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RESEARCH ARTICLE

Potential Interaction of Propyl Gallate and Butylated Hydroxyanisole with EGFR–PI3K–Akt–mTOR Proteins in Oral and Gastrointestinal Carcinogenic Signaling Pathway: An *in silico* Molecular Docking Study

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Abstract

BACKGROUND: Synthetic food preservatives are widely used to improve food stability and shelf life, but prolonged exposure may contribute to oral and gastrointestinal carcinogenesis. Epidermal growth factor receptor (EGFR)–phosphoinositide 3-kinase (PI3K)–protein kinase B (Akt)–mammalian target of rapamycin (mTOR) axis plays a pivotal role in regulating tumor initiation and progression; however, the potential interactions with cancer-related signaling proteins remain poorly understood. This study computationally evaluated the predicted binding interactions of commonly used synthetic food preservatives with proteins using molecular docking.

METHODS: Propyl gallate (PG), butylated hydroxyanisole (BHA), tertiary-butylhydroquinone (TBHQ), potassium sorbate (PS), sodium benzoate (SB), and sodium metabisulfite (SMB) were evaluated for physicochemical properties using SwissADME. Molecular docking with EGFR, PI3K, Akt-1, and mTOR was performed using CB-Dock 2.0. Predicted ligand–protein interactions were analyzed using BIOVIA Discovery Studio 2016 and root mean square fluctuation (RMSF) was evaluated using CABS-flex 3.0.

RESULTS: PG and BHA exhibited the most predicted binding affinities among the investigated preservatives. PG showed the strongest interactions with EGFR (−6.1 kcal/mol), PI3K (−6.8 kcal/mol), and mTOR (−6.7 kcal/mol), whereas BHA demonstrated the highest affinity toward PI3K (−6.8 kcal/mol) and Akt-1 (−6.5 kcal/mol). These interactions were supported by multiple hydrogen bonds, hydrophobic interactions, and van der Waals contacts.

CONCLUSION: PG and BHA exhibited the highest binding affinity toward proteins of the EGFR–PI3K–Akt–mTOR associated with oral and gastrointestinal carcinogenesis. These computational findings provide a basis for future experimental studies to determine the biological relevance of the predicted protein–ligand interactions under long-term dietary exposure.

KEYWORDS: synthetic food preservatives, molecular docking, oral carcinogenesis, gastrointestinal carcinogenesis

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Introduction

The widespread consumption of processed foods has substantially increased the use of synthetic food preservatives to maintain product quality, inhibit microbial contamination, and prolong shelf life. Among the most frequently used preservatives are tert-butylhydroquinone (TBHQ), butylated hydroxyanisole (BHA), propyl gallate (PG), potassium sorbate (PS), sodium benzoate (SB), and

sodium metabisulfite (SMB), all of which are approved for food applications within specific regulatory limits.(1) Although these compounds are generally considered safe at acceptable daily intake levels, increasing experimental evidence suggests that prolonged or excessive exposure may induce oxidative stress, DNA damage, chronic inflammation, and tumor-promoting activities under certain biological conditions, thereby raising concerns regarding their long-term safety.(2,3) Consequently, understanding the molecular mechanisms underlying the biological effects of synthetic food preservatives has become an important research priority in food safety and computational toxicology.(4,5)

Following ingestion, food preservatives come into direct contact with the epithelial lining of the oral cavity, esophagus, stomach, small intestine, and colon, making the gastrointestinal tract the primary site of exposure.(6) Continuous exposure to compounds capable of disturbing cellular redox balance may increase the production of reactive oxygen species (ROS), resulting in oxidative stress, DNA instability, and persistent inflammatory responses.(7,8) These biological alterations are recognized as important contributors to the initiation and progression of gastrointestinal malignancies, particularly oral squamous cell carcinoma (OSCC), esophageal carcinoma, gastric cancer, and colorectal cancer.(9,10) Recent evidence has highlighted oxidative stress as a central mechanism linking environmental and dietary exposures with carcinogenic signaling pathways involved in the development and progression of cancers throughout the gastrointestinal tract.(11,5)

Among the signaling pathways associated with oral and gastrointestinal cancers, the epidermal growth factor receptor (EGFR)–phosphoinositide 3-kinase (PI3K)–protein kinase B (AKT)–mammalian target of rapamycin (mTOR) signaling axis is one of the most frequently dysregulated pathways. Activation of EGFR sequentially stimulates PI3K, AKT, and mTOR, thereby regulating cell proliferation, survival, angiogenesis, metabolic reprogramming, epithelial–mesenchymal transition, invasion, metastasis, and resistance to apoptosis. Dysregulation of this pathway has been widely reported in oral squamous cell carcinoma as well as esophageal, gastric, and colorectal cancers, making the EGFR–PI3K–AKT–mTOR axis an important molecular target for mechanistic and therapeutic cancer research.(12–20)

Despite considerable advances in toxicological and epidemiological studies evaluating the safety of synthetic food preservatives, previous investigations have primarily focused on cytotoxicity, oxidative stress, genotoxicity, metabolic disturbances, and animal toxicity. However, the potential molecular interactions of commonly used synthetic food preservatives with proteins across the EGFR–PI3K–AKT–mTOR signaling pathway have not been systematically investigated. Therefore, the present study was conducted to evaluate the predicted interactions of six commonly used synthetic food preservatives (TBHQ, BHA, PG, PS, SB, and SMB) with EGFR, PI3K, AKT, and mTOR proteins using molecular docking analysis.

Methods

Collection and Preparation of Ligand and Protein Structures

All active molecule data including TBHQ (Pubchem CID: 16043), BHA (Pubchem CID: 8456), PG (Pubchem CID: 4947), PS (Pubchem CID: 23676745), SB (Pubchem CID: 517055), and SMB (Pubchem CID: 124202468) were retrieved from the PubChem database along with their Canonical Simplified Molecular Input Line Entry System (SMILES) representations and downloaded in SDF format. Active molecules were selected based on their structural relevance, representing for subsequent computational analysis. Target protein data of EGFR (PDB ID: 2ITY), PI3K (PDB ID: 6PYS), Akt-1 (PDB ID: 8UW2), and mTOR (PDB ID: 4JSV) were obtained from the Protein Data Bank and downloaded in PDB format. Protein selection criteria included high structural quality, defined by a resolution range of 2.0–2.5 Å, absence of mutations, ≥90% of residues in favored regions, and no residues in disallowed regions.

To provide a benchmark for docking performance and binding affinity interpretation, established inhibitors of EGFR, PI3K, Akt-1, and mTOR were included as reference ligands. These inhibitors were used solely as positive docking controls because their binding modes within the ATP-binding pockets have been experimentally validated. The comparison was intended to contextualize the binding affinity of the investigated food additives rather than to imply inhibitory activity. Specifically, gefitinib (PubChem CID: 123631) was selected as the reference ligand for EGFR, alpelisib (PubChem CID: 56649450) for PI3K, capivasertib (PubChem CID: 25227436) for Akt-1, and torin (PubChem CID: 51358113) for mTOR. These reference inhibitors were chosen because they are well-characterized inhibitors with experimentally validated binding to their respective target proteins and are widely employed as standard reference compounds in structural biology, molecular docking, and anticancer drug discovery studies.

SwissADME-Based Pharmacokinetic Evaluation

Pharmacokinetic properties were subsequently assessed using SwissADME (Molecular Modelling Group, Lausanne, Switzerland, http://www.swissadme.ch). Canonical SMILES served as input to evaluate physicochemical properties, including molecular weight, molar refractivity, lipophilicity (Log P), aqueous solubility, number of heavy atoms, rotatable bonds, hydrogen bond acceptors, and hydrogen bond donors.

Preparation and Energy Minimization of Ligands and Proteins

Each active molecule was prepared through energy minimization using PyRx–Virtual Screening Tool 1.2 (FastSpring, Amsterdam, Netherlands). Molecular structures were imported into the workspace and optimized using the Universal Force Field (UFF). Energy minimization was performed employing the conjugate gradient algorithm with a maximum of 200 iterations. Convergence was achieved when the energy gradient reached <0.01 kcal/mol·Å, ensuring a stable three-dimensional conformation. The optimized structures were subsequently exported in .pdb format for further analysis. Protein preparation was carried out using BIOVIA Discovery Studio 2016 (Dassault Systèmes, Vélizy-Villacoublay, France). Prior to docking, protein structures were inspected to remove crystallographic water molecules, co-crystallized ligands, and non-essential heteroatoms that could interfere with ligand binding. The cleaned protein structures were subsequently saved in Protein Data Bank (PDB) format and used for molecular docking analysis.

Molecular Docking and Binding Interaction Analysis

Molecular docking was carried out using CB-Dock 2.0 (https://cadd.labshare.cn/cb-dock2/php/index.php). Prepared ligands and target proteins were uploaded to predict binding interactions. The platform automatically detected up to five potential binding cavities and conducted docking simulations using AutoDock Vina as the docking engine. For each cavity, multiple binding poses were generated, and the optimal pose was selected based on the lowest binding affinity (Vina score, kcal/mol) and cavity suitability. Docking results were subsequently evaluated by considering the predicted binding affinity together with the consistency of ligand localization within the predicted binding cavity and the interaction profiles with key amino acid residues surrounding the binding pocket. This approach provides confidence that the selected docking poses represent energetically favorable and structurally plausible ligand–protein interactions. Ligand–protein interactions were subsequently visualized in both three-dimensional (3D) and two-dimensional (2D) formats using BIOVIA Discovery Studio 2016.

Root Mean Square Fluctuation Analysis

The structural flexibility of the selected protein–ligand complexes was evaluated using the CABS-flex 3.0 web server (https://lcbio.pl/cabsflex3/). The complexes exhibiting the lowest Vina scores for each protein target were analyzed using the default CABS-flex 3.0 simulation settings. During the analysis, the docked small-molecule ligands were explicitly retained and modeled as part of the protein–ligand complexes, allowing residue fluctuations to be evaluated in the ligand-bound state. Root mean square fluctuation (RMSF) values were calculated for each amino acid residue to assess residue-level flexibility following ligand binding. Lower RMSF values indicate reduced residue mobility of the ligand-bound protein and provide complementary information to the docking results.

Results

PG Exhibits the Most Favorable Physicochemical Profile for Protein Binding

The physicochemical characteristics of the selected food additives were analyzed using the SwissADME web server (Table 1). All compounds exhibited relatively low molecular weights, ranging from 112.13 to 212.20 g/mol. PG possessed the highest molecular weight (212.20 g/mol), the greatest number of heavy atoms (15), hydrogen bond acceptors (5), hydrogen bond donors (3), and rotatable bonds (4), suggesting a greater structural flexibility and higher potential to establish intermolecular interactions with target proteins. In contrast, potassium sorbate and sodium benzoate displayed comparatively simpler molecular structures with fewer heavy atoms and hydrogen bonding sites.

Lipophilicity analysis demonstrated that BHA exhibited the highest Log P value (2.69), followed by TBHQ (2.34), whereas PG showed a moderate Log P value (1.24), indicating a more balanced hydrophilic–lipophilic profile. Water solubility analysis revealed that BHA was the least soluble compound (Log S = −3.15), while PS exhibited the highest aqueous solubility (Log S = −1.24). Overall, the physicochemical profiles suggest that PG combines moderate lipophilicity with the highest hydrogen-bonding capacity among the investigated food additives,

Table 1. Physiochemical properties of active molecules using SwissADME web-based platform.

Physiochemical	Ligand					
	TBHQ	BHA	PG	PS	SB	SMB
Molecular weight (g/mol)	166.22	180.24	212.30	150.22	144.10	190.10
Number of heavy atoms	12	13	15	9	10	9
Number of rotatable bonds	1	2	4	2	1	1
Number of HBA	2	2	5	2	2	2
Number of HBD	2	1	3	0	0	2
Molar refractivity	49.76	54.23	53.40	29.84	31.46	22.50
Lipophilicity (Log P)	2.34	2.69	1.24	1.02	1.35	1.98
Water solubility (Log S / ESOL)	-2.96	-3.15	-2.32	-2.25	-2.71	-2.15

characteristics that may contribute to stronger ligand–protein interactions during molecular docking.

PG and BHA Consistently Achieve the Lowest Docking Scores Across Multiple Cancer-Protein Related Targets

Among all investigated compounds, PG and BHA exhibited the most binding affinities across multiple protein targets. PG produced the strongest interaction with EGFR, showing the lowest Vina score of −6.1 kcal/mol, while also demonstrating the highest affinity toward mTOR with a Vina score of −6.7 kcal/mol. Furthermore, PG achieved one of the lowest docking scores against PI3K (−6.8 kcal/mol), indicating a strong interaction with this key signaling protein. Similarly, BHA exhibited highly favorable docking results, producing the lowest Vina score against Akt-1 (−6.5 kcal/mol) and sharing the strongest binding affinity toward PI3K with PG (−6.8 kcal/mol). In comparison, TBHQ showed moderate binding affinities across all protein targets. Meanwhile, PS, SB, and SMB consistently displayed weaker interactions (Table 2).

PG and BHA Achieve Stable Protein Binding Through Extensive Hydrogen Bonding and Hydrophobic Interactions

Interaction profiles demonstrated that PG and BHA established multiple stabilizing interactions within the binding pockets of their respective target proteins through combinations of hydrogen bonds, van der Waals interactions, and hydrophobic contacts. The PG–EGFR complex exhibited a highly stabilized binding mode through three hydrogen bonds involving GLN791, ARG776, and VAL774. Additional stabilization was provided by extensive van der Waals interactions, together with π-anion and π-alkyl interaction. The presence of multiple hydrogen bonds combined with hydrophobic interactions may explain the binding affinity of PG toward EGFR (Table 3, Figure 1).

Table 2. Vina score interactions of food additives with cancer-related protein targets.

Active Molecules	Protein Target (Vina Score)			
	EGFR	PI_3K	Akt-1	mTOR
TBHQ	-5.8	-6.6	-6.2	-6.1
BHA	-5.7	**-6.8**	**-6.5**	-6.0
PG	**-6.1**	**-6.8**	-6.4	**-6.7**
PS	-4.3	-4.9	-4.8	-4.7
SB	-5.1	-5.8	-5.7	-5.3
SMB	-4.5	-5.0	-4.6	-4.5
Control ligand	-6.7 (Gefitnib)	-7.0 (Alpelisib)	-6.8 (Capivasertib)	-9.1 (Torin)

Value written in bolds are compounds with the lowest predicted binding energies (Vina scores).

For PI3K, both PG and BHA demonstrated identical docking scores but exhibited distinct interaction patterns. BHA formed a hydrogen bond with GLN661, accompanied by multiple van der Waals interactions involving LEU752, TYR698, HIS665, ARG662, PRO168, GLU259, VAL166, ASP258, and TYR167, as well as π-alkyl interactions with ALA758 and PRO757. Conversely, PG interacted predominantly through extensive hydrophobic contacts with GLN661, PRO757, VAL166, ALA758, ASP258, TYR260, GLU259, and ASN170, while forming several π-alkyl interactions with TYR167, LEU752, ARG662, and PRO168. These complementary interaction profiles suggest that both compounds can be accommodated efficiently within the PI3K binding pocket despite their structural differences (Table 3, Figure 1).

The strongest interaction with Akt-1 was observed for BHA, which formed a hydrogen bond with SER205 and additional van der Waals interactions. Moreover, π–π stacking and π-alkyl interactions further stabilized the ligand within the catalytic pocket, supporting its docking score. The PG–mTOR complex displayed the most favorable binding affinity among all mTOR docked complexes. PG established four hydrogen bonds with GLN225, LEU318, LEU48, and VAL316, together with van der Waals interactions. Additional stabilization was provided through π-alkyl interactions, as well as a π-sulfur interaction. Collectively, molecular interaction analyses demonstrate that the superior docking performance of PG and BHA is associated with their ability to establish multiple complementary intermolecular interactions within the active sites of EGFR, PI3K, Akt-1, and mTOR (Table 3, Figure 1).

RMSF Analysis Revealed Differences in Residue-Level Flexibility Among Ligand-Protein Structures

The residue-level flexibility of the selected ligand-bound proteins was evaluated using RMSF analysis in CABS-flex 3.0, with the docked small-molecule ligands retained throughout the analysis. RMSF profiles varied among the five protein–ligand complexes, indicating differences in residue mobility following ligand binding. The PG–PI3K complex exhibited the lowest average RMSF value (1.76 Å), followed by BHA–PI3K (1.80 Å), PG–mTOR (1.87 Å), and BHA–Akt-1 (1.92 Å), whereas the PG–EGFR complex showed the highest average RMSF value (3.16 Å) (Figure 2). These RMSF profiles describe the flexibility of the ligand-bound protein structures and complement the molecular docking results by providing information on residue mobility following ligand binding.

Discussion

Molecular docking analysis identified PG and BHA as the compounds showing the lowest predicted Vina scores across the investigated synthetic food preservatives. PG showed the most prominent predicted interactions with EGFR, PI3K, and mTOR, whereas BHA showed prominent predicted interactions with PI3K and Akt-1 (Table 2). These findings were further supported by molecular interaction analysis, which revealed multiple hydrogen bonds, hydrophobic contacts, and van der Waals interactions within the predicted binding pockets (Table 3, Figure 1). In addition, interaction profiles of PG and BHA may be related, at least in part,

Table 3. Molecular docking interactions between synthetic food preservatives and cancer-related proteins.

Interaction	Hydrogen Bond Details	Van Der Waals Bonds	Other Bonds
PG - EGFR	GLN791, ARG776, VAL774	LEU1017, ALA1013, LEU778, LYS852, CYS775, PRO772, ASN771, ASP770, TYR1016	Pi-anion: ASP1014 Pi-Alkyl: ILE1018
BHA - PI_3K	GLN661	LEU752, TYR698, HIS665, ARG662, PRO168, GLU259, VAL166, ASP258, TYR167	Pi-alkyl: ALA758, PRO757
PG - PI_3K	-	GLN661, PRO757, VAL166, ALA758, ASP258, TYR260, GLU259, ASN170	Pi-alkyl: TYR167, LEU752, ARG662, PRO168
BHA - Akt-1	SER205	LYS268, LEU210, ASP292, TYR272, GLN79	Pi-Pi Stacked: TRP80 Pi-alkyl: VAL270, LEU264
PG - mTOR	GLN225, LEU318, LEU48, VAL316	ARG227, GLU49, ALA319, ASN46, SER90, SER175	Pi-alkyl: HIS177, ALA47 Pi-sulfur: CYS317

The displayed ligand–protein complexes represent those with the highest binding affinities for each target protein.

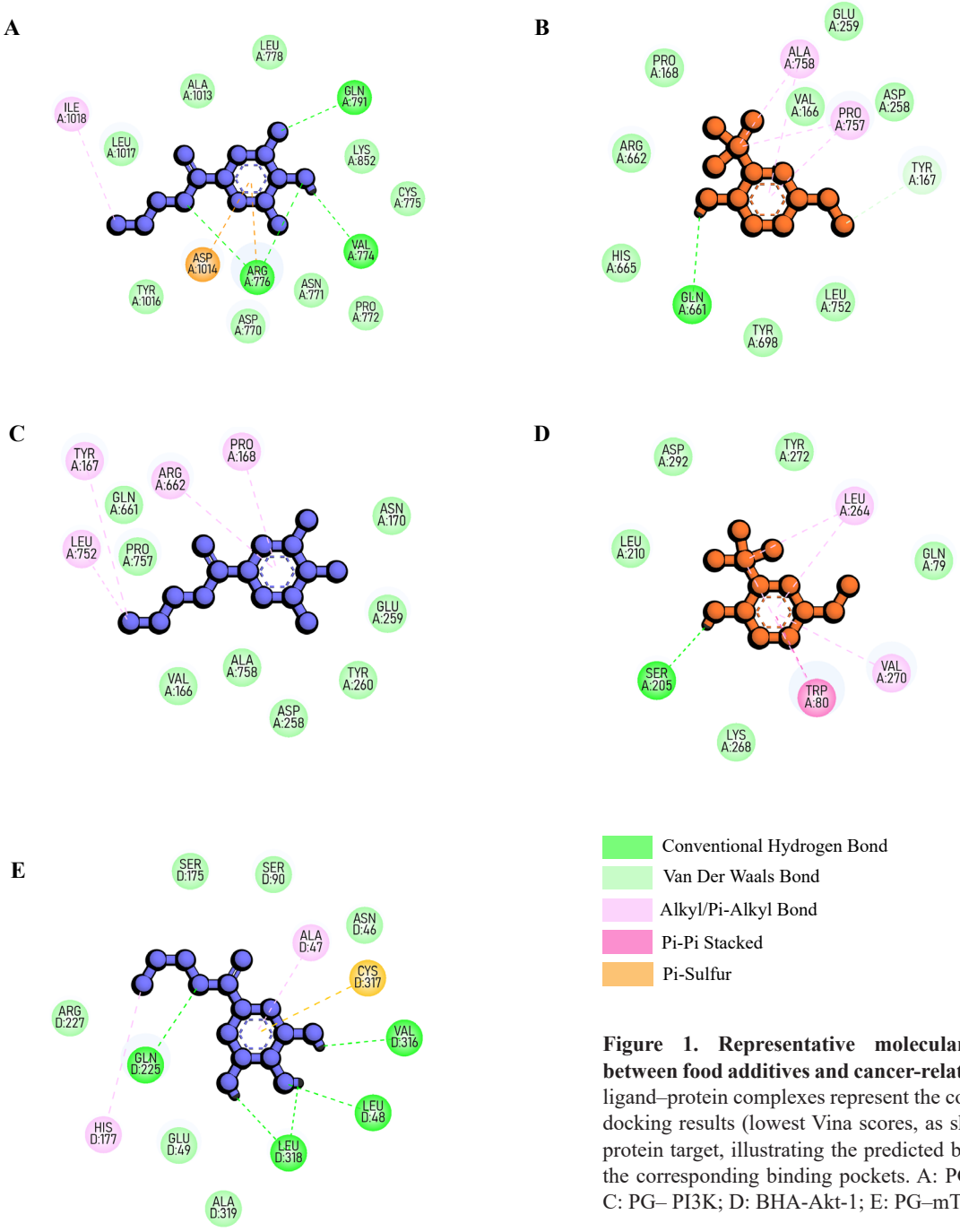

Figure 1. Representative molecular docking interactions between food additives and cancer-related protein. The displayed ligand–protein complexes represent the compounds with the highest docking results (lowest Vina scores, as shown in Table 2) for each protein target, illustrating the predicted binding orientations within the corresponding binding pockets. A: PG–EGFR; B: BHA–PI3K; C: PG– PI3K; D: BHA-Akt-1; E: PG–mTOR.

to their physicochemical characteristics, particularly their lipophilicity, hydrogen-bonding capacity, and structural properties (Table 1), which can influence ligand recognition and interactions within protein binding sites.(21,22)

Among all investigated targets, EGFR exhibited the strongest predicted interaction with PG, as indicated by its Vina score (Table 2). EGFR is an important upstream component of the EGFR–PI3K–Akt–mTOR signaling pathway and is frequently dysregulated in oral and gastrointestinal cancers. Through its downstream signaling, EGFR regulates cellular processes associated with tumor development, including proliferation, survival, migration, and resistance to apoptosis. In the present study, the predicted PG–EGFR interaction therefore indicates a potential molecular association with an important signaling regulator. (23,24) However, molecular docking cannot determine whether PG activates, inhibits, or otherwise modulates EGFR, and the biological significance of this predicted interaction remains to be experimentally established.

In addition to EGFR, PI3K showed prominent predicted interactions with both PG and BHA (Table 2). PI3K is an important intracellular component of the signaling network

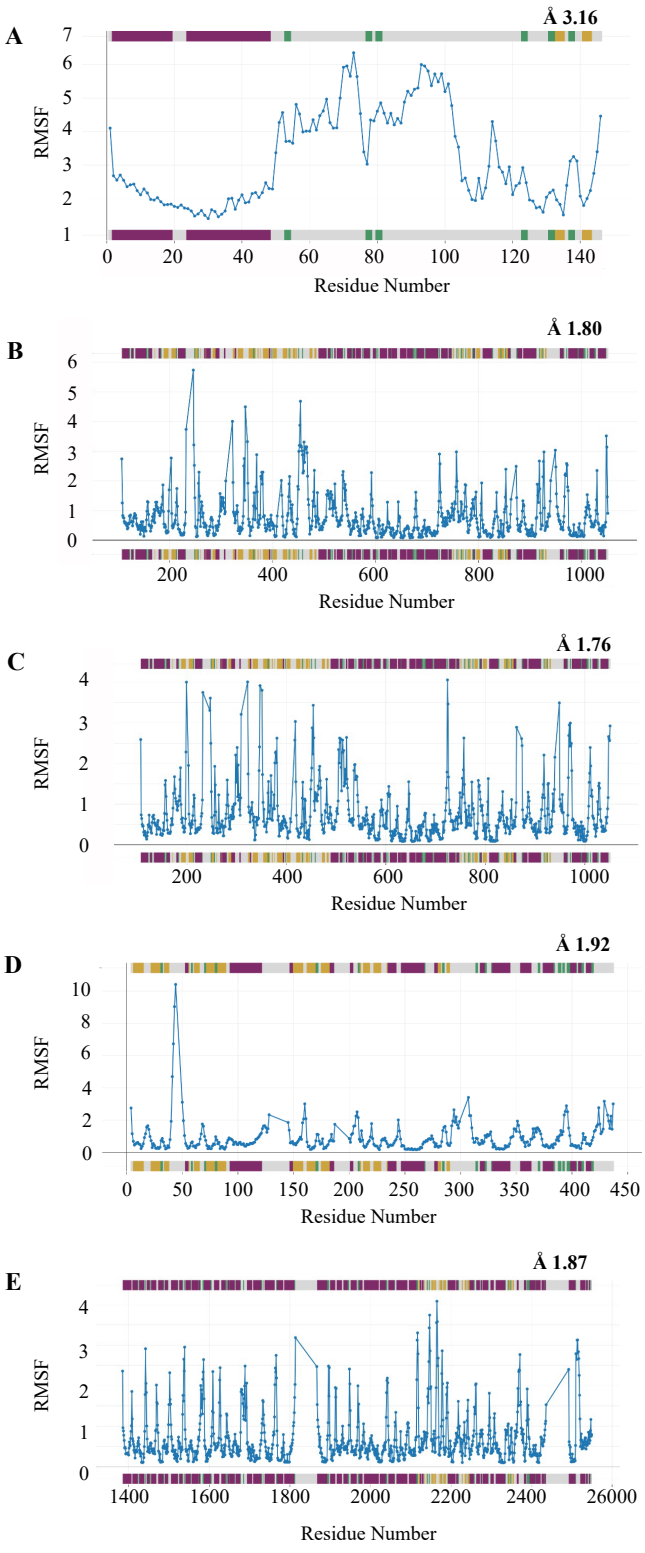

Figure 2. RMSF analysis of selected food additive–protein complexes exhibiting the strongest binding affinities. The figure presents RMSF profiles of ligand–protein complexes with the lowest Vina scores among all investigated food preservatives. RMSF plots describe residue fluctuations during molecular dynamics simulations, providing an assessment of structural flexibility and complex stability. A: PG–EGFR; B: BHA–PI3K; C: PG–PI3K; D: BHA–Akt-1; E: PG–mTOR.

and regulates cellular processes including proliferation, survival, metabolism, and migration.(25) Dysregulation of PI3K signaling, including alterations involving PIK3CA, has been reported in oral, esophageal, gastric, and colorectal cancers and has been associated with tumor progression and therapeutic resistance.(26,27) The predicted interactions of PG and BHA with PI3K therefore extend the observed docking pattern beyond the upstream receptor and suggest potential associations with an intracellular component of the same signaling network.

A similar pattern was observed for Akt-1, with BHA showing one of the more prominent predicted interactions among the investigated preservatives (Table 2). Akt-1 is an important signaling regulator involved in cell-cycle progression, metabolism, protein synthesis, and resistance to apoptosis.(28) Altered Akt signaling has been reported in oral squamous cell carcinoma, esophageal carcinoma, gastric cancer, and colorectal cancer and has been associated with tumor progression and unfavorable clinical characteristics.(29,30) The predicted interaction between BHA and Akt-1, together with its interaction with PI3K, suggests that BHA may associate with multiple components of the same signaling network.

PG also showed a prominent predicted interaction with mTOR (Table 2), providing an additional interaction involving a downstream component of the EGFR–PI3K–Akt–mTOR pathway. mTOR regulates cellular growth, metabolism, protein synthesis, and proliferation, and its dysregulation has been reported in oral and gastrointestinal cancers.(31–34) This finding is further supported by previous evidence indicating that the PI3K/Akt/mTOR signaling axis plays a crucial role in cell survival, growth, and proliferation in various tumor cells.(35) The predicted PG–mTOR interaction, together with the interactions observed between PG and EGFR and PI3K, indicates that PG showed predicted associations with multiple components distributed across the signaling pathway. Nevertheless, this computational finding represents a predicted molecular association and should not be interpreted as evidence that PG modulates mTOR activity.

RMSF analysis provided complementary information regarding residue-level flexibility in the selected ligand-bound protein structures (Figure 2). The different RMSF profiles observed among the five complexes indicate variations in residue mobility across the ligand-bound protein structures. The PI3K-bound complexes generally showed lower residue fluctuations, whereas the EGFR-bound complex exhibited greater fluctuations, with Akt-1 and mTOR showing intermediate profiles. These findings

these compounds activate, inhibit, or otherwise modulate the target proteins. Furthermore, the biological effects of long-term dietary exposure are influenced by absorption, metabolism, distribution, and tissue exposure. Experimental studies, including enzyme activity assays, phosphoprotein analyses, cell-based signaling studies, and *in vivo* exposure models, are therefore needed to establish the biological relevance of the predicted interactions.

Conclusion

The present molecular docking study showed that PG and BHA exhibited the highest binding affinities toward multiple proteins within the EGFR–PI3K–Akt–mTOR compared with the other investigated synthetic food preservatives. These findings provide a computational basis for prioritizing these compounds for future mechanistic investigations. Further experimental studies are needed to determine the biological relevance of the predicted interactions and their potential implications in oral and gastrointestinal cancer-related signaling following long-term dietary exposure.

Authors Contribution

The study was conceived and designed by FS, with valuable contributions from VEP, JH, DR, and KHL. Data collection, analysis, manuscript drafting, and figure preparation were carried out by FS and VEP. All authors critically revised the manuscript and approved the final version.

Ethical Statement

Ethical approval and informed consent were not required for this work.

Conflict of Interest

All authors declare that they have no competing interests.

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