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Computational Study of Natural Phenolic Acid Solubility and Their Interactions with Chitosan

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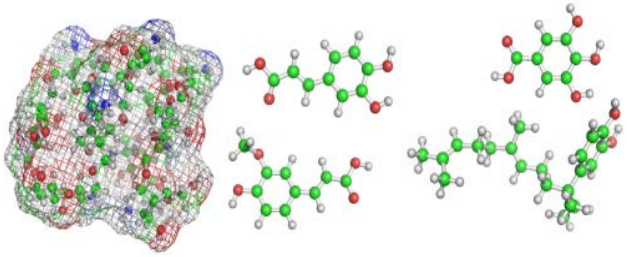
Abstract: *Natural phenolic acids such as gallic, caffeic, ferulic and sinapic acids, have received great attention due to their biological activities, like antioxidant, anti-inflammatory and others. These properties put them as good candidates for the new controlled drug release systems. Among the various types of polymeric materials used in the development of controlled release systems for active drugs and films, chitosan is highlighted because it has many favorable characteristics, such as biocompatibility and biodegradability. To verify the behavior of such phenolic acids in hydrophilic biological fluids and hydrophobic biological barriers aimed at the production of new systems of modified drug release, in the present work it was conducted in silico simulation of solubility in water and in 1-octanol by molecular dynamics. The interaction of these phenolic compounds with chitosan was also investigated by molecular docking. The results showed that all investigated phenolic acids showed adequate solubility and good interaction with chitosan. The results show that the methodology applied in the present work can be well used for the development of pharmacologically active compounds and can aid the understanding of the interaction of such compounds with polymers, saving time and resources.*

Keywords: *phenolic acids, chitosan, molecular dynamics, molecular docking*

Graphical Abstract:



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Introduction:

Natural phenolic acids, such as ferulic, gallic, caffeic and sinapic acids have received great attention due to their biological properties, such as antioxidant action [1,2], antithrombotic antitumor and anti-inflammatory [3,4].

The biological properties of phenolic acids make them good drug candidates for new systems of modified drug release, and the antioxidant property make them good candidates for additives to the new active films development for food packaging, because the antioxidants, in addition to being known to remove or inhibit free radicals production in the body [5], also play an important role in preventing oxidative damage to food during the processing and storage [6].

There is a growing interest in the new and effective modified drug delivery systems development, which are driven by the need to increase the therapeutic effect and minimize the drugs side effects [7]. In simplified form, drugs modified release may be defined as the process of releasing a bioactive substance in a specific quantity at a specific site [8]. These modified drug delivery systems, usually, are constituted by the drug addiction in a polymer base, forming a drug-polymer complex [9]. In addition to the interest in new modified drug delivery systems, there is also the new materials development interest that can be used as active packaging in the food industry, maintaining food integrity for a long time [10, 11]. As with modified drug delivery systems, much of the active packaging is also characterized by the addition of some additive to a polymer base. Among the materials used in the new systems development of active drugs and films modified release, chitosan has gained prominence. Chitosan is a polysaccharide with favorable characteristics and properties for novel modified drug delivery systems synthesis and active films for food packaging, because it is a natural polymer, renewable, biodegradable, biofunctional, biocompatible and non-toxic [12], besides having a cationic polymeric character and gel properties and film forming [13-15].

Natural compounds isolated from plant sources have an extensive use from the past and continues being well used today in several areas, because besides serving as interest compounds by their natural form, can also serve as models for the analogues synthesis with higher activity and lower toxicity [16].

Molecular modeling studies (*in silico*) have been increasingly used to elucidate the natural compounds physicochemical properties, such as solubility, a highly important aspect for the active substances bioavailability [17] and for predicting the such compounds interaction with a polymer base, providing better characteristics understanding of the compounds and the drug-polymer complex formation [18,19].

Motivated by the chitosan features and the phenolic acids biological properties, the present study sought to investigate in silico, by molecular dynamics and machine learning algorithm, the water and 1-octanol solubility of the ferulic acid compounds, Gallic acid, caffeic acid and sinapic acid, besides observing how these compounds interaction occurs with chitosan, through molecular docking, aiming at a better compounds behavior understanding in biological fluids (hydrophilic) and cell membrane (hydrophobic) and in interaction with chitosan (drug-polymer).

Materials and Methods:

Quantum Mechanic Optimization

The geometric optimization of gallic, ferulic, caffeic and sinapic acid molecules (**Figure 1**) was performed using the Density Functional Theory method (DFT), which is a theory based on electronic density, with B3LYP [20, 21] and 6-31G basis set. For the ab initio calculation, the GAMESS-US software was used [22] with the GABEDIT graphical interface aid 2.4.8 [23].

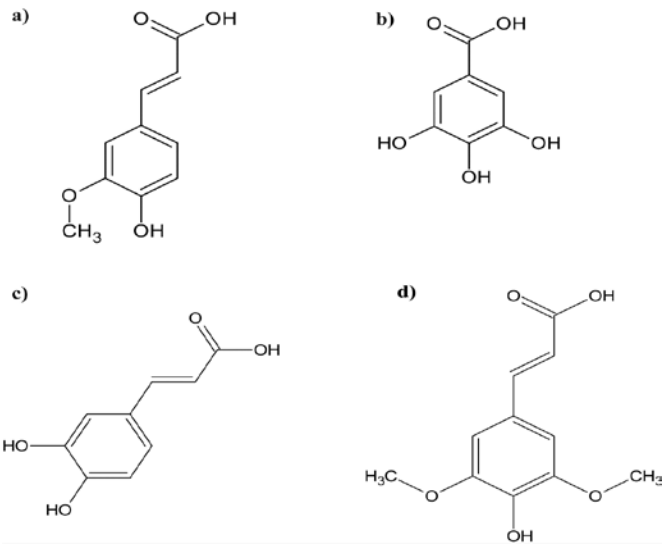

Figure 1. Chemical structure of phenolic compounds a) ferulic acid b) gallic acid c) caffeic acid and d) sinapic acid

Binders solubility study

Based on the compounds solubility importance for their pharmacological activity, the present study investigated the phenolic acids solubility in aqueous and lipophilic medium, as well as the behavior after being solubilized. The ALOGPS 2.1 software was used for partition coefficient (log P) and water solubility (log S) calculations [24]. The ALOGPS was built on the Associative Neural Network (ASNN), which is a machine learning algorithm that combines neural network with k-neighbors [25].

The software GROMACS 4.5.5 [26] was used to simulate the phenolic acids in solvated water and 1-octanol, by molecular dynamics calculations. For the organic compounds energy minimization and simulation in solvated medium the field of force OPLS-AA [27]. The set temperature for simulation was constant at 300 K and the pressure was kept constant at 1 bar. The free energy of solvation in water (ΔG water) and in 1-octanol (ΔG oct) was obtained by the Bennet Acceptance Ratio (BAR) method. The solvation free energy was calculated by creating 21 points: 0; 0.05; 0.1; 0.15; 0.2; 0.25; 0.3; 0.35; 0.4; 0.45; 0.5; 0.55; 0.6; 0.65; 0.7; 0.75; 0.8; 0.85; 0.9; 0.95 and 1.00. The system was balanced over time in 2 ns, while the points simulation occurred in 20 ns. The electrostatic interactions were obtained by PME with cutoff space at 1.3 nm. The details on solvation simulation setup details are given on **Table 1**. The coulombic energies and Lennard-Jones interactions, solvent accessible surface, solvation free energy and root mean square fluctuation (RMSF) of phenolic acids were calculated using the g_energy, g_sas, G_bar and g_rmsf, respectively. Both present in the GROMACS package.

Docking

For the molecular docking simulations, two chitosan molecules were used, one with nine and one with 12-meres acquired in the PDB format through the "Human Metabolome Data Base" banks [28] and "PolySac3DB" [29] respectively. After download, the structures were submitted to molecular mechanical optimization (MM), with the AMBER force field [30], present in GABEDIT.

The software Autodock 4.2 [31] was used as the choice to perform the molecular docking study.

In Autodock 4.2, Gasteiger partial loads and hydrogens needed for the calculation were added in the chitosan molecules. The rotational bonds of the binders have been automatically defined and their nonpolar hydrogens suppressed. Autogrid 4.2 software was used to generate the pre-calculated three-dimensional map around the chitosan molecule. For the 12-meres structure, the grid was positioned around the entire molecule with dimensions of 46 Å on the X-axis, 126 Å on the Y-axis and 28 Å on the Z- axis, In 0.503 Å spacing. For the nine-meter structure, the grid was positioned around any molecule with 126 Å dimensions in the X-axis, 40 Å in the Y-axis and 40 Å in the Z-axis, spaced 0.375 Å.

To find the most stable conformations of the ligands, we used the Lamarckian genetic algorithm (LGA). The initial population was defined as 150 and the search process occurred through random initial conformations. The maximum value of energy assessments chosen was 25,000,000, while the maximum number of generations was maintained at 27,000, just as the number of elitism was kept at 1. The genetic mutation and crossover rates were respectively 0.02 and 0.80. After completing the calculations, 100 different conformations were obtained and grouped into different clusters, defined by energy

proximity and RMS (Root Mean Square deviation) values, according to the *AutoDock* default. During the search process, chitosan was kept rigid and the binders flexible.

Table 1. The solvation simulation system description

System	Components (number of molecules in parentheses)	Box size (Å)
A	(1) Gallic acid + (4134) Water	5 x 5 x 5
B	(1) Ferulic acid + (4134) Water	5 x 5 x 5
C	(1) Ácido cafeico + (4132) Water	5 x 5 x 5
D	(1) Sinapic acid + (4131) Water	5 x 5 x 5
E	(1) Gallic acid + (512) 1-Octanol	5 x 5 x 5
F	(1) Ferulic acid + (512) 1-Octanol	5 x 5 x 5
G	(1) Caffeic acid + (512) 1-Octanol	5 x 5 x 5
H	(1) Sinapic acid + (512) 1-Octanol	5 x 5 x 5

Results and Discussion:

In relation to the octanol/water partition coefficient (LogP) calculated by ALOGPS 2.1, the values found for sinapic acid, caffeic acid and ferulic acid were very close (**Table 2**). Gallic acid was the compound that presented the lowest logP value, representing greater solubility in water when compared to the other compounds. In relation to the water solubility (LogS) calculated by the software ALOGPS 2.1, the sinapic acid was the one that presented the lowest value (less soluble in water), whereas gallic acid had the highest value (greater solubility in water).

LogS values above -1 are related to very polar molecules and have difficulty permeabilizing on hydrophobic surfaces. Empirically, it can be said that compounds with logS values between -1 and -5 present hydrophilicity required for aqueous solubility and lipophilicity to interact with hydrophobic surfaces [32].

Table 2. LogP and logS the compounds values calculated by ALOGPS 2.1 and their experimental values.

Compound	Log P	Log S	Log P $_{exp}$	Log S $_{exp}$
Ferulic acid	1.58	-2.33	1.42 [32]	-
Gallic acid	1.17	-1.54	0.89 [33]	-
Sinapic acid	1.63	-2.55	-	-
Caffeic acid	1.67	-2.05	1.24 [34]	-

Drugs or drug candidates must have hydrophilicity and lipophilicity to interact with biological fluids and cross some biological barriers, such as the plasma membrane that is extremely lipophilic. Based on this assumption, all phenolic acids included in the study have adequate solubility for the pharmacokinetic requirements, as they have sufficient hydrophilicity for aqueous solubility and sufficient lipophilicity to interact with

hydrophobic surfaces.

It is observed that the logP and logS values do not present linearity, despite having a connection in their results. This is because logP shows compounds solubility relation in inorganic (water) and organic (1-octanol) solvents, whereas logS is related only to the compounds solubility in water.

In the free energy calculation of solvation performed by GROMACS 4.5.5, it was observed that gallic acid presented the best solubility in water and in 1-octanol (**Table 3**).

Table 3. Solvation free energy in water and 1-octanol

Compound	Solvation free energy in water	Solvation free energy in 1-octanol
Gallic acid	-6.16 +/- 0.22	-6.45 +/- 1.14
Caffeic acid	- 0.36 +/- 0.17	-3.10 +/- 0.57
Ferulic acid	3.67 +/- 0.04	-3.34 +/- 0.54
Sinapic acid	5.87 +/- 0.02	-4.05 +/- 0.21

The free energy obtained for ferulic and sinapic acids in water indicates that the compounds are practically insoluble in water. The high gallic acid solubility in both solvents may be due to the high polar interactions density formed between the phenolic and gallic acid carboxylic hydroxyls with the water and the hydroxyls of 1-octanol.

It can also be observed that all compounds were more soluble in 1-octanol than in water. In **Table 4** the solvent accessible area of the phenolic compounds studied is presented. The solvent accessible surface area is divided into hydrophilic and hydrophobic based on the atomic partial charges.

Figure 2 shows the hydrogen bonds formed between phenolic acids and water. From the figure, it can be observed that the oxygens of

Table 4. Solvent Accessible Surface Area of phenolic compounds

Compound	Hydrophilic area (nm^2)	Hydrophobic area (nm^2)	Total (nm^2)
Gallic acid	1.82	1.02	2.84
Caffeic acid	1.43	1.77	3.20
Ferulic acid	1.28	2.09	3.37
Sinapic acid	1.22	3.13	4.35

the phenolic hydroxyls of all compounds tend to form hydrogen bonding with water. In all cases, too, the carboxylic group oxygens promote hydrogen bonding with water. It can also be observed that ferulic, sinapic and caffeic acids undergo a twist close to the carboxylic group when binding to the solvent.

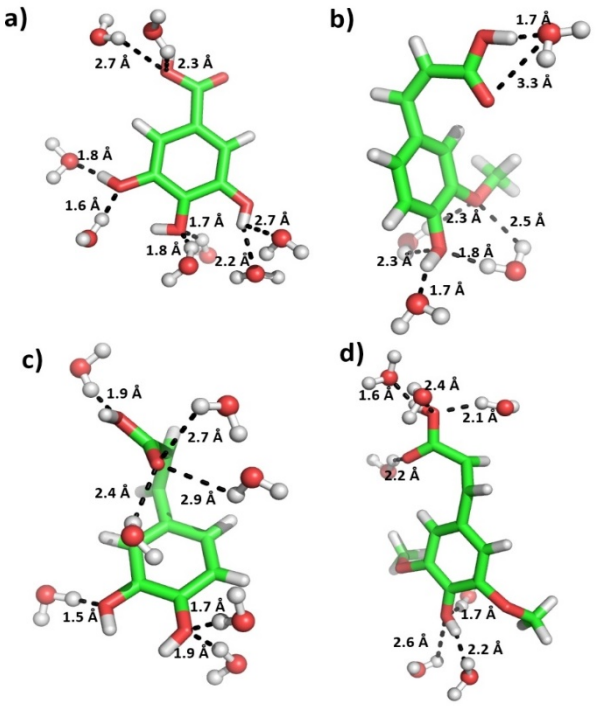

Figure 2. Hydrogen bonds of phenolic compounds in water. a) Gallic acid, b) Ferulic acid, c) Caffeic acid d) Sinapic acid

In **Figure 3** the hydrogen interactions formed between the phenolic compounds and the 1-octanol solvent can be observed. Note that even

promoting less hydrogen bonding, caffeic, ferulic and sinapic acids suffer the same twists as when they are in aqueous medium. To verify the behavior of the compounds in solvated medium, specifically their structural stability in solvated medium, the quadratic mean root fluctuation (RMSF) per atom of the phenolic acid molecules was calculated during the simulation of the compounds in water solvent and 1-octanol.

In **Figure 4** it can be observed that gallic acid has greater fluctuation in the -COOH group in both solvents, however, it is also observed, small fluctuations in the hydrogens of the phenolic hydroxyls when the compounds are in water. It is also observed that caffeic, ferulic and sinapic acids undergo fluctuations in the -COOH groups and the phenolic -OH and -OCH_3 groups, in addition to a considerable fluctuation in the aliphatic chain linking the -COOH group in the phenolic ring, in both solvents. As expected, fluctuations occur more strongly when phenolic acids are in the presence of water.

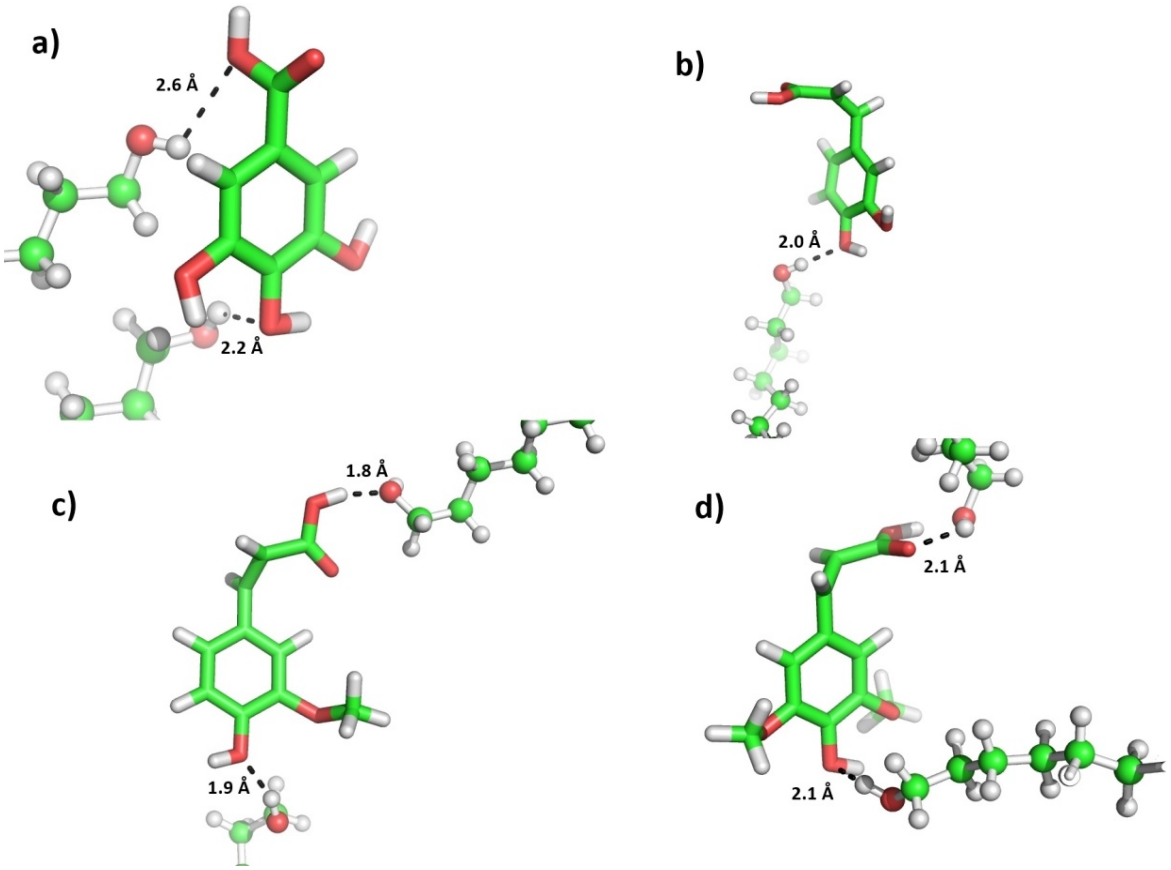

Figure 3. Hydrogen bonds of phenolic compounds to 1-octanol. a) Gallic acid, b) Caffeic acid, c) Ferulic acid, d) Sinapic acid.

By evaluating pharmacokinetic aspects, RMSF calculations show that the compounds although more soluble in organic solvents, promote denser polar interactions with water, adding to the notion that compounds interact in a stable way with biological fluids without compromising the absorption of these substances. The solubility study of the compounds shows that even though the compounds exhibit better solubility in contact with hydrophobic surfaces, they can interact with aqueous fluids through the polar interactions between phenolic hydroxyls, carboxyl and methoxyl groups with water, which is of great significance for the biological effect of these compounds, since they act in an aqueous medium from the beginning to the end of their pharmacokinetic cycle.

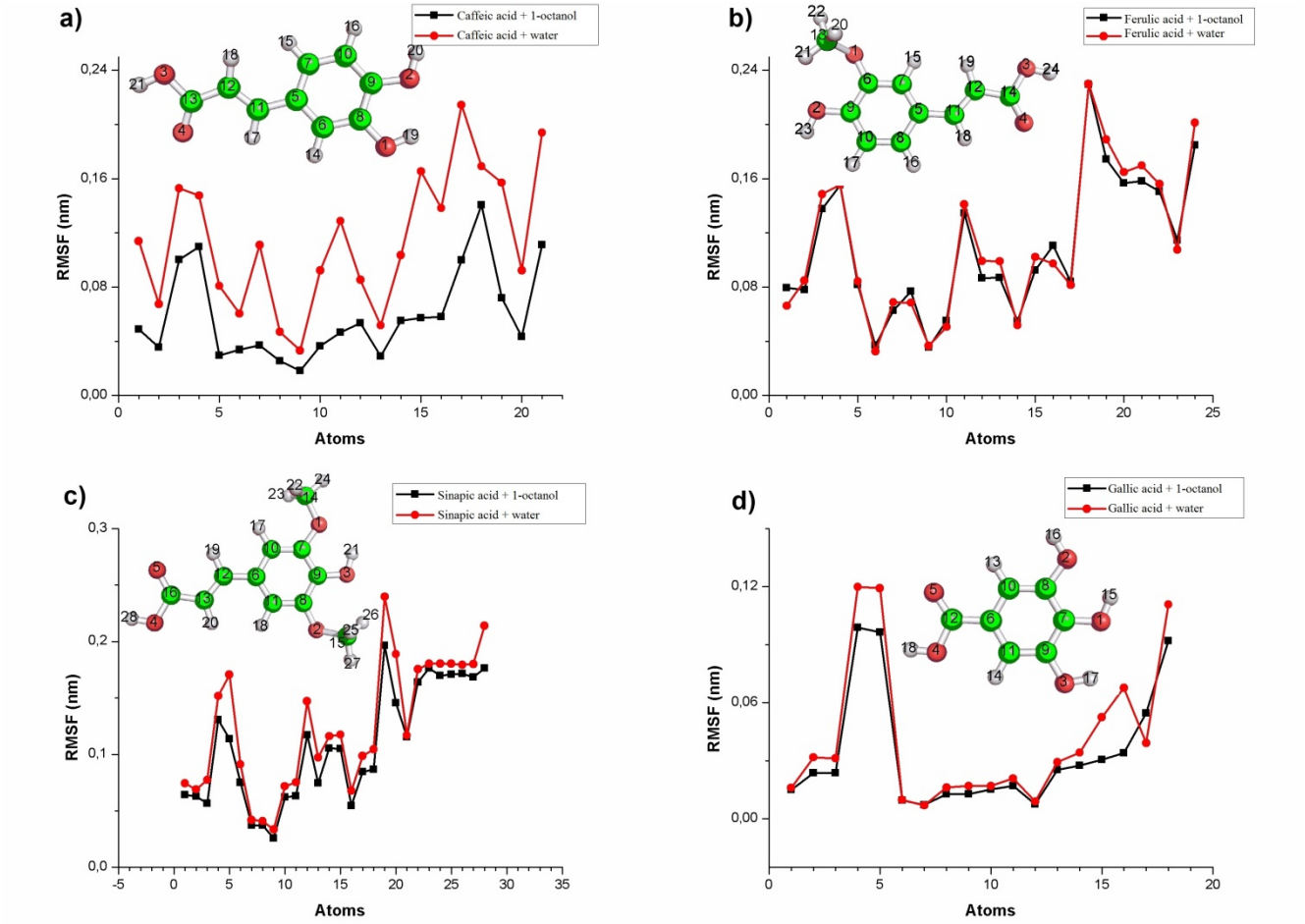

Figure 4. Quadratic mean root fluctuation (RMSF) per atom of the phenolic acid molecules. a) Caffeic acid; b) ferulic acid; c) gallic acid; d) sinapic acid.

Docking Study

In **Table 4** are shown the results of the interaction free energy of phenolic compounds with chitosan (12 meres) obtained through the molecular docking study, besides the torsional energy of the ligands and energy of the electrostatic interactions. Lee et al. [33] investigated the antioxidant activity of sinapic, gallic and ferulic acids alone and conjugated with chitosan. The results proved that the antioxidant capacity of the conjugates was superior to the antioxidant activity of the chitosan alone. The study published by Lee and co-workers also showed that the conjugates have good antimicrobial activity when tested in food pathogens, as well as good cytocompatibility in hepatic cells of mice. In another study conducted by Panwar et al. [34] the antifungal activity of chitosan microcapsules with conjugated ferulic acid was tested. In the Panwar study it was observed that the microcapsules have good activity against *Candida albicans*. Among the phenolic compounds targeted by this study, caffeic and gallic acids were the ones that obtained lower binding energy, being more stable in complexes with chitosan, but the interaction energies of sinapic acid and ferulic acid were also strong.

In **Figure 5** it can be observed five hydrogen bonds between caffeic acid and chitosan through the -COOH and -OH group of caffeic acid and the -OH and -O- groups of chitosan. It can also be observed that the interaction between the hydroxyl of the carboxylic acid and the chitosan occurs with the shortest distance. It can also be observed that the formation of two hydrogen bonds between sinapic acid and chitosan occurs, one through the -COOH group with -OH group of chitosan and another through the -OH group of sinapic acid with a -O- of chitosan. It is also observed that two repulsive polar interactions occur between

the oxygen of the carbonyl of the sinapic acid with -OH and -O- groups of the chitosan. Gallic acid promotes five hydrogen bonds with chitosan, one through the -COOH group of gallic acid with the -OH group of chitosan and another four through the phenolic -OH groups of gallic acid with a -OH and -O- of chitosan.

Table 4. Result of the study of docking of phenolic compounds with chitosan of 12 mer (kcal/mol)

Complexes	Interaction free energy (ΔG interaction)	Vdw_hb_desolv energy (ΔG vdw+hb+desolv)	Electrostatic Energy	Torsional Energy
Ferulic acid + Chitosan	-2.11	-3.66	0.06	1.49
Caffeic acid + Chitosan	-2.95	-4.10	-0.34	1.49
Sinapic + Chitosan	-2.52	-4.06	-0.24	1.79
Gallic acid + Chitosan	-2.88	-3.87	-0.05	1.49

The present study is close to the experimental study carried out by Rosa et al. [35] which, when characterizing microcapsules with conjugated gallic acid through FTIR and NMR spectra, identified possible hydrogen bonds between the phenolic hydroxyls of gallic acid and chitosan. Ferulic acid promotes two hydrogen bonds with chitosan, one through the -COOH group of ferulic acid with -O- group of chitosan and another through the -OH group of ferulic acid with a -O- group of chitosan. It can also be observed that the two hydrogen bonds have the same distance. In the study published by Panwar and collaborators [34], where microcapsules of chitosan with conjugated ferulic acid were developed, the authors propose the possible electrostatic interactions between the carboxylic group of ferulic acid and chitosan amines. The results obtained by molecular docking show that there are polar interactions between the carboxyl group with polar groups of chitosan.

Another important detail, presented in **Figure 6**, is that the caffeic, ferulic and sinapic acids bond in the same site of the chitosan. Gallic acid, however, was bond up somewhere else. In the docking simulation, it was observed that caffeic and gallic acids presented greater stability when complexed with chitosan, due to lower binding energy, but it should be taken into account that sinapic and ferulic acids also have attractive interaction. It was also observed that in all cases they had hydrophilic interactions, which shows the importance of the polar groups of phenolic compounds for interaction with chitosan.

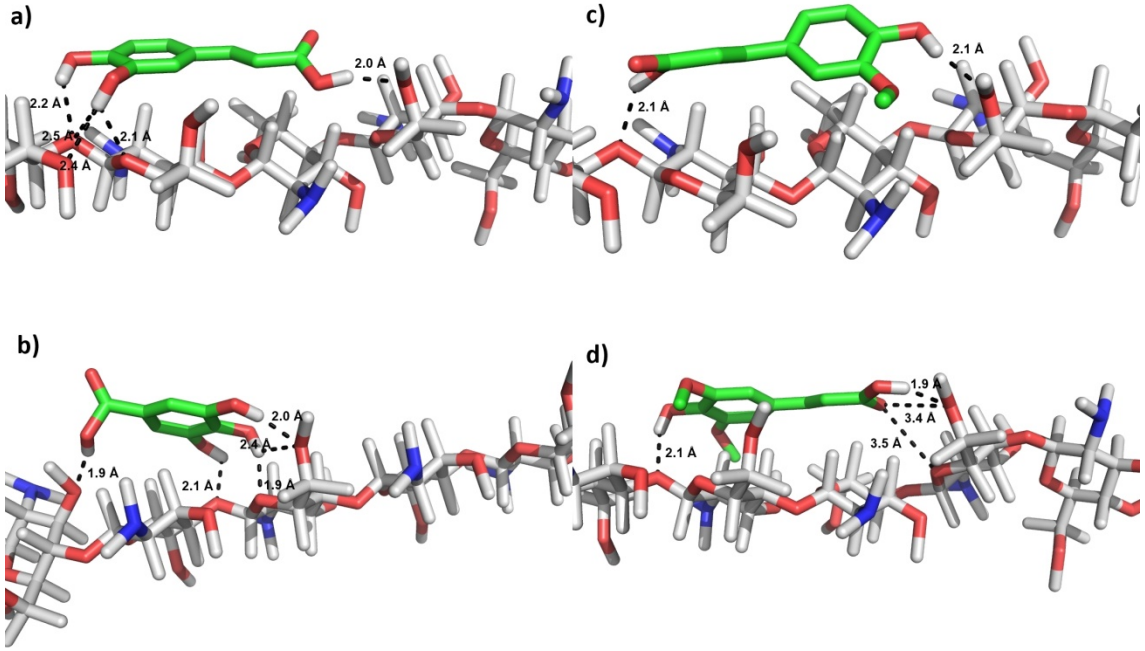

Figure 5. More stable conformation of phenolic acids in complex with 12 mers chitosan.a) caffeic acid; b) gallic acid; c) ferulic acid; d) sinapic acid.

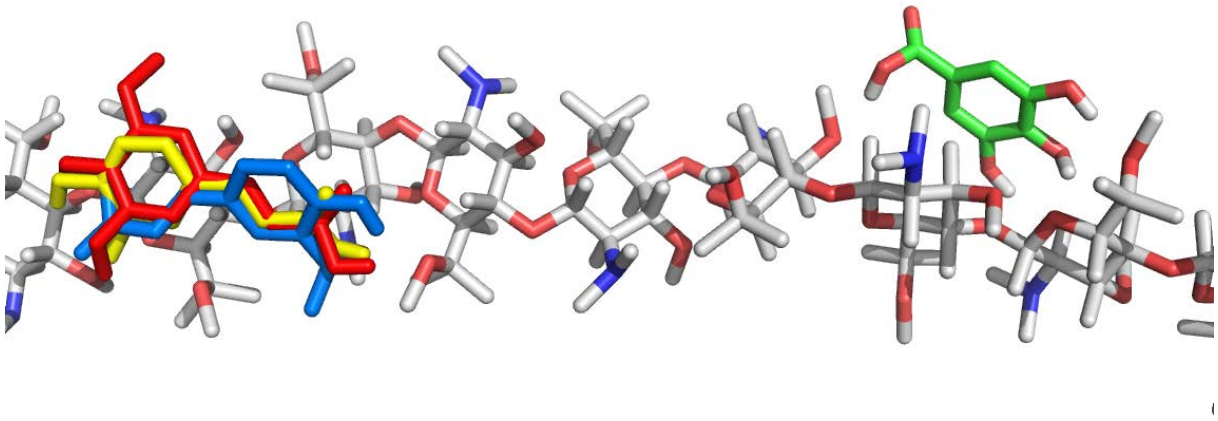

Figure 6. Overlap of sinapic acid, ferulic acid and caffeic acid complexed with chitosan. The caffeic acid is represented in yellow; Ferulic acid in blue and sinapic acid in red.

In **Table 5** are shown the results of the interaction free energy of phenolic compounds with chitosan (nine meres) obtained through the molecular docking study, as well as the torsional energy of the binders and energy of the electrostatic interactions obtained in the docking study. As can be seen in **Table 5**, all the compounds interacted with the chitosan in an attractive manner, with caffeic and ferulic acids having the lowest energies. It is noteworthy that gallic and sinapic acids also presented negative energies, which represents the attractive interaction between the compounds and the chitosan of nine meres.

Figure 7 shows the most stable conformation of the interaction of phenolic acids with chitosan. It is observed that caffeic acid interacts by hydrogen bonds through the phenolic hydroxyl and carboxylic hydroxyl with chitosan. No interaction of hydrogen between ferulic acid and chitosan was observed through the docking study, however, it is observed that the hydrogens of hydroxyls are directed to the oxygen of chitosan, characterizing polar interactions between ferulic acid and chitosan. As with chitosan of 12 meres,

sinapic acid also promotes polar interactions with chitosan nine meres. As in the docking study between gallic acid and chitosan of 12 meres, gallic acid also promoted hydrogen bonding between the phenolic hydroxyls and chitosan, with distances varying from 2.1 to 2.8 Å.

Table 5. Result of the docking study of the phenolic compounds with nine mers chitosan (kcal/mol)

Complexes	Interaction free energy (ΔG interaction)	Vdw_hb_desolv energy (ΔG vdw+hb+desolv)	Electrostatic Energy	Torsional Energy
Ferulic acid + Chitosan	-2.94	-4.28	-0.15	1.49
Caffeic acid + Chitosan	-3.05	-4.45	-0.09	1.49
Sinapic + Chitosan	-2.83	-4.45	-0.16	1.79
Gallic acid + Chitosan	-2.85	-4.16	-0.19	1.49

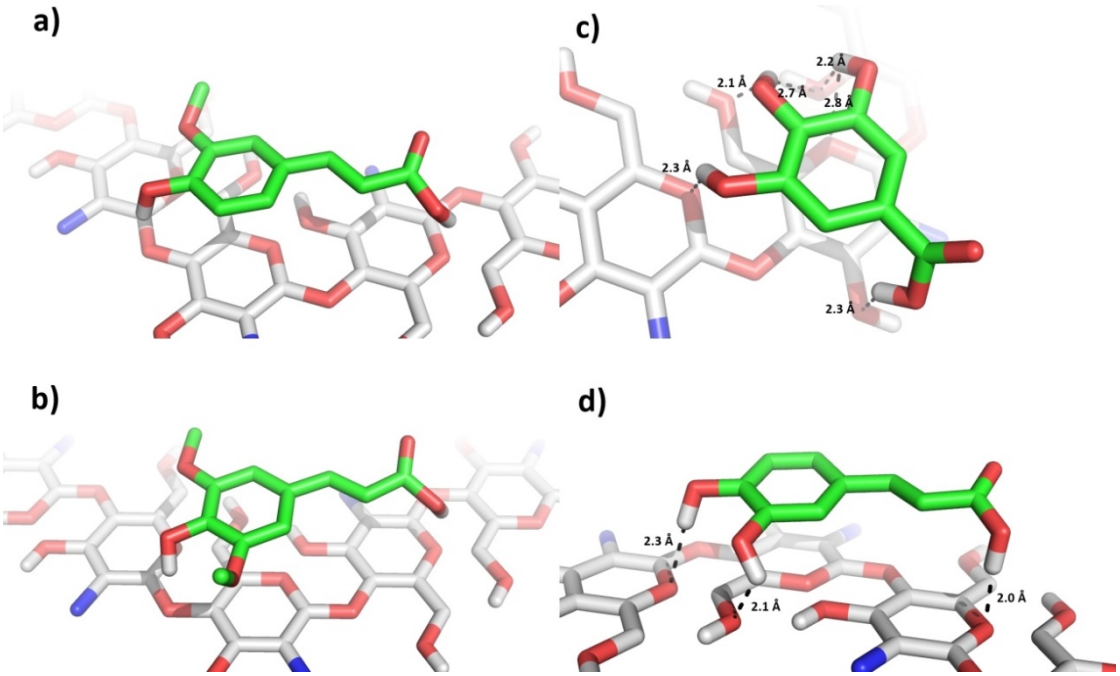

Figure 7. More stable conformation of phenolic acids in complex with nine meres chitosan. a) ferulic acid; b) sinapic acid; c) gallic acid; d) caffeic acid.

Conclusions:

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. The present study investigated the solubility of gallic, ferulic, caffeic and sinapic acids, in order to verify the behavior of these compounds in contact with aqueous biological fluids and with hydrophobic barriers, such as the plasma membrane, for example. This work also investigated the interaction of these compounds with chitosan, to understand how these substances complex with the polymer in the formation of a controlled release system of drugs (film, microcapsule and others) and active films.

It concluded from the *in silico* simulations that caffeic, ferulic, sinapic and gallic acids have adequate solubility to cross hydrophobic

biological barriers and to interact with hydrophilic biological fluids. It was also verified that the phenolic acids involved in the study are good candidates to the development of controlled release systems for active drugs, in the form of microcapsules or films, since they presented strong interaction energy when complexed with chitosan.

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Conflicts of Interest:
The authors declare no conflict of interest

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