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In-silico molecular docking of sodium erythorbate and phytate into cyclooxygenase enzymes

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Abstract:

Sodium erythorbate and phytate are compounds known for their antioxidant and metal-chelating properties, respectively. This study used in-silico molecular docking to examine the interaction of sodium erythorbate and phytate with the cyclooxygenase enzymes COX-1 and COX-2, and to assess their potential as anti-inflammatory agents. Docking was evaluated through binding energy, root mean square deviation (RMSD) and the amino acid residues involved. Sodium erythorbate bound weakly to both isoforms, with binding energies of −5.2630 kcal/mol for COX-1 and −5.4070 kcal/mol for COX-2, whereas phytate bound more strongly, with −7.2871 kcal/mol for COX-1 and −7.3935 kcal/mol for COX-2. In the combined docking, the binding of phytate was slightly strengthened at COX-1 (−7.4457 kcal/mol) but weakened at COX-2 (−6.3569 kcal/mol), suggesting that sodium erythorbate destabilises the binding of phytate to COX-2. All RMSD values were below 2.0 Å, indicating reliable docking poses. The reference NSAIDs celecoxib and ibuprofen gave binding energies between those of the two test compounds. Phytate is therefore the more promising candidate for COX inhibition, whereas sodium erythorbate appears unsuitable for combination use because it reduces the binding stability of phytate at COX-2. Future work should examine alternative antioxidant combinations that do not reduce the affinity of phytate, and should validate these computational predictions experimentally.

Keywords: Anti-inflammatory; binding energy; cyclooxygenase enzymes; molecular docking; phytate; sodium erythorbate

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Introduction

Cyclooxygenase (COX) is a bifunctional enzyme that converts arachidonic acid (AA) into prostaglandin H2 (PGH2), which plays an important role in inflammation and pain. Non-steroidal anti-inflammatory drugs (NSAIDs) such as celecoxib (COX-2 selective) and ibuprofen (non-selective) are often used as first-line therapy for inflammatory conditions [1]. COX-1 is constitutively expressed in various tissues, including the gastrointestinal tract, kidney, platelets, brain and spleen [2]. COX-2, in contrast, is an inducible enzyme that is upregulated in response to inflammatory stimuli, leading to increased synthesis of pro-inflammatory prostaglandins, which contribute to pain, fever and oedema [3].

Sodium erythorbate is a synthetic antioxidant used as a food additive and authorised by the US Food and Drug Administration (FDA) [4]. It exerts antioxidant activity by reducing lipid oxidation, a process influenced by factors including high temperature, enzymatic activity, metal complexes and free radicals [5,6]. Its ability to scavenge radicals directly and to increase cellular antioxidant capacity makes it a candidate for the management of diseases driven by oxidative stress [7].

Phytate, or phytic acid (myo-inositol hexakisphosphate, IP6), is a naturally occurring compound found mainly in plant seeds, grains, legumes and nuts. Phytate chelates metal

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ions including zinc, calcium and iron, and this metal-chelating action mitigates oxidative stress at the cellular level, thereby protecting biological molecules [8]. Phytate has also been shown to stabilise cell membranes and inhibit lipid peroxidation, reinforcing its role as a natural antioxidant [9].

Molecular docking is a structure-based computational technique that predicts the binding conformation and affinity between a ligand and its target [10]. Docking studies typically follow a standard workflow that begins with selection and preparation of a suitable protein, followed by grid generation and ligand preparation, and concludes with analysis of the docking results and of the ligand–receptor interaction patterns [11]. Binding energy is central to drug design, as it helps identify compounds worth taking forward [12]. The root mean square deviation (RMSD), measured in ångströms (Å), assesses docking precision from the average displacement between equivalent atoms in two structures [13]; values below 2 Å indicate good agreement with experimental data, whereas larger deviations imply less reliable predictions. This study therefore used molecular docking to determine the binding energies of sodium erythorbate and phytate, individually and in combination, and to analyse their interactions with the amino acid residues of COX-1 and COX-2.

Materials and Methods

Protein and Ligand Preparation

Docking was carried out in Molecular Operating Environment (MOE) 2015 using the crystal structures of human COX-1 (PDB ID: 6Y3C) and murine COX-2 (PDB ID: 3LN1). All ligand structures were retrieved from the PubChem database using their compound identifiers (CIDs): sodium erythorbate (CID 23683938), phytate (CID 66391), celecoxib (CID 2662) and ibuprofen (CID 3672).

Docking Protocol and Pose Selection

Sodium erythorbate and phytate were docked individually into COX-1 and COX-2, and then together into both isoforms. Celecoxib and ibuprofen were docked into both isoforms as reference NSAIDs for comparison. For each ligand, the pose with the lowest binding energy and an RMSD below 2.0 Å was selected for analysis.

Visualisation of Interactions

The best-scoring poses were then exported to BIOVIA Discovery Studio Visualizer 4.5 to generate the 2D and 3D interaction diagrams showing the amino acid residues involved.

Results and Discussion

In-silico molecular docking was performed in MOE 2015 to investigate the interactions of sodium erythorbate and phytate with COX-1 and COX-2, both individually and in combination. The binding energies, RMSD values and interacting residues are given in Table 1, and the residues shared between ligand pairs are summarised in Table 2 for COX-1 and Table 3 for COX-2.

Table 1. Binding energies, RMSD values and interacting residues of the ligands docked individually and in combination into COX-1 and COX-2

Ligand	Enzyme	Binding energy (kcal/mol)	RMSD (Å)	Hydrogen bonding		Hydrophobic and other interactions	
				Conventional	Carbon hydrogen	Alkyl and pi-alkyl	Others
Sodium erythorbate	COX-1	−5.2630	0.8475	GLU A:465	GLY A:45; CYS A:41	–	CYS A:47 (metal acceptor)
	COX-2	−5.4070	1.3230	CYS A:26; GLU A:451; ARG A:29	GLN A:27	–	ASN A:24 (metal acceptor)
Phytate	COX-1	−7.2871	1.4621	ARG A:79; ASN A:122; GLN A:44; LYS A:468	GLY A:471; HIS A:43	–	–
	COX-2	−7.3935	1.3580	SER A:112; TYR A:108; ASP A:111; ARG A:29; GLU A:31; ARG A:46; LYS A:123	PRO A:113	–	–
Celecoxib	COX-1	−6.5849	1.4772	GLN A:44	CYS A:47	PRO A:153; LEU A:152; ILE A:46	CYS A:41; GLU A:465 (halogen, F)
	COX-2	−7.0136	1.0974	ARG A:29	ALA A:142; CYS A:32	TYR A:116; LEU A:138; PRO A:139; ARG A:455; LYS A:454	ASP A:111; GLU A:31 (halogen, F)
Ibuprofen	COX-1	−6.1806	1.7799	HIS A:43; GLN A:42; CYS A:41	–	LEU A:152; ARG A:469; CYS A:47; PRO A:153	–
	COX-2	−6.4148	0.9654	–	–	ARG A:29; CYS A:32; CYS A:26; PRO A:25; LEU A:138; LYS A:454	–
Combination: sodium erythorbate	COX-1	−5.2631	0.8478	GLU A:465	GLY A:45; CYS A:41	–	CYS A:47 (metal acceptor)
Combination: phytate	COX-1	−7.4457	1.1204	VAL A:119; ASN A:122; GLN A:44; ARG A:469; THR A:62; ARG A:79; THR A:76; ASN A:80; TYR A:64; ARG A:83	HIS A:43	–	–
Combination: sodium erythorbate	COX-2	−5.4071	1.3229	CYS A:26; ARG A:29; GLU A:451	GLN A:27	–	ASN A:24 (metal acceptor)
Combination: phytate	COX-2	−6.3569	1.0540	TYR A:116; GLY A:121; GLY A:30; CYS A:26; ASN A:24; GLN A:447; PRO A:140; ALA A:142	PRO A:25; PRO A:139; GLU A:31; CYS A:22; CYS A:21	–	–

RMSD, root mean square deviation. Residue numbering follows the deposited PDB entries 6Y3C (COX-1) and 3LN1 (COX-2). –, no interaction of this type observed.

Individual Ligand Docking

Sodium erythorbate gave binding energies of −5.2630 kcal/mol with COX-1 and −5.4070 kcal/mol with COX-2, indicating weak binding to both isoforms. The less negative the binding energy, the weaker the affinity between ligand and target protein; values below −6.0 kcal/mol are generally considered favourable for effective binding [14], although affinity also depends on the nature of the interactions formed [15]. The docked poses showed conventional hydrogen bonds, carbon–hydrogen bonds and metal-acceptor contacts in both COX-1 (Figure 1) and COX-2 (Figure 2). Hydrogen bonding is generally associated with higher binding affinity [16], yet sodium erythorbate bound weakly despite forming such bonds. This is most likely because it is a small molecule with limited surface area and few functional groups, which restricts the number and strength of the interactions it can form within the enzyme active site. On the basis of these results alone, sodium erythorbate shows only weak, non-selective binding to both COX isoforms, and any anti-inflammatory potential would require experimental verification.

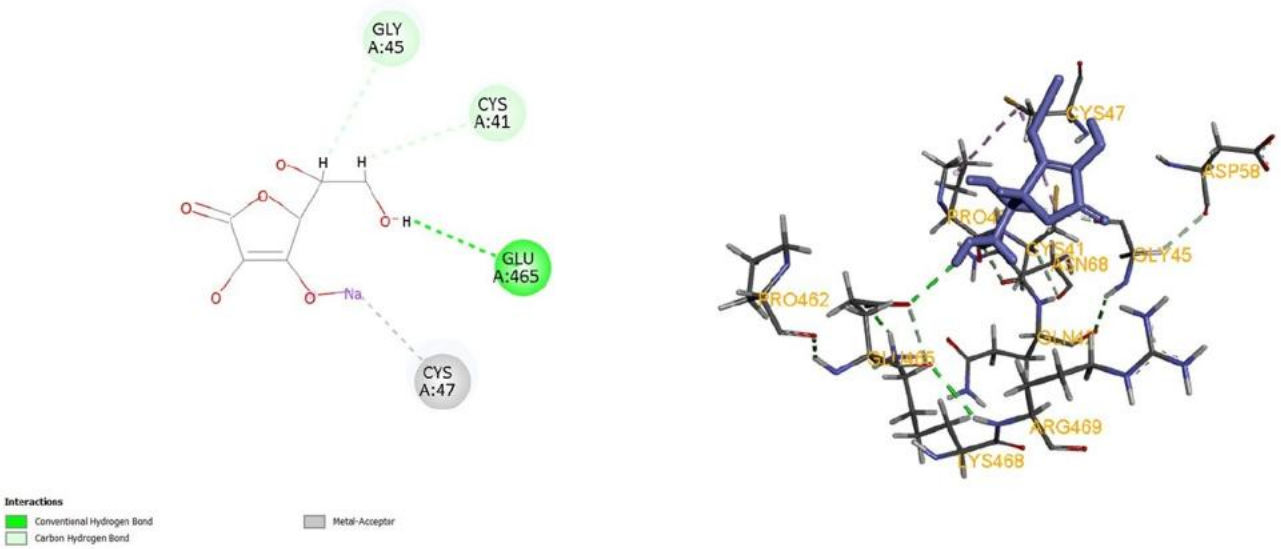


Figure 1. Docking interactions of sodium erythorbate in COX-1 (left, 2D; right, 3D).

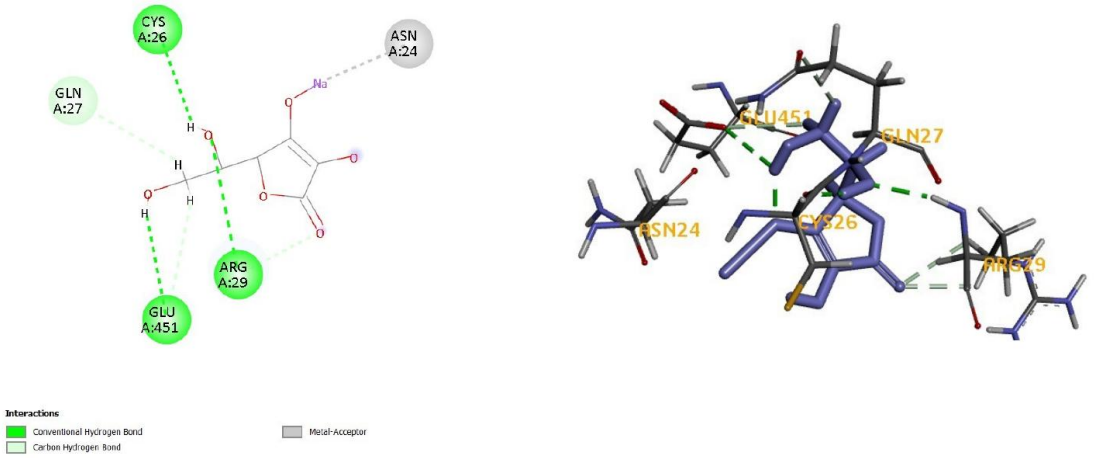


Figure 2. Docking interactions of sodium erythorbate in COX-2 (left, 2D; right, 3D).

Phytate gave binding energies of −7.2871 kcal/mol with COX-1 (Figure 3) and −7.3935 kcal/mol with COX-2 (Figure 4), indicating stronger binding than sodium erythorbate. Phytate formed only conventional and carbon–hydrogen bonds with both isoforms. Its highly phosphorylated, negatively charged structure allows it to form numerous hydrogen bonds with the COX enzymes, which is consistent with the higher affinity observed [17]. Phytate also shared more residues with celecoxib in COX-2 than in COX-1, namely ASP A:111, ARG A:29 and GLU A:31 (Table 3), which suggests that it occupies part of the celecoxib-binding region. However, its binding energies for the two isoforms differ by only about 0.1 kcal/mol, which is within the error of the scoring function and does not by itself establish selectivity. Enzyme inhibition assays would be required to confirm any preference.

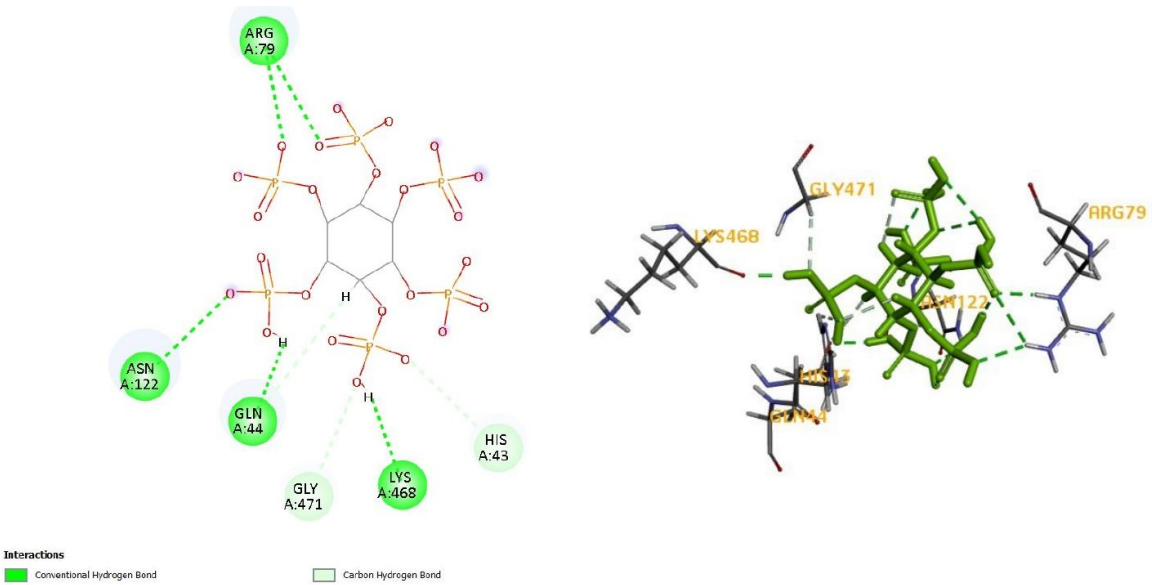


Figure 3. Docking interactions of phytate in COX-1 (left, 2D; right, 3D).

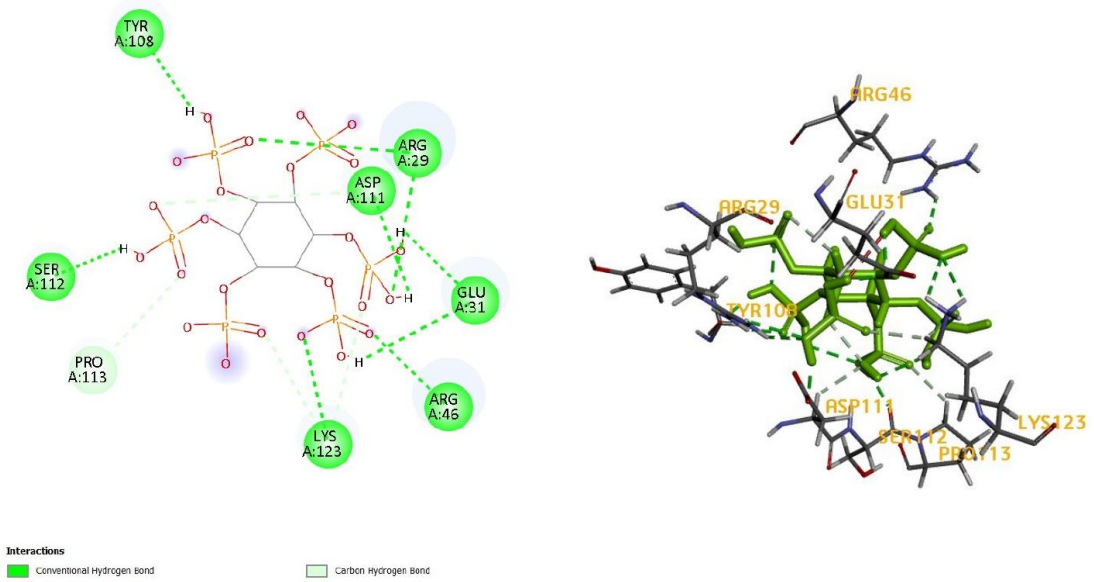


Figure 4. Docking interactions of phytate in COX-2 (left, 2D; right, 3D).

Celecoxib gave binding energies of −6.5849 kcal/mol with COX-1 (Figure 5) and −7.0136 kcal/mol with COX-2 (Figure 6). The more negative value for COX-2 indicates stronger binding to that isoform, which is consistent with the known clinical COX-2 selectivity of celecoxib. Celecoxib also formed more alkyl, pi-alkyl and halogen interactions with COX-2 than with COX-1, consistent with its occupancy of the COX-2 side pocket [18].

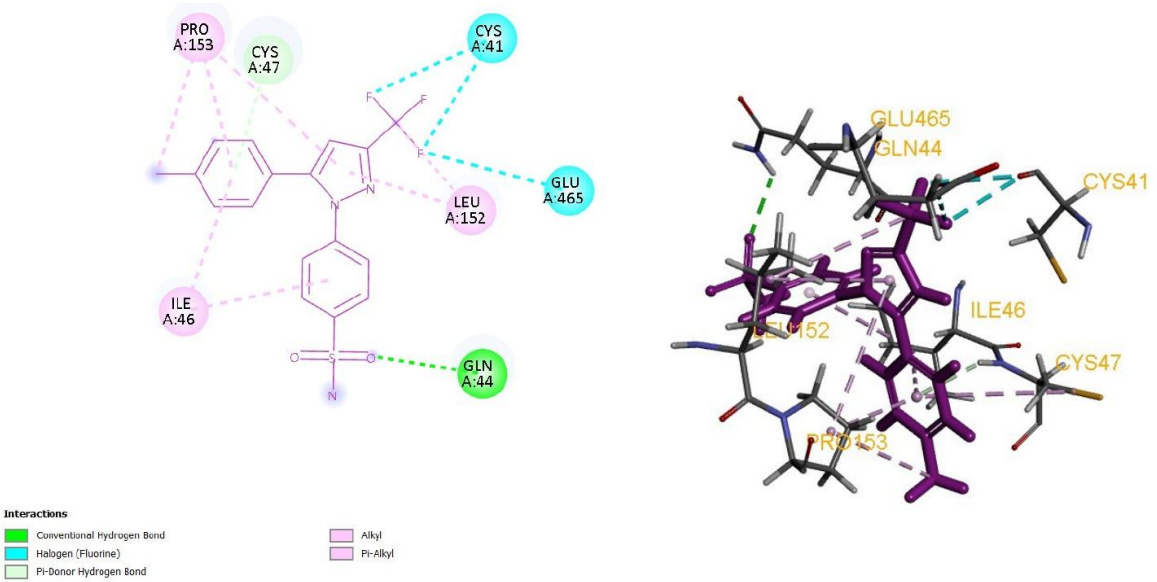


Figure 5. Docking interactions of celecoxib in COX-1 (left, 2D; right, 3D).

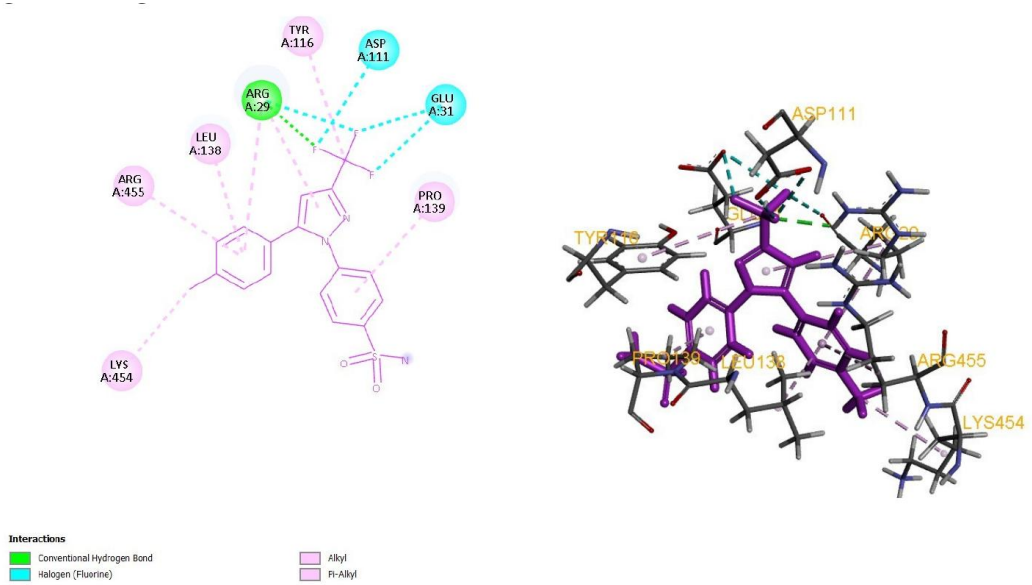


Figure 6. Docking interactions of celecoxib in COX-2 (left, 2D; right, 3D).

Ibuprofen gave binding energies of −6.1806 kcal/mol with COX-1 (Figure 7) and −6.4148 kcal/mol with COX-2 (Figure 8). These comparable values are consistent with its known action as a non-selective NSAID.

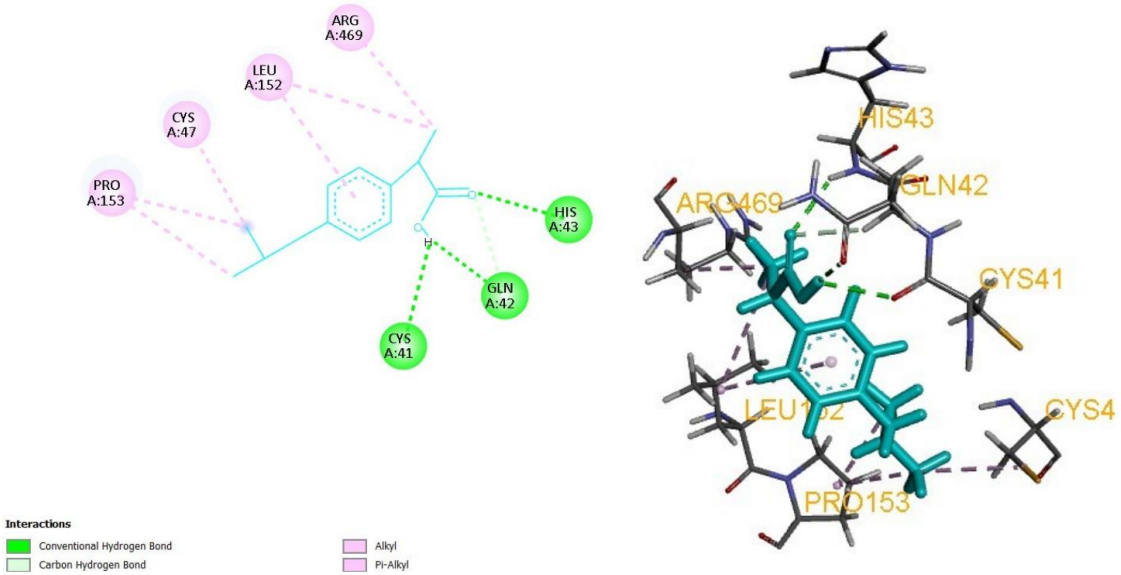


Figure 7. Docking interactions of ibuprofen in COX-1 (left, 2D; right, 3D).

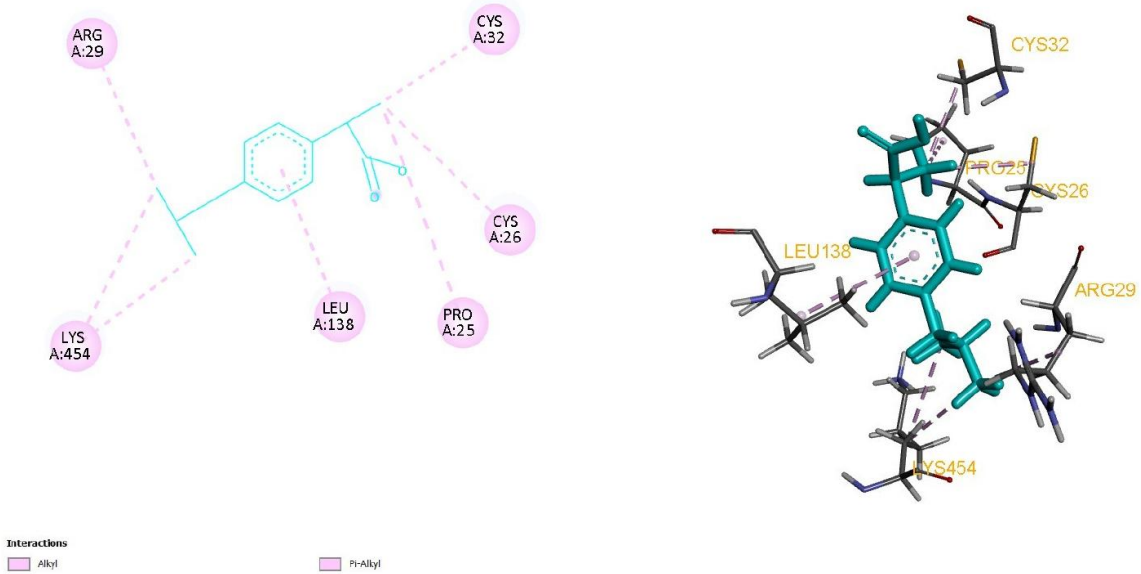


Figure 8. Docking interactions of ibuprofen in COX-2 (left, 2D; right, 3D).

Combination Ligand Docking

In the combined docking with COX-1 (Figure 9), sodium erythorbate gave a binding energy of −5.2631 kcal/mol and phytate −7.4457 kcal/mol. Sodium erythorbate was essentially unchanged from its individual value, whereas the binding energy of phytate became slightly more negative, from −7.2871 to −7.4457 kcal/mol, a marginal improvement in affinity in the presence of sodium erythorbate. Within COX-1, phytate formed hydrogen bonds with residues including VAL A:119, ASN A:122, GLN A:44, ARG A:469 and ARG A:83, while sodium erythorbate contributed a conventional hydrogen bond with GLU A:465, carbon–hydrogen bonds with GLY A:45 and CYS A:41, and a metal-acceptor contact with CYS A:47. The extensive hydrogen-bond network and the involvement of positively charged arginine residues appear to increase binding stability, which may favour inhibition of COX-1 by this ligand combination.

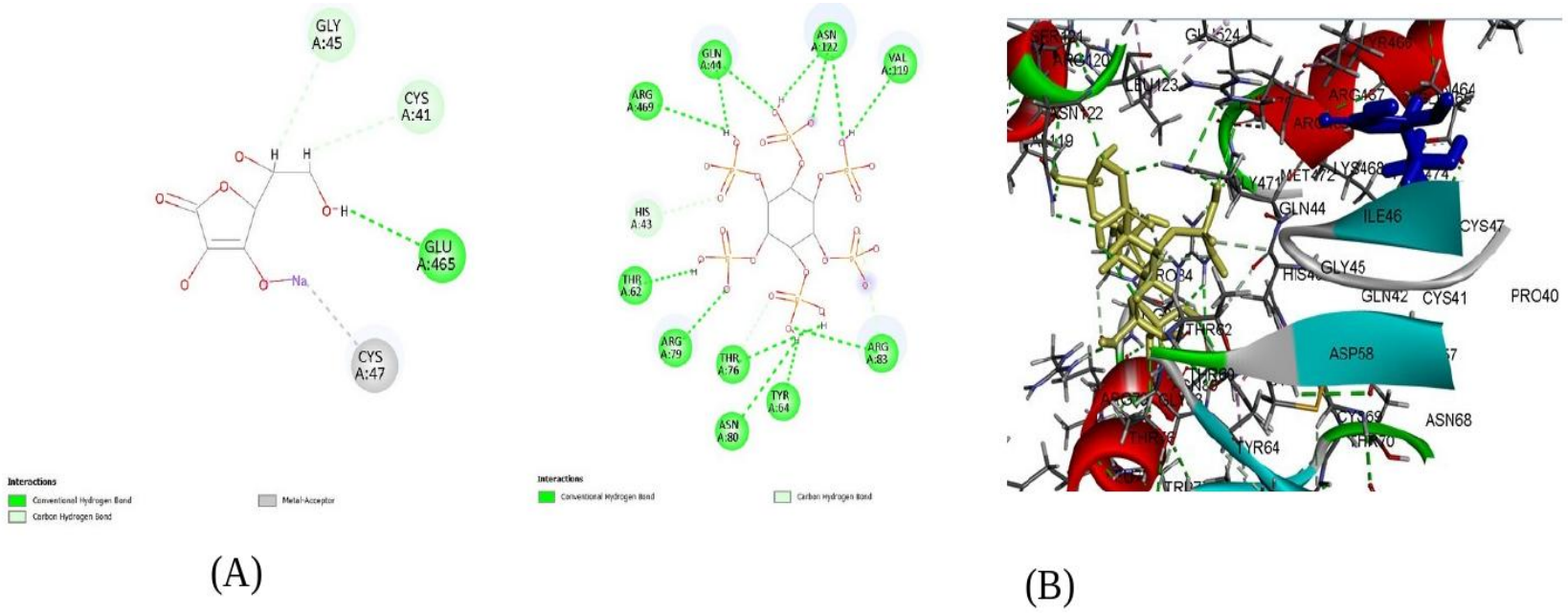


Figure 9. Docking interactions of sodium erythorbate (A) and phytate (B) in the combined docking with COX-1.

In COX-2 (Figure 10), the combination showed a different pattern. The binding energy of phytate became less negative, from −7.3935 to −6.3569 kcal/mol, indicating reduced affinity in the presence of sodium erythorbate and therefore an antagonistic effect at this isoform. The binding energy of sodium erythorbate was unchanged between the individual and combined docking. This suggests that sodium erythorbate retains its own binding mode while destabilising that of phytate, probably through steric or electrostatic interference within the COX-2 binding pocket. Nonetheless, the combination shared more residues with celecoxib in COX-2, namely TYR A:116, ALA A:142 and PRO A:139 (Table 3),

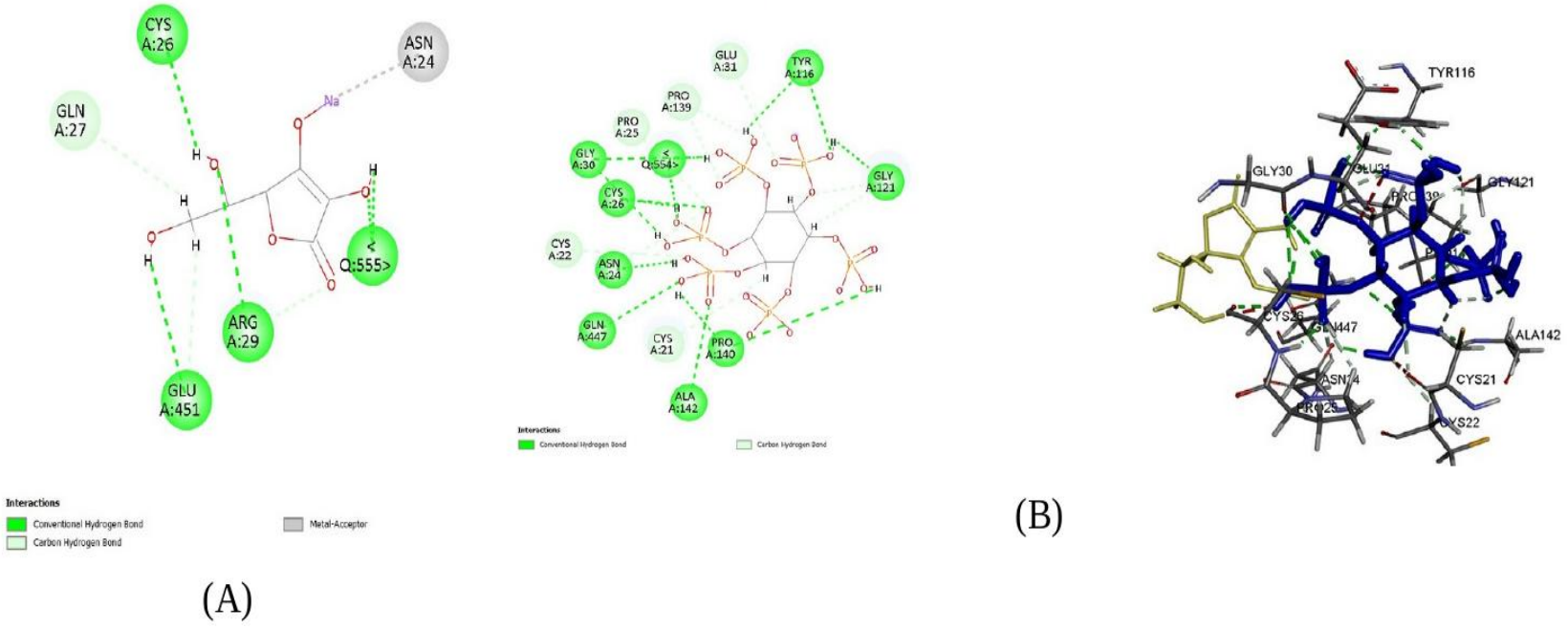


Figure 10. Docking interactions of sodium erythorbate (A) and phytate (B) in the combined docking with COX-2.

Table 2. Amino acid residues shared between different pairs of ligands in COX-1

Ligand pair	Common interactions (COX-1)
Phytate, combination and celecoxib	GLN A:44
Phytate, combination and ibuprofen	HIS A:43
Phytate and combination	ASN A:122, ARG A:79
Sodium erythorbate, combination, ibuprofen and celecoxib	CYS A:41
Sodium erythorbate and combination	GLY A:45
Sodium erythorbate and celecoxib	CYS A:47
Sodium erythorbate, combination and celecoxib	GLU A:465
Ibuprofen and celecoxib	LEU A:152, PRO A:153
Combination and celecoxib	ARG A:469

Table 3. Amino acid residues shared between different pairs of ligands in COX-2

Ligand pair	Common interactions (COX-2)
Sodium erythorbate, phytate, combination, ibuprofen and celecoxib	ARG A:29
Sodium erythorbate, combination and ibuprofen	CYS A:26
Sodium erythorbate and combination	GLU A:451, GLN A:27, ASN A:24
Combination and celecoxib	TYR A:116, ALA A:142, PRO A:139
Combination and ibuprofen	PRO A:25
Phytate and celecoxib	ASP A:111
Phytate, combination and celecoxib	GLU A:31
Celecoxib and ibuprofen	CYS A:32, LYS A:454

Conclusion

In summary, phytate bound comparatively strongly to both COX isoforms, whereas sodium erythorbate bound weakly while still forming hydrogen bonds and metal-acceptor contacts. In the combined docking, binding was favoured at COX-1, and the binding of phytate at COX-2 was destabilised, indicating an antagonistic effect. This combination is therefore unlikely to meet the therapeutic aim of reducing the adverse effects associated with current NSAIDs, and replacing sodium erythorbate with a more compatible antioxidant may better support the activity of phytate at COX-2. These findings are computational predictions only, generated with a single scoring function and without molecular dynamics simulation or experimental validation; in vitro COX-1 and COX-2 inhibition assays are required before any pharmacological conclusion can be drawn.

Conflict of interest

The authors declare no conflict of interest

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