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Quantum Chemical Analyses of Methylated Derivatives of Gallic Acid and *In Silico* Evaluations of their Interactions with the Cyclooxygenase-2 Enzyme

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Abstract: Structural and electronic features of methylated derivatives of gallic acid were analyzed by performing quantum chemical density functional theory (DFT) calculations. Subsequently, interactions of each stabilized structure of gallic acid (ligand) were evaluated towards the cyclooxygenase-2 (COX-2) enzyme target by performing *in silico*-based molecular docking simulations to approach a point of exploring new sets of anti-inflammatory agents. The available OH groups of gallic acid were substituted by one, two, three, and four methyl groups to yield the new OMe groups for the derivatives. Accordingly, their electronic features indicated the impacts of such structural modifications on the electronic properties of gallic acid. The results of stabilizations and electronic features evaluations indicated the majority of structural modification of gallic acid for achieving more specific ligand structures. Additionally, the results of molecular docking simulations of interacting ligand-target complexes indicated a benefit of structural modification of gallic acid for approaching a higher strength level of interaction with the COX-2 enzyme target compared with the original gallic acid compound. As a remarkable achievement of this work, the methylation of gallic acid could yield more efficient ligands for interacting with the COX-2 enzyme target.

Keywords: gallic acid; COX-2; anti-inflammatory; ligand-target interaction; DFT; *in silico*.

1. Introduction

Performing quantum chemical calculations could help to analyze chemical compounds to provide insights into their physical and chemical features [1-3]. Accordingly, structural conformations and their corresponding properties could be evaluated for designing novel materials or optimizing them for approaching desired purposes [4-7]. Within this work, such quantum chemical analyses were done on methylated derivatives of gallic acid (Figures 1 and 2) to reveal their properties for approaching a structural investigation. Gallic acid is indeed a polyphenolic acid with the formula $C_7H_6O_5$, which is found in natural products of plants such as tea leaves and sumac [8]. Additionally, gallic acid could be chemically synthesized as 3,4,5-

trihydroxy benzoic acid [9]. Several works reported various applications of gallic acid from industries up to the high level of pharmaceutical treatments [10, 11]. Earlier results indicated the benefits of employing gallic acid for maintaining human health-related systems by treating cancer cells and tumors [12].

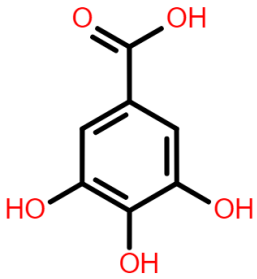


Figure 1. Gallic acid (ChemSpider ID: 361) [13].

Anti-inflammatory activities were also reported for gallic acid by the earlier works [14-17]. Accordingly, this work was done to recognize the stabilities and properties of gallic acid methylated derivatives to evaluate their interactions with the cyclooxygenase-2 enzyme target. Cyclooxygenase-2, or COX-2, is an enzyme involved in converting arachidonic acid to prostaglandin H2, as expressed in inflammation [18]. In this regard, inhibiting the activity of COX-2 could reduce or control severe impacts of inflammation [19]. Several anti-inflammatory agents have been reported, but the topic is still open to new investigations for approving more efficient anti-inflammatory agents [20-23]. Within this work, such an issue of exploring new anti-inflammatory agents was done by means of evaluating interactions of the methylated derivatives of gallic acid with the COX-2 enzyme target (Figure 3). In silico-based molecular docking simulations were performed to yield the interacting ligand-target complexes [24-28] to approach this goal. Furthermore, of the importance of discovering efficient drugs, various types of studies were done for developing new drug substances [29-32]. Additionally, learning details of human body-related systems could provide helpful insights into approaching such therapeutic goals [33-36].

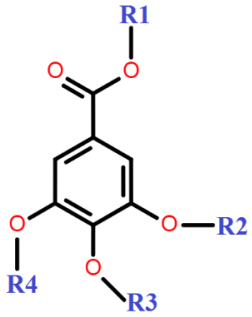
2. Materials and Methods

Quantum chemical analyses of methylated derivatives of gallic acid were done by performing the B3LYP/6-31G* density functional theory calculations using the Gaussian program [37]. As described in Table 1, the OH groups of gallic acid were methylated to produce the desired derivatives. 0 means the original gallic acid with the polyphenolic structure (Figure 1). 1, 2, and 3 mean one-OH methylated derivatives. 12, 13, 23, and 24 mean two-OH methylated derivatives. 123, 124, and 234 mean three-OH derivatives. And 1234 means four-OH derivatives of gallic acid. Twelve compounds of gallic acid were investigated in this with the role of ligands for interacting with the enzyme target. Their stabilized energies and electronic molecular orbital features were evaluated by optimizing the structures. The exhibited features of Table 1 include E: stabilized energy, HOMO: energy of the highest occupied molecular orbital, LUMO: energy of the lowest unoccupied molecular orbital, GAP: energy gap of HOMO and LUMO levels, η: chemical hardness, μ: chemical potential, and ω: electrophilicity index; as described by another work how to be evaluated [38]. The calculated distribution patterns of HOMO and LUMO of gallic acid derivatives are exhibited in Figure 2. Next, the macromolecular structure of COX-2 was obtained from the protein data bank (PDB ID: 3NT1) [39, 40], and it was prepared as the enzyme target for running the molecular docking simulations. The ligands were individually submitted to the SwissDock web server [41] to

interact with the target in an accurate model of a molecular docking simulation. The results were extracted, and values of their binding energies (BE) were summarized in Table 2, besides exhibiting the interacting ligand-target complexes in Figure 3.

Consequently, the ligand models of gallic acid were optimized by DFT calculations first. Their *in silico*-based interactions with the COX-2 enzyme target were evaluated by molecular docking simulations next to see the benefits of employing the methylated derivatives of gallic acid as possible anti-inflammatory agents. It should be mentioned that several methodologies have been developed for investigating biological-related systems up to now [42-45]. In the current research work, the required information was evaluated using the computational methodology as a beneficial tool for investigating complicated systems [46-50].

Table 1. Descriptions and the obtained features (all in eV) of methylated derivatives of gallic acid.



Ligand	R1	R2	R3	R4	E	HOMO	LUMO	GAP	η	μ	ω
0	H	H	H	H	-17591.70	-6.15	-1.23	4.92	2.46	-3.69	2.77
1	Me	H	H	H	-18661.31	-6.07	-1.11	4.96	2.48	-3.59	2.60
2	H	Me	H	H	-18661.46	-5.91	-1.00	4.91	2.45	-3.46	2.44
3	H	H	Me	H	-18661.32	-6.14	-1.21	4.92	2.46	-3.68	2.74
12	Me	Me	H	H	-19731.07	-5.83	-0.89	4.94	2.47	-3.36	2.29
13	Me	H	Me	H	-19730.93	-6.06	-1.10	4.96	2.48	-3.58	2.58
23	H	Me	Me	H	-19730.80	-6.17	-1.20	4.96	2.48	-3.69	2.74
24	H	Me	H	Me	-19730.88	-5.95	-1.01	4.93	2.47	-3.48	2.46
123	Me	Me	Me	H	-20800.41	-6.09	-1.09	5.00	2.50	-3.59	2.58
124	Me	Me	H	Me	-20800.49	-5.86	-0.90	4.96	2.48	-3.38	2.31
234	H	Me	Me	Me	-20800.16	-6.52	-1.25	5.27	2.64	-3.89	2.87
1234	Me	Me	Me	Me	-21869.77	-6.45	-1.14	5.31	2.66	-3.80	2.71

3. Results and Discussion

Within this work, the methylated derivatives of gallic acid were analyzed (Table 1), and their interactions with the COX-2 enzyme were investigated (Table 2) regarding the development of anti-inflammatory agents. Gallic acid is a naturally originated compound placed as a lead compound in this work for undertaking structural modifications. Earlier works indicated the benefits of exploring natural products or herbal compounds for developing novel therapeutic agents [51-55]. Accordingly, the features of gallic acid and its methylated derivatives were investigated in this work to provide new insights on the topic of anti-inflammations. The OH groups of gallic acid were substituted with the methyl (Me) groups to yield new OMe-modified gallic acid derivatives. The four OH groups in the structure were modified by the additional Me groups, in which eleven derivatives were found beside the original gallic acid as indicated by 0. The Me group modified one OH group of gallic acid to create 1, 2, and 3 derivative compounds. The Me group modified two OH groups of gallic acid to create 12, 13, 23, and 24 derivative compounds. The Me group modified three OH groups of gallic acid to create 123, 124, and 234 derivative compounds. The Me group modified all four OH groups of gallic acid to create 1234 derivative compounds. Consequently, the ligand

structures were prepared by adding Me groups instead of each of the OH groups of the gallic acid. All structures were optimized to obtain the stabilized geometries to evaluate their energy and related electronic features. As could be found by the obtained values of E, even the models with similar numbers of additional Me groups showed different energy stabilities. For the one Me group modified models, the order of stability was found as 2 > 3 > 1. For the two Me groups modified models, the order of stability was found as 12 > 13 > 24 > 23. For the three Me groups modified models, the order of stability was found as 142 > 123 > 234. Accordingly, their related electronic molecular orbital features varied among the optimized models.

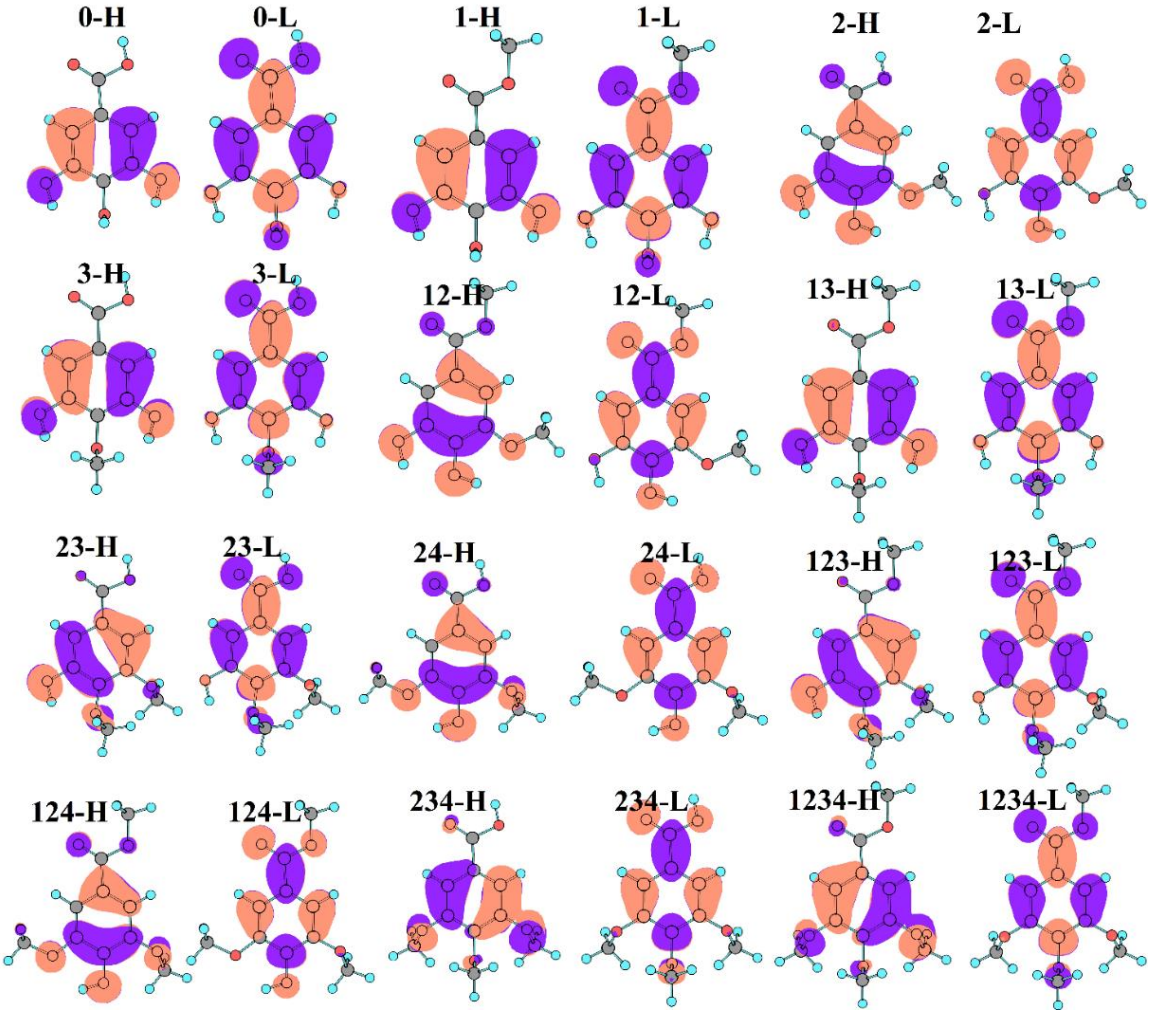


Figure 2. The evaluated HOMO (H) and LUMO (L) distribution patterns of methylated derivatives of gallic acid.

It is known that the energy levels of HOMO and LUMO are very important regarding the electron transferring of a molecule inside and outside the chemical system. In this regard, the effects of methylation on the electronic feature of gallic acid were obvious by observing changes in HOMO and LUMO levels in both quantities of Table 1 and qualitative representations of Figure 2. Subsequently, the obtained values of GAP showed the energy distances of HOMO and LUMO levels, in which the models were different in the related values of η, μ, and ω. Furthermore, the results of DFT calculations on stabilizations and electronic feature evaluations indicated the effects of methylation on the specified properties of the models. Accordingly, these different electronic features of gallic acid derivative structures could change their future interaction activities, followed by the results of molecular docking simulations.

Additionally, the represented results of Figure 2 also showed variations of localizations of HOMO and LUMO among the methylated derivatives of gallic acid. Such movements of HOMO and LUMO distribution patterns of a molecule could lead to changes in its electronic tendency to participate in interactions with other substances. Consequently, the idea of modifying the lead compound of gallic acid was reasonable regarding the obtained achievements of electronic features of the derivative structures.

Table 2. Values of binding energies (BE in kcal/mol) of the interacting ligand-target complexes (Figure 3).

	0-T	1-T	2-T	3-T	12-T	13-T	23-T	24-T	123-T	124-T	234-T	1234-T
BE	-6.48	-6.96	-6.79	-6.81	-7.05	-6.91	-7.05	-6.90	-7.32	-7.19	-7.07	-7.53

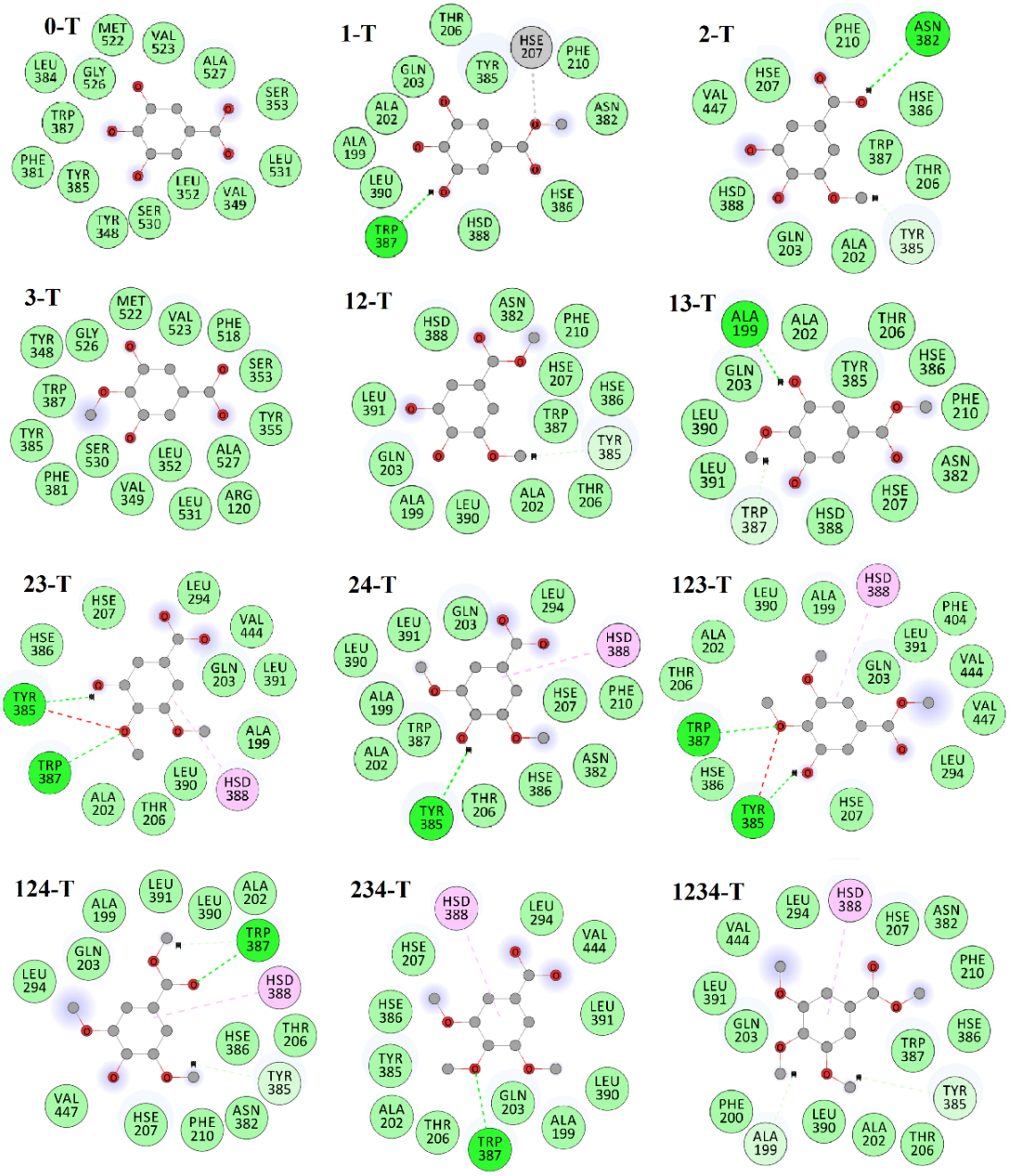


Figure 3. The evaluated interacting ligand-target complexes by molecular docking simulations.

To evaluate the interactions of gallic acid ligands with the COX-2 enzyme, molecular docking simulations were performed to assess the formations of ligand-target complexes. The evaluated values of binding energies (BE) were summarized in Table 2, and the obtained

ligand-target complexes were visualized in Figure 3. Based on the results of BE values, the strengths of ligand-target complexes differed among the investigated models. One important achievement could be mentioned about the higher strengths of all methylated derivatives of gallic acid for interacting with the COX-2 target compared with the original gallic acid ligand. In this regard, a benefit of methylation of gallic acid for obtaining a higher strength of interaction between the ligand and target was found here as the majority of lead compound optimization for achieving more efficient conditions. Among the models of methylated derivatives of gallic acid, increasing the number of substituted methyl groups could increase the strength of interaction between the ligand and target. In this regard, 1234 was found as a ligand at the highest interaction energy strength with the COX-2 target as found for the 1234-T complex. The next level of strength was found for models 123, 124, and 234, and the other two methyl groups and one methyl group modified models were placed at the next steps of strengths. Comparing the results of interaction energy strengths of the current ligands towards the COX-2 enzyme target in comparison with the other available results in the literature could show the comparability of the current ligands of gallic acid with those other proposed inhibitors [56-59]. Based on the evaluated results of this work, the ligand-target complex models were categorized by the evaluated values of BE of interaction strengths.

Additionally, the graphical representations of complexes could show reasonable surrounding environments of amino acids around the central ligand. Accordingly, the modes of interactions and the involving amino acids showed a rational similarity of surrounding amino acids around the ligands revealing the convergence of ligands for interactions with a specified zone of the target. However, a specific mode of interaction was found for each ligand toward the COX-2 enzyme target based on the structural and electronic features of ligands. Consequently, the stabilized models of methylated gallic acid were stabilized by performing DFT calculations, and their features showed the impacts of modifications on the original structure of gallic acid. Additionally, the interacting ligand-target complexes of molecular docking simulations indicated a benefit of such structural modification for approaching a higher strength of interaction and formation. The obtained interacting complexes were in a physical mode of interactions, resembling a reversible enzyme inhibition.

4. Conclusions

The main goal of this work was to investigate the methylated derivatives of gallic acid in accordance with analyzing their properties and evaluating their interactions with the COX-2 enzyme target. In this regard, developing a new set of possible anti-inflammatory agents was explored within this work. The models of methylated gallic acids were stabilized, and their properties were evaluated to recognize their electronic features based on DFT calculations. Next, molecular docking simulations were performed to examine the formation of interacting ligand-target complexes between the methylated gallic acids and the COX-2 enzyme. The results indicated the stabilities of the investigated ligands, and their features showed the impacts of structural modification on their electronic properties. Subsequently, molecular docking simulations evaluated results showed the benefits of modifications of gallic acid derivatives for approaching a higher strength of interaction with the target compared with the original gallic acid. Additionally, the obtained values of binding energies of the ligands towards the target were reasonable compared to other earlier works in this field. The involved interactions were in a physical mode. A reversible inhibition could be expected for the function

of methylated derivatives of gallic acid towards the COX-2 enzyme for approaching a possible anti-inflammatory condition.

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Conflicts of Interest

The authors declare no conflict of interest.

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