



Computational Repurposing of Flavokawain B as a Novel p38 MAPK Inhibitor for Triple-Negative Breast Cancer Therapy

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Abstract

Background: Triple-Negative Breast Cancer (TNBC) is an aggressive and therapeutically challenging subtype with poor clinical outcomes. Among various oncogenic targets, p38 MAPK α (MAPK14) regulates key pathways in cell survival, apoptosis, and inflammatory responses. Despite its therapeutic relevance, MAPK14 remains underexplored in the context of natural compound-based interventions for TNBC. This study aims to fill that gap by evaluating plant-derived ligands with multi-targeted potential and better safety profiles as novel MAPK14 inhibitors for targeted cancer therapy. **Methods:** This study employed a comprehensive in silico strategy to evaluate two phytochemicals, Epigallocatechin-3-gallate (EGCG) and Flavokawain B (FKB), as potential MAPK14 inhibitors. Molecular docking was performed using AutoDock Vina against the MAPK14 protein (PDB ID: 1A9U), followed by interaction visualization. ADME-Tox profiling was conducted using SwissADME and ProTox-II, while pathway analysis was performed via Cytoscape to explore downstream network connectivity. **Results:** EGCG demonstrated high binding affinity (-8.0 kcal/mol) and diverse hydrogen bonding and π -type interactions, but showed limitations in GI absorption and bioavailability. In

contrast, FKB exhibited slightly lower binding energy (-7.7 kcal/mol) but greater structural stability across docking poses, with superior pharmacokinetic features, including high GI absorption, BBB permeability, and low predicted toxicity. Network analysis indicated both compounds may influence apoptotic signaling via MAP2K3, TP53, and STAT1 pathways. **Conclusion:** The results suggest that while EGCG shows strong molecular interactions, FKB presents a more balanced therapeutic profile. These findings support FKB as a promising natural inhibitor of MAPK14, warranting further in vitro and in vivo validation for TNBC therapy.

Keywords: Triple-Negative Breast Cancer (TNBC), p38 MAPK α (MAPK14), Epigallocatechin-3-gallate (EGCG), Flavokawain B (FKB), Molecular docking

1. Introduction

Cancer remains the second leading cause of death globally, with breast cancer being the most frequently diagnosed malignancy among women (Arnold et al., 2022). Among its subtypes, Triple-Negative Breast Cancer (TNBC) is particularly aggressive, complex, and resistant to standard therapies. TNBC accounts for approximately 15-20% of all breast cancer cases and is characterized by the absence of estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2), rendering it unresponsive to hormonal or HER2-targeted therapies (van Barele et al., 2021). Due to this limitation, patients with TNBC primarily rely on chemotherapy, which is often associated with adverse effects, drug resistance, and a high risk of relapse (Maqbool et al., 2022). Even with advances in treatment, the five-year survival

Significance | Flavokawain B's inhibition of MAPK14 suggests its potential as a novel, natural therapeutic candidate against TNBC progression.

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rate for TNBC patients remains significantly lower compared to other breast cancer subtypes (Baranova et al., 2022). Recent studies have identified Mitogen-Activated Protein Kinase 14 (MAPK14), also known as p38 MAPK α , as a critical oncogenic regulator in Triple-Negative Breast Cancer (TNBC). This kinase plays a central role in modulating cellular inflammation, oxidative stress responses, cell cycle regulation, and apoptosis (Wang et al., 2022). In TNBC cells, overexpression or hyperactivation of the p38 MAPK α pathway has been associated with enhanced tumor cell survival and metastatic potential (H. Chen et al., 2021; Kudravalli et al., 2022). Importantly, inhibition of this pathway has been shown to induce growth arrest and apoptosis in cancer cells, suggesting its therapeutic relevance (Cetraro et al., 2022). Consequently, MAPK14 is increasingly recognized as a promising molecular target for the development of targeted therapies in TNBC treatment.

Despite the therapeutic relevance of p38 MAPK α in cancer biology, most of its known inhibitors have failed to achieve clinical success due to significant drawbacks such as off-target toxicity, poor aqueous solubility, metabolic instability, and limited bioavailability (García-Hernández et al., 2021; Phan et al., 2023). These pharmacokinetic and pharmacodynamic limitations have shifted the research focus towards bioactive natural products, which are structurally diverse, biologically accessible, and generally well-tolerated. Natural compounds with anti-inflammatory and anticancer properties offer unique advantages in targeting dysregulated pathways like MAPK14, especially in hard-to-treat cancers such as TNBC (W. Xu et al., 2021). Moreover, several plant-derived molecules have demonstrated the ability to modulate multiple signaling pathways simultaneously, making them attractive candidates for multi-targeted therapy (Ganguly et al., 2023). Hence, identifying safe and effective natural MAPK14 inhibitors could offer a promising therapeutic strategy for TNBC management.

In this study, we selected two naturally derived compounds: Epigallocatechin-3-gallate (EGCG) and Flavokawain B (FKB), based on their well-documented anticancer properties. EGCG, the principal polyphenol found in green tea, has been extensively studied for its anti-proliferative, anti-angiogenic, and pro-apoptotic effects in various cancer types, including breast cancer (Kciuk et al., 2023). It is known to modulate key signaling pathways such as PI3K/Akt, JAK/STAT, and NF- κ B, which are often dysregulated in TNBC (Farghadani & Naidu, 2021; Fultang et al., 2021). EGCG also exhibits low systemic toxicity, making it an attractive candidate for therapeutic repurposing.

On the other hand, Flavokawain B (FKB) is a naturally occurring chalcone compound derived from the kava plant (*Piper methysticum*), known for its ability to induce cell cycle arrest at the G2/M phase and activate caspase-mediated apoptotic pathways (Zhao et al., 2023). FKB has shown promising activity against drug-resistant cancer cell lines and is gaining attention as a potent anti-

tumor agent (Szymczyk et al., 2021). However, despite these encouraging findings, the potential of both EGCG and FKB to inhibit the MAPK14 (p38 MAPK α) pathway remains underexplored, particularly in the context of TNBC. This presents a significant literature gap, which this study aims to address through computational modeling and comparative analysis with known reference inhibitors.

In this study, two naturally occurring compounds-Epigallocatechin-3-gallate (EGCG) and Flavokawain B (FKB)-were selected for their reported anticancer activities and favorable safety profiles. EGCG, the major polyphenol in green tea, has demonstrated anti-proliferative and apoptosis-inducing effects through modulation of signaling pathways like PI3K/Akt and NF- κ B (Ferrari et al., 2022). FKB, a chalcone from *Piper methysticum*, is known to induce G2/M cell cycle arrest and caspase-mediated apoptosis in cancer cells (Michalkova et al., 2023). Despite their promising profiles, their potential to inhibit MAPK14 (p38 MAPK α), a key target in TNBC progression, remains poorly studied. This study addresses that gap by evaluating their binding affinity, interaction stability, and pharmacokinetic features, using SB203580 as a reference inhibitor.

The present study aimed to identify Epigallocatechin-3-gallate (EGCG) and Flavokawain B (FKB) as potential natural inhibitors of p38 MAPK α , a key molecular target implicated in Triple-Negative Breast Cancer (TNBC) progression. Using a structure-based molecular docking approach and biological network/pathway analysis, the interaction profiles and therapeutic relevance of these compounds were comprehensively evaluated (Marín et al., 2023).

By focusing on compounds that are both biologically active and naturally sourced, this research fills a critical literature gap in targeted drug discovery for TNBC. It sets a foundation for future in vitro and in vivo validation and offers insights that may contribute to the broader fields of oncology, natural product pharmacology, and precision therapeutics. If validated further, these compounds could offer a safer and more effective therapeutic alternative for TNBC patients.

2. Materials and Methods

2.1 Study Design

This study used a structure-based computational approach to explore natural compounds as potential inhibitors of p38 MAPK α , a key protein in TNBC. The 3D structure of MAPK14 was retrieved from the Protein Data Bank and prepared for docking. Epigallocatechin-3-gallate (EGCG) and Flavokawain B (FKB) were selected as test ligands, with SB203580 as a reference inhibitor. Molecular docking was performed using AutoDock Vina via PyRx to assess binding affinity. ADME and toxicity profiles were predicted using SwissADME and ProTox-II. Pathway involvement of MAPK14 was analyzed using KEGG and visualized with Cytoscape.

This workflow aimed to identify safe and effective natural inhibitors for further TNBC therapy development.

2.2 Protein Preparation

The three-dimensional crystal structure of the human p38 MAPK α protein (MAPK14) was retrieved from the Protein Data Bank (PDB ID: 1A9U). This structure, resolved at 2.5 Å, includes the active form of the kinase domain bound with a known inhibitor, SB203580. It was selected based on its completeness and relevance to inhibitor binding studies. Using Discovery Studio Visualizer, all non-essential molecules-including water, ions, and the co-crystallized ligand-were removed. The structure was inspected for missing atoms or chains and confirmed to be suitable for docking analysis.

Further optimization was carried out using AutoDock Tools (v1.5.7). Polar hydrogens were added, and Gasteiger charges were assigned to ensure proper electrostatic calculations. The cleaned structure was saved in PDBQT format, compatible with AutoDock Vina. A grid box was generated to cover the active site based on the coordinates of the native ligand binding region. This preparation ensured that the receptor structure was properly formatted, chemically optimized, and ready for accurate molecular docking simulations with selected ligands.

2.3 Ligand Selection and Preparation

Two bioactive natural compounds-Epigallocatechin-3-gallate (EGCG) and Flavokawain B (FKB)-were selected for this study based on previous reports of their anticancer potential. EGCG (PubChem CID: 65064) is a major polyphenol from green tea, known for its ability to modulate cell signaling, induce apoptosis, and inhibit tumor growth. Flavokawain B (PubChem CID: 5318984) is a chalcone derivative reported to induce G2/M cell cycle arrest and promote caspase mediated cell death. The known p38 MAPK α inhibitor SB203580 (PubChem CID: 5353947) was used as a reference to benchmark docking results and validate the method. The 2D structures of all ligands were downloaded from the PubChem database in SDF format. Using Open Babel and PyRx (v0.8), the structures were converted to 3D, and energy minimization was performed using the Universal Force Field (UFF) to obtain a stable conformation. Hydrogen atoms were added, and torsions were adjusted as needed. The ligands were then saved in PDBQT format, suitable for docking in AutoDock Vina. These prepared ligands were further used to study their molecular interactions with the active site of p38 MAPK α .

2.4 Molecular Docking Protocol

Molecular docking was performed to evaluate the binding affinity and interaction patterns of the selected ligands (EGCG and Flavokawain B) with the p38 MAPK α (MAPK14) protein. Docking simulations were carried out using AutoDock Vina integrated within PyRx (v0.8), which applies a Lamarckian Genetic Algorithm to predict the most stable binding conformations. The protein (PDB ID: 1A9U) was loaded in PDBQT format, and the docking grid box

was defined around the native ligand-binding site to include key active residues. The reference inhibitor SB203580 was also docked under identical conditions to serve as a positive control.

All ligands were docked in their minimized 3D conformations, and the binding affinity (expressed in kcal/mol) was recorded for each compound. The top-ranked pose with the lowest binding energy was selected for further interaction analysis. The resulting ligand-protein complexes were visualized in both 2D and 3D using Discovery Studio Visualizer and LigPlot+, allowing identification of key hydrogen bonds, hydrophobic contacts, and π -interactions. These docking results provided critical insights into the binding strength and mode of each ligand with the MAPK14 protein.

2.5 Drug-Likeness and Toxicity Prediction

The drug-likeness of the selected ligands-Epigallocatechin-3-gallate (EGCG), Flavokawain B (FKB), and the reference compound SB203580-was evaluated using the SwissADME web server. Key physicochemical properties such as molecular weight, number of hydrogen bond donors and acceptors, rotatable bonds, topological polar surface area (TPSA), and lipophilicity (LogP) were analyzed. Each compound was further assessed against Lipinski's Rule of Five to determine its potential for oral bioavailability. Additional parameters such as bioavailability score and gastrointestinal (GI) absorption were also predicted. These analyses provided insight into whether the ligands possess desirable features for drug development.

Toxicity-related properties were predicted using ProTox-II and pkCSM web tools. Parameters including LD₅₀ values (mg/kg), hepatotoxicity, blood-brain barrier (BBB) permeability, and potential inhibition of cytochrome P450 (CYP) isoenzymes (e.g., CYP1A2, CYP2C9, CYP3A4) were evaluated. These predictions helped estimate the safety profile of each compound in terms of systemic toxicity, metabolic interactions, and brain exposure. The integrated data from both drug-likeness and toxicity predictions guided the prioritization of EGCG and Flavokawain B as safe and effective candidates for further development as MAPK14 inhibitors.

2.6 Pathway and Network Analysis

To better understand the role of p38 MAPK α (MAPK14) in cancer-related signaling, pathway mapping and network analysis were performed using curated databases and visualization tools. The MAPK signaling pathway was explored through the KEGG database, focusing on MAPK14 and its upstream and downstream interactions relevant to cell proliferation, survival, and inflammation. The gene-protein interaction data were extracted from STRING (v11.5) with a high confidence score (≥ 0.7) to ensure reliability.

The extracted interaction network was imported into Cytoscape (v3.9.1) for topological analysis and visualization. Key network features such as node degree, clustering coefficient, and hub proteins were analyzed to identify central regulators within the MAPK

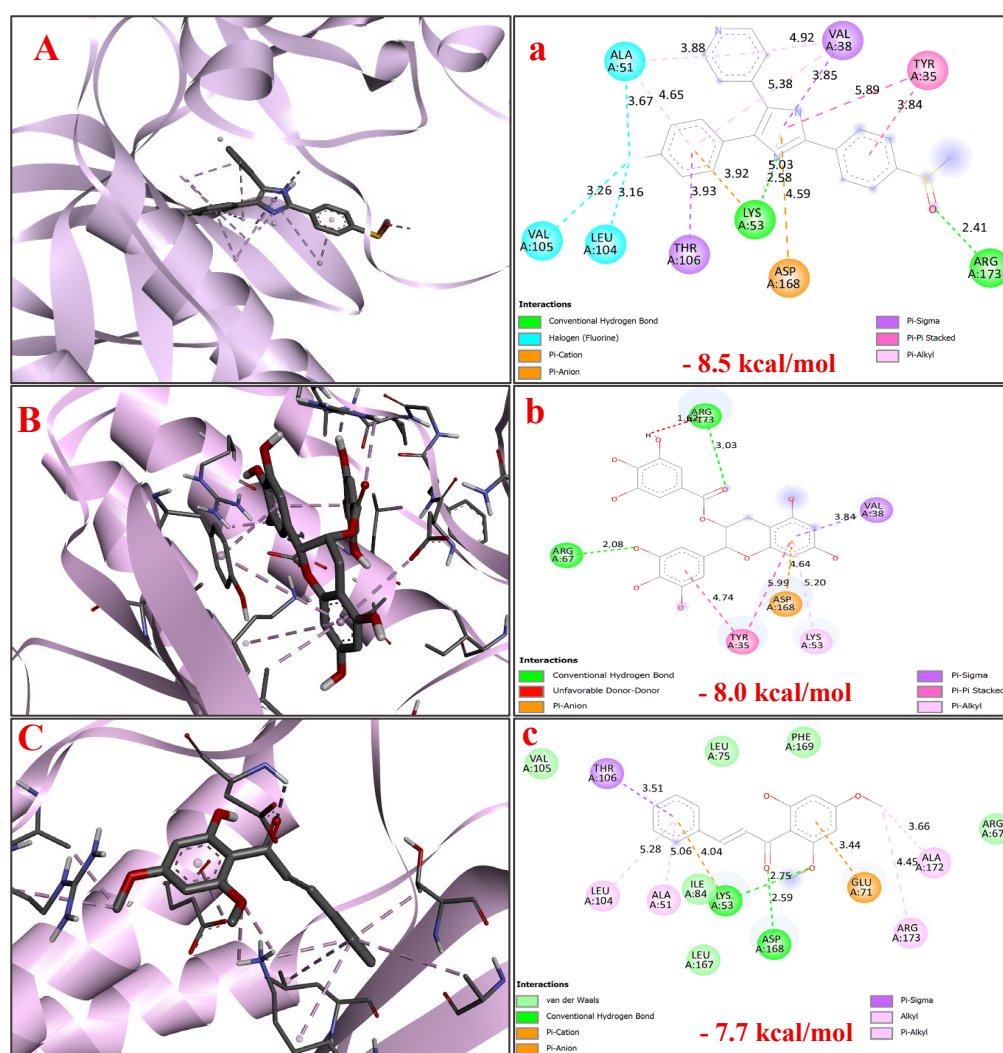


Figure 1. Three-dimensional (left) and two-dimensional (right) interaction diagrams of the complexes formed between the target protein and the selected ligands (SB203580, Epigallocatechin-3-gallate, and Flavokawain B). (A/a) SB203580, (B/b) Epigallocatechin-3-gallate, and (C/c) Flavokawain B. The binding energy of each ligand is indicated in red in the corresponding 2D interaction diagram. The interactions include hydrogen bonding, π - π stacking, π -cation, and van der Waals forces.

pathway. MAPK14's connectivity with other oncogenic nodes (e.g., MAPK3, MAP2K6, JUN, TP53) was highlighted to illustrate its biological importance. This network-based approach supported the hypothesis that inhibiting MAPK14 could disrupt multiple cancer-related processes, especially in aggressive cancers like triple-negative breast cancer (TNBC).

2.7 Statistical Analysis

Docking scores, RMSD values, and toxicity data were analyzed using one-way ANOVA followed by Tukey's post hoc test to assess statistical significance. Results were expressed as mean $\pm$ standard deviation (SD), with $p < 0.05$ considered significant. Significance levels were denoted as: $p < 0.01$ (*), $p < 0.01$ (**), and $p < 0.001$ (***); "ns" indicated non-significance. All analyses and plots were performed using GraphPad Prism (v9.5).

3. Results

3.1 Interaction Analysis through Molecular Docking

Through molecular docking analysis, the binding patterns and affinities of two potential natural inhibitors-Epigallocatechin-3-gallate (EGCG) and Flavokawain B-were evaluated with the active site of the target protein. To facilitate comparative assessment, a well-established reference inhibitor, SB203580, was included; however, the primary focus of this study remained on the inhibitory performance of EGCG and Flavokawain B.

EGCG exhibited a notable binding affinity, with a docking energy of -8.0 kcal/mol. It showed strong interaction within the active site, primarily through multiple hydrogen bonds formed with ARG67, ARG95, and LYS53. Additionally, π - π stacking with TYR35 and a π -cation interaction with ASP168 contributed to the overall stability of the complex. Although an unexpected donor-donor type interaction was observed, it did not significantly impact the overall inhibitory profile. Instead, EGCG's structural features and deep interactions within the active site support its potential as a promising natural inhibitor (Figure 1).

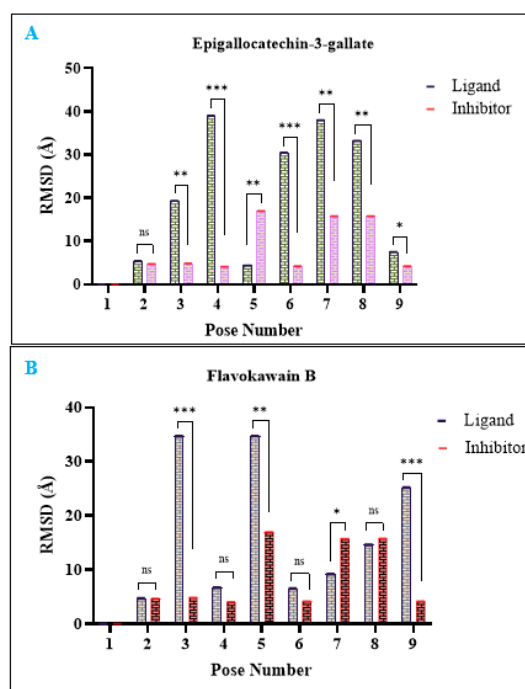


Figure 2. Comparative root-mean-square-deviation (RMSD) values of the docked ligand and reference inhibitor SB203580 for Epigallocatechin-3-gallate (A) and Flavokawain B (B) across nine docking poses. RMSD values were calculated for each pose based on the deviation from the initial conformation. Statistically significant differences between the ligand and the inhibitor at each pose are indicated as follows: $p < 0.01$ (*), $p < 0.01$ (**), and $p < 0.001$ (***); ns denotes non-significant differences.

Flavokawain B, although displaying a slightly lower binding energy (-7.7 kcal/mol), also established a stable interaction within the active site. It formed several hydrogen bonds with ALA51, ILE75, ARG67, and ARG173, alongside van der Waals and π -alkyl interactions with VAL105, LEU104, and LYS53. Notably, a π -cation interaction with GLU171 added to the stability of the complex. Its precise fit within the active site and diverse interaction profile position Flavokawain B as another key inhibitor candidate following EGCG. The reference inhibitor SB203580 showed a binding energy of -8.5 kcal/mol. It formed conventional hydrogen bonds with ALA51, VAL105, and LEU104, and was also involved in π -alkyl and π -anion interactions with TYR35 and ASP168, respectively. Additional van der Waals contacts with LYS53 and ARG173 were also observed.

3.2 Molecular RMSD Analysis of Ligand-Protein Complexes

Root Mean Square Deviation (RMSD) analysis was used to evaluate the conformational variability of Epigallocatechin-3-gallate (EGCG) and Flavokawain B in their docking poses, with SB203580 serving as the reference inhibitor (Figure 2).

For EGCG, the RMSD values of the ligand were significantly higher than those of the inhibitor in most docking poses. Specifically, in poses 3, 4, 5, 6, 7, and 9, the differences were statistically highly significant ($p < 0.01$ to $p < 0.001$). Pose 8 showed a very strong difference ($p < 0.001$), while pose 9 showed a notable difference ($p < 0.01$). Only pose 2 did not show any statistically significant variation (ns). These results suggest that EGCG exhibited diverse binding orientations within the active site during docking, leading

to comparatively higher RMSD values. This elevated RMSD indicates considerable conformational flexibility, which, while sometimes advantageous, may negatively influence binding stability if variability becomes excessive.

In the case of Flavokawain B, most poses did not show significant differences in RMSD values compared to the inhibitor. Notable differences were observed only in poses 3, 4, and 9 ($p < 0.01$ to $p < 0.001$), while pose 7 showed a moderate difference ($p < 0.01$). The remaining poses (2, 5, 6, and 8) did not exhibit any significant statistical differences (ns). These observations indicate that Flavokawain B maintained relatively stable conformations across most docking poses, with RMSD values comparable to those of the reference inhibitor SB203580. Overall, the findings highlight that EGCG displayed greater conformational flexibility, potentially reflecting binding variability, whereas Flavokawain B showed more structural stability across docking orientations.

3.3 Analysis of the MAPK Signaling Network

In Figure 3, an interaction network was constructed using Cytoscape to analyze the functional interconnectivity among the key proteins and genes involved in the Mitogen-Activated Protein Kinase (MAPK) signaling cascade. The active connections and signaling flow between associated genes and proteins were clearly visualized. The network analysis revealed two distinct functional axes: apoptosis (programmed cell death) and proliferation (cell division and survival).

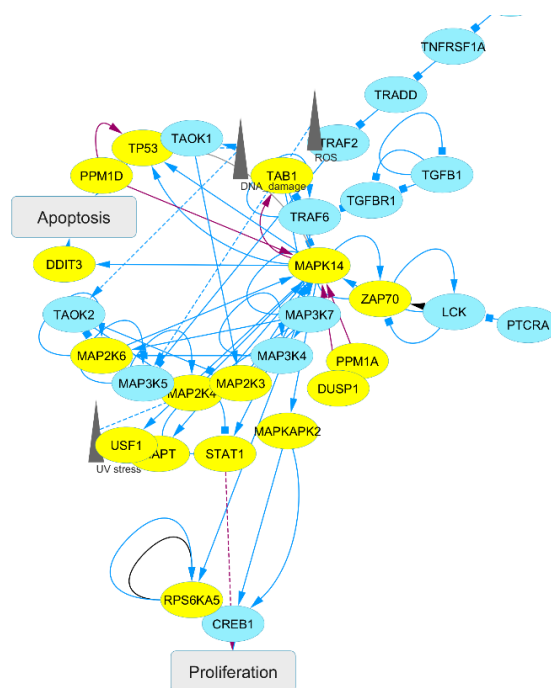


Figure 3. Cytoscape-based network representation of the MAPK signaling pathway. The diagram illustrates core interactions among kinases, phosphatases, and transcription factors, highlighting two major outcomes: apoptosis (via MAPK14, TP53) and proliferation (via MAPKAPK2, CREB1). Central nodes such as MAPK14 and STAT1 integrate signals from ROS and DNA damage.

Within the network, MAPK14 (p38 MAPK), MAP2K3, MAP3K7, MAPKAPK2, and STAT1 appeared as major hub nodes. MAPK14 functioned as a central component, activated via TRAF6 and TAB1, responding to upstream signals related to reactive oxygen species (ROS) and DNA damage. It subsequently promoted the apoptosis pathway by activating downstream regulators such as TP53 and DDIT3. Upstream kinases like MAP2K3, MAP3K5, and MAP2K6 contributed to this apoptotic signaling cascade.

On the other hand, CREB1 activation was observed through MAPKAPK2 and RPS6KA5, suggesting involvement in cellular proliferation-related activities. Notably, STAT1 exhibited a bifunctional role, participating in both apoptotic and proliferative signaling routes.

Several phosphatases present in the network, including DUSP1, PPM1A, and PPM1D, acted as negative regulators, playing essential roles in preventing MAPK pathway hyperactivation. Furthermore, adaptor proteins such as TRAF2, TRAF6, and TAB1 served as crucial connectors in signal transduction by linking various MAPK kinases within the cascade.

3.4 Comparative Analysis of Drug-Likeness and ADME Properties

The physicochemical, lipophilicity, solubility, pharmacokinetic, and drug-likeness properties of SB203580 (reference inhibitor), Epigallocatechin-3-gallate (EGCG), and Flavokawain B were comparatively analyzed. These parameters are crucial indicators for assessing a compound's potential as an orally bioavailable and bioactive drug candidate (Table 1).

In terms of physicochemical characteristics, EGCG exhibited the highest molecular weight (458.37 g/mol) and the largest Topological Polar Surface Area (TPSA: 197.37 Å²), reflecting its highly hydrophilic nature. It possesses 8 hydrogen bond donors and 11 acceptors, exceeding the conventional permeability limits, which may negatively impact gastrointestinal (GI) absorption. In contrast, Flavokawain B had the lowest TPSA (55.76 Å²), which may favor membrane permeability.

Regarding lipophilicity, both Flavokawain B and SB203580 showed relatively high XlogP values (3.83 and 3.20, respectively) and WLogP values (3.20 and 5.97, respectively), suggesting good potential for membrane permeation. On the other hand, EGCG displayed lower lipophilicity (XlogP: 1.17; WLogP: 1.91), indicating better solubility in water but potential limitations in penetrating lipophilic environments. In water solubility assessment, EGCG was identified as the most soluble compound (Silicos-IT LogS: -2.50; Class: Soluble), whereas Flavokawain B and SB203580 exhibited moderate to low solubility profiles.

In the pharmacokinetic profile, Flavokawain B and SB203580 demonstrated high GI absorption, while EGCG showed low absorption, likely due to its high polarity and hydrogen bonding capacity. Notably, Flavokawain B was the only compound predicted to cross the Blood-Brain Barrier (BBB), suggesting its relevance in potential neurological applications. For drug-likeness evaluation, EGCG violated two of Lipinski's rules, which may limit its oral bioavailability. In contrast, Flavokawain B and SB203580 fully

Table 1. ADME and drug-likeness profiles of SB203580, Epigallocatechin-3-gallate, and Flavokawain B, including physicochemical properties, lipophilicity, solubility, GI absorption, BBB permeability, Lipinski’s rule compliance, and bioavailability score.

Properties		SB203580	Epigallocatechin-3-gallate	Flavokawain B
Physicochemical Properties	Molecular wt. (g/mol)	377.43	458.37	284.31
	Rotatable Bond	4	4	5
	H-Bond Acceptors	4	11	4
	H-Bond Donors	1	8	1
	TPSA (Å2)	77.85	197.37	55.76
Lipophilicity	XlogP3	3.20	1.17	3.83
	WLogP	5.97	1.91	3.20
Water Solubility	ESOL LogS	-4.56	-3.56	-4.11
	ESOL Class	MS	S	MS
	Ali LogS	-4.51	-4.91	-4.70
	Ali Class	MS	MS	MS
	Silicos-IT LogS	-9.04	-2.50	-4.63
	Silicos-IT Class	PS	S	MS
Pharmacokinetics	GI Absorption	H	L	H
	Blood Brain Barrier	N/A	N/A	Yes
Druglikeness	Lipinski’s Violation	Y, 0	No, 2	Y, 0
	Bioavailability Score	0.55	0.17	0.55

Table 2. In silico prediction of acute toxicity (LD₅₀), cytochrome P450 enzyme inhibition potential, blood-brain barrier (BBB) permeability, and hepatotoxicity for SB203580, Epigallocatechin-3-gallate, and Flavokawain B.

Ligand	LD ₅₀ (mg/kg)	Cytochrom e CYP1A2	Cytochrome CYP2C19	Cytochrome CYP2C9	Cytochrome CYP3A4	BBB-barrier	Hepatotoxic ity
SB203580	2000	0.92	0.93	0.83	0.93	0.90	0.56
Epigallocatechi n-3-gallate	1000	-	-	-	-	0.53	-
Flavokawain B	3000	0.85	0.80	0.68	0.93	0.79	-

complied with Lipinski’s criteria (no violations), and both showed a bioavailability score of 0.55, significantly higher than that of EGCG (0.17).

3.5 In Silico Toxicity and CYP450 Enzyme Interaction Prediction

Toxicological risk and cytochrome P450 enzyme interaction potential of SB203580, Epigallocatechin-3-gallate (EGCG), and Flavokawain B were assessed using computational prediction tools. Key parameters included predicted median lethal dose (LD₅₀), inhibition potential across major CYP isoenzymes (CYP1A2, CYP2C19, CYP2C9, CYP3A4), blood-brain barrier (BBB) permeability, and hepatotoxicity likelihood (Table 2). The predicted oral LD₅₀ values (in mg/kg, rat) suggest that Flavokawain B exhibits the highest threshold (3000 mg/kg), followed by SB203580 (2000 mg/kg) and EGCG (1000 mg/kg), indicating low to moderate acute toxicity for all compounds. Notably, EGCG showed the lowest predicted LD₅₀, which may relate to its higher number of hydrogen bond donors and large polar surface area, possibly affecting its bioaccumulation. Regarding Cytochrome P450 enzyme interactions, SB203580 displayed high inhibitory probabilities across CYP1A2 (0.92),

CYP2C19 (0.93), CYP2C9 (0.83), and CYP3A4 (0.93), indicating a high potential to interfere with hepatic drug metabolism. Flavokawain B showed moderate inhibition scores ranging from 0.68 to 0.93, suggesting possible CYP-mediated drug interactions. EGCG did not return predictive scores in this dataset, which may reflect either low inhibitory likelihood or insufficient data within the prediction model. BBB permeability scores were highest for SB203580 (0.90) and Flavokawain B (0.79), indicating strong likelihood of crossing the blood-brain barrier. EGCG had a markedly lower score (0.53), consistent with its hydrophilic nature and high TPSA. Predicted hepatotoxicity risk was reported only for SB203580 (score: 0.56), suggesting a moderate probability of liver toxicity, while no significant hepatotoxic signal was predicted for EGCG or Flavokawain B.

4. Discussion

This study was conducted with the objective of identifying potential protein-targeted therapeutic strategies for treating Triple-Negative Breast Cancer (TNBC), an aggressive subtype of breast cancer that

lacks hormone receptors and HER2 expression. Due to the ineffectiveness of conventional targeted therapies in TNBC, the mitogen-activated protein kinase alpha (p38 MAPK α or MAPK14) protein has been selected as a promising therapeutic target, given its crucial role in cell proliferation, apoptosis, and inflammatory signaling (Zheng et al., 2023). To investigate this, two naturally derived compounds-Epigallocatechin-3-gallate (EGCG) and Flavokawain B (FKB)-were evaluated for their inhibitory potential against MAPK14. Additionally, SB203580, a well-established MAPK inhibitor, was used as a reference standard to facilitate comparative analysis. The overall findings provide a comprehensive understanding of the structural binding efficiency, conformational stability, pharmacokinetic behavior (ADME-Tox), and potential pathway modulation associated with these natural ligands, suggesting their relevance in future TNBC therapeutic development (Liskova et al., 2021).

The molecular docking results for Epigallocatechin-3-gallate (EGCG) demonstrated a strong binding affinity (-8.0 kcal/mol) and a series of stabilizing hydrogen bonds and π - π interactions with key residues in the MAPK14 active site. Although EGCG has been previously reported to affect p38 MAPK signaling pathways (Mhatre et al., 2021; Manica et al., 2022), the present study uniquely investigates its pose-specific docking behavior and structural interaction profile with MAPK14 in the context of TNBC. Furthermore, similar polyphenolic compounds, particularly catechin derivatives, have been shown to modulate kinase signaling pathways, including MAPK and ERK cascades (Mokra et al., 2022), supporting the plausibility of EGCG as a natural MAPK14 modulator.

In the case of Flavokawain B, although its docking energy was slightly lower (-7.7 kcal/mol), its compact structure and π -cation interactions contributed to stable docking across multiple poses. Darwish et al. (2023) have reported that FKB induces caspase-mediated apoptosis in TNBC cells, possibly through modulation of upstream MAPK pathways (Darwish et al., 2023). This aligns with our computational findings, which suggest effective binding of FKB to MAPK14. Moreover, previous studies have indicated that chalcone-derived compounds, structurally similar to FKB, can activate apoptotic pathways by targeting MAPK kinases (L.-C. Chen et al., 2023), providing further supportive evidence for the mechanism proposed in our study.

In the RMSD-based docking analysis, Epigallocatechin-3-gallate (EGCG) exhibited considerable conformational flexibility across multiple poses. This suggests that the ligand is capable of adapting to the protein's active site through varied orientations, likely due to its polyphenolic structure and multiple hydrogen bond donors and acceptors. Similar behavior has been reported in previous studies where ligands with extended hydrogen bonding networks demonstrated pose-specific binding flexibility (Lomas & Rosenberg,

2023; Song et al., 2021; Akter et al., 2022). While such adaptability can be advantageous for dynamic binding, our results indicate that excessive conformational variability may negatively impact binding stability, as evidenced by EGCG's relatively higher RMSD values across several poses.

Conversely, Flavokawain B displayed lower RMSD variance across docking poses, suggesting greater pose stability. This may be attributed to its rigid molecular framework and lower topological polar surface area (TPSA). Prior computational findings have highlighted that rigid ligands with compact structures tend to show higher binding predictability and spatial stability (Savasapun et al., 2023; Islam et al., 2023). These observations align with our current results, indicating that Flavokawain B could potentially serve as a structurally stable and consistent MAPK14-binding candidate.

Although Epigallocatechin-3-gallate (EGCG) demonstrated a notable binding affinity to MAPK14 in molecular docking analysis, its pharmacokinetic profile reveals potential limitations. Specifically, poor gastrointestinal (GI) absorption and two violations of Lipinski's rule suggest restricted oral bioavailability. This is supported by in vivo pharmacokinetic studies (Kciuk et al., 2023; Ke et al., 2023), which reported EGCG's rapid metabolism and limited systemic availability-findings that align with our computational ADME results.

In contrast, Flavokawain B (FKB) was found to comply fully with Lipinski's criteria and displayed high predicted GI absorption as well as Blood-Brain Barrier (BBB) permeability. Manica et al. (2023) previously reported that ligands with lower topological polar surface area (TPSA) and moderate lipophilicity tend to exhibit better BBB penetration a pattern that supports our observation for FKB (Manica et al., 2023).

A clinically significant aspect is that Triple-Negative Breast Cancer (TNBC) frequently leads to brain metastasis, where many conventional chemotherapeutics fail to reach due to limited brain permeability (Steeg, 2016). Thus, the ability of FKB to potentially cross the BBB positions it as a promising candidate for addressing metastatic TNBC, meriting further investigation.

Toxicity predictions revealed a distinct difference in the biosafety profiles of Epigallocatechin-3-gallate (EGCG) and Flavokawain B (FKB). EGCG was predicted to have a lower LD₅₀ value and a potential for hepatotoxicity. This aligns with previous toxicological reports on catechin-based natural products; for instance, Manica et al. (2024) observed that repeated exposure to green tea catechins at high doses could induce hepatic stress, highlighting the risk of metabolic burden-consistent with our computational findings (Manica et al., 2024).

In contrast, FKB demonstrated a higher predicted LD₅₀ and no signs of hepatotoxicity, suggesting that it may be a safer and better-tolerated therapeutic candidate. Flavonoid-based chalcones with similar structural and physicochemical properties (e.g., TPSA, logP)

have been reported to exhibit lower predicted toxicity in computational platforms like ProTox-II (Mvondo et al., 2021; Oner et al., 2023). The toxicological profile of FKB in our study conforms to these prior modeling validations. Taken together, although both compounds originate from natural sources, their predicted biosafety parameters differ substantially, and such distinctions are effectively captured through in silico toxicity modeling approaches.

The Cytoscape-based pathway network analysis revealed that MAPK14 (p38 MAPK α) acts as a central regulatory protein, influencing two key cellular processes - apoptosis and proliferation - through downstream interactions with MAP2K3, MAP3K7, TP53, and STAT1. According to the network topology, inhibition of MAPK14 can activate apoptotic pathways, particularly via downstream effectors such as TP53 and DDIT3 (Whitaker & Cook, 2021; Amin et al., 2024).

Our molecular findings suggest that both EGCG and Flavokawain B, through their predicted inhibition of MAPK14, may promote pro-apoptotic signaling. Prior studies have demonstrated similar effects: D. Xu et al. (2019) reported that EGCG suppresses p38 MAPK and promotes caspase-mediated apoptosis, while Manica et al. (2024) observed that Flavokawain B can induce apoptosis in TNBC cells through MAPK pathway regulation (D. Xu et al., 2021; Manica et al., 2024).

Notably, STAT1 emerged in our network as a bifunctional node with potential involvement in both apoptotic and proliferative signaling. This dual role reflects the complexity of the MAPK signaling cascade and suggests that inhibition of MAPK14 - via EGCG or FKB - may yield context-dependent therapeutic outcomes. Such insights are crucial for understanding the dual-edged nature of targeted inhibitors within intricate signaling networks (Tolomeo et al., 2022). This study successfully identified and evaluated the MAPK14 (p38 MAPK α) inhibitory potential of two plant-derived compounds - Epigallocatechin-3-gallate (EGCG) and Flavokawain B (FKB)-using a comprehensive computational strategy. While EGCG exhibited high binding affinity and a diverse range of protein-ligand interactions at the active site, its overall pharmacokinetic limitations-including low GI absorption, violations of Lipinski's rule, and potential hepatotoxicity may restrict its applicability, particularly in oral therapeutic contexts. In contrast, Flavokawain B demonstrated a more balanced and clinically favorable profile. It showed high predicted GI absorption, the ability to cross the blood-brain barrier (BBB), structural docking stability, and lower toxicity risk. These characteristics suggest that FKB may hold greater promise as a safe and effective MAPK14 inhibitor.

5. Limitation

Although this study offers promising insights through robust computational analyses, several limitations remain. All results are based solely on in silico predictions, and thus the actual biological

efficacy of EGCG and Flavokawain B could not be experimentally validated. The ADME-Tox profiles and molecular docking outcomes are predictive and may not fully translate to cellular or physiological environments. Additionally, the MAPK14 signaling pathway is complex and highly context-dependent, with potential variations across different cell types and conditions. Therefore, further experimental validation, including in vitro and in vivo studies, is essential to confirm the therapeutic relevance of the findings.

6. Conclusion

This study identified Epigallocatechin-3-gallate (EGCG) and Flavokawain B (FKB) as potential inhibitors of p38 MAPK α (MAPK14), a key target in Triple-Negative Breast Cancer. While EGCG showed strong binding affinity, its pharmacokinetic limitations may affect therapeutic application. In contrast, FKB demonstrated a more favorable profile, with high GI absorption, BBB permeability, and low predicted toxicity. Overall, the integrated molecular docking, ADME-Tox evaluation, and pathway analysis suggest that FKB may serve as a promising natural therapeutic candidate, meriting further in vitro and in vivo validation for effective MAPK14-targeted cancer treatment.

Author contributions

A.B. conceived and designed the study, supervised the project, and prepared the initial manuscript draft. S.H. performed molecular docking and computational analyses and contributed to data interpretation. M.U.P. carried out data validation, software support, and assisted in manuscript editing. S.A.M. contributed to methodology development, data visualization, and result interpretation. T.H.T. assisted in literature review, data curation, and manuscript formatting and proofreading. All authors reviewed and approved the final manuscript.

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Competing financial interests

The authors have no conflict of interest.

References

- Akter, M. F., Islam, M. R., Manica, A. K., Siddique, M. A. B., Tufael (2022). "Structural and Pharmacological Insights into Withaferin A Binding to Mutant p53 (R248Q): Multi-Faceted Inhibitor in Cancer Treatment", *Journal of Angiotherapy*, 6(2), 1-8, 10432. <https://doi.org/10.25163/angiotherapy.6210432>
- Amin, M. S., Rahman, A., Prapty, A. N., Numan, A. A., Rahman, M. M., Ahmed, B., Shabuj, M. M. H., Aunni, S. A. A. (2024). "Nanomedicine in Cancer Therapy: From Preclinical Promise to Clinical Applications", *Journal of Precision Biosciences*, 6(1), 1-14, 10064 <https://doi.org/10.25163/biosciences.6110064>

- Arnold, M., Morgan, E., Rumgay, H., Mafra, A., Singh, D., Laversanne, M., Vignat, J., Gralow, J. R., Cardoso, F., Siesling, S., & Soerjomataram, I. (2022). Current and future burden of breast cancer: Global statistics for 2020 and 2040. *The Breast*, 66, 15–23. <https://doi.org/10.1016/j.breast.2022.08.010>
- Baranova, A., Krasnoselskiy, M., Starikov, V., Kartashov, S., Zhulkevych, I., Vlasenko, V., Oleshko, K., Bilodid, O., Sadchikova, M., & Vinnyk, Y. (2022). Triple-negative breast cancer: current treatment strategies and factors of negative prognosis. *Journal of Medicine and Life*, 15(2), 153–161. <https://doi.org/10.25122/jml-2021-0108>
- Cetraro, P., Plaza-Diaz, J., MacKenzie, A., & Abadía-Molina, F. (2022). A Review of the Current Impact of Inhibitors of Apoptosis Proteins and Their Repression in Cancer. *Cancers*, 14(7), 1671. <https://doi.org/10.3390/cancers14071671>
- Chen, H., Padia, R., Li, T., Li, Y., Li, B., Jin, L., & Huang, S. (2021). Signaling of MK2 sustains robust AP1 activity for triple negative breast cancer tumorigenesis through direct phosphorylation of JAB1. *Npj Breast Cancer*, 7(1), 91. <https://doi.org/10.1038/s41523-021-00300-1>
- Chen, L.-C., Mokgautsi, N., Kuo, Y.-C., Wu, A. T. H., & Huang, H.-S. (2023). In Silico Evaluation of HN-N07 Small Molecule as an Inhibitor of Angiogenesis and Lymphangiogenesis Oncogenic Signatures in Non-Small Cell Lung Cancer. *Biomedicines*, 11(7), 2011. <https://doi.org/10.3390/biomedicines11072011>
- Darwish, M. I. M., Moustafa, A. M., Youssef, A. M., Mansour, M., Yousef, A. I., El Omri, A., Shawki, H. H., Mohamed, M. F., Hassaneen, H. M., Abdelhamid, I. A., & Oishi, H. (2023). Novel Tetrahydro-[1,2,4]triazolo[3,4-a]isoquinoline Chalcones Suppress Breast Carcinoma through Cell Cycle Arrests and Apoptosis. *Molecules*, 28(8), 3338. <https://doi.org/10.3390/molecules28083338>
- Farghadani, R., & Naidu, R. (2021). Curcumin: Modulator of Key Molecular Signaling Pathways in Hormone-Independent Breast Cancer. *Cancers*, 13(14), 3427. <https://doi.org/10.3390/cancers13143427>
- Ferrari, E., Bettuzzi, S., & Naponelli, V. (2022). The Potential of Epigallocatechin Gallate (EGCG) in Targeting Autophagy for Cancer Treatment: A Narrative Review. *International Journal of Molecular Sciences*, 23(11), 6075. <https://doi.org/10.3390/ijms23116075>
- Fultang, N., Chakraborty, M., & Peethambaran, B. (2021). Regulation of cancer stem cells in triple negative breast cancer. *Cancer Drug Resistance*. <https://doi.org/10.20517/cdr.2020.106>
- Ganguly, P., Macleod, T., Wong, C., Harland, M., & McGonagle, D. (2023). Revisiting p38 Mitogen-Activated Protein Kinases (MAPK) in Inflammatory Arthritis: A Narrative of the Emergence of MAPK-Activated Protein Kinase Inhibitors (MK2i). *Pharmaceuticals*, 16(9), 1286. <https://doi.org/10.3390/ph16091286>
- García-Hernández, L., García-Ortega, M. B., Ruiz-Alcalá, G., Carrillo, E., Marchal, J. A., & García, M. Á. (2021). The p38 MAPK Components and Modulators as Biomarkers and Molecular Targets in Cancer. *International Journal of Molecular Sciences*, 23(1), 370. <https://doi.org/10.3390/ijms23010370>
- Islam, M. R., Manica, A. K., Akter, M. F., Siddique, M. A. B., Tufael (2023). "In Silico Drug-Likeness and Safety Profiling of Tinosporaside: A Natural Alternative to Celecoxib for COX-2 Inhibition", *Journal of Primeasia*, 4(1),1-8,10434. <https://doi.org/10.25163/primeasia.4110434>
- Kciuk, M., Alam, M., Ali, N., Rashid, S., Głowacka, P., Sundaraj, R., Celik, I., Yahya, E. B., Dubey, A., Zerroug, E., & Kontek, R. (2023). Epigallocatechin-3-Gallate Therapeutic Potential in Cancer: Mechanism of Action and Clinical Implications. *Molecules*, 28(13), 5246. <https://doi.org/10.3390/molecules28135246>
- Ke, Q., Duan, K., Cheng, Y., Xu, S., Xiao, S., & Fang, L. (2023). Sanguinarine Exhibits Antiviral Activity against Porcine Reproductive and Respiratory Syndrome Virus via Multisite Inhibition Mechanisms. *Viruses*, 15(3), 688. <https://doi.org/10.3390/v15030688>
- Kudaravalli, S., den Hollander, P., & Mani, S. A. (2022). Role of p38 MAP kinase in cancer stem cells and metastasis. *Oncogene*, 41(23), 3177–3185. <https://doi.org/10.1038/s41388-022-02329-3>
- Liskova, A., Samec, M., Koklesova, L., Brockmueller, A., Zhai, K., Abdellatif, B., Siddiqui, M., Biringer, K., Kudela, E., Pec, M., Gadanec, L. K., Šudomová, M., Hassan, S. T. S., Zulli, A., Shakibaei, M., Giordano, F. A., Büsselberg, D., Golubnitschaja, O., & Kubatka, P. (2021). Flavonoids as an effective sensitizer for anti-cancer therapy: insights into multi-faceted mechanisms and applicability towards individualized patient profiles. *EPMA Journal*, 12(2), 155–176. <https://doi.org/10.1007/s13167-021-00242-5>
- Lomas, J. S., & Rosenberg, R. E. (2023). Cooperativity and intermolecular hydrogen bonding in donor-acceptor complexes of phenol and polyhydroxybenzenes. *Journal of Physical Organic Chemistry*, 36(7). <https://doi.org/10.1002/poc.4506>
- Manica, A. K., Akter, M. F., Islam, M. R., Tufael, Siddique, M. A. B. (2022). "Computational Exploration of Xanthohumol as a Safer Natural Substitute for Tamoxifen in Estrogen Receptor-Positive Breast Cancer", *Journal of Angiotherapy*, 6(2),1-8,10431. <https://doi.org/10.25163/angiotherapy.6210431>
- Manica, A. K., Tufael, Siddique, M. A. B., Akter, M. F., Islam, M. R. (2023). "In Silico Repurposing of FDA-approved Drugs Targeting Keap1-NRF2 Axis in Hepatocellular Carcinoma for Precision Therapy", *Journal of Precision Biosciences*, 5(1),1-8,10436 <https://doi.org/10.25163/biosciences.5110436>
- Manica, A. K., Siddique, M. A. B., Tufael, Akter, M. F., Islam, M. R. (2024). "Targeted Drug Repurposing in Precision Oncology Reveals Celecoxib as a GSK-3 β Inhibitor in Hepatocellular Carcinoma", *Journal of Precision Biosciences*, 6(1),1-8,10440 <https://doi.org/10.25163/biosciences.6110440>
- Manica, A. K., Islam, M. R., Siddique, M. A. B., Akter, M. F., Tufael (2024). "Tanshinone IIA as a Promising Natural Inhibitor of the STING Pathway: A Computational Exploration Toward Neuroinflammatory Therapy", *Australian Herbal Insight*, 7(1),1-8,10441 <https://doi.org/10.25163/herbal.7110441>
- Maqbool, M., Bekele, F., & Fekadu, G. (2022). Treatment Strategies Against Triple-Negative Breast Cancer: An Updated Review. *Breast Cancer: Targets and Therapy*, Volume 14, 15–24. <https://doi.org/10.2147/BCTT.S348060>
- Marín, V., Burgos, V., Pérez, R., Maria, D. A., Pardi, P., & Paz, C. (2023). The Potential Role of Epigallocatechin-3-Gallate (EGCG) in Breast Cancer Treatment. *International Journal of Molecular Sciences*, 24(13), 10737. <https://doi.org/10.3390/ijms241310737>
- Mhatre, S., Naik, S., & Patravale, V. (2021). A molecular docking study of EGCG and theaflavin digallate with the druggable targets of SARS-CoV-2. *Computers in Biology and Medicine*, 129, 104137. <https://doi.org/10.1016/j.compbiomed.2020.104137>
- Michalkova, R., Kello, M., Cizmarikova, M., Bardelcikova, A., Mirossay, L., & Mojzis, J. (2023). Chalcones and Gastrointestinal Cancers: Experimental Evidence. *International*

- Journal of Molecular Sciences, 24(6), 5964. <https://doi.org/10.3390/ijms24065964>
- Mokra, D., Joskova, M., & Mokry, J. (2022). Therapeutic Effects of Green Tea Polyphenol (–)-Epigallocatechin-3-Gallate (EGCG) in Relation to Molecular Pathways Controlling Inflammation, Oxidative Stress, and Apoptosis. *International Journal of Molecular Sciences*, 24(1), 340. <https://doi.org/10.3390/ijms24010340>
- Mvondo, J. G. M., Matondo, A., Mawete, D. T., Bambi, S.-M. N., Mbala, B. M., & Lohohola, P. O. (2021). In Silico ADME/T Properties of Quinine Derivatives using SwissADME and pkCSM Webservers. *International Journal of TROPICAL DISEASE & Health*, 1–12. <https://doi.org/10.9734/ijtdh/2021/v42i1130492>
- Oner, E., Al-Khafaji, K., Mezher, M. H., Demirhan, I., Suhail Wadi, J., Belge Kurutas, E., Yalin, S., & Choowongkamon, K. (2023). Investigation of berberine and its derivatives in Sars Cov-2 main protease structure by molecular docking, PROTOX-II and ADMET methods: in machine learning and in silico study. *Journal of Biomolecular Structure and Dynamics*, 41(19), 9366–9381. <https://doi.org/10.1080/07391102.2022.2142848>
- Phan, T., Zhang, X. H., Rosen, S., & Melstrom, L. G. (2023). P38 kinase in gastrointestinal cancers. *Cancer Gene Therapy*, 30(9), 1181–1189. <https://doi.org/10.1038/s41417-023-00622-1>
- Savaspun, K., Boonchaisri, S., Chaisuriya, P., Srisomsap, C., Svasti, J., Ardkhean, R., Phanumartwiwath, A., & Sam-ang, P. (2023). Cytotoxicity and molecular docking to DNA topoisomerase II of chalcone flavokawain B isolated from *Kaempferia elegans* rhizomes. *ScienceAsia*, 49(3), 421. <https://doi.org/10.2306/scienceasia1513-1874.2023.036>
- Song, X., Ni, M., Zhang, Y., Zhang, G., Pan, J., & Gong, D. (2021). Comparing the inhibitory abilities of epigallocatechin-3-gallate and gallic acid against tyrosinase and their combined effects with kojic acid. *Food Chemistry*, 349, 129172. <https://doi.org/10.1016/j.foodchem.2021.129172>
- Szymczyk, J., Sluzalska, K., Materla, I., Opalinski, L., Otlewski, J., & Zakrzewska, M. (2021). FGF/FGFR-Dependent Molecular Mechanisms Underlying Anti-Cancer Drug Resistance. *Cancers*, 13(22), 5796. <https://doi.org/10.3390/cancers13225796>
- Tolomeo, M., Cavalli, A., & Cascio, A. (2022). STAT1 and Its Crucial Role in the Control of Viral Infections. *International Journal of Molecular Sciences*, 23(8), 4095. <https://doi.org/10.3390/ijms23084095>
- van Barelle, M., Heemskerk-Gerritsen, B. A. M., Louwers, Y. V., Vastbinder, M. B., Martens, J. W. M., Hooning, M. J., & Jager, A. (2021). Estrogens and Progestogens in Triple Negative Breast Cancer: Do They Harm? *Cancers*, 13(11), 2506. <https://doi.org/10.3390/cancers13112506>
- Wang, W., Han, D., Cai, Q., Shen, T., Dong, B., Lewis, M. T., Wang, R., Meng, Y., Zhou, W., Yi, P., Creighton, C. J., Moore, D. D., & Yang, F. (2022). MAPK4 promotes triple negative breast cancer growth and reduces tumor sensitivity to PI3K blockade. *Nature Communications*, 13(1), 245. <https://doi.org/10.1038/s41467-021-27921-1>
- Whitaker, R. H., & Cook, J. G. (2021). Stress Relief Techniques: p38 MAPK Determines the Balance of Cell Cycle and Apoptosis Pathways. *Biomolecules*, 11(10), 1444. <https://doi.org/10.3390/biom11101444>
- Xu, D., Peng, S., Guo, R., Yao, L., Mo, H., Li, H., Song, H., & Hu, L. (2021). EGCG Alleviates Oxidative Stress and Inhibits Aflatoxin B1 Biosynthesis via MAPK Signaling Pathway. *Toxins*, 13(10), 693. <https://doi.org/10.3390/toxins13100693>
- Xu, W., Liu, R., Dai, Y., Hong, S., Dong, H., & Wang, H. (2021). The Role of p38 γ in Cancer: From review to outlook. *International Journal of Biological Sciences*, 17(14), 4036–4046. <https://doi.org/10.7150/ijbs.63537>
- Zhao, M., Jiang, X., Fang, J., Lin, Y., Li, Y., Pei, R., Ye, P., Lu, Y., & Jiang, L. (2023). The kava chalcone flavokawain B exerts inhibitory activity and synergizes with BCL-2 inhibition in malignant B-cell lymphoma. *Phytomedicine*, 120, 155074. <https://doi.org/10.1016/j.phymed.2023.155074>
- Zheng, Q., Li, S., Wang, A., Zhe, M., Yang, P., Wu, Y., Zhao, M., Zhu, Y., Luo, Y., Wang, G., & Ouyang, L. (2023). p38 mitogen-activated protein kinase: Functions and targeted therapy in diseases. *MedComm – Oncology*, 2(3). <https://doi.org/10.1002/mog2.53>