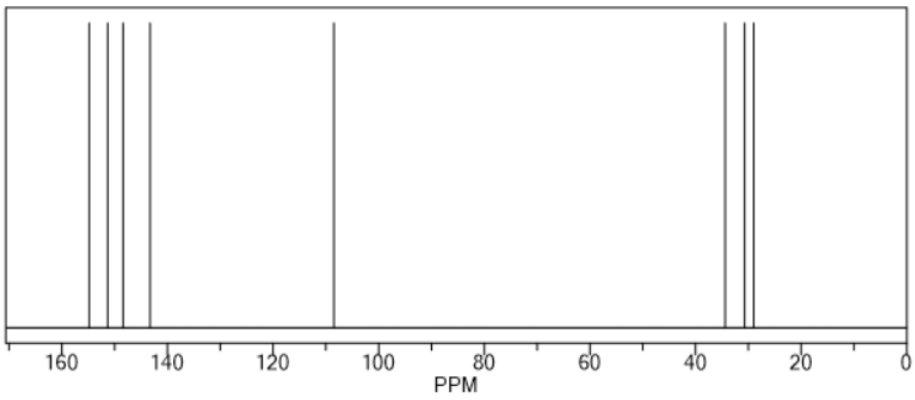
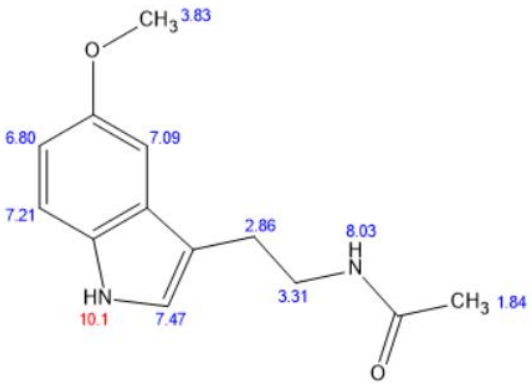


Fig. 5: Carbon multiplicity diagram.

Fig. 6 and 7 show the results of the simulated characterization of Nuclear Magnetic Resonance H and its scientific name according to MLT's UIPAC.



N-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)acetamide

Fig. 6: IUPAC scientific name and Nuclear Magnetic Resonance of H, with its quantified protons.

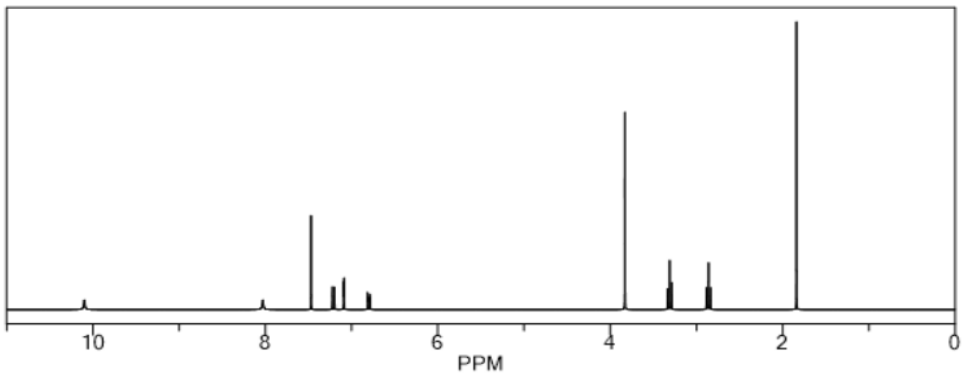
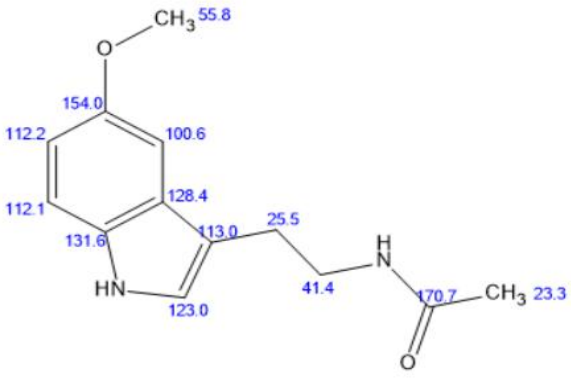


Fig. 7: Proton multiplicity diagram.

Fig. 8 and 9 show the results of the simulated characterization of C13 Nuclear Magnetic Resonance and its scientific name according to MLT's UIPAC.



N-(2-(5-methoxy-1*H*-indol-3-yl)ethyl)acetamide

Fig. 8. C13 nuclear magnetic resonance. The molecule is shown with its quantification.

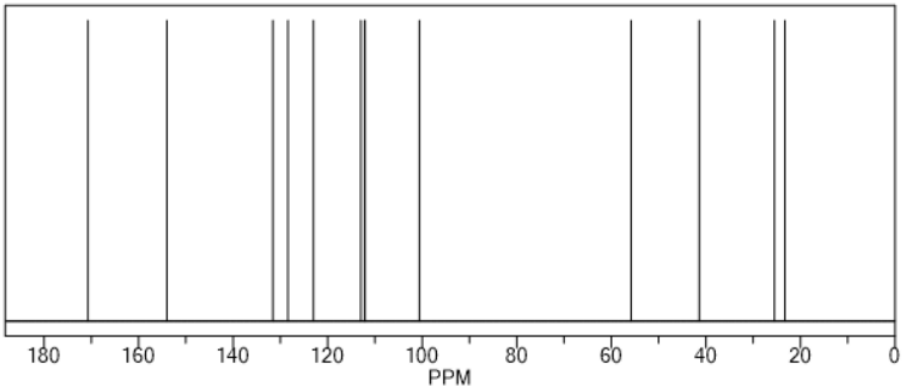
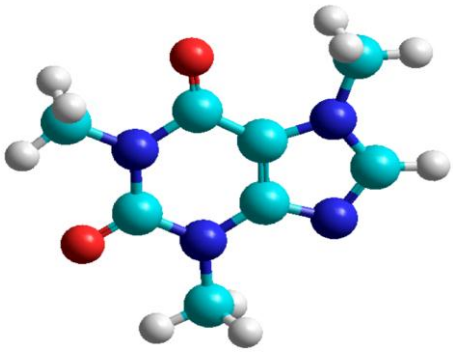


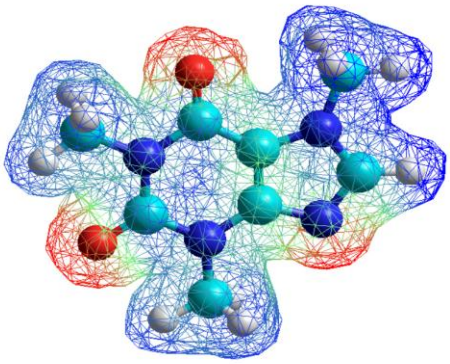
Fig. 9: PPM diagram.

Quantum characterization

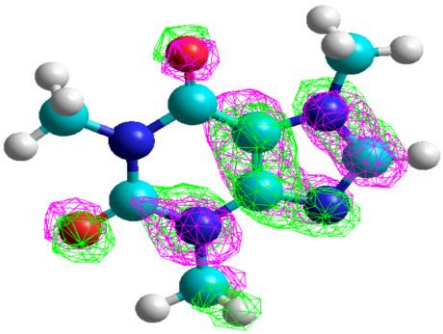
Fig. 10 shows us the CFI molecule characterized by its different quantum concepts. This molecule presents a quantum superposition of HOMO and LUMO. This quantum property infers that it has spheres or micelles.



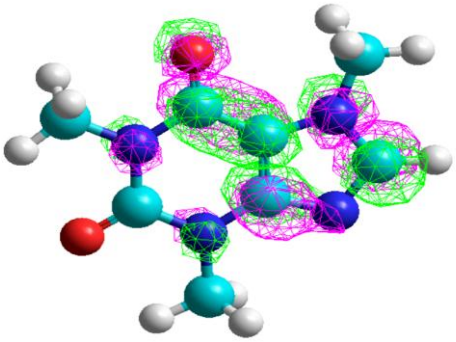
a) CFI. HyperChem



b) CFI. Electrostatic potential. -E= - 0.128 eV/a°; +E = 0.132 eV/a°.



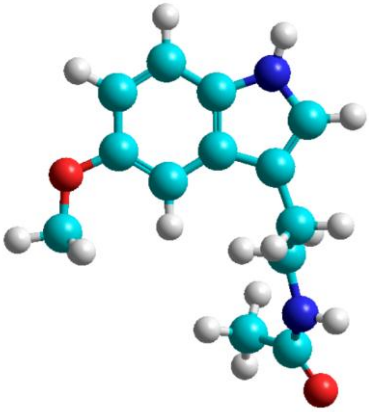
c) CFI. HOMO. -8.895807 eV



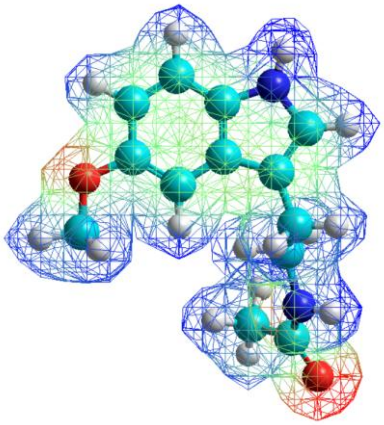
d) CFI. LUMO. - 0.4871098 eV

Fig. 10: Quantum characterization. A) Cyan = C; White = Y; Blue = Nitrogen; Red = Oxygen; B) Electrostatic Potential; C) HOMO; D) LUMO.

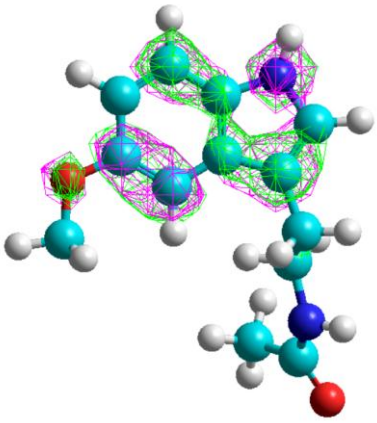
Fig. 11 shows us the MLT molecule characterized by its different quantum concepts. Like CFI, this molecule presents a quantum superposition of HOMO and LUMO. This quantum property infers that it has spheres or micelles.



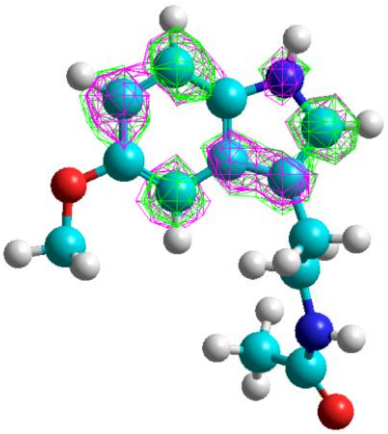
a) MLT. HyperChem



b) MLT. Electrostatic potential. -d= - 0.128 eV/a°; +d = 0.137 eV/a°.



c) MLT. HOMO. -8.482016 eV



d) MLT. LUMO. - 0.1503941 eV

Fig. 11: Quantum characterization. A) Cyan = C; White = Y; Blue = N; Red = O; B) Electrostatic Potential; C) HOMO; D) LUMO.

Interaction of CFI with MLT

The Oxide-Reduction diagram and graph were used to show a summary of interactions between CFI and MLT.

In Table 3, we can see the HOMO and LUMO data for CFI and MLT; the ETC is slightly lower when CFI acts as an oxidant. With this, we can confirm that CFI oxidizes MLT; in fact, it competes with it. We confirm that CFI blocks sleep hormone (MLT) production.

Table 3: Interaction between CFI and MLT. Oxide-Reduction.										
DATA	**Name**	**Reduzing agent**	**Oxidizing agent**	**HOMO**	**LUMO**	**Bg**	**E-**	**E+**	**EP**	**ETC**
SD10	Cafeína	CFI	CFI	-8.895807	-0.4871098	8.4086972	-0.128	0.132	0.26	32.3411431
SD77	MLTa	MLT	MLT	-8.482016	-0.1503941	8.3316219	-0.128	0.137	0.265	31.4400826
Opción 1	CFI:MT	CFI	MLT	-8.895807	-0.1503941	8.7454129	-0.128	0.137	0.265	33.0015581
Opción 2	MT:CFI	MLT	CFI	-8.482016	-0.4871098	7.9949062	-0.128	0.132	0.26	30.7496392

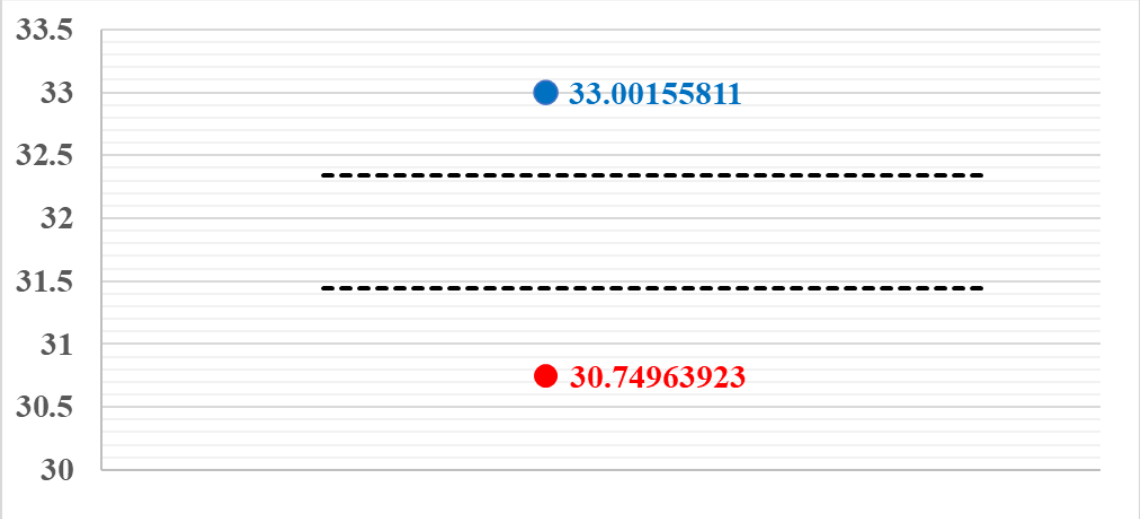


Fig. 12: Oxide-Reduction Graph.

Interaction of CFI with Adrenaline

Adrenaline, also called epinephrine, is a chemical compound that the body secretes through the adrenal glands to react quickly in dangerous situations that require alertness and activity.

Table 4 reaffirms our key points: the HOMO-LUMO gap is around 8.5 eV in both cases. The ETC is consistently lower when CFI acts as an antioxidant or reducer, providing strong evidence for the exceptional antioxidant properties of CFI on adrenaline. These findings, which are robust and reliable, reinforce our understanding of the interaction between CFI and adrenaline, instilling confidence in the validity of our research.

Table 4: CFI – Adrenaline interaction. Oxide-Reduction.										
DATA	**Nombre**	**Reductor**	**Oxidante**	**HOMO**	**LUMO**	**Bg**	**E-**	**E+**	**EP**	**ETC**
SD10	Cafeina	CFI	CFI	-8.895807	-0.4871098	8.4086972	-0.128	0.132	0.26	32.3411431
NT1	ADRENALIN	ADR	ADR	-8.998369	0.09176242	9.09013142	-0.117	0.198	0.315	28.8575601
Opción 1	CFI:ADR	CFI	ADR	-8.895807	0.09176242	8.98756942	-0.128	0.198	0.326	27.5692313
Opción 2	ADR:CFI	ADR	CFI	-8.998369	-0.4871098	8.5112592	-0.117	0.132	0.249	34.1817639

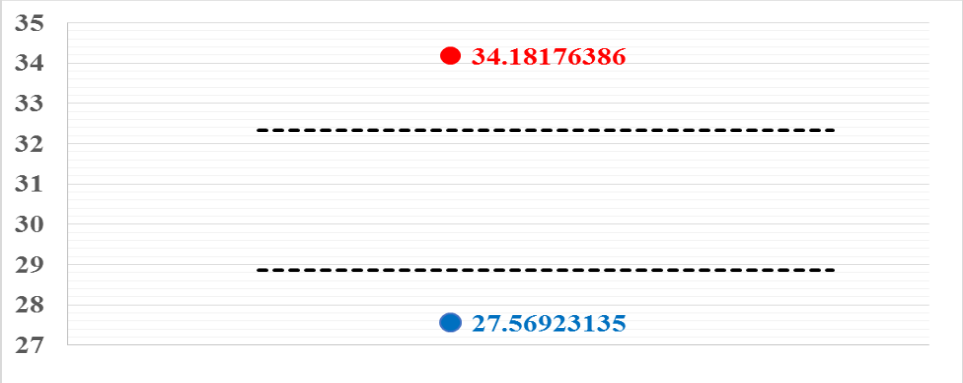


Fig. 13: Oxide-Reduction Graph.

As observed in the interaction, CFI has a lower ETC when it functions as a reducer. This confirms that CFI is an excellent antioxidant of Adrenaline.

CONCLUSIONS

Aim. Analyze the interaction between CFI and the sleep hormone (MLT) using quantum analysis.

Thesis. Table 2 shows the interactions between CFI and MLT. We observe that when CFI is used as an oxidant, the electron transfer coefficient is lower than when used as an antioxidant or reducer. This confirms that CFI reduces or completely blocks the production of MLT, which is why it decreases the total quantity and quality of sleep.

Corollary. Beyond our initial objective, we uncovered intriguing interactions between CFI and neurotransmitters. In some instances, CFI functions as an antioxidant, while in others as a reducer. However, in the case of its interaction with glutamic acid, CFI maintains a dynamic equilibrium, a finding that underscores the complexity of CFI's behavior and its potential implications.

THANKS

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CONFLICT OF INTERESTS

We declare that there is no conflict of interest, neither in our educational institutions nor among authors.

REFERENCIAS.

1. Jee, H. J., Lee, S. G., Bormate, K. J., & Jung, Y. S. (2020). Effect of Caffeine Consumption on the Risk for Neurological and Psychiatric Disorders: Sex Differences in Human. Nutrients, 12(10): 3080.
2. Ribeiro, J. A., & Sebastião, A. M. (2010). Caffeine and adenosine. Journal of Alzheimer's disease: JAD, 20(1): S3–S15.
3. Lozano, R. P., García, Y. A., Tafalla, D. B., & Albaladejo, M. F. (2007). Cafeína: un nutriente, un fármaco, o una droga de abuso. Adicciones, 19(3): 225-238.
4. Nehlig, A., Daval, J. L., & Debry, G. (1992). Caffeine and the central nervous system: mechanisms of action, biochemical, metabolic and psychostimulant effects. Brain research. Brain research reviews, 17(2): 139–170.
5. Schubert, M. M., Irwin, C., Seay, R. F., Clarke, H. E., Allegro, D., & Desbrow, B. (2017). Caffeine, coffee, and appetite control: a review. International journal of food sciences and nutrition, 68(8): 901–912.
6. Cappelletti, S., Piacentino, D., Sani, G., & Aromatario, M. (2015). Caffeine: cognitive and physical performance enhancer or psychoactive drug?. Current neuropharmacology, 13(1): 71–88.
7. Shilo, L., Sabbah, H., Hadari, R., Kovatz, S., Weinberg, U., Dolev, S., ... & Shenkman, L. (2002). The effects of coffee consumption on sleep and melatonin secretion. Sleep medicine, 3(3): 271-273.
8. O'Callaghan, F., Muurlink, O., & Reid, N. (2018). Effects of caffeine on sleep quality and daytime functioning. Risk management and healthcare policy, 11: 263–271.
9. M Yelanchezian, Y. M., Waldvogel, H. J., Faull, R. L. M., & Kwakowsky, A. (2022). Neuroprotective Effect of Caffeine in Alzheimer's Disease. Molecules (Basel, Switzerland), 27(12): 3737.
10. Merighi, S., Travagli, A., Nigro, M., Pasquini, S., Cappello, M., Contri, C., Varani, K., Vincenzi, F., Borea, P. A., & Gessi, S. (2023). Caffeine for Prevention of Alzheimer's Disease: Is the A2A Adenosine Receptor Its Target?. Biomolecules, 13(6): 967.

11. M Yelanchezian, Y. M., Waldvogel, H. J., Faull, R. L. M., & Kwakowsky, A. (2022). Neuroprotective Effect of Caffeine in Alzheimer's Disease. Molecules (Basel, Switzerland), 27(12): 3737.
12. Ferreira, S. E., de Mello, M. T., Pompéia, S., & de Souza-Formigoni, M. L. O. (2006). Effects of energy drink ingestion on alcohol intoxication. Alcoholism: Clinical and Experimental Research, 30(4): 598-605.
13. Roca, D. J., Schiller, G. D., & Farb, D. H. (1988). Chronic caffeine or theophylline exposure reduces gamma-aminobutyric acidA receptor function. Molecular Pharmacology, 33(6): 481-486.
14. Fawaz Alasmari (2020). Caffeine induces neurobehavioral effects through modulating neurotransmitters. Saudi Pharmaceutical Journal, 28(4): 445-451.
15. Isokawa, M. (2016). Caffeine-induced suppression of GABAergic inhibition and calcium-independent metaplasticity. Molecular Brain, 9(1): 1-12.
16. Mukhopadhyay, S., & Poddar, M. K. (1998). Caffeine-induced changes in the levels of monoamine neurotransmitters in discrete brain regions of young and adult rats. Neurochemical Research, 23(9): 1171-1178.
17. Alasmari F. Caffeine induces neurobehavioral effects through modulating neurotransmitters. Saudi Pharm J., 2020 Apr; 28(4): 445-451. doi: 10.1016/j.jsps.2020.02.005. Epub 2020 Feb 17. PMID: 32273803; PMCID: PMC7132598.
18. Jeliński, T., Kubsik, M., & Cysewski, P. (2022). Application of the Solute-Solvent Intermolecular Interactions as Indicator of Caffeine Solubility in Aqueous Binary Aprotic and Proton Acceptor Solvents: Measurements and Quantum Chemistry Computations. Materials (Basel, Switzerland), 15(7): 2472.
19. Sacristán, H., & García, J. G. La melatonina y su papel en la enfermedad de Alzheimer.
20. J.J. Poza, M. Pujol, J.J. Ortega-Albás, O. Romero, Melatonina en los trastornos de sueño, Neurología, 2022; 37(7): 575-585, ISSN 0213-4853.
21. Poza, J. J., Pujol, M., Ortega-Albás, J. J., & Romero, O. (2022). Melatonina en los trastornos de sueño. Neurología, 37(7): 575-585.
22. Escames, G., & Acuña Castroviejo, D. (2009). Melatonina, análogos sintéticos y el ritmo sueño/vigilia. Rev. neurol.(Ed. impr.), 245-254.
23. Smith, J., & Jones, A. (2022). The effects of caffeine on melatonin and sleep quality. Journal of Sleep Research, 15(3): 123-134.

24. García, A., & Fernández, L. (2020). Efectos del consumo de cafeína sobre la calidad del sueño. Revista de Neurología, 55(3): 123-134.
25. Ramírez, A., Sánchez, M., & Gómez, P. (2018). Mecanismos de acción de la cafeína sobre la regulación del sueño. Fisiología, 45(3): 89-101.
26. Gómez, P., Sánchez, R., & Díaz, M. (2021). Interacción entre melatonina y cafeína: implicaciones en el estrés oxidativo y los trastornos del sueño. Farmacología Experimental, 15(2): 45-56.
27. Martínez, C., Gómez, L., & Fernández, J. (2020). Relación entre melatonina, cafeína y química cuántica. Revista de Neurociencias, 25(1): 12-23.
28. de Lima Menezes, G., Sales Bezerra, K., Nobre Oliveira, J.I., et al. (2024). Quantum mechanics insights into melatonin and analogs binding to melatonin MT1 and MT2 receptors. Scientific Reports, 14: 10922.
29. Fedor-Freybergh, P., & Peter, B. (2007). Melatonin, consciousness, and traumatic stress. Journal of Pineal Research, 43(4): 335-353.
30. Martínez, C., Gómez, L., & Fernández, J. (2020). Relación entre melatonina, cafeína y química cuántica. Revista de Neurociencias, 25(1): 12-23.
31. Velkov, Z.A., Velkov, Y.Z., Galunska, B.T., Paskalev, D.N., & Tadjer, A.V. (2009). Melatonin: Quantum-chemical and biochemical investigation of antioxidant activity. Journal of Molecular Structure, 930(1-3): 52-56.
32. van Mourik T. (2004). First-principles quantum chemistry in the life sciences. Philosophical transactions. Series A, Mathematical, physical, and engineering sciences, 362(1825): 2653–2670.