RESEARCH PAPER

Evaluation of Glyphosate Interaction with Nrf2 and Heme Oxygenase-1 and Its Implications for Oxidative Stress in Early Childhood Caries: An In Silico Study

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ABSTRACT

Background: Early childhood caries (ECC) is increasingly associated with oxidative stress and dysregulation of antioxidant defense pathways. Glyphosate, a widely used environmental herbicide, has been reported to induce oxidative stress; however, its molecular interaction with key antioxidant regulators in ECC remains unclear.

Aim: To evaluate the interaction of glyphosate with KEAP1 and heme oxygenase-1 (HO-1) using molecular docking and explore its implications in oxidative stress pathways related to ECC.

Materials and Methods: An in silico docking study was performed using AutoDock Vina. The KEAP1 Kelch domain (PDB ID: 2FLU) and HO-1 (PDB ID: 1N45) were selected as targets. Glyphosate (PubChem CID: 3496) was docked into the active sites, and interactions were analyzed using PyMOL and Discovery Studio.

Results: Glyphosate exhibited moderate binding affinity toward KEAP1 (−5.0 kcal/mol) and HO-1 (−4.5 kcal/mol), with interactions predominantly mediated by hydrogen bonding, electrostatic forces, and water-mediated contacts. A relatively higher affinity was observed for KEAP1.

Conclusion: Glyphosate may weakly modulate the KEAP1–Nrf2–HO-1 pathway, potentially contributing to oxidative stress in ECC. Further experimental validation is required..

Keywords: Early childhood caries, oxidative stress, glyphosate, nuclear factor erythroid 2-related factor 2 (Nrf2), heme oxygenase-1, reactive oxygen species, antioxidants, environmental exposure, Good Health and Well-being.

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INTRODUCTION

Early childhood caries (ECC) remains one of the most prevalent chronic diseases affecting children worldwide, characterized by rapid progression and significant impact on oral and systemic health. Traditionally attributed to microbial dysbiosis and dietary factors, ECC is now increasingly recognized as a disease influenced by host immune responses and oxidative stress mechanisms. Emerging evidence suggests that an imbalance between reactive oxygen species (ROS) and antioxidant defenses contributes to tissue damage, inflammatory amplification, and progression of carious lesions. Clinical and systematic studies have demonstrated altered salivary antioxidant capacity and elevated oxidative stress biomarkers in children with ECC, reinforcing the role of redox dysregulation in disease pathogenesis.[1], [2]

At the molecular level, the nuclear factor erythroid 2–related factor 2 (Nrf2) signaling pathway plays a central role in cellular defense against oxidative stress. Nrf2 regulates the transcription of multiple cytoprotective genes, including heme oxygenase-1 (HO-1), which is a key enzyme involved in mitigating oxidative injury and inflammation. Activation of the Nrf2/HO-1 axis is considered a crucial adaptive response in maintaining redox homeostasis under pathological conditions. Although this pathway has been extensively studied in systemic inflammatory and metabolic disorders, its specific role in ECC and its modulation by external environmental factors remain inadequately explored.[3], [4], [5]

Glyphosate, a widely used herbicide, has gained significant attention due to its potential biological effects beyond its intended agricultural applications. Several experimental studies have demonstrated that glyphosate exposure can induce oxidative stress, disrupt mitochondrial function, and alter antioxidant defense systems. In vitro and in vivo investigations have shown increased ROS production and modulation of oxidative stress–related genes, including

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Nrf2 and HO-1, following glyphosate exposure.[6], [7], [8] These findings indicate that glyphosate may interfere with critical cellular defense mechanisms, potentially exacerbating oxidative damage in susceptible tissues.

Despite these advances, a critical gap exists in the literature linking environmental toxicants such as glyphosate with oxidative stress pathways in oral diseases, particularly ECC. Most studies on ECC have focused on salivary biomarkers and clinical indices, while glyphosate-related research has primarily been confined to hepatic, intestinal, or aquatic models. Notably, there is a lack of molecular-level evidence investigating the direct interaction between glyphosate and key antioxidant regulators such as Nrf2 and HO-1 within the context of oral pathology. Furthermore, no studies to date have employed computational docking approaches to explore these interactions and their potential implications in ECC progression.

Therefore, the present study aims to evaluate the interaction of glyphosate with Nrf2 and HO-1 using in silico molecular docking approaches, to elucidate its potential role in modulating oxidative stress pathways relevant to ECC. Understanding these interactions may provide novel mechanistic insights into how environmental exposures contribute to disease progression and may help identify potential therapeutic targets for mitigating oxidative stress in pediatric dental conditions. This integrative approach bridges environmental toxicology and oral disease biology, addressing a significant gap in current scientific knowledge and laying the groundwork for future translational research.

MATERIALS AND METHODS

Study Design

This in silico study was designed to evaluate the interaction of glyphosate with key proteins of the antioxidant signaling pathway, namely the Kelch domain of Kelch-like ECH-associated protein 1 (KEAP1) and human heme oxygenase-1 (HO-1), using molecular docking and structural analysis.

Protein Selection and Preparation

The three-dimensional crystal structure of the KEAP1 Kelch domain in complex with an Nrf2-derived peptide (PDB ID: 2FLU) was retrieved from the Protein Data Bank (RCSB-PDB). This structure was selected due to its well-characterized Nrf2-binding interface, which is critical for redox regulation.[9] Similarly, the crystal structure of human heme oxygenase-1 (HO-1) complexed with its native ligand heme (PDB ID: 1N45) was selected, as it represents the functional catalytic configuration of the enzyme.[10], [11]

Protein preparation was carried out using AutoDock Tools (version 1.5.6). All water molecules and co-crystallized ligands were removed, except for those required for validation studies. Polar hydrogens were added, and Kollman united atom charges were assigned. The proteins were then converted to PDBQT format for docking analysis.

Ligand Preparation

The three-dimensional structure of glyphosate (CID: 3496) was obtained from the PubChem database. The ligand was energy-minimized using the Universal Force Field (UFF) and prepared using AutoDock Tools by adding polar hydrogens and assigning Gasteiger charges. Rotatable bonds were defined to allow conformational flexibility during docking.

Molecular Docking Procedure

Molecular docking was performed using AutoDock Vina (version 1.1.2) owing to its reliable scoring function and computational efficiency. For KEAP1, the docking grid box was defined around the Nrf2-binding pocket within the Kelch domain, specifically encompassing the ETGE motif recognition region. The grid was centered at coordinates x = 10.5, y = 22.3, and z = 35.7, with a grid box size of 40 × 40 × 40 Å and a grid spacing of 0.375 Å. Similarly, for heme oxygenase-1 (HO-1), the docking grid was positioned over the heme-binding catalytic cavity, with center coordinates set at x = 15.2, y = 8.6, and z = 24.1, maintaining the same grid box dimensions and spacing. Docking simulations were carried out with standard parameters, including 10 binding modes, an exhaustiveness value of 8, and an energy range of 3 kcal/mol. Each docking run generated multiple ligand conformations, and the optimal binding pose was selected based on the lowest binding affinity (kcal/mol) along with a favorable interaction profile within the active site.

Post-Docking Analysis

The docked protein–ligand complexes were visualized and analyzed using PyMOL and BIOVIA Discovery Studio Visualizer to elucidate the molecular interaction patterns. Detailed interaction analysis was performed to identify key binding features, including hydrogen bonds, electrostatic interactions, van der Waals forces, and hydrophobic contacts between glyphosate and the amino acid residues within the active binding pockets. Special emphasis was placed on interactions with critical residues involved in Nrf2 recognition within the KEAP1 Kelch domain, particularly Arg415, Ser508, and Tyr525, which are known to play a central role in ligand binding and stabilization. For heme oxygenase-1, attention was directed toward interactions within the catalytic and substrate-binding regions, which are essential for enzymatic activity and ligand accommodation. This comprehensive interaction profiling enabled a deeper understanding of the binding affinity and potential mechanistic implications of glyphosate within the Nrf2/HO-1 antioxidant pathway.

Study Workflow

The overall workflow included protein and ligand preparation, validation through redocking, molecular docking using AutoDock Vina, and post-docking interaction analysis. This dual-target approach enabled evaluation of glyphosate interaction at both the regulatory level (KEAP1–Nrf2 axis) and effector level (HO-1), providing a comprehensive understanding of its potential impact on oxidative stress pathways.

RESULTS

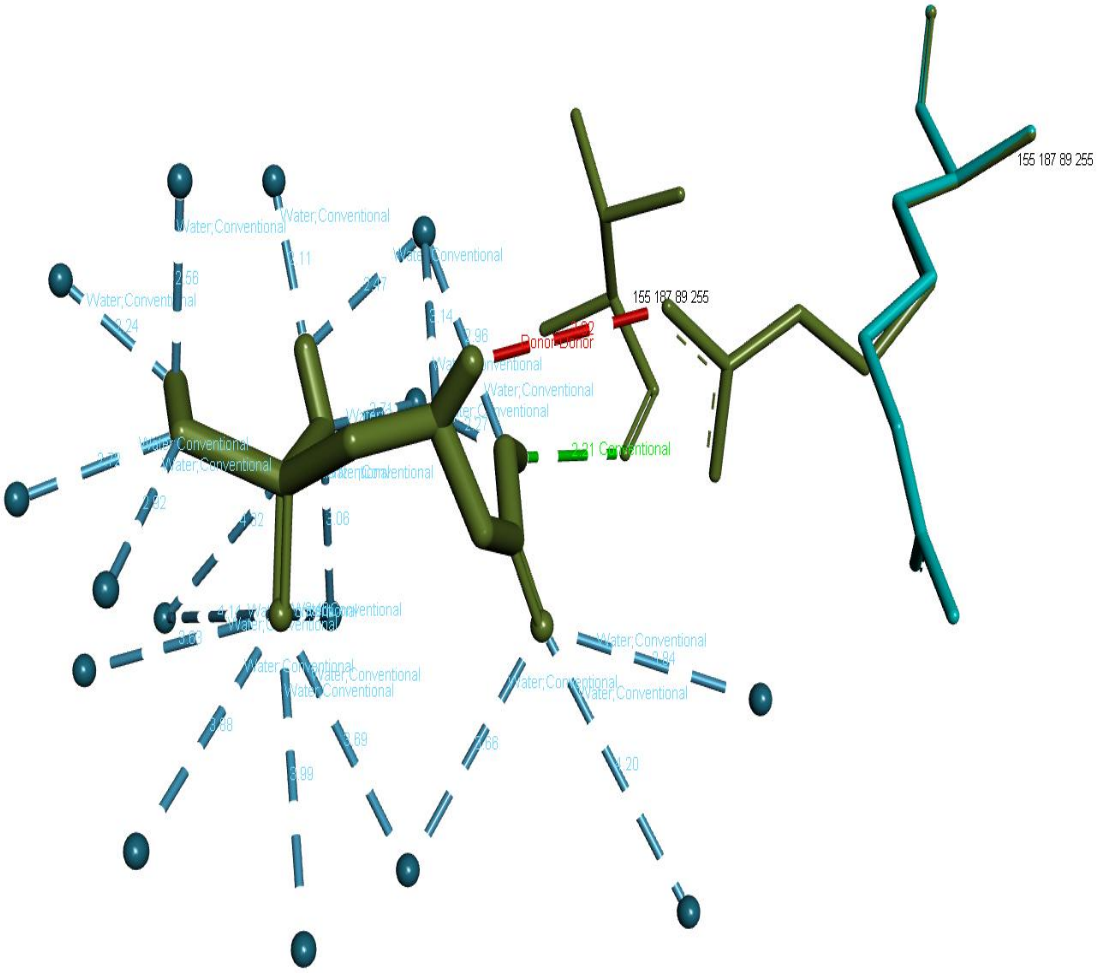

Figure 1A: Three-dimensional representation of glyphosate docked within the KEAP1 Kelch domain showing its orientation in the Nrf2-binding pocket. The ligand (green) is stabilized through multiple hydrogen bonds and water-mediated interactions (blue spheres and dashed lines). Key interacting residues and distances are indicated, highlighting the role of polar interactions in ligand stabilization.

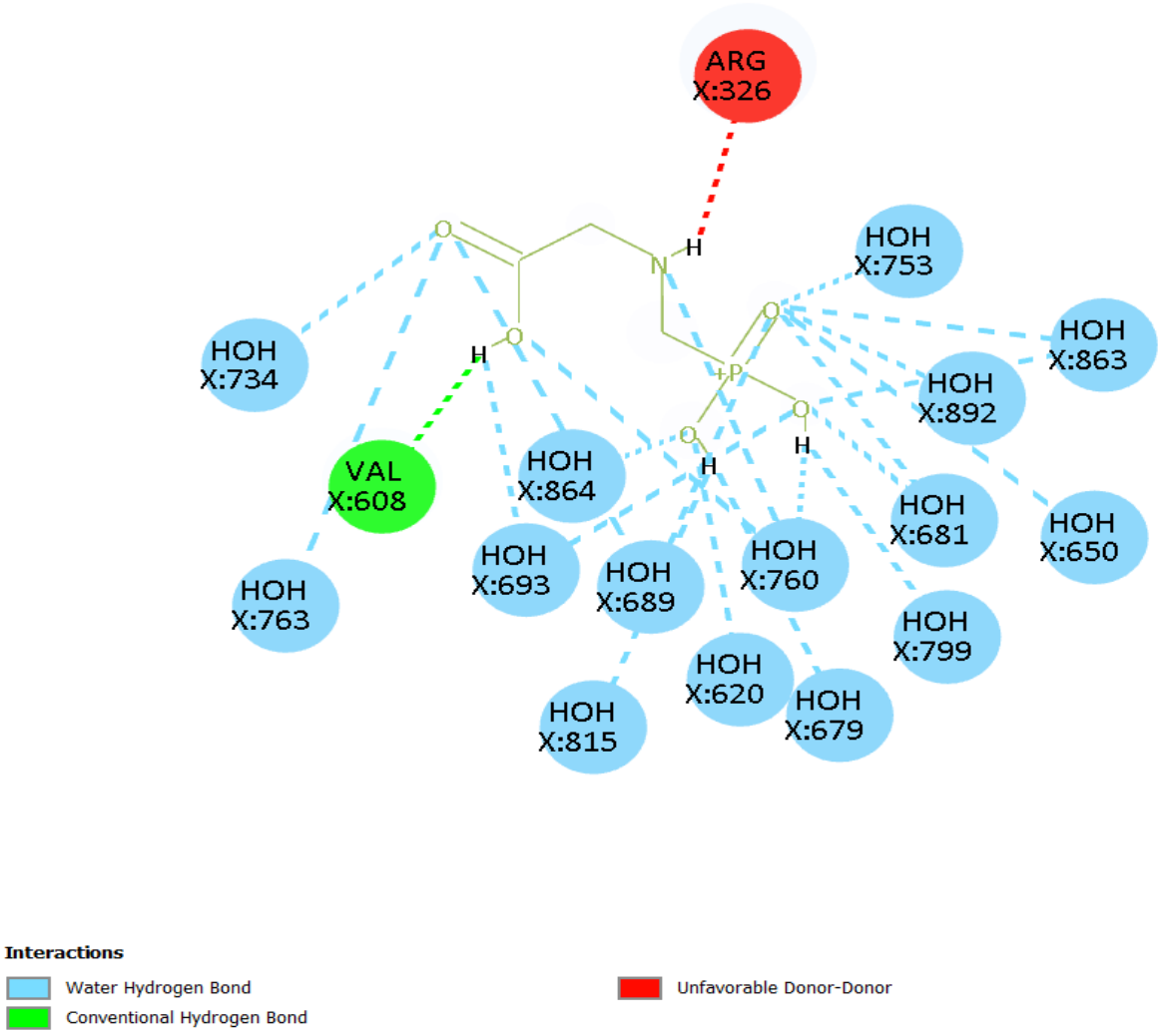

Figure 1B: Two-dimensional interaction diagram illustrating the binding interactions between glyphosate and amino acid residues within the KEAP1 Kelch domain. Conventional hydrogen bonding with Val608 is observed (green dashed line), while an unfavorable donor–donor interaction with Arg326 is indicated (red dashed line). Numerous water-mediated hydrogen bonds (blue dashed lines) are seen involving surrounding HOH molecules, suggesting a solvent-dependent binding mechanism.

The molecular docking analysis of glyphosate (PubChem CID: 3496) with the KEAP1 Kelch domain (PDB ID: 2FLU) demonstrated moderate binding affinity within the Nrf2-binding pocket, with the best docking pose exhibiting a binding energy of −5.0 kcal/mol (Fig. 1). Multiple conformations were generated, with binding energies ranging from −5.0 to −4.0 kcal/mol, indicating relatively consistent but modest interaction strength. The top-ranked pose showed an RMSD value of 0 Å, confirming it as the most stable reference conformation, while other poses exhibited RMSD variations ranging from 1.699 to 4.185 Å, suggesting similar binding orientations within the active site. A few poses displayed significantly higher RMSD values (>26 Å), indicating less stable or non-relevant binding conformations outside the optimal binding region

Interaction analysis revealed that glyphosate binding is primarily governed by polar interactions, including hydrogen bonding and extensive water-mediated contacts within the KEAP1 binding pocket. A key stabilizing interaction was observed with Val608, while proximity to Arg326 resulted in an unfavorable donor–donor interaction, indicating localized steric or electrostatic constraints. Despite this, the ligand maintained stable binding through compensatory van der Waals and hydration-mediated interactions. This docking results suggest that glyphosate exhibits moderate affinity toward the KEAP1 Kelch domain and may interact within the Nrf2-binding interface predominantly through solvent-assisted and polar interaction mechanisms (Fig. 1)
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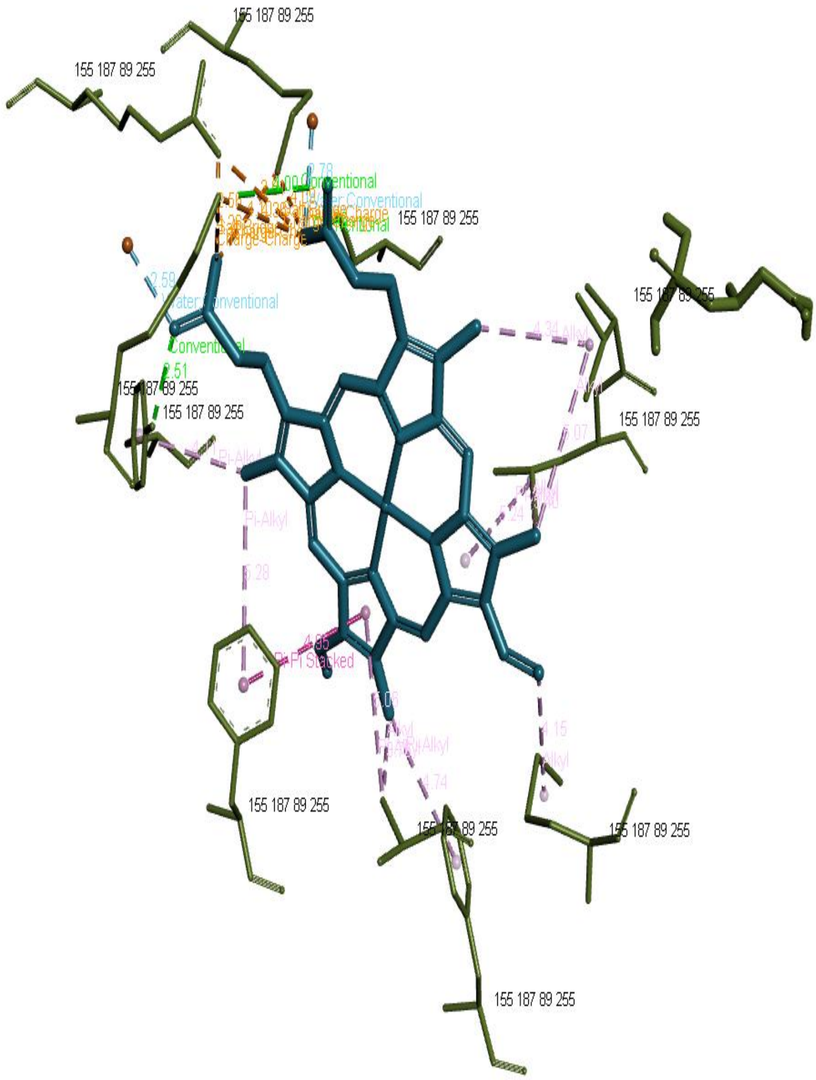

Figure 2A: Three-dimensional representation of glyphosate (PubChem CID: 3496) docked within the catalytic heme-binding pocket of heme oxygenase-1. The ligand is stabilized through conventional hydrogen bonds with Ser142 and Tyr134, electrostatic interactions with Lys18, Lys179, and Arg183, and additional hydrophobic contacts with surrounding residues. Water-mediated hydrogen bonds further contribute to ligand stabilization within the active site.

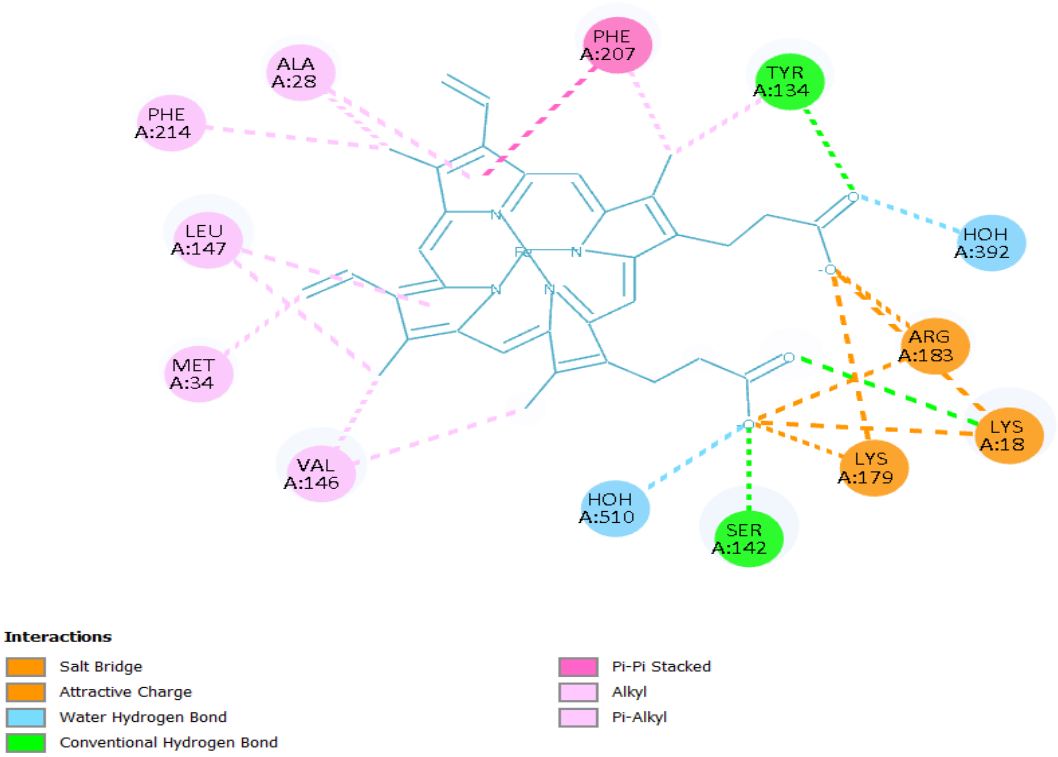

Figure 2B: Two-dimensional interaction diagram illustrating the binding interactions between glyphosate (PubChem CID: 3496) and HO-1. Conventional hydrogen bonds are observed with Ser142 and Tyr134 (green dashed lines), while strong electrostatic interactions, including salt bridges and attractive charge interactions, are noted with Lys18, Lys179, and Arg183 (orange dashed lines). Hydrophobic interactions, including π–π stacking and π–alkyl contacts with residues such as Phe207, Phe214, Leu147, Val146, and Met34, are also present, along with multiple water-mediated hydrogen bonds (blue dashed lines).

The molecular docking analysis of glyphosate (PubChem CID: 3496) with human heme oxygenase-1 (HO-1; PDB ID: 1N45) demonstrated moderate binding within the catalytic heme-binding pocket (Fig. 2A&B). The best docking pose showed a binding affinity of −4.5 kcal/mol with an RMSD value of 0 Å, indicating the most stable conformation, while other poses ranged from −4.5 to −3.7 kcal/mol, suggesting relatively consistent but low binding strength. Several conformations exhibited RMSD values between 2.311 and 12.367 Å, indicating similar binding orientations, whereas a few poses showed significantly higher RMSD values (>40 Å), reflecting unstable or non-specific interactions. Interaction analysis revealed that glyphosate binding is primarily driven by polar and electrostatic interactions, including conventional hydrogen bonds with Ser142 and Tyr134. Strong electrostatic interactions, such as salt bridges and attractive charge interactions, were observed with Lys18, Lys179, and Arg183, which likely stabilize the negatively charged functional groups of glyphosate. Additionally, multiple water-mediated hydrogen bonds were identified, further supporting ligand stabilization within the binding cavity. Hydrophobic interactions, including π–π stacking and π–alkyl contacts with

residues such as Phe207, Phe214, Leu147, Val146, and Met34, also contributed to binding stability. These findings indicate that glyphosate interacts with the HO-1 active site through a combination of hydrogen bonding, electrostatic, and hydrophobic interactions, although the moderate binding affinity suggests a relatively weak or transient interaction.

Target Protein	PDB ID	Best Binding Affinity (kcal/mol)	Binding Energy Range (kcal/mol)	RMSD Range (Å)	Interpretation
KEAP1 Kelch domain	2FLU	-5	-5.0 to -4.0	0 – 27.25	Moderate binding within Nrf2-binding pocket
Heme oxygenase-1	1N45	-4.5	-4.5 to -3.7	0 – 42.39	Moderate binding within catalytic pocket

Table 1: Summary of molecular docking results of glyphosate (PubChem CID: 3496) with KEAP1 Kelch domain (PDB ID: 2FLU) and heme oxygenase-1 (PDB ID: 1N45), showing best binding affinity, range of docking energies, and RMSD values indicating conformational stability and variability of the ligand within the respective binding pockets.

Glyphosate (PubChem CID: 3496) exhibited moderate binding affinity toward both KEAP1 (PDB ID: 2FLU) and HO-1 (PDB ID: 1N45), with the best docking scores of −5.0 kcal/mol and −4.5 kcal/mol, respectively. The binding energy ranges and RMSD values indicated relatively stable conformations along with some variability, suggesting flexible binding within the active sites. Comparatively, glyphosate showed slightly higher affinity toward KEAP1, indicating a greater potential to interact with the Nrf2 regulatory interface. These interactions were predominantly governed by polar and electrostatic forces, reflecting the hydrophilic nature of the ligand and suggesting transient modulatory binding rather than strong inhibition. Glyphosate shows moderate, mainly polar binding to both KEAP1 and HO-1, with slightly higher affinity for KEAP1, suggesting it may weakly and transiently modulate the Nrf2/HO-1 antioxidant pathway rather than strongly inhibit it.

DISCUSSION

This docking study findings demonstrating moderate binding of glyphosate toward KEAP1 and HO-1 are consistent with existing experimental evidence indicating that glyphosate primarily acts as a modulator of oxidative stress pathways rather than a strong direct inhibitor. Studies by Zheng T et al. reported that chronic glyphosate exposure significantly reduced antioxidant enzyme activity, including SOD, GSH, and CAT, and altered the expression of key redox-regulating genes such as Nrf2, Keap1, and HO-1, thereby disrupting cellular redox homeostasis.[12] Similarly, Bai G et al. demonstrated that glyphosate-based herbicides induce oxidative stress and activate the Nrf2/HO-1 signaling pathway as a compensatory response, while Mehtiyev T et al. observed increased ROS production and upregulation of HO-1 and Nrf2 in HepG2 cells, further supporting stress-mediated pathway activation rather than direct inhibition.[2], [3]

The slightly higher binding affinity of glyphosate toward KEAP1 observed in the present study suggests a potential to interfere with the KEAP1–Nrf2 interaction, thereby influencing Nrf2 stabilization and downstream antioxidant signaling. This observation aligns with findings from Qiu S et al., who reported that glyphosate induces oxidative damage and disrupts intestinal barrier integrity, likely through modulation of antioxidant pathways.[13] Bai G et al. (2023) demonstrated that glyphosate exposure activates Nrf2-mediated antioxidant signaling along with mitochondrial dysfunction and inflammatory responses, reinforcing its role in redox pathway modulation.[14] Reviews by Mesnage R et al. and Peillex C and Pelletier M further support that glyphosate induces oxidative stress, immune dysregulation, and inflammatory responses across multiple biological systems, highlighting oxidative stress as a central mechanism of toxicity.[15], [16]

In relation to HO-1, the moderate binding affinity observed in this study is in agreement with previous reports indicating that glyphosate influences HO-1 expression indirectly. Rather than acting as a strong inhibitor, glyphosate appears to induce HO-1 as part of an adaptive antioxidant response to oxidative injury, as evidenced in multiple in vitro and in vivo studies. This supports the interpretation that glyphosate interaction with HO-1 is likely transient and regulatory in nature.

From a clinical perspective, these findings gain significance when correlated with studies on early childhood caries (ECC), where oxidative stress imbalance has been extensively documented. Hegde AM et al. and Kumar D et al. reported altered salivary total antioxidant capacity (TAC) in children with ECC, indicating disruption of redox balance.[17], [18] Mahjoub S et al. and da Silva PV et al. demonstrated significant changes in antioxidant activity and oxidative stress markers in ECC-affected children, suggesting a compensatory antioxidant response to chronic cariogenic challenge.[19], [20] Further studies by Ahmadi-Motamayel F et al., Pyati SA et al., and AlAnazi H et al. confirmed alterations in both salivary and systemic

oxidative stress markers, including increased lipid peroxidation and changes in TAC levels.[21], [22] A systematic review by Martins JR et al. further concluded that oxidative stress biomarkers are consistently altered in children with dental caries, reinforcing the role of redox imbalance in disease progression.[23], [24]

Taken together, the present findings provide a mechanistic bridge between environmental exposure and oral disease, suggesting that glyphosate may contribute to oxidative stress pathways implicated in ECC through weak but biologically relevant interactions with the KEAP1–Nrf2–HO-1 axis. Importantly, the literature reveals a significant gap, as no previous studies have directly evaluated glyphosate interaction with these targets in the context of ECC, highlighting the novelty and relevance of the current in silico investigation.

This study provides a novel mechanistic insight by integrating environmental toxicology with oral disease through molecular docking of glyphosate on the KEAP1–Nrf2–HO-1 pathway; however, the findings are limited by their reliance on in silico analysis without in vitro or in vivo validation, which restricts direct biological interpretation. Therefore, future studies involving cell-based assays, gene expression analysis, and clinical correlation are necessary to validate the role of glyphosate in modulating oxidative stress pathways in early childhood caries.

CONCLUSION

This in silico investigation reveals that glyphosate exhibits moderate binding affinity toward both KEAP1 and heme oxygenase-1, predominantly mediated through polar and electrostatic interactions, with a relatively higher affinity for the KEAP1 Kelch domain. These findings suggest that glyphosate may act as a weak modulator of the KEAP1–Nrf2–HO-1 antioxidant signaling axis rather than a direct inhibitor. In the context of early childhood caries, where oxidative stress plays a critical role in disease progression, such interactions may contribute to subtle alterations in redox homeostasis. Although the binding affinities indicate transient interactions, the potential cumulative effect of environmental exposure cannot be overlooked. Therefore, this study provides a novel mechanistic perspective linking environmental toxicants with oral disease and highlights the need for further experimental validation to establish the biological and clinical relevance of these findings.

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