

Semi-empirical study of the molecular interaction of paracetamol with lignosulfonated ammonium, sulfur, calcium and sodium in acidic and basic aqueous environments

Pablo Javier Salazar Valencia

pjsalazar@unicauca.edu.co

University of Cauca

Luz Elena Bolívar Marínez

University of Cauca

Servio Tulio Perez Merchancao

University of Cauca

Research Article

Keywords:

Posted Date: October 23rd, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10923908/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Additional Declarations: No competing interests reported.

Semi-empirical study of the molecular interaction of paracetamol with lignosulfonated ammonium, sulfur, calcium and sodium in acidic and basic aqueous environments

P J Salazar Valencia, L E Bolivar Marinez and S T Perez Mechancano

SENUMA group, Departamento de Física, Universidad del Cauca, Popayán, Colombia

*Corresponding author. E-mail: pjsalazar@unicauca.edu.co

All the authors contributed equally to this work

Abstract

Currently, a significant and frequently overlooked issue in the management of wastewater is the increasing presence of molecular residues from pharmacologically active substances, originating from all sorts of human activities.[1] These residues, or PSA, present themselves as a huge family of small molecular fragments, that can't be effectively eliminated in treatment facilities or by natural photodegradation in the water bodies due to their small size, they can and will bypass ultrafiltration processes, remaining within the water cycle and integrating into ecosystems. This integration disrupts living organisms by altering, sometimes to a notable degree, their metabolism, reproduction, and behavior [2]. Ultimately, these residues and the changes they induce find their way back into the human population through the carbon cycle, leading to severe health concerns such as drug resistance in pathogens and allergic reactions [3]. Among the pharmacologically active substances that are prevalent in wastewater due to their affordability and overuse are analgesics like paracetamol or acetaminophen; these compounds are never completely absorbed by the human body and are expelled via the urinary system [5]. In this study, we have examined the interactions between paracetamol molecular residues and lignosulfonates or lignin sulfates, which serve as binding and flocculating agents widely utilized in various industries, employing semiempirical methods from the NDO (Neglect of Differential Overlap) family to determine whether these agents can facilitate the removal of paracetamol molecular waste from wastewater.

1 Introduction

A significant challenge in the domain of water treatment for human consumption is the increasing presence of molecular contaminants known as pharmacologically active substances (PAS) [6]. These substances enter the water cycle through the excretion of living organisms

via domestic, industrial, and healthcare related wastewater [7]. Among these PAS, over-the-counter analgesics are particularly prevalent due to their affordability and accessibility. [8]

One such analgesic is paracetamol, also referred to as acetaminophen. Paracetamol is recognized for its analgesic properties, although it lacks clinically significant anti-inflammatory effects. It functions by inhibiting the production of prostaglandins, which are cellular mediators that trigger pain [9]. Additionally, it possesses antipyretic properties, helping to reduce fever. Paracetamol is commonly available in various forms, including capsules, tablets, suppositories, and oral drops, and is frequently included in numerous cold and flu medications [10]. While it is generally safe at standard doses, its low cost and easy availability have led to numerous instances of overdose [11]. At recommended doses, paracetamol does not adversely affect the gastric mucosa, blood clotting, or renal function; however, even a slight increase beyond the prescribed dosage can result in liver damage. [12]

Unlike opioid analgesics, paracetamol does not induce euphoria or alter the mood of the patient. The terms paracetamol and acetaminophen reflect the historical nomenclature of this compound, with N-acetyl-para-aminophenol and para-acetyl-aminophenol being used interchangeably. The molecular structure of paracetamol or acetaminophen is illustrated in Figure 1.

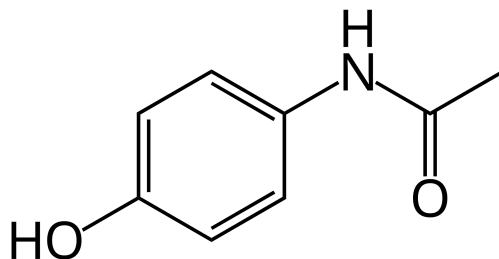


Figure 1: Molecular structure of paracetamol (acetaminophen).

Paracetamol undergoes metabolism primarily in the liver, where it is converted into both toxic and non-toxic metabolites. The three principal metabolic pathways identified are: [13].

- • Glucuronidation, which involves the addition of glucuronic acid, it accounts for 40% to 60% of the metabolites.
- Sulfation, which may represent 20 % and 40% of all metabolites.
- • N-hydroxylation and subsequent rearrangement, followed by GSH conjugation, which constitutes less than 15% of the metabolites. .

The first two pathways yield inactive, non-toxic end products that are ultimately excreted by the kidneys. In contrast, the third pathway produces a toxic intermediate known as

NAPQI or N-acetyl-p-benzoquinone imine, which is primarily responsible for the toxic effects associated with paracetamol, exemplifying a case of intoxication. [14] Figure 2 shows the molecular species resulting from the acetaminophen degradation by liver metabolism.

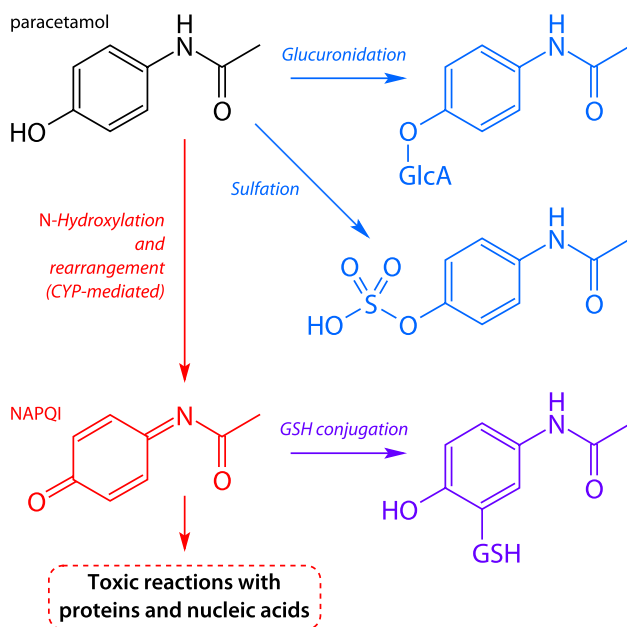


Figure 2: Molecular structure of the paracetamol metabolites after they are processed in the liver

Lignosulfonates (LS), also referred to as lignin sulfonates or lignin sulfites, are essentially sulfonated forms of lignin derived from sulfite liquors, which are byproducts of the paper pulp extraction process in the wood derivatives industry [15]. Their primary utility stems from their diverse properties, allowing them to serve as additives, dispersants, binders, fluidizing agents, and more across various sectors, including food, fertilizers, and the production of ion exchange membranes [16]. Due to their relatively simple and rapid manufacturing process, as well as the ability to manipulate their molecular size to create low molecular weight fragments, they are utilized as transport agents in the food, cosmetic, and pharmaceutical industries, as well as in the development of drugs and molecular components for addressing health issues. [17]

The extraction of LS is known as delignification, which involves breaking the ester bonds (C-O-C) that link the components of lignin [18]. The electrophilic carbocations generated during this bond cleavage react with bisulfite ions to form sulfonates, facilitating the incorporation of functional groups into the molecular structure. Ions such as Calcium, Sodium, Magnesium, and Ammonium are among those incorporated, as briefly illustrated in Figure 3. [19]

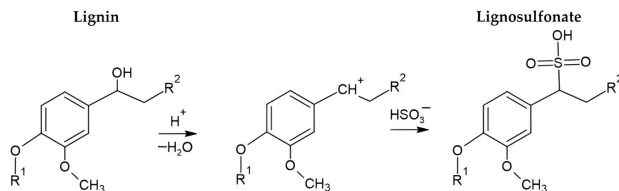


Figure 3: Lignosulfonate (LS) formation process.

During this process, the removal of the adhering components from the woody tissue leads to the creation of a type of polyelectrolyte polymers characterized by high acidity, attributed to the presence of highly dissociated sulfonic acid groups within their molecular framework [20]. Unlike lignin, which is typically found in cell walls, these sulfonic acid groups exhibit solubility in water; collectively, these molecules are referred to as lignins. [21]

Empirical observations have indicated that LS exhibit properties that enable them to function effectively as free radical scavengers and antioxidants. The significance of investigating the interaction between LS and free radicals stems from the involvement of oxygen-derived free radicals in the onset of various diseases, including cancer, rheumatoid arthritis, and arteriosclerosis, as well as in degenerative processes associated with aging. These free radicals are produced through metabolic activities and from external sources such as food, pharmaceuticals, ultraviolet radiation, and environmental pollutants. [22]

The characteristics of LS, like any other molecular system, are a consequence of their structural composition and the properties of their individual components, sharing fundamental precursor forms and binding mechanisms with lignin. Upon examining their molecular structure, one can observe a series of small aggregates comprising two or three precursor units linked by Carbon-Oxygen bonds, predominantly of the β -O-4 type, which connect the aromatic segments to a carbon chain. This carbon chain is further modified by the attachment of various substituent groups, including sulfonates (functional groups containing an SO_3 ion). Additional functional groups may be connected to the sulfonates, occupy available positions on the carbon chain, or exist in proximity to the molecular structure. An example of a LS complex with calcium is depicted in Figure 4, showcasing a fundamental unit with a nearby Ca atom, which may be ionized or not. [23]

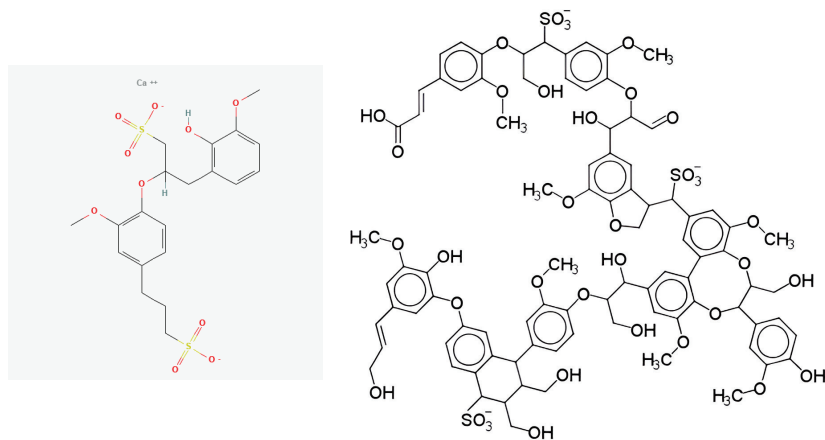


Figure 4: Example of a Calcium LS, consisting of two fundamental units that take the form of a macromolecule..

This macromolecule subsequently expands through a process of random polymerization, resulting in an amorphous, three-dimensional biopolymer. Just like in lignin, this structure poses challenges for study due to its size and the inherent randomness of its formation. However, prior research has indicated that the properties of the fundamental units or precursors of lignins can be reliably extrapolated to accurately characterize the macrostructure's attributes and behavior.[24]

2 Methodology

The methodology employed in this research involves the examination of molecular geometries and properties derived from prior studies. Specifically, the paracetamol molecule will be integrated with small fragments of three fundamental LS units that include Ammonium, Sulfur, Calcium, and Sodium functional groups. This integration will occur in aqueous, acidic, and basic environments to analyze the interactions among the molecular systems, focusing on parameters such as atomic distances, heat or enthalpy of formation, and simulations of electrostatic potentials. We will use the molecular modeling software Hyperchem 5 [25], applying the semiempirical methods AM1 and PM3 from the NDO (Neglect of Differential Overlap) family to assess structural properties. Additionally, the electronic and optical properties will be evaluated using the semiempirical ZINDO/CI method. A gradient RMS convergence criterion with a limit of 10-3 will be implemented throughout all calculations. [26] The electronic and optical properties will be determined in single point mode using the ZINDO/CI method, with a search criterion of six occupied and six unoccupied orbitals. The initial phase will involve a semiempirical characterization of paracetamol utilizing the aforementioned methods to ascertain its fundamental structural, electronic, and optical characteristics in both vacuum and acidic and basic aqueous environments. Subsequently, the paracetamol molecule will be combined with the specified LS units, allowing for further

observation of the characteristics of the resulting molecular systems in the designated media. [27]

3 Results

Table 1 presents the enthalpy of formation values derived from geometry optimizations of paracetamol, utilizing the three primary methods of the NDDO approach. The PM3 method yields the most accurate result, differing by approximately 10 kcal/mol from the AM1 and MNDO methods. The enthalpy of formation quantifies the energy change associated with the formation of one mole of a compound from its constituent elements, all in their standard states. A more negative value indicates a greater likelihood of the structure’s existence and stability.

Method	Heat of Formation
MDNO	-58.01
AM1	-56.97
PM3	-67.12

Table 1: presents the heat of formation in kcal/mol for paracetamol in its neutral state and in a vacuum.

Given that PM3 yields the most accurate results, it was chosen as the method for conducting the subsequent geometry optimizations in this study. The geometrical structure derived from these calculations is illustrated in Figure 5.

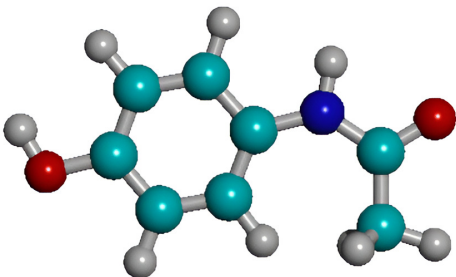


Figure 5: Molecular structure of Paracetamol, derived from geometry optimization using the PM3 semiempirical method.

It is important to note that the graphical representations of the geometries for the molecular systems examined in this study are two-dimensional projections of their three-dimensional counterparts, which inherently leads to visualization challenges. For instance, the depicted geometry reveals a predominantly planar molecule, measuring approximately 6.5 Å in length

and 2.42 Å in width, with a minor side chain extending out of the plane at a torsion angle of roughly -27°. The molecular mass is recorded at 151.15 amu (atomic mass units). However, Figure 5 does not fully convey all this information; therefore, it is essential to consider additional parameters, such as the heat of formation, to gain a more comprehensive understanding of the molecular systems under investigation.

Charge	Heat of Formation	
	Vacuum	Aqueous Environment
+1	117.73	-1147.02
0	-67.12	-1409.72
-1	-77.71	-1401.16

Table 2: Heat of formation in kcal/mol for paracetamol in both vacuum and aqueous environments across various charge states, with results derived from the PM3 method.

Next, geometry optimizations were conducted in a solution containing 50 water molecules within a periodic box. This system was initially analyzed in a charge-neutral state and later ionized by adding one proton and one electron to assess the molecule’s behavior as either an electron acceptor or donor. The findings, detailed in Table 2, reveal a significant reduction in the heat of formation when transitioning from vacuum to an aqueous environment, indicating a strong affinity of paracetamol for water. Notably, in a vacuum, paracetamol acts as an electron acceptor, whereas in water, it neither accepts nor donates electrons, suggesting that the free radical bonding mechanism is not applicable for this structure.

The electronic properties were evaluated using the ZINDOS/CI method, with relevant data presented in Table 3, indicating that paracetamol functions as an electrical insulator regardless of the surrounding medium, and this insulating behavior remains unchanged upon ionization. However, ionization does influence the electronegativity of the structure, as illustrated in Figure 6. The energy gap, defined as the difference between the self-energy values of the highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO), provides insight into the electrical conduction properties of the molecular structure, enabling classification into conductors, semiconductors, and insulators.

Environment	Charge	HOMO	LUMO	GAP
Vacuum	+1	-9.87	-4.03	5.84
	0	-8.36	0.44	8.80
	-1	2.47	4.65	2.18
Water	+1	-10.53	-3.51	7.02
	0	-8.31	0.44	8.75
	-1	1.06	3.11	2.05

Table 3: HOMO, LUMO, and GAP energy values in electron volts (eV) for paracetamol in both vacuum and aqueous environments across various charge states, with values derived from the ZINDO/CI computational method.

The graphical depictions of electrostatic potential, commonly referred to as potential energy maps, serve to illustrate the distribution of molecular charges in two or three dimensions. These visualizations facilitate an understanding of the spatial arrangement and behavior of charged regions within molecules, thereby enabling the assessment of molecular interactions. Furthermore, these representations elucidate additional properties such as polarity, electronegativity, and bonding characteristics, leveraging the intrinsic connection between charge distribution and these properties.

Given the absence of precise equations to predict such properties for complex molecules, these visual tools emerge as the most effective means of analyzing the aforementioned characteristics. In the realm of organic chemistry, these representations prove particularly valuable, as they compensate for the lack of equations that adequately describe the complexities of molecular interactions. They provide a robust framework for identifying the most reactive sites, whether nucleophilic (associated with proton affinity) or electrophilic (linked to electron affinity), and illustrate how these sites evolve during molecular interactions.

The significance of these reactive sites is underscored by their role in the gain or loss of functional groups within molecules, as well as their indication of regions within the molecular system that exhibit greater repulsion or attraction. This is particularly relevant in identifying areas with a higher likelihood of interaction and bond formation between different molecular systems. In the context of paracetamol, analysis reveals that in its neutral charge state, the most reactive sites are associated with the nitrogen and oxygen atoms. Upon ionization through electron removal, resulting in a -1 charge state, the reactivity of these regions expands, encompassing the vicinity of the aromatic ring.

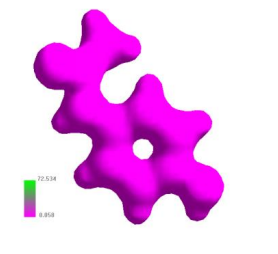
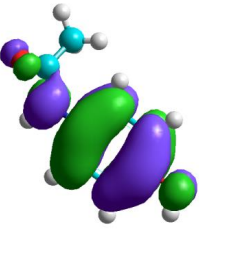
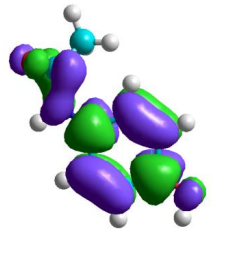
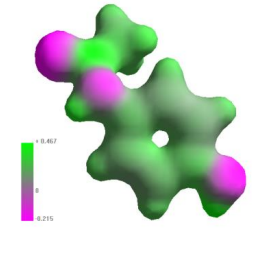
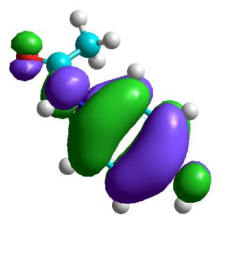
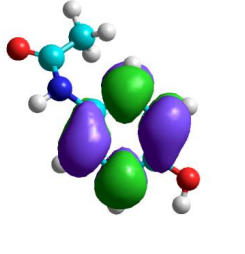
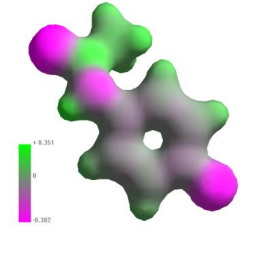
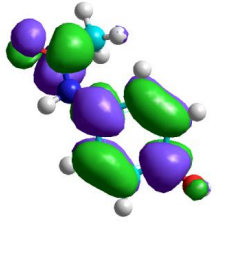
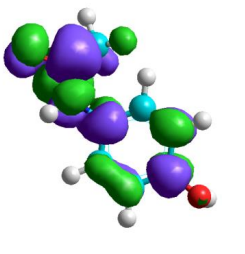
Charge	Electrostatic Potential	HOMO	LUMO
+1			
0			
-1			

Figure 6: Graphical representation of the electrostatic potential, HOMO and LUMO orbitals for paracetamol in various ionization states. Results obtained from the application of the ZINDO/CI method.

The state in which the molecule exhibits the highest reactivity corresponds to +1 ionization, indicating the presence of a proton. In this scenario, the entire molecule is reactive; however, the heat of formation values for this charged state suggest that the likelihood of the molecular system existing in this state, whether in a vacuum or in water, is quite low.

The interaction of paracetamol with various acidic and basic aqueous environments was examined by focusing on the solvents typically utilized in conventional laboratories. This combination leads to an expansion of the molecular system under investigation, as the paracetamol molecule integrates with a mixture of water molecules and solvents. Consequently, the simulation time increases significantly. Nevertheless, this challenge has highlighted the remarkable adaptability of semiempirical methods, as a satisfactory balance between simulation duration and result quality was achieved.

Environment	Heat of Formation
Water	-1409.72
Water + Sulfuric Acid	-3005.23
Water + Hydrochloric Acid	-1315.55
Water + Nitric Acid	-1773.51
Water + Sodium Hydroxide	-2311.37
Water + Ammonium	-1063.92

Table 4: Heat of formation in kcal/mol for paracetamol in the different media considered. Values found with the AM1 method.

The information presented in Table 4 illustrates the heat of formation values for the newly developed molecular systems, indicating the affinity of paracetamol with the environments examined in this study. It is evident that the optimal medium comprises both water and sulfuric acid molecules. Furthermore, the electronic properties of these combinations were analyzed using the ZINDOS/CI method, with the results detailed in Table 5. The energetic gap values consistently indicate an insulating behavior. Notably, the paracetamol-water and nitric acid combination exhibits a lower gap value, nearly 2 eV less than the other combinations, while the analysis involving sodium hydroxide is inconclusive due to insufficient parameters for system resolution.

Environment	HOMO	LUMO	GAP
Water	-8.31	0.44	8.75
Water + Sulfuric Acid	-7.97	0.37	8.34
Water + Hydrochloric Acid	-8.34	0.25	8.59
Water + Nitric Acid	-8.27	-1.98	6.29
Water + Sodium Hydroxide	FAILED	FAILED	FAILED
Water + Ammonium	-8.39	0.22	8.61

Table 5: Energy of the HOMO and LUMO orbitals, GAP energy in eV for the paracetamol studied in the presence of different solvents, values obtained with the ZINDO/CI method..

Failures of this nature frequently occur when working with elements that are not entirely parameterized within semiempirical methods. It is important to emphasize that this does not undermine the validity of the findings; rather, it highlights the necessity for further development in this area. The advantages of these methodologies, as discussed in this research, reinforce this viewpoint.

We will now proceed to examine the interaction between paracetamol and the lignin structures (LS) analyzed in this study, whose properties have been previously investigated in other literature. In these novel molecular systems, the LS were integrated as they were synthesized, ranging from 1 to 3 precursor units; larger LS were not utilized due to the constraints of the computational resources available. Nevertheless, this limitation does not

diminish the validity of the results, as commercial LS products exhibit a vast array of molecular sizes. By sharing characteristics with lignin, the properties of these macromolecules can be extrapolated from those of the precursors and smaller polymeric fragments.

LS with:	Charge	1 Unit	2 Units	3 Units
Ammonia	+1	-108.79	-305.67	-502.14
	0	-287.27	-484.87	-683.88
	-1	-332.97	-532.37	-739.16
Sulfur	+1	-58.68	-289.52	-478.23
	0	-234.33	-459.50	-643.75
	-1	-282.38	-520.73	-706.33
Calcium	+1	-719.48	-1624.85	-1775.58
	0	-834.01	-1723.80	-1889.31
	-1	-887.65	-1774.03	-1963.21
Sodium	+1	-234.34	-491.21	-834.89
	0	-367.08	-605.69	-871.60
	-1	-423.99	-656.13	-896.27

Table 6: Heat of formation values in kcal/mol for paracetamol in combination with the LS studied, in vacuum and different charge states. Values obtained with the semiempirical methods AM1 and PM3.

In vacuum, the values obtained show that the molecular systems become more stable as the LS fragments grow, with a significant decrease in the values of the heat of formation, and when these systems are ionized, a tendency to behave as electron acceptors is observed, although the difference between the neutral and -1 charge states decreases progressively, it is reasonable to expect that eventually systems containing larger LS do not present this behavior. This information is given in Table 6.

Paracetamol + LS with:	Charge	1 Unit	2 Units	3 Units
Ammonia	+1	-2431.56	-2751.04	-3066.47
	0	-2598.47	-2925.17	-3238.89
	-1	-2655.64	-2972.61	-3298.66
Sulfur	+1	-1227.12	-1909.37	-1761.92
	0	-1393.80	-2080.49	-1912.14
	-1	-1395.41	-2140.02	-1982.37
Calcium	+1	-2281.54	-2237.26	-3221.10
	0	-2395.78	-2325.86	-3294.02
	-1	-2457.71	-2378.06	-3391.93
Sodium	+1	-2017.37	-2165.54	-2324.93
	0	-2141.27	-2216.92	-2350.97
	-1	-2214.57	-2291.46	-2433.58

Table 7: Heats of formation values in kcal/mol for paracetamol in combination with the studied LS, in aqueous medium and different charge states. Values obtained by semi-empirical methods AM1 and PM3..

Previous works [28] have reported a coupling phenomenon between the aromatic parts of paracetamol structures and lignin fragments from softwoods in their natural unprocessed form and have proposed that this mechanism can be used to trap analgesic molecules in aqueous environments. In this work, this possibility has been explored since the considered LSs share many characteristics and properties with natural lignin, the only significant difference being that LSs are water soluble while natural lignin is not. [29]

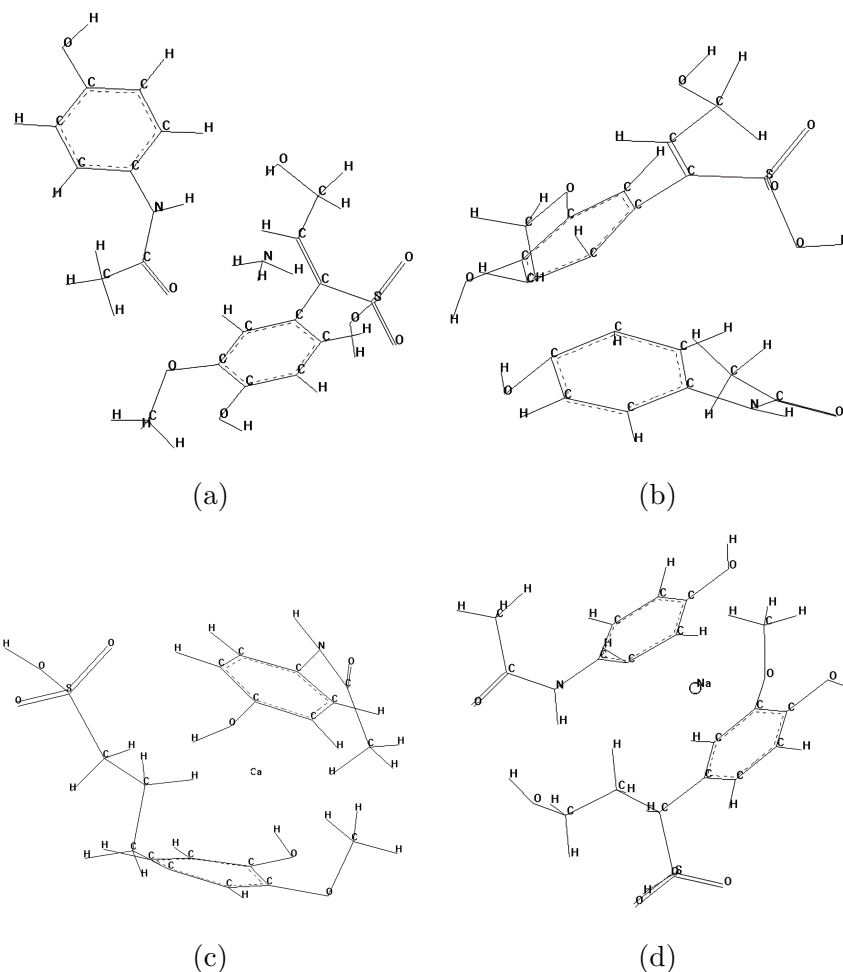


Figure 7: Graphical representations of the molecular interactions between acetaminophen and monomeric fragments of the studied LS in water. (a) LS with ammonium. (b) LS with sulfur. (c) LS with calcium. (d) LS with sodium.

These interactions are graphically represented in Figure 7, where it should be clarified that the water molecules of the medium are not included to facilitate the visualization. The graphical representations of the molecular geometry of the systems studied show that the phenomenon of alignment does indeed occur, only that it is not as significant as that observed for lignin in natural form; of all the LS studied, only the one combined with ammonium doesn't present the phenomenon of alignment, and of the remaining three, the one that presents the best results is the LS with sulfur, in which the distance between the planes containing the aromatic rings is of the order of 1.5 Å, but the rings tend to join on one of their sides.

For the other two LS, with calcium and with sodium, the observed coupling is much better, with the aromatic rings located on top of each other aligning almost perfectly, this phenomenon can be explained in terms of the interaction between the conjugated π bonds of the molecules involved, together with the involved substituent atoms corresponding to

the LS, these calcium and sodium atoms tend to locate between the two molecules acting as linking elements between them.

The resulting distances between the aromatic parts range from 2.1 Å for the LS with Calcium to 3.1 Å for the LS with Sodium, and a closer observation shows an interesting phenomenon, the fact that the LS try to form bonds by any possible means within their reach, in the case of the LS with Ammonium it is appreciated that although the aromatic parts don't align, the edges of the molecules tend to form bonds through the hydrogens and other functional groups present. This feature once again demonstrates the incredible diversity and versatility of LSs for the development of all types of products and applications.

By observing the interaction of the larger LS (3 units), we can see (Figure 8) that the molecular structures in an aqueous medium have a more varied behavior, presenting interactions that go beyond the coupling between aromatic structures observed in the combinations of paracetamol and LS precursors. The combinations containing LS with ammonium (a) and sulfur (b), show a scenario in which the LS tend to stretch longitudinally, while the paracetamol molecule is parallel to them and tends to bond to the LS by one of its ends; the geometry found shows that there is a tendency to form bonds between the oxygen atoms and it is very likely that the shape of the alienation between the molecules is due to the repulsion caused by the size difference between them. [30]

In the case of combinations incorporating LS with calcium (c) and sodium (d), however, a radical difference is observed. The geometries obtained show a tendency for LS to close on itself, almost surrounding nearby molecules, independent of whether they are substituent groups or paracetamol. The way molecules "close" on each other is determined by the nature of the ions that act as substituent groups. In this case, the atoms of calcium and sodium, which are more electronegative than sulfur and ammonium, tend to attract other atomic elements more intensely.

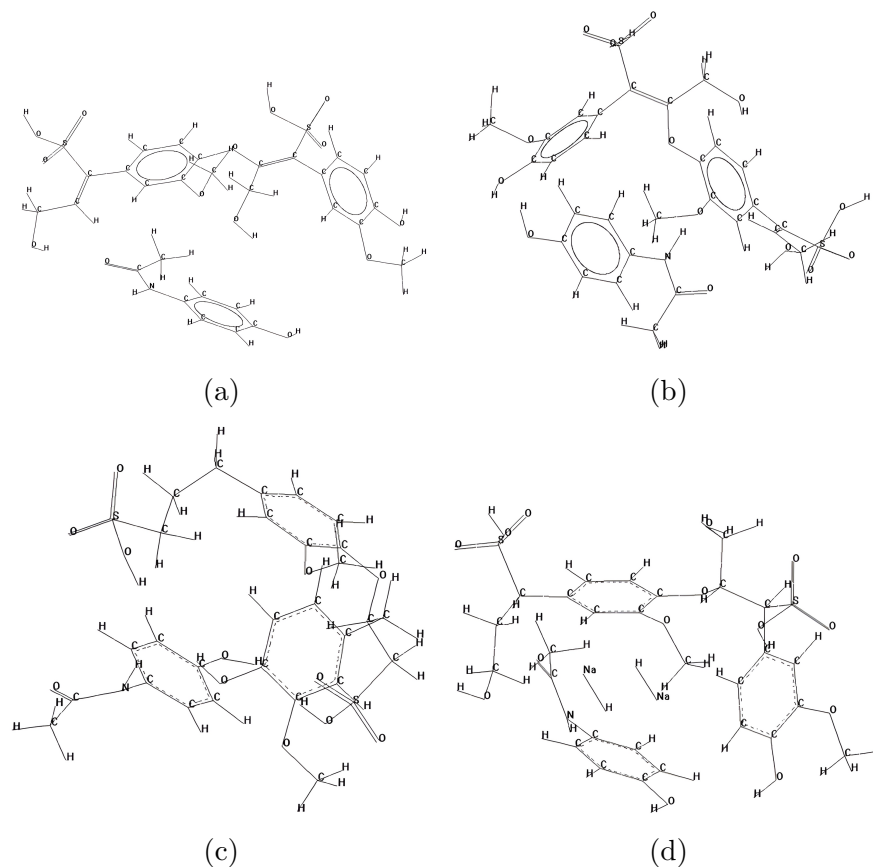


Figure 8: Graphical representations of the molecular structures of the LS studied in combination with paracetamol in an aqueous medium. Water molecules not shown to facilitate visualization. (a) LS with Ammonium. (b) LS with Sulfur. (c) LS with Calcium. (d) LS with Sodium.

Environment	LS with Ammonium	LS with Sulfur	LS with Calcium	LS with Sodium
Vacuum	7.87	7.63	7.49	6.38
Water	7.86	7.82	7.51	7.02
Water + Sulfuric Acid	7.79	8.04	5.58	6.73
Water + Hydrochloric Acid	7.82	8.08	5.59	5.19
Water + Nitric Acid	6.13	6.77	5.63	6.11
Water + Sodium Hydroxide	7.80	7.94	6.10	5.54

Table 8: Energy gap in electron volts for paracetamol in combination with the studied LS was measured in all the environments studied. The values obtained with the semiempirical ZINDOS method in CI configuration, LS fragments are 3 units in size..

This observation is further substantiated by the reactivity of the systems, as evidenced by the information obtained from the optical GAP values (Table 8) and the electrostatic

potential values (Figure 9) derived from the ZINDOS/CI method. The GAP values consistently exhibit insulating behavior, irrespective of the combination, a finding that aligns with the observations made for isolated LS and paracetamol.

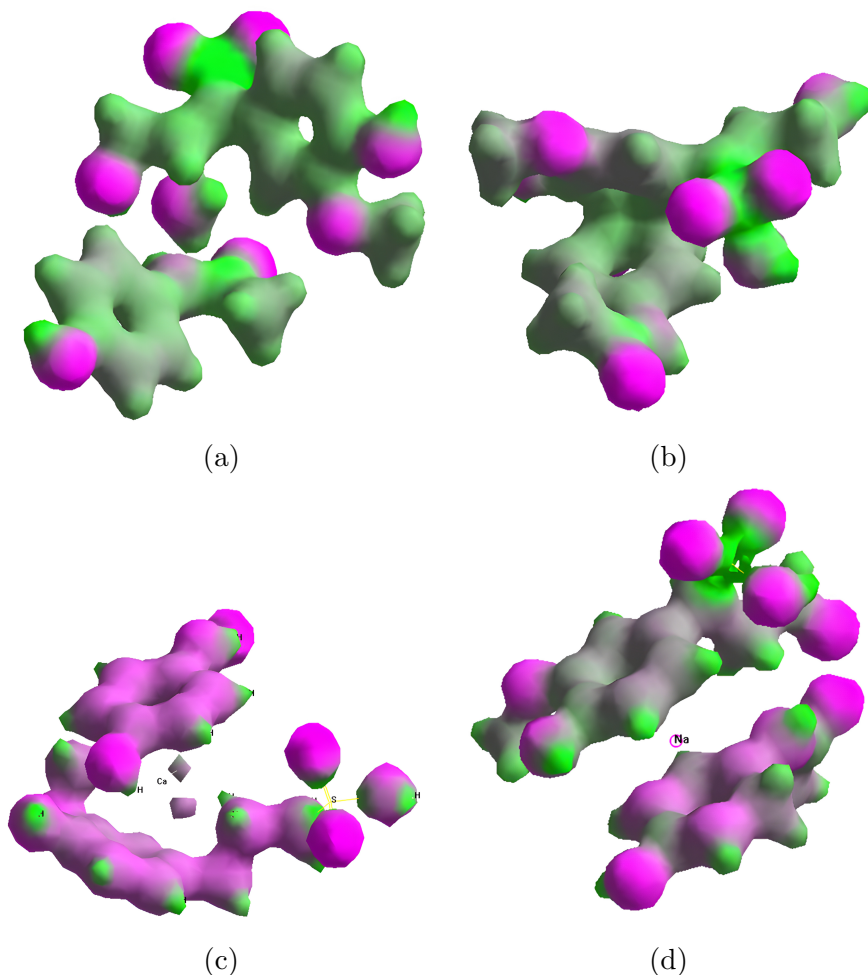


Figure 9: Graphical representations of the electrostatic potential of the molecular interactions between paracetamol and monomeric fragments of the LS studied. (a) LS with Ammonium. (b) LS with Sulfur. (c) LS with Calcium. (d) LS with Sodium.

As illustrated in Figure 9, the graphical representation of the electrostatic potential for the combination of paracetamol with LS and Ammonium reveals that the most reactive sites, indicated in the figure by the purple-colored regions, are located within the atoms of oxygen, sulfur, and nitrogen in the separated molecules. The combination of LS with sulfur demonstrates that the two molecules have become so close that they essentially become a single entity with their own reactive sites. This phenomenon is primarily attributed to the alignment between the aromatic parts and the formation of hydrogen bonds at the edges of the molecules. However, this phenomenon does not recur with the other two LSs. The separation between them is such that the molecules do not bond. The reactivity in the case of the molecular system incorporating the LS with calcium is very good and extends over

practically all the atoms that form it. In the instance of the combination with the LS and sodium, the molecules exhibit near-perfect alignment and demonstrate high reactivity.

To gain a comprehensive understanding of the subject, a study was conducted on the molecular systems of paracetamol and LS when placed in the acidic and basic media under consideration in this work. The values of the heat of formation obtained (see Table 9) demonstrate that transitioning from a vacuum to an aqueous environment significantly enhances the stability of molecular combinations. It is also evident that the medium in which the systems studied demonstrate optimal performance is the combination of water and sulfuric acid, irrespective of the type of LS present. In conclusion, the system demonstrating optimal energetic behavior is the one in which paracetamol and a LS with calcium are combined in a water and sulfuric acid environment.

Environment	LS with Ammonium	LS with Sulfur	LS with Calcium	LS with Sodium
Vacuum	-683.88	-643.75	-1889.31	-871.60
Water	-3238.89	-1912.14	-3294.02	-2350.97
Water + Sulfuric Acid	-3337.89	-3153.88	-6867.12	-5104.75
Water + Hydrochloric Acid	-2905.82	-2236.06	-6323.04	-3911.85
Water + Nitric Acid	-2884.61	-2297.74	-5994.98	-3791.55
Water + Sodium Hydroxide	-2927.21	-2478.21	-6515.86	-3728.60

Table 9: Heat of formation in kilocalories per mole for paracetamol in combination with the studied LS, in all the studied media. Values obtained through the utilization of the semi-empirical methods AM1 and PM3, all LS fragments have three precursor units.

It had previously been observed [31] that the LS with calcium presents a structure in which the molecule tends to close around itself, thereby attracting the molecular elements of its environment. This behavior remained constant when combined with paracetamol. According to the values of heat of formation assigned in Table 9, the energetic behavior is optimal even in a vacuum. These characteristics suggest that, in scenarios where the aqueous medium becomes acidic, whether through the addition of sulfuric acid or a comparable substance (bleach or sodium hypochlorite), LS with calcium would effectively fulfill the role of molecular capture investigated in this study. Given the availability of LS with calcium as a commercially viable alternative, with price points ranging from 200 to 500 per ton, the incorporation of this substance into water treatment processes is both feasible and economically sound.

When visualizing the molecular structure of this combination (Figure 10), it is observed that the LS with calcium tends to "surround" the paracetamol molecule. Furthermore, the molecules of the medium, which were initially uniformly distributed and filled the box, are now grouped around the LS and paracetamol. The observed clustering can be explained by the high electronegativity of LS with calcium, as illustrated in Figure 9(c). The calcium and sulfur atoms function as linking elements between the larger molecules, as previously observed.

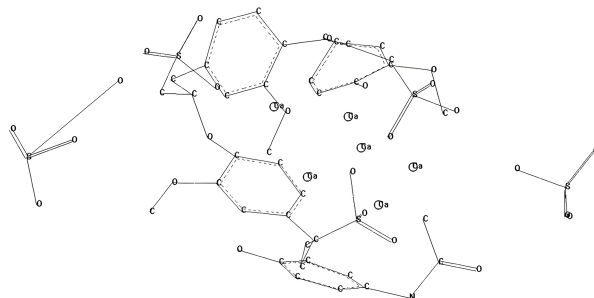


Figure 10: Best combination found: Paracetamol + LS with Calcium + Water + Sulfuric Acid.

Finally, there is a representation of the optical or ultraviolet absorption spectrum (Figure 11) for a hypothetical water sample that includes paracetamol with LS with calcium in an environment of water and sulfuric acid, the most intense transition appears in the region of 270 nm and is considered a distinctive mark of the presence of lignin-derived products. It should be clarified that LS with calcium are widely used in the food industry as binding agents and are therefore perfectly safe in terms of toxicity, which reinforces the possibility of using it for the objectives proposed in this work.

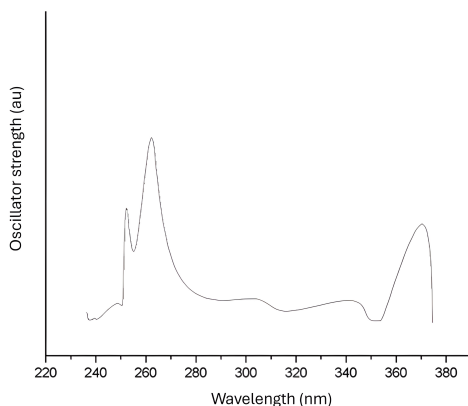


Figure 11: Optical absorption spectrum corresponding to the best combination found: Paracetamol + LS with Calcium + Water + Sulfuric Acid. Applied method: ZINDOS/CI..

The feasibility of implementing a cleaning process that utilizes LS in a wastewater treatment stage is a reasonable proposition. This stage can be implemented in either settling or sedimentation tanks. The utilization of lime in these tanks is typically employed for the purpose of agglutinating and precipitating the small solids that have eluded the mesh filters. The incorporation of LS at this stage would be both feasible and economically viable, given its relatively low commercial cost. The findings of this study indicate that sulfuric acid, the acid solvent that exhibited a propensity for molecular capture, poses significant drawbacks

due to its high toxicity. However, the study’s results also demonstrate that, in general, any acid medium can be effective, thereby facilitating the exploration of alternative additives.

4 Conclusions

- The findings regarding the heat of formation of paracetamol, measured in both vacuum and aqueous conditions, indicate a strong preference of the molecule for aqueous environments. Additionally, the electronic characteristics reveal that paracetamol functions as an insulator.
- The graphical representations of the electrostatic potential highlight that the most reactive sites are associated with the Nitrogen and Oxygen atoms. Furthermore, upon ionization with a single electron, resulting in a -1 charge state, the reactivity of these regions increases, expanding to include the vicinity of the aromatic ring.
- The findings regarding the heat of formation for paracetamol across various acidic and basic environments examined in this study indicate that the optimal medium for the stability of the molecular system is one that includes a combination of water and sulfuric acid. Furthermore, it was noted that this specific environment enhances the insulating properties of the system.
- Additionally, it was determined that the medium or environment with the Lewis Structures (LS) that exhibits the highest affinity for paracetamol is characterized by the presence of Calcium and Sodium substituent groups or ions. Prior research has demonstrated that LS containing Calcium and Sodium exhibit a mimetic behavior, effectively surrounding the accompanying molecules in a manner akin to an 'embrace'. This behavior was consistently observed in both vacuum and aqueous environments, contrasting with the behavior of LS containing Ammonium and Sulfur, which tend to align longitudinally in parallel with adjacent molecules.
- An observed alignment phenomenon was noted between the aromatic components of the lignin structures (LS) examined in conjunction with paracetamol, particularly pronounced in the interaction with the sulfur-containing LS, where this alignment promotes the development of a novel molecular entity. In contrast, for the other LS analyzed, while alignment is present, it does not facilitate the proximity necessary for the establishment of more substantial bonds or interactions. Previous studies have proposed this phenomenon as a potential mechanism for a lignin molecule to 'capture' paracetamol; however, this investigation has revealed the existence of more effective capture mechanisms, specifically the manner in which the LS containing Calcium and Sodium envelop the contaminant molecule, independent of the alignment of aromatic planes, and instead forming bonds through hydrogen and other functional groups, thereby leveraging their electronegativity.
- The mechanism of 'capture' identified in the examination of paracetamol’s interaction with LS containing Calcium and Sodium in an aqueous environment appears to be

enhanced by the presence of sulfuric acid molecules. In this scenario, it is evident that the LS not only 'envelops' the paracetamol but also results in a further reduction in the calculated heat of formation values. A geometric analysis of these interactions reveals that the introduction of H₂SO₄ facilitates the clustering of all molecules in the medium around the LS.

Acknowledgements.

The authors wish to thank the Vicerrectoría de Investigaciones of the University of Cauca for the support to the development of this work under the research grand ID 4524

Declarations

- **Funding:** This work was developed thanks to the support of the *Vicerrectoría de Investigaciones* of the University of Cauca under the research grant ID 4524.
- **Conflict of interest/Competing interests:** Not applicable.
- **Ethics approval and consent to participate:** Not applicable.
- **Consent for publication:** All authors consent to the publication policies of the Brazilian Journal of Physics.
- **Data availability:** The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.
- **Materials availability:** Not applicable.
- **Code availability:** Not applicable.
- **Author contribution:** All authors contributed equally to the development of this work.

References

- [1] Vieira, Y., Spode, J. E., Dotto, G. L., Georgin, J., Franco, D. S. P., Reis, G. S., & Lima, E. C. (2024). Paracetamol environmental remediation and ecotoxicology: A review. *Environmental Chemistry Letters*, 22, 2343–2373. <https://doi.org/10.1007/s10311-024-01751-1>
- [2] Yisau, Y. S., Al-Makishah, N. H., & Barakat, M. A. E. F. (2024). Microbial degradation of paracetamol in pharmaceutical wastewater: A review. *American Journal of Environmental Sciences*, 20(2), 31–47. <https://thescipub.com/pdf/ajessp.2024.31.47.pdf>

- [3] Bano, A., Prasad, B., Kumari, M., Meili, L., & Prasad, K. S. (2025). Pharmaceuticals in water and wastewater: A review on ecological risk and sustainable treatment options. *Water, Air, & Soil Pollution*, 236, Article 516. <https://doi.org/10.1007/s11270-025-08181-x>
- [4] Agarwal, N. (2022). Paracetamol – A contaminant of high concern: Existence in environment and adverse effects. *Pharmaceutical Drug Regulatory Affairs Journal*, 4(1), Article 000128. <https://medwinpublishers.com/PDRAJ/paracetamol--a-contaminant-of-high-concern-existence-in-environment-and-adverse-effects.pdf>
- [5] Franjić, S. (2024). An allergic reaction can occur to any drug. *Mathews Journal of Immunology & Allergy*, 8(2), 30. <https://www.mathewsopenaccess.com/full-text/an-allergic-reaction-can-occur-to-any-drug>
- [6] Bangia, S., Bangia, R., & Daverey, A. (2023). Pharmaceutically active compounds in aqueous environment: Recent developments in their fate, occurrence and elimination for efficient water purification. *Environmental Monitoring and Assessment*, 195, 1344. <https://doi.org/10.1007/s10661-023-11858-7>
- [7] Anderson, B. J. (2008). Paracetamol (acetaminophen): Mechanisms of action. *Pediatric Anesthesia*, 18(9), 915–921. <https://doi.org/10.1111/j.1460-9592.2008.02764.x>
- [8] Chidiac, A. S., Buckley, N. A., Nogrehchi, F., & Cairns, R. (2023). Paracetamol (acetaminophen) overdose and hepatotoxicity: Mechanism, treatment, prevention measures, and estimates of burden of disease. *Expert Opinion on Drug Metabolism & Toxicology*, 19(5), 297–317. <https://doi.org/10.1080/17425255.2023.2223959>
- [9] Arout, C. A., & Sofuoglu, M. (2019). Opioids. In F. R. Frankenburg (Ed.), *Addictions: Elements, history, treatments, and research* (pp. 107–126). Praeger/ABC-CLIO. <https://psycnet.apa.org/record/2018-40424-006>
- [10] Graham, G. G., Davies, M. J., Day, R. O., Mohamudally, A., & Scott, K. F. (2013). The modern pharmacology of paracetamol: Therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. *Inflammopharmacology*, 21(3), 201–232. <https://doi.org/10.1007/s10787-013-0172-x>
- [11] Athersuch, T. J., Antoine, D. J., Boobis, A. R., Coen, M., Daly, A. K., Possamai, L., Nicholson, J. K., & Wilson, I. D. (2018). Paracetamol metabolism, hepatotoxicity, biomarkers and therapeutic interventions: A perspective. *Toxicology Research*, 7(3), 347–357. <https://doi.org/10.1039/c7tx00340d>
- [12] Kim, S. H., Choi, H. J., Seo, H., Kwon, D., Yun, J., & Jung, Y. S. (2021). Down-regulation of glutathione-mediated detoxification capacity by binge drinking aggravates acetaminophen-induced liver injury through IRE1 α ER stress signaling. *Antioxidants*, 10(12), 1949. <https://doi.org/10.3390/antiox10121949>

- [13] Aro, T., & Fatehi, P. (2017). Production and application of lignosulfonates and sulfonated lignin. *ChemSusChem*, 10(1), 186–205. <https://doi.org/10.1002/cssc.201700082>
- [14] Ruwoldt, J. (2020). A critical review of the physicochemical properties of lignosulfonates: Chemical structure and behavior in aqueous solution, at surfaces and interfaces. *Surfaces*, 3(4), 622–648. <https://doi.org/10.3390/surfaces3040042>
- [15] Karagoz, P., Khiawjan, S., Marques, M. P. C., Santzouk, S., Bugg, T. D. H., & Lye, G. J. (2024). Pharmaceutical applications of lignin-derived chemicals and lignin-based materials: Linking lignin source and processing with clinical indication. *Biomass Conversion and Biorefinery*, 14, 26553–26574. <https://doi.org/10.1007/s13399-023-03745-5>
- [16] Jeevanantham, V., Jagatheesan, R., Vinitha, M., & Snega, P. (2025). Functionalization of lignin by sulfonation. In *Handbook of Lignin* (pp. 1–22). Springer. https://doi.org/10.1007/978-981-97-2664-6_27-1
- [17] Permata, D. A., Kasim, A., Asben, A., & Yusniwati. (2021). Delignification of lignocellulosic biomass. *World Journal of Advanced Research and Reviews*, 12(2), 462–469. <https://doi.org/10.30574/wjarr.2021.12.2.0618>
- [18] Ruwoldt, J. (2020). A critical review of the physicochemical properties of lignosulfonates: Chemical structure and behavior in aqueous solution, at surfaces and interfaces. *Surfaces*, 3(4), 622–648. <https://doi.org/10.3390/surfaces3040042>
- [19] Sadeghifar, H., & Ragauskas, A. J. (2025). Lignin as a natural antioxidant: Chemistry and applications. *Macromol*, 5(1), 5. <https://doi.org/10.3390/macromol5010005>
- [20] Gori, P., Singh, S., & Patel, P. (2025). Oxidative stress and free radicals in disease pathogenesis: A review. *Discover Medicine*, 2, Article 104. <https://doi.org/10.1007/s44337-025-00303-y>
- [21] Erfani Jazi, M., Narayanan, G., Aghabozorgi, F., Farajidizaji, B., Aghaei, A., Kamyabi, M. A., Navarathna, C. M., & Mlsna, T. E. (2019). Structure, chemistry and physico-chemistry of lignin for material functionalization. *SN Applied Sciences*, 1, Article 1094. <https://doi.org/10.1007/s42452-019-1126-8>
- [22] Lu, Y.-C., Lu, Y., & Fan, X. (2020). Structure and characteristics of lignin. In *Springer Series on Polymer and Composite Materials* (pp. 17–75). Springer. https://doi.org/10.1007/978-3-030-40663-9_2
- [23] Adebayo, A. J., & Olanrewaju, A. (2025). A complete review of lignin’s extraction, analysis, applications, and future outlook. *Chemistry Africa*, 8, 1711–1741. <https://doi.org/10.1007/s42250-025-01323-y>
- [24] Zeng, Y., Lin, K.-T., Happs, R. M., Leal, J. H., Kang, X., Dou, C., Kruger, J. S., Ding, L., Sale, K. L., Semelsberger, T. A., Ray, A. E., Sun, N., & Donohoe, B. S. (2025). Storage-induced collapse of lignin macromolecular structure and its impacts

- on the biorefinery. *ACS Sustainable Chemistry & Engineering*. <https://doi.org/10.1021/acssuschemeng.5c04284>
- [25] Hypercube, Inc. (2007). *HyperChem molecular modeling software* (Version 8.0) [Computer software]. <http://hypercubeusa.com>
 - [26] Stewart, J. J. P. (1989). Optimization of parameters for semiempirical methods I. Method. *Journal of Computational Chemistry*, 10(2), 209–220. <https://doi.org/10.1002/jcc.540100208>
 - [27] Frisch, M. J., Trucks, G. W., Schlegel, H. B., Scuseria, G. E., Robb, M. A., Cheeseman, J. R., ... Fox, D. J. (2016). *Gaussian 16, Revision A.03* [Software]. Gaussian, Inc.
 - [28] Doczekalska, B., Kuśmierek, K., & Swiatkowski, A. (2025). The adsorptive removal of paracetamol as a model pollutant from an aqueous environment using activated carbons made from selected nutshells as agricultural waste. *Processes*, 13(7), 2198. <https://doi.org/10.3390/pr13072198>
 - [29] Athersuch, T. J., Antoine, D. J., Boobis, A. R., Coen, M., Daly, A. K., Possamai, L., Nicholson, J. K., & Wilson, I. D. (2018). Paracetamol metabolism, hepatotoxicity, biomarkers and therapeutic interventions: A perspective. *Toxicology Research*, 7(3), 347–357. <https://doi.org/10.1039/c7tx00340d>
 - [30] Ruwoldt, J. (2020). A critical review of the physicochemical properties of lignosulfonates: Chemical structure and behavior in aqueous solution, at surfaces and interfaces. *Surfaces*, 3(4), 622–648. <https://doi.org/10.3390/surfaces3040042>
 - [31] Musl, O., Sulaeva, I., Sumerskii, I., Mahler, A. K., Rosenau, T., Falkenhagen, J., & Potthast, A. (2021). Mapping of the hydrophobic composition of lignosulfonates. *ACS Sustainable Chemistry & Engineering*, 9(46), 16786–16795. <https://doi.org/10.1021/acssuschemeng.1c06469>