Scientific Research Publishing

International Journal of Organic Chemistry, 2023, 13, 96-108
https://www.scirp.org/journal/ijoc
ISSN Online: 2161-4695
ISSN Print: 2161-4687

Electronic Aspects of the Synergistic Antioxidant Interaction of Various Pairs "Phenolic Food Acid and Glutathione" in Their Reactions with the Stable Radical Cation ABTS$^{+\bullet}$

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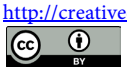
How to cite this paper: Gorbachev, M.Yu., Gorinchoy, N.N. and Balan, I.I. (2023) Electronic Aspects of the Synergistic Antioxidant Interaction of Various Pairs "Phenolic Food Acid and Glutathione" in Their Reactions with the Stable Radical Cation ABTS$^{+\bullet}$. *International Journal of Organic Chemistry*, **13**, 96-108.
https://doi.org/10.4236/ijoc.2023.133008

Received: June 15, 2023
Accepted: September 23, 2023
Published: September 26, 2023



Abstract

In the present work, for the first time, the main details of the electronic mechanism of the synergistic antioxidant interaction between different pairs: phenolic food acid and glutathione and the stable radical cation ABTS$^{+\bullet}$ were revealed on the basis of a rigorous analysis of the DFT calculated data. It was shown that among all the studied food acids, only caffeic acid exhibits a clear-cut significant synergistic effect with glutathione. It established the electronic and structural factors underlying the mechanism of the synergistic interaction of the mixture caffeic acid and glutathione in its reaction with ABTS$^{+\bullet}$. The main causes of this considered synergistic effect are, firstly, the presence of the 3-OH and 4-OH hydroxyl groups in the structure of caffeic acid, secondly, the greater stability of its anion which contains the deprotonated 4-OH hydroxyl group. All other phenolic food acids under study do not possess the given structural particularity and therefore do not show such synergistic effects with glutathione.

Keywords

Synergistic Effect, Caffeic Acid and Glutathione, ABTS$^{+\bullet}$ Test, Electronic Mechanism, DFT Calculations

1. Introduction

One of the most practically important and theoretically interesting effects of the simultaneous action of two (or more) antioxidants on one oxidant is the synergistic effect [1] [2]. It lies in the fact that the value of antioxidant activity measured for the above mixture of antioxidants exceeds the sum of the values of their

antioxidant activity when they are used separately. It is obvious that a theoretical understanding of the mechanism of the occurrence of a synergistic effect in each specific case opens up wide opportunities for the formation of the most effective antioxidant mixtures in terms of their antioxidant activity. However, as a rule, the mechanisms responsible for synergistic antioxidant activity are not explained due to the complex nature of the simultaneous reaction of compositions of antioxidants with one common oxidant compound (for instance, the review [1]). Thus, in view of the complexity of the interaction between synergistic systems of antioxidants and the corresponding oxidants, the possible factors of their synergistic action can be: 1) regeneration of a stronger antioxidant by a less powerful one; 2) formation by antioxidants of a joint complex with greater antioxidant activity; 3) the interaction of the reaction products of the studied antioxidants with their original forms with the formation of more active antioxidant systems than the original ones; 4) difference in solubility and interfacial distribution of initial antioxidants and their molecular complexes (including their complexes noted above with products of corresponding redox reactions); and, finally, 5) various random molecular interactions in the systems under study, including interactions with solvent molecules. The putative implementation of the named explanations reasons for the occurrence of a synergistic effect in binary mixtures of antioxidants is considered in [2] on a large sample of specific examples.

It is clear that any problem of revealing the mechanisms of synergistic interaction of antioxidants in their mixtures is very difficult to solve at the modern experimental level, and even more so on the basis of existing theoretical (quantum-chemical) methods for studying all possible intermolecular interactions in the process of redox reactions. It is for this reason that in this work we limited our DFT study of the synergistic effect to a small sample of binary mixtures of low molecular weight antioxidants interacting with the $ABTS^{+\bullet}$ cation-radical. We are talking about binary mixtures of natural phenolic food antioxidant acids (gallic, vanilla, coumaric, etc.) with glutathione, which, in turn, is also known as a powerful natural antioxidant. Plant phenolic acids belong to vital human dietary components and have a pronounced antioxidant activity [3]. It should also be noted here that in recent years there has been a steady trend towards replacing synthetic antioxidants with natural ones present in plant products. Natural antioxidants practically do not harm the human body and, obviously, there is no need to synthesize them (see the review [4]). Practically very important is the task of quantum-chemical study of the mechanism of synergistic interaction of phenolic food acids with antioxidants produced in the human body itself. One of the most powerful antioxidants produced in the human body is glutathione. The structure of the reduced (and active) form of glutathione (hereinafter denoted as GSH) is shown below in **Figure 1**.

The GSH structure presented in **Figure 1** shows that glutathione (gamma-L-glutamyl-L-cysteinylglycine) is the tripeptide which is synthesized from glutamic acid, cysteine, and glycine. Glutathione is synthesized in human erythrocytes from

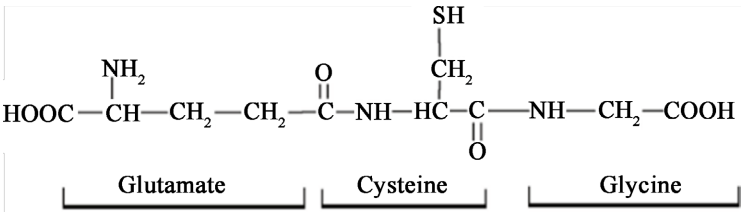


Figure 1. The structural formula of the reduced form (GSH) of glutathione.

the above three acids under the successive action of the enzymes: glutamyl cysteine synthetase and glutathione synthetase in the presence of adenosine triphosphate and Mg^{2+} cations [5] [6].

The antioxidant power of glutathione in its reduced GSH form is so great that inside red blood cells. It is able to restore the oxidized form of vitamin C (see [7]). That is, it is an even stronger antioxidant than vitamin C. Glutathione formed inside erythrocytes is able to leave its intracellular environment and thus enter the blood plasma, where it still retains its antioxidant functions [8].

Along with the reduced form of glutathione, human blood plasma contains almost all dietary phenolic antioxidant acids that enter it through human consumption of plant foods (see the work [9]). The simultaneous presence of antioxidants of different chemical natures (glutathione and phenolic food acids) in the same medium makes it legitimate to ask about the possible presence of their synergistic interaction with free radical particles. The interaction of various binary mixtures of the glutathione + phenolic acid type in their joint reaction with the $ABTS^{+\bullet}$ radical cation was studied in Ref. [10]. It was shown (see the work [10]) that among all the studied food acids, the only acid that exhibits a clear-cut significant synergistic effect is caffeic acid. In this regard, it seems very important to identify the electronic and structural factors underlying the synergistic interaction during the reaction between the glutathione + caffeic acid mixture with the $ABTS^{+\bullet}$ radical cation. The purpose of the present paper is the determination of the main stages of the above synergistic effects mechanism.

2. Theoretical Aspects and Computational Details

In the present Section we have to consider some theoretical and experimental data which are important for the following solving of the studied problem. First of all, this concerns the results of our previous work [11], in which the mechanism of the reaction between some food acids and the radical cation $ABTS^{+\bullet}$ was established on the basis of DFT B3LYP calculations. The main results received in [11] are:

1) Electron transfer to the radical cation $ABTS^{+\bullet}$ occurs not from the neutral food phenolic acid molecule, but from its anion;

2) The above-mentioned anion binds by hydrogen bonding to one of the two sulfo-groups of the given radical cation;

3) The anion that binds to the sulfo-group is in its lowest energy tautomeric form (in the presence of several of its tautomeric forms);

4) The solvent (ethanol) has a significant effect on the magnitude of the charge transferred from the given anion to the radical cation;

5) The greater the value of the negative charge transferred from the anion to the radical cation, the higher the activity of the corresponding phenolic acid.

Below, in the bottom row of **Figure 2**, the lowest energy tautomeric forms of anions of caffeic, and gallic acids are shown. The energy differences of the anionic forms of caffeic and gallic acids shown in **Figure 2** are equal to 9.66 kcal/mol and 9.82 kcal/mol, respectively.

The corresponding energy values (obtained by the DFT B3LYP method in the basis 6 - 31 G(d)) are given below the structural formulas. All calculations were carried out taking into account the solvent (ethanol) based on the IEFPCM option of the Gaussian 09 program package. Here it is to be noted that the DFT definition of the most stable anionic forms of caffeic and gallic acids in the gas-phase and water was performed in the work [12]. It was shown in [12] that, for the both above cases, the most stable anions of the acids arise by elimination of the protons which belong to the hydroxyl group 4-OH in the structures of the given acids. Thus, our results performed for ethanol and presented in **Figure 2** are consistent with the results of this work. Further, the 4-OH and 3-OH hydroxyl groups of caffeic acid are responsible not only for its electrolytic dissociation in polar media but also for antioxidant activity of this compound. So, as it was shown in Ref. [13], namely both these groups (when one of them is deprotonated) take part in the reaction of caffeic acid with hydroxyl radicals. The considered reaction occurs in water and is carried out through the SPLET mechanism. At the same time the phenolate anion arising due to the dissociation of the 4-OH group is more stable due to the delocalization of its electron density over its entire structure (see [13]). In the work [14], in the test with $ABTS^{+\bullet}$, the antioxidant activities

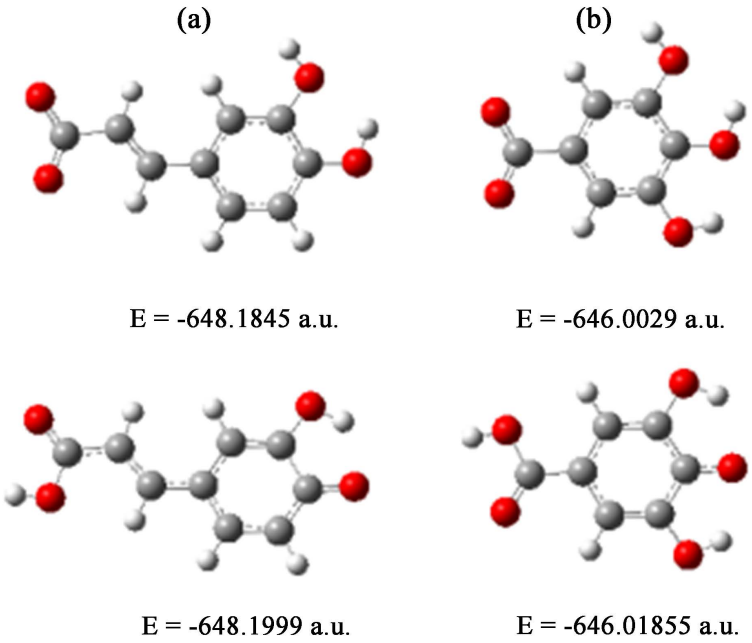


Figure 2. The relative stability of the anionic forms of caffeic (a) and gallic (b) acids.

of caffeic acid-4-O-sulfate, and caffeic acid-3-O-sulfate, which are metabolites of caffeic acid, were studied. It was shown, that the above monosulfate derivatives of caffeic acid were 4-fold less efficient as the antioxidant than caffeic acid. Thus, in work [14] the importance of both hydroxyl groups 4-OH and 3-OH of caffeic acid for its antioxidant activity in the test with the $ABTS^{+\bullet}$ radical cation was clearly demonstrated.

In connection with the above-mentioned data of Ref. [14], it should be noted that in work [15] it was shown that the coordination of caffeic acid anions to the cation Eu^{3+} is carried out mainly through its hydroxyl groups 4-OH and 3-OH. Thus, these two hydroxyl groups of caffeic acid are responsible both for its coordination with positively charged molecular systems and for its antioxidant activity in the test with the $ABTS^{+\bullet}$ radical cation.

All the electronic and geometry characteristics of the molecules of all the studied molecular systems have been calculated by means of the DFT method using the Becke's three-parameter non-local exchange functional [16] with the corresponding correlation functional proposed by Lee, C., Yang, W. and Parr, R.G. (B3LYP) in [17]. The full geometry optimization of the investigated compounds was carried out with the 6-31 G^* basis sets [18] which include polarization functions for all the atoms in the systems under consideration. All the studied molecular systems possessing unpaired electrons have been calculated by means of the unrestricted B3LYP method (UB3LYP). The calculations were performed by using of the GAUSSIAN09 program package [19]. The effect of the solvent (ethanol) on the electronic distribution in the studied molecular systems was taken into account using the IEFPCM model. This model is present as a standard option in the GAUSSIAN09 program package.

3. Results and Discussion

The main results of our DFT study of the mechanism of the antioxidant synergistic effect between glutathione and caffeic acid in their joint reaction with the $ABTS^{+\bullet}$ radical-cation are presented below in **Figures 3-12**.

3.1. The Particularities of Interactions of Some Phenolic Acids and Its Anions with Cation-Radical $ABTS^{+\bullet}$

First of all, it is to be noted that in contrast to all the studied phenolic food acids, whose anions connect with the $ABTS^{+\bullet}$ radical-cation due to their carboxylic groups, in the case of caffeic acid its anion connects with $ABTS^{+\bullet}$ by means of the atoms of its hydroxyl groups. One of these hydroxyl groups of caffeic acid is deprotonated as it is shown in **Figure 2**. **Figure 3** shows the DFT optimized geometries of the complexes formed by the lowest-energy anions of gallic and caffeic acids with $ABTS^{+\bullet}$. One can see that only in the case of the low-energy caffeic anion its interaction with $ABTS^{+\bullet}$ is realized by means of the atoms belonging to its hydroxyl groups.

In its turn **Figure 4** demonstrates the distribution of the electronic density of

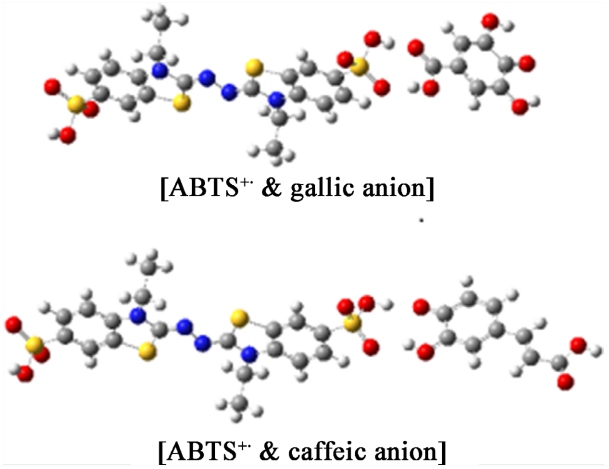


Figure 3. Different ways of coordination of the lowest-energy gallic and caffeic acids anions to one of the SO_3H groups of $ABTS^{+\bullet}$.

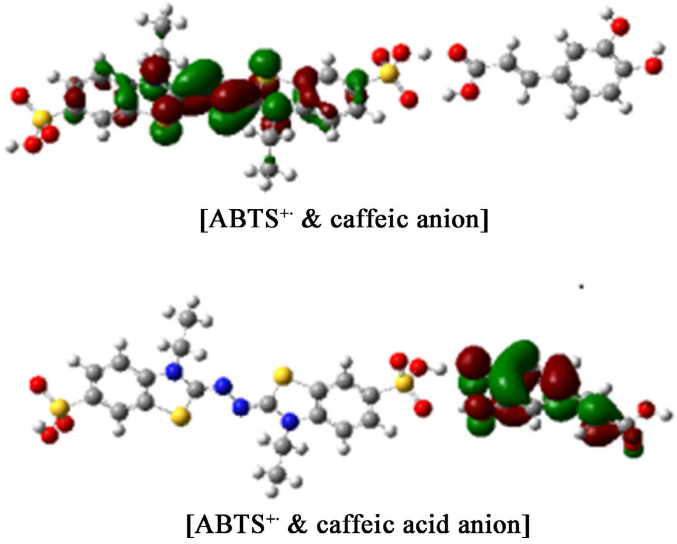


Figure 4. Spin density distrubutions in the complexes between $ABTS^{+\bullet}$ and caffeic acid (at the top) and $ABTS^{+\bullet}$ with caffeic acid anion (at the bottom).

the unpaired electrons in two complexes of caffeic acid and its anion with the cation-radical $ABTS^{+\bullet}$.

The first complex [$ABTS^{+\bullet}$ & caffeic acid] at the top of **Figure 4** is formed due to the interaction between one sulfo-group of $ABTS^{+\bullet}$ and the carboxyl group of a neutral caffeic acid molecule; the second complex in **Figure 4**, [$ABTS^{+\bullet}$ & caffeic acid anion], is generated by the interaction of $ABTS^{+\bullet}$ with the most stable caffeic acid anion arising by deprotonation of the para-hydroxyl group of this acid (see **Figure 2**). One can see that only in the second case due to the electron density transfer from the anion to the $ABTS^{+\bullet}$ cation radical, the latter is transformed into its diamagnetic derivative. However, it should be noted, that in the ethanol medium (as in the aqueous one) only some insignificant part of molecules of caffeic acid is dissociated. Thus, the greater part of the $ABTS^{+\bullet}$ radical-cations reacts with non-dissociated molecules of caffeic acid and, therefore, remains un-

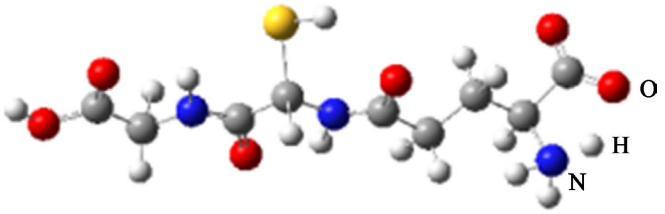
changed, *i.e.* paramagnetic (see the top of Figure 4).

3.2. Effect of Glutathione on Enhancing the Antioxidant Activity of Caffeic Acid

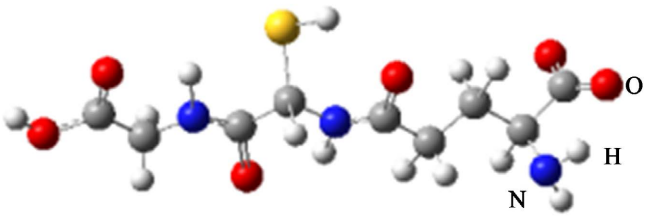
Further, let us consider the DFT optimized structures of glutathione and its anion. Both these structures are shown in Figure 5.

One can see that the neutral glutathione molecule exists in the zwitter-ionic form which contains the $-NH_3^+$ and $-COO^-$ groups. In the glutathione anionic structure (Figure 5, at the bottom) the above $-NH_3^+$ group is being transformed into the corresponding amino-group $-NH_2$, which forms the intra-molecular hydrogen bond with the above-considered $-COO^-$ group. The following DFT calculations show that the glutathione anion can interact with the complex [$ABTS^{+\bullet}$ & caffeic acid] (Figure 4) generating the new complex shown at the bottom of Figure 6. The molecular systems presented at the top and the bottom of Figure 6 are respectively the initial and end points of the corresponding geometry optimization process. It can be seen that as a result of the intra-complex proton transfer, the anionic form of glutathione interacting with [$ABTS^{+\bullet}$ & caffeic acid] becomes the neutral glutathione molecule. At the same time, the neutral caffeic acid structural fragment of the [$ABTS^{+\bullet}$ & caffeic acid] complex transforms in the corresponding anion of caffeic acid.

The result of the mentioned transformations is given in Figure 7 which shows the unpaired electron density distribution in the common complex presented at the bottom of Figure 6. One can easily see that due to the intra-complex one-electron transfer from the considered caffeic acid anion to the $ABTS^{+\bullet}$ this anion becomes the corresponding free radical. This transfer process is also accompanied by transformation of the radical $ABTS^{+\bullet}$ to its diamagnetic derivative (cf. with the bottom



R(N-H) = 1.073Å R(O-H) = 1.663Å



R(N-H) = 1.026Å R(N-H) = 2.093Å

Figure 5. The optimized geometry structures of the neutral glutathione molecule (at the top) and its anion (at the bottom).

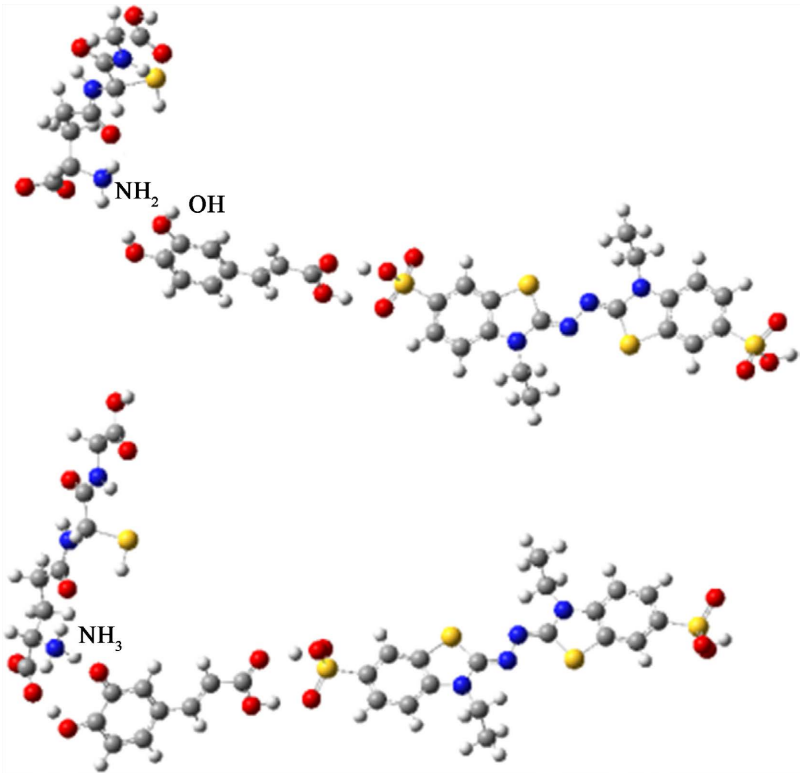


Figure 6. Interaction of the glutatione anion with [$ABTS^{+\bullet}$ & caffeic acid] (at the top) and the formation of their common complex (at the bottom).

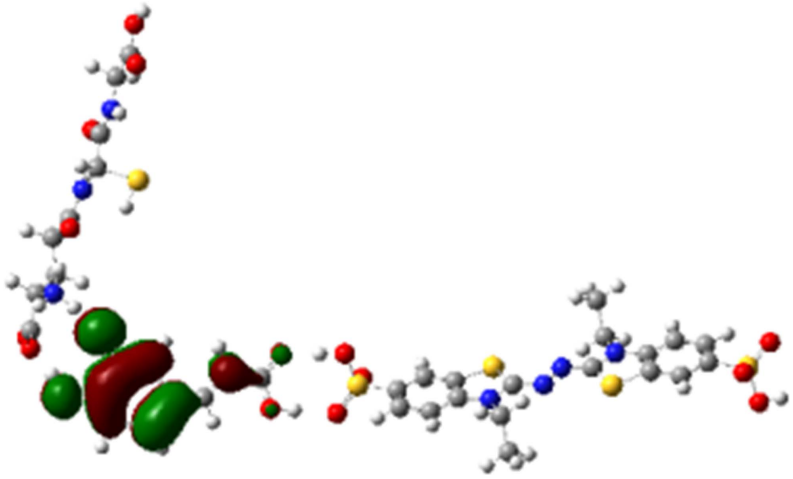


Figure 7. Unpaired electron density distribution in the common complex shown at the bottom of **Figure 6**.

of **Figure 4**).

Thus, all of the above considered makes it possible to understand the influence of glutathione on the inactive complex [$ABTS^{+\bullet}$ & caffeic acid].

3.3. Effect of Caffeic Acid on Enhancing the Antioxidant Activity of Glutathione

The similar (to the above considered) situation takes place when caffeic acid en-

hances antioxidant activity of glutathione interacting with $ABTS^{+\bullet}$. Figure 8 shows that the interaction of a neutral molecule of glutathione with the cation-radical $ABTS^{+\bullet}$ does not lead to any electron density transfer from glutathione to the given cation-radical. It means that this interaction does not transform the latter into its diamagnetic derivative.

Moreover, unlike the case of the interaction between the caffeic acid anion and $ABTS^{+\bullet}$ transforming $ABTS^{+\bullet}$ into its diamagnetic form, the reaction of the glutathione anion with $ABTS^{+\bullet}$ results in the charge transfer complex (shown at the top of Figure 8) in which, however, its unpaired electron is delocalized over both its structural fragments (see the bottom of Figure 9).

Nevertheless, our further DFT calculations have shown that the complex presented at the top of Figure 9 can easily react with a neutral molecule of caffeic acid. At the top of Figure 10 it is shown the most reasonable initial mutual spatial orientation of the interacting molecular systems. The corresponding DFT optimized structure of this joint system is at the bottom of Figure 10.

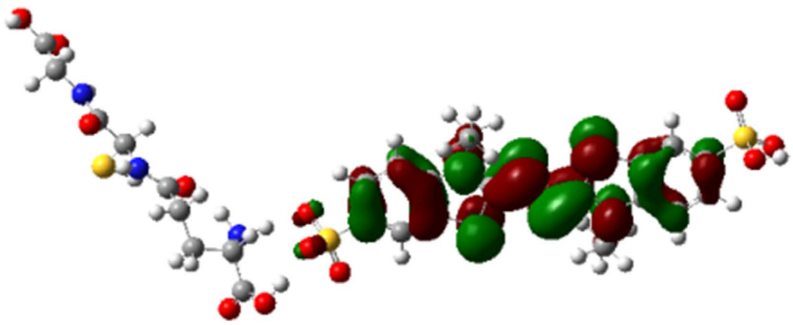


Figure 8. Unpaired electron density distribution in the complex [$ABTS^{+\bullet}$ & glutathione].

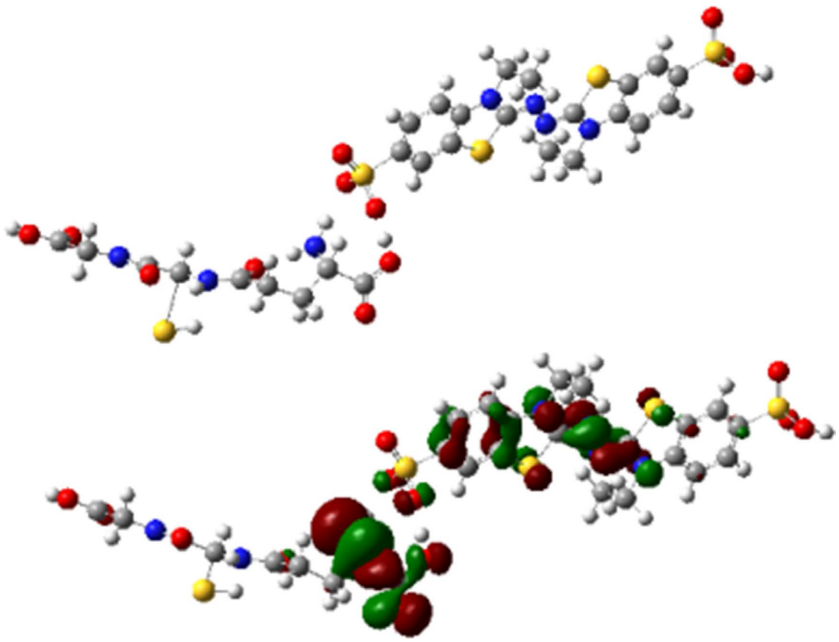


Figure 9. The structure of the complex [$ABTS^{+\bullet}$ & glutathione anion] (at the top) and the unpaired electron density distribution in it (at the bottom).

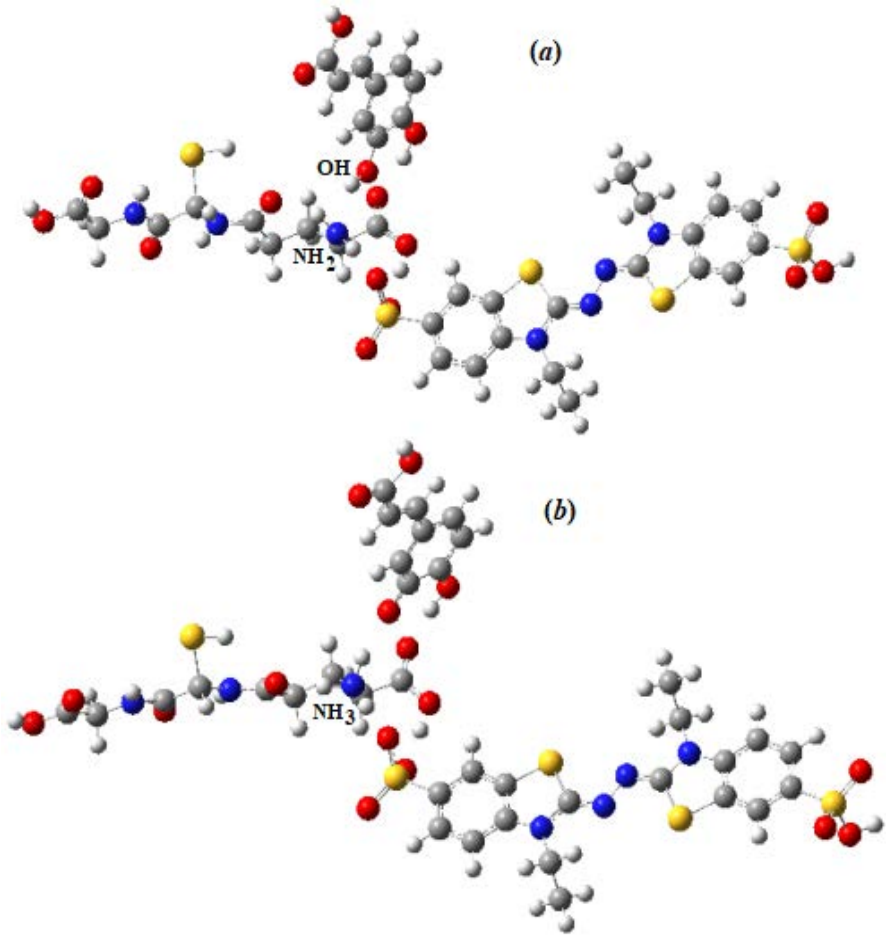


Figure 10. Interaction of the neutral molecule of caffeic acid with [$ABTS^{+\bullet}$ & glutathione anion] complex: the initial (a) and DFT optimized structures of the joint system (b).

One can see that the neutral molecule of caffeic acid interacts with the complex [glutathione anion & $ABTS^{+\bullet}$] by means of its two phenolic hydroxyl groups. The main result of this interaction is the transfer of the hydroxyl proton belonging to the 3-OH group of caffeic acid to the NH_2 group of the glutathione anion, accompanied by the simultaneous transfer of the electron density from the caffeic acid residue to the structural fragment of the complex [$ABTS^{+\bullet}$ & glutathione anion]. At the same time, the neutral caffeic acid molecule is transformed into the corresponding radical. **Figure 11** demonstrates that the unpaired electron of the whole system under consideration is completely localized on the above caffeic acid radical.

The practically identical final electron density distribution as in **Figure 11** is generated due to the interaction between the complex [glutathione & $ABTS^{+\bullet}$] shown in **Figure 8** and a caffeic acid anion (**Figure 12**). This interaction includes the -NH_2 and -COOH groups of the [glutathione & $ABTS^{+\bullet}$] complex and two hydroxyl groups of the anion, one of which is deprotonated.

Thus, the above-considered results of our DFT calculations show that caffeic acid in its both the neutral and anionic forms enhances the antioxidant activity

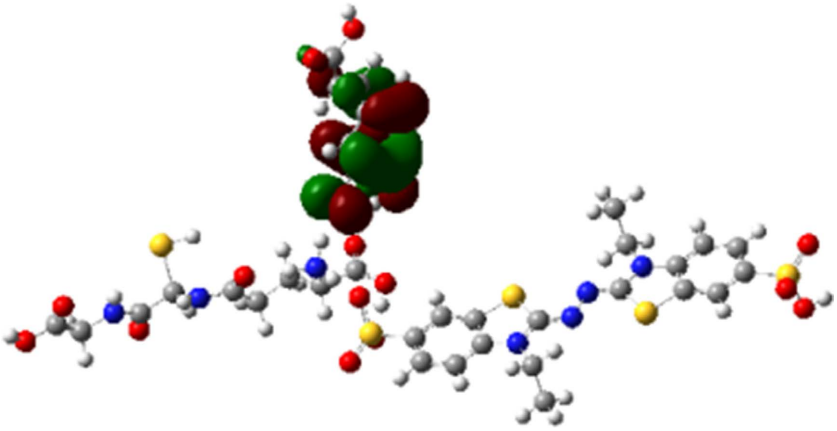


Figure 11. Unpaired electron density localization in the joint complex [$ABTS^{+\bullet}$ & glutathione anion & caffeic acid].

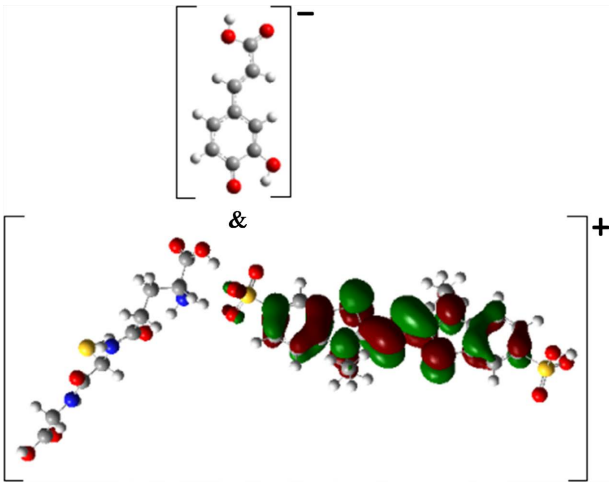


Figure 12. Formation of the complex [glutathione & $ABTS^{+\bullet}$ & caffeic acid anion] due to interaction between [glutathione & $ABTS^{+\bullet}$] and a caffeic acid anion.

of glutathione, transforming the cation-radical $ABTS^{+\bullet}$ in the complexes [glutathione anion & $ABTS^{+\bullet}$] and [glutathione & $ABTS^{+\bullet}$] into its diamagnetic derivative. The above theoretical results are in full agreement with the experimental data presented in the work [10]. This agreement also confirms the previously revealed efficiency of the DFT method for describing the antioxidant activity of food phenolic acids in their reaction with the cation-radical $ABTS^{+\bullet}$ [11].

4. Conclusions

Summarizing all the above-considered calculation data, one can say that in the case of the joint reaction of caffeic acid and glutathione with the cation-radical $ABTS^{+\bullet}$ it takes place the mutual enhancement of the antiradical activities of both these antioxidant compounds; *i.e.* it takes place the synergistic effect between them. It is shown that this synergistic effect is realized solely due to the presence of 3-OH and 4-OH hydroxyl groups in the structure of caffeic acid and the formation of the caffeic acid anion due to the deprotonation of the 4-OH hydroxyl group. The

present study allows us to understand why other phenolic food acids that do not contain such hydroxyl groups in their structure do not show a synergistic effect with glutathione. It should be noted that the same synergistic effect could be expected in the case of gallic acid, which also contains 3-OH and 4-OH hydroxyl groups in its structure. However, in the anion of this acid, its deprotonated 4-OH hydroxyl group is shielded from both sides by two intramolecular hydrogen bonds, which excludes the possibility of the synergistic effect.

The present work stimulated our further studies of the possibility of the synergistic effect of the combined action of food acids and flavonoids in their joint reaction with the cation-radical $ABTS^{+\bullet}$, which will be the subject of our next paper.

Acknowledgements

This work was performed under the Moldovan National Research Project Nr. 20.80009.5007.27, "Physico-chemical mechanisms of redox processes with electron transfer involved in vital, technological and environmental systems".

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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