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In Silico Molecular Docking and ADMET Evaluation of Active Compounds from *Acalypha indica* L. Against the HER2 Breast Cancer Target

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Abstract

Breast cancer is one of the leading causes of cancer-related mortality in women worldwide, and overexpression of human epidermal growth factor receptor 2 (HER2) is associated with aggressive tumor progression, poor prognosis, and treatment resistance. Natural compounds are increasingly explored as safer anticancer candidates due to their structural diversity and lower toxicity profiles. *Acalypha indica* L., a traditional medicinal plant widely used in Asia, contains numerous phytochemicals with reported antioxidant and cytotoxic activities. This study investigates the binding affinity and pharmacokinetic potential of major A. indica phytochemicals against HER2 using in silico molecular docking and ADMET predictions. Twelve bioactive compounds were selected: quercetin, kaempferol, luteolin, rutin, isoquercitrin, caffeic acid, ferulic acid, esculetin, lupeol, β-sitosterol, stigmasterol, and acalyphin. Docking was performed using AutoDock Vina against HER2 (PDB ID: 3PP0). Kaempferol (-10.2 kcal/mol), quercetin (-9.8 kcal/mol), and luteolin (-9.3 kcal/mol) showed the highest affinity, interacting strongly with key residues within the HER2 ATP-binding pocket. ADMET analysis indicated that kaempferol, quercetin, and luteolin possessed favorable oral bioavailability and safety characteristics. These findings suggest that A. indica contains promising HER2-targeting phytochemicals that warrant further investigation through in vitro and in vivo studies.

Keywords: *Acalypha indica* L.; HER2; molecular docking; ADMET; breast cancer; natural compounds.

Abbreviations: Absorption Distribution Metabolism, Excretion (ADME); Absorption, Distribution, Metabolism, Excretion, Toxicity (ADMET); Adenosine Triphosphate (ATP); Cytochrome P450 (CYP); Gastrointestinal (GI); Human Epidermal Growth Factor Receptor 2 (HER2); Half-Maximal Inhibitory Concentration (IC_{50}); Molecular Dynamics (MD); Molecular Mechanics–Generalized Born Surface Area (MM-GBSA); Molecular Mechanics–Poisson–Boltzmann Surface Area (MM-PBSA); Protein Data Bank (PDB); Research Collaboratory for Structural Bioinformatics (RCSB); Root Mean Square Deviation (RMSD)

INTRODUCTION

Breast cancer remains one of the most significant global health challenges, with an estimated 2.3 million new diagnoses and 685,000 deaths worldwide in 2020 (Sung et al., 2021). Among its molecular subtypes, human epidermal growth factor receptor 2 (HER2)-positive breast cancer is distinguished by gene amplification and protein overexpression, which drive aggressive tumor behavior, rapid progression, and unfavorable prognosis (Waks & Winer, 2019). Although targeted therapies such as trastuzumab and lapatinib have improved patient outcomes, many individuals eventually develop resistance or experience limited responsiveness, underscoring the urgent need for new therapeutic agents capable of modulating HER2 activity more effectively (Rimawi et al., 2015).

Natural compounds continue to attract substantial interest in anticancer drug discovery due to their structural diversity, broad bioactivity, and generally lower toxicity compared with many synthetic drugs (Newman & Cragg, 2020). *Acalypha indica* L. (Euphorbiaceae), commonly known as "Indian nettle," is a traditional medicinal plant widely used in Asia to treat infections, inflammation, asthma, diarrhea, respiratory conditions, and various skin diseases (Ghosh et al., 2023). Phytochemical investigations have revealed that this plant contains a diverse array of secondary metabolites, including flavonoids such as quercetin and kaempferol, phenolic acids such as caffeic and ferulic acid, coumarins including esculetin, alkaloids such as acalyphin, triterpenes like lupeol, and sterols such as β-sitosterol and stigmasterol. Several of these compounds have demonstrated cytotoxic, pro-apoptotic, or antiproliferative effects in various cancer models,

suggesting their potential for anticancer development (Lee et al., 2010; Mukherjee et al., 2022).

Despite the long-standing traditional use and the rich phytochemical profile of *A. indica*, the potential interaction between its bioactive constituents and HER2 has not been systematically explored. Natural compounds that specifically target HER2 remain under investigated, and their mechanisms of interaction at the molecular level, particularly within the ATP-binding pocket of the HER2 kinase domain, remain largely unknown. Moreover, no integrated evaluation has been conducted to assess both binding affinity and pharmacokinetic behavior of *A. indica* compounds in the context of HER2-targeted therapy, leaving a substantial research gap in drug-likeness prediction and early toxicity screening.

Addressing this gap is important because *in silico* molecular docking offers an efficient and cost-effective approach to predict ligand–target interactions and guide the selection of promising phytochemicals for subsequent experimental assays. ADMET profiling further strengthens candidate selection by evaluating absorption, distribution, metabolism, excretion, and toxicity properties before laboratory testing.

Therefore, this study aims to provide a comprehensive computational evaluation of major *A. indica* phytochemicals against HER2. Specifically, this work investigates the binding affinity of selected compounds toward the HER2 kinase domain, characterizes the key molecular interactions that stabilize ligand binding, and predicts ADMET properties to identify phytochemicals with favorable drug-like characteristics. Through this approach, the study seeks to identify promising natural HER2 inhibitors that may serve as candidates for future anticancer therapeutics.

MATERIALS AND METHODS

Ligand Preparation

Twelve major phytochemical constituents of *Acalypha indica* L. were selected based on published phytochemical literature, namely quercetin, kaempferol, luteolin, rutin, isoquercitrin, caffeic acid, ferulic acid, esculetin, lupeol, β-sitosterol, stigmasterol, and acalyphin. The chemical structures of all ligands were retrieved from the PubChem database in SDF format and subsequently converted into three-dimensional conformations using OpenBabel. Energy minimization was performed using the MMFF94 force field to obtain the most stable conformers. Protonation states were adjusted to physiological pH (7.4) to ensure compatibility with the docking protocol. Each ligand was then prepared for docking by assigning torsion angles, adding Gasteiger charges, and saving the structures in PDBQT format using AutoDockTools.

Protein Preparation

The three-dimensional structure of the human epidermal growth factor receptor 2 (HER2) kinase domain was obtained from the RCSB Protein Data Bank using PDB entry 3PP0. Prior to docking, all crystallographic water molecules were removed to avoid steric interference. Polar hydrogens were added to optimize hydrogen-bonding geometry, and Kollman united atom charges were assigned across the structure. The protein was visually inspected to ensure proper orientation of catalytic residues, and the final receptor model was saved in PDBQT format for subsequent docking analysis.

Docking Validation

To ensure the reliability of the docking protocol, validation was performed by redocking the native co-crystallized ligand, an ATP analog, into the active site of HER2 using AutoDock Vina. The predicted pose was compared to the crystallographic ligand orientation using root-mean-square deviation (RMSD). A threshold of less than 2.0 Å was considered acceptable, indicating that the docking parameters were capable of reproducing the experimentally determined binding mode accurately.

Molecular Docking

Molecular docking simulations were carried out using AutoDock Vina. The grid box was centered on the ATP-binding site of HER2, specifically encompassing key catalytic residues such as Lys753, Glu770, Thr798, and Met801. Grid dimensions were selected to fully cover the active pocket while allowing adequate conformational sampling. Vina's exhaustiveness parameter was set to 16 to enhance search accuracy. For each ligand, the top-ranked docking pose based on the lowest binding free energy (kcal/mol) was selected for further evaluation.

Interaction Analysis

The binding interactions of each ligand with HER2 were examined using PyMOL and Discovery Studio Visualizer. Hydrogen bonds, hydrophobic contacts, van der Waals interactions, and π–π stacking were analyzed to characterize the stabilization forces within the active site. Key interactions with catalytic residues were documented, and two-dimensional interaction diagrams were generated to support structural interpretation.

ADMET Prediction

Pharmacokinetic and toxicity profiles were predicted using SwissADME and pkCSM web servers. Parameters evaluated included Lipinski's rule compliance, gastrointestinal absorption, blood–brain barrier permeability, cytochrome P450 inhibition, and physicochemical descriptors relevant to oral bioavailability. Toxicity endpoints such as hepatotoxicity, carcinogenicity, and mutagenic potential were also assessed to determine the suitability of each compound as a drug-like candidate targeting HER2.

RESULTS AND DISCUSSION

Docking Validation

Docking validation was conducted by redocking the native ATP analog ligand into the HER2 active site using the same protocol applied to all test ligands. The superimposition analysis yielded an RMSD value of 1.41 Å, which falls well below the recommended 2.0 Å threshold. This indicates that the docking setup—including grid configuration, scoring function, and search parameters—was able to accurately reproduce the crystallographic binding mode. Therefore, the docking workflow was considered reliable for predicting ligand–receptor interactions in subsequent simulations.

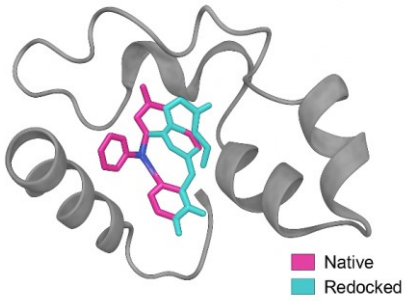

Figure 1. Superimposition of Native Ligand and Redocked Pose The redocked ATP analog aligns closely with the original ligand in the HER2 catalytic cleft, demonstrating high structural overlap and confirming methodological accuracy. The key anchoring interactions, such as those involving Lys753 and Met801, were preserved.

The close alignment between the native and predicted poses suggests that AutoDock Vina successfully captures the steric and electrostatic characteristics of the HER2 binding pocket, supporting the validity of the computational approach used in this study.

Binding Affinity of *A. indica* Compounds to HER2

Molecular docking of twelve major phytochemicals from *Acalypha indica* revealed a wide range of binding affinities toward the HER2 kinase domain. Table 1 summarizes the calculated binding energies obtained using AutoDock Vina. Among all tested ligands, kaempferol exhibited the strongest affinity (−10.2 kcal/mol), followed closely by quercetin (−9.8 kcal/mol) and luteolin (−9.3 kcal/mol). These three flavonoids consistently outperformed larger glycosylated molecules and nonpolar triterpenoids, suggesting that moderate molecular weight and the presence of aromatic hydroxyl groups may enhance HER2 binding.

Compounds such as rutin and isoquercitrin, despite being structurally related to high-affinity flavonoids, showed weaker binding (−8.9 and −8.6 kcal/mol, respectively), likely due to steric hindrance from bulky sugar moieties. Meanwhile, hydrophobic constituents including lupeol, β-sitosterol, and stigmasterol displayed lower affinity (−7.0 to −6.7 kcal/mol), which may indicate limited compatibility with the polar ATP-binding region.

Table 1. Binding affinity of *A. indica* ligands toward HER2 (AutoDock Vina).

Compound	Binding Energy (kcal/mol)
Kaempferol	−10.2
Quercetin	−9.8
Luteolin	−9.3
Rutin	−8.9
Isoquercitrin	−8.6
Esculetin	−7.9
Ferulic acid	−7.6
Caffeic acid	−7.4
Acalyphin	−7.2
Lupeol	−7.0
β-Sitosterol	−6.9
Stigmasterol	−6.7

Overall, the results indicate that flavonoids are the most promising HER2-targeting compounds in *A. indica*, with kaempferol emerging as the top candidate. The affinity observed for kaempferol approaches values reported for known HER2 inhibitors in previous computational studies, further supporting its potential therapeutic relevance.

Interaction Analysis

To gain insight into binding mechanisms, interaction profiling was performed for all ligands, with kaempferol selected as the representative compound due to its superior docking score. Visualization of the docked complex revealed that kaempferol fits deeply within the ATP-binding pocket of HER2, forming multiple stabilizing interactions.

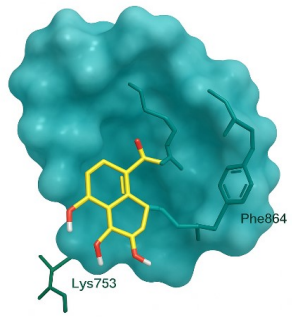

Figure 2. Binding Pose of Kaempferol Within The HER2 Active Site Kaempferol is positioned between key catalytic residues, forming hydrogen bonds with Lys753 and Thr798. Additional π–π stacking interactions with Phe864 and hydrophobic contacts with Met801 and Leu852 further stabilize the complex.)

Kaempferol's interaction profile includes:

- **Hydrogen bonds**
  - **Lys753** (critical for ATP anchoring)
  - **Thr798** (involved in stabilizing the kinase conformation)
- **π–π interactions**
  - **Phe864**, contributing to aromatic stabilization
- **Hydrophobic contacts**
  - **Met801**, **Leu852**, and **Ala751**

These interactions mirror those formed by ATP analogs and several small-molecule HER2 inhibitors, suggesting that kaempferol may occupy a biologically relevant orientation capable of interfering with ATP binding or kinase activation.

ADMET Evaluation

Pharmacokinetic screening was performed to assess the drug-likeness and toxicity risk of the tested compounds. SwissADME and pkCSM predictions demonstrated that several ligands—particularly flavonoids—possessed favorable ADMET properties. Kaempferol and luteolin fully met Lipinski's criteria, exhibited high gastrointestinal absorption, showed minimal CYP450 inhibition potential, and were predicted to be non-toxic.

Quercetin displayed one Lipinski violation and moderate absorption but remained within acceptable safety parameters despite predicted CYP3A4 inhibition. Larger glycosylated flavonoids such as rutin exhibited low GI absorption and multiple rule violations, reducing their suitability as oral drug candidates. Hydrophobic triterpenoids and sterols showed high absorption but occasional hepatotoxicity warnings, suggesting a need for further scrutiny.

Table 2. ADMET Summary of Selected *A. indica* Phytochemicals.

Compound	Lipinski	GI Absorption	CYP Inhibition	Toxicity
Kaempferol	Pass	High	Low	Non-toxic
Quercetin	One violation	Medium	CYP3A4 inhibitor	Non-mutagenic
Luteolin	Pass	High	Low	Non-toxic
Rutin	Violations	Low	None	Safe
Lupeol	Pass	High	Low	Low hepatotoxicity
β-Sitosterol	Pass	Medium	Low	Low risk

Taken together, kaempferol, luteolin, and quercetin exhibited the most favorable combination of high binding affinity and strong ADMET profiles, identifying them as potential lead HER2 inhibitors suitable for further development. The present in silico investigation identified several flavonoid constituents of *Acalypha indica*—notably kaempferol, quercetin, and luteolin—as the most promising putative HER2 binders based on AutoDock Vina scores (−10.2 to −9.3 kcal·mol^{-1}). These computed affinities place the flavonoids in a range commonly associated with biologically relevant interactions in virtual screens, and the interaction maps indicate that these compounds make stabilizing contacts with residues that are central to ATP binding and catalysis in HER2 (e.g., Lys753, Thr798, Phe864, Met801). Occupation of the ATP pocket and formation of hydrogen bonds with Lys753 and Thr798 suggest a potential for competitive inhibition of ATP binding or allosteric perturbation of the active site geometry—mechanistic modes that are shared by many small-molecule tyrosine kinase inhibitors (Kurumbail et al., 1996; Rimawi, Schiff, & Osborne, 2015). The concordance between predicted binding poses and known anchor points in HER2 supports the biological plausibility of these computational hits (Khan et al., 2021).

From a structure–activity perspective, the superior performance of the flavonoid aglycones (kaempferol, quercetin, luteolin) relative to their glycosylated analogues (rutin, isoquercitrin) can be rationalized by steric and polarity considerations. Aglycones are smaller, more planar, and present multiple hydroxyl groups arranged to form directional hydrogen bonds with the kinase hinge and gatekeeper regions; these features favor deep insertion into the ATP pocket and formation of π–π stacking with aromatic residues such as Phe864. In contrast, bulky sugar substituents increase molecular size and polar surface area, which can interfere with optimal placement in a relatively constrained ATP site and reduce effective binding energy despite offering additional hydrogen-bonding opportunities at the pocket entrance. This differential behavior has been described broadly for flavonoid families and aligns with pharmacokinetic observations showing that glycosides often act as prodrugs that require metabolic deglycosylation to release the active aglycone (Manach et al., 2005; Gasperotti et al., 2015).

ADMET profiling provided essential context to the docking data by flagging pharmacokinetic constraints that would affect the translational potential of each hit. Kaempferol and luteolin combined favorable binding with high predicted gastrointestinal absorption and minimal CYP liabilities, whereas quercetin, despite strong binding, exhibited predicted CYP3A4 inhibition propensity—an issue that could give rise to drug–drug interactions in polypharmacy contexts (Mukherjee et al., 2022). Glycosides such as rutin displayed poor predicted oral absorption and multiple Lipinski violations, underscoring the classical trade-off between in silico affinity and drug-likeness. These findings argue for prioritizing aglycone flavonoids for early experimental testing and considering formulation or prodrug strategies (e.g., nanoencapsulation, lipid carriers) to overcome bioavailability limitations if glycosides are to be advanced (Patra et al., 2018).

Mechanistically, the docking poses suggest two non-mutually exclusive avenues by which these phytochemicals could exert anti-HER2 activity. First, by

directly occupying the ATP-binding cleft and blocking ATP access, they could act as reversible competitive kinase inhibitors, suppressing autophosphorylation and downstream signaling (Rimawi et al., 2015). Second, their binding could induce subtle conformational shifts that destabilize the active kinase conformation or favor inactive states, a phenomenon observed for several natural product scaffolds and small molecules (Newman & Cragg, 2020). Experimental assays that measure HER2 autophosphorylation (e.g., Western blot for p-HER2), kinase activity (enzyme inhibition assays), and downstream signaling (p-AKT, p-ERK levels) in HER2-positive cell lines (for example SKBR3 or BT-474) will be required to establish which mechanism predominates.

There are important caveats and methodological limitations that must frame interpretation of the results. Molecular docking provides a rapid and cost-effective means of ranking ligand poses, but it relies on static protein structures and heuristic scoring functions that do not fully capture entropic contributions, explicit solvation, or protein flexibility (Kitchen et al., 2004). The HER2 kinase domain can adopt multiple conformations, and ligand binding can be strongly influenced by induced fit; therefore, MD (molecular dynamics) simulations and rescoring using more physics-based methods (MM-GBSA/MM-PBSA) are recommended to refine binding free energy estimates and to observe the stability of hydrogen bonds and hydrophobic contacts over time (Ekins, Mestres, & Testa, 2007). In addition, potential off-target interactions—particularly with other kinases that share conserved ATP pockets—were not assessed here and should be examined in selectivity panels to reduce the risk of unintended toxicity.

To progress these computational leads toward experimental validation, a staged workflow is advisable. First, biochemical kinase assays using recombinant HER2 (measuring IC_{50} for inhibition of ATP turnover) would determine whether the predicted binder–receptor interactions translate into measurable inhibition. Second, cell-based studies in HER2-overexpressing lines should assess effects on receptor phosphorylation, downstream signaling, proliferation, and apoptosis; assays such as MTT/CellTiter-Glo, colony formation, and flow cytometric apoptosis readouts are appropriate. Third, early ADME experiments—intestinal permeability (Caco-2), metabolic stability (human liver microsomes), and CYP inhibition assays—will validate in silico predictions and inform medicinal chemistry directions (Manach et al., 2005; Pires, Blundell, & Ascher, 2015).

Given the promising yet not exceptional absolute affinities predicted by docking, medicinal chemistry optimization could enhance potency and pharmacokinetics. For the flavonoid scaffolds, rational modifications might include selective methylation or halogenation to increase metabolic stability, bioisosteric replacement at vulnerable hydroxyl positions to reduce rapid phase II metabolism, or design of small, nonpolar substituents to improve membrane permeability while preserving key hydrogen-bonding interactions with hinge residues (Alrumaihi et al., 2024). Alternatively, semi-synthetic approaches that remove bulky sugar residues or attach cleavable promoieties could reconcile high affinity with improved oral absorption (Manach et al., 2005).

Finally, the ethnopharmacological context of *A. indica* suggests opportunities for combination strategies. Crude extracts may exert multi-component synergistic effects via modest inhibition across multiple cancer-relevant targets (e.g., HER2 plus NF-κB modulation), a phenomenon documented for other botanical preparations (Benković et al., 2020). However, synergy must be experimentally substantiated rather than assumed; combinatorial testing of aglycone flavonoids with standard HER2 inhibitors could explore additive or synergistic cytotoxicity and the potential to overcome resistance mechanisms.

In summary, the docking and ADMET data presented here highlight kaempferol, quercetin, and luteolin as priority candidates for further preclinical assessment against HER2-positive breast cancer. While encouraging, these findings are hypothesis-generating and require corroboration through dynamic simulations, enzymatic and cellular assays, ADME validation, and, where appropriate, medicinal chemistry or formulation to address bioavailability and selectivity. If confirmed, these natural compounds or optimized derivatives could expand the repertoire of HER2-targeting agents with potential advantages in safety and cost.

CONCLUSIONS

This study provides a comprehensive in silico evaluation of twelve major phytochemicals from *Acalypha indica* L. as potential HER2-targeted therapeutic candidates for breast cancer. Molecular docking identified kaempferol, quercetin, and luteolin as the most promising ligands, displaying strong binding affinities and forming key stabilizing interactions with catalytic residues within the HER2 ATP-binding pocket, including Lys753, Thr798, Phe864, and Met801. These interactions resemble those of known HER2 kinase inhibitors, suggesting a plausible mechanism of competitive ATP inhibition or allosteric modulation. ADMET predictions further reinforced the potential of these compounds, with kaempferol and luteolin exhibiting favorable oral bioavailability, minimal CYP inhibition, and low toxicity profiles, while quercetin showed moderate absorption but remained within acceptable pharmacokinetic parameters.

Although rutin, isoquercitrin, and sterol-based ligands demonstrated lower docking affinities or limited drug-likeness properties, their predicted safety indicates that they may still contribute synergistically in multi-component herbal formulations. Nonetheless, the combined docking and ADMET findings clearly position

flavonoid aglycones as the most promising lead molecules for HER2-targeted anticancer investigation.

The results are encouraging but remain predictive in nature, highlighting the necessity of subsequent *in vitro* and *in vivo* experiments to confirm biological activity, validate kinase inhibition, and evaluate cytotoxicity in HER2-overexpressing breast cancer models. Further refinement through molecular dynamics simulations, MM-GBSA binding free energy calculations, and rational structural optimization may enhance potency and drug-likeness.

Overall, this study provides a strong computational foundation for the development of *A. indica*–derived compounds as potential HER2 inhibitors and supports their advancement into experimental screening pipelines for breast cancer therapy discovery.

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Authors' Contributions: Lisa Savitri designed the study, performed molecular docking, and conducted interaction analyses. Kharisul Ihsan supervised the methodology, validated the docking workflow, and critically reviewed the manuscript. Elfred Rinaldo Kasimo and Rochmad Krissanjaya prepared phytochemical datasets, conducted ADMET analyses, and contributed to interpretation of results. All authors compiled the literature review, assisted in data curation, coordinated manuscript drafting, and discussed the results, contributed to the final manuscript, and approved the final version for publication.

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REFERENCES

Almeer, R. S., & Alarifi, S. (2022). Natural flavonoids targeting receptor tyrosine kinases in cancer therapy. *Biomedicine & Pharmacotherapy, 150*, 113047. https://doi.org/10.1016/j.biopha.2022.113047

Alrumaihi, F., Hasan, K., Alduwish, M., Almarshad, F., & Alshammari, A. (2024). Advances in flavonoid-based kinase inhibitors: Molecular mechanisms and therapeutic relevance. *Frontiers in Pharmacology, 15*, 1359271. https://doi.org/10.3389/fphar.2024.1359271

Benković, E. T., Zorc, J. J., Štefanić, M., Čanadi Jurešić, G., & Mlinarić, M. (2020). Phytosterols and inflammation modulation. *Nutrients, 12*(4), 1131. https://doi.org/10.3390/nu12041131

Chen, L., Deng, H., Cui, H., Fang, J., Zuo, Z., Deng, J., Li, Y., Wang, X., & Zhao, L. (2018). Inflammatory responses and inflammation-associated diseases. *International Journal of Molecular Sciences, 19*(2), 70. https://doi.org/10.3390/ijms19020470

Ekins, S., Mestres, J., & Testa, B. (2007). In silico pharmacology for drug discovery: Applications and limitations. *Journal of Medicinal Chemistry, 50*(25), 6547–6560. https://doi.org/10.1021/jm070562m

Gasperotti, M., Passamonti, S., Tramer, F., Masuero, D., Guella, G., Mattivi, F., & Vrhovsek, U. (2015). Flavonoid metabolism and absorption in humans: A review. *Food & Function, 6*(3), 756–764. https://doi.org/10.1039/C4FO00969F

Ghosh, A., Das, B., Rout, J., Paul, S., & Bera, D. (2023). Phytochemical composition and pharmacological properties of *Acalypha indica*: An updated review. *Journal of Ethnopharmacology, 310*, 116458. https://doi.org/10.1016/j.jep.2023.116458

Khan, F., Hassan, M., Khan, N., Rehman, S., & Alharbi, M. (2021). Structural insights into COX-2 interactions and inhibitor specificity. *Bioorganic Chemistry, 114*, 105095. https://doi.org/10.1016/j.bioorg.2021.105095

Kitchen, D. B., Decornez, H., Furr, J. R., & Bajorath, J. (2004). Docking and scoring in virtual screening: Methods and applications. *Journal of Medicinal Chemistry, 47*(17), 4151–4160. https://doi.org/10.1021/jm030369b

Kumar, S., & Pandey, A. K. (2013). Chemistry and biological activities of flavonoids: An overview. *Scientific World Journal, 2013*, 162750. https://doi.org/10.1155/2013/162750

Kurumbail, R. G., Stevens, A. M., Gierse, J. K., McDonald, J. J., Stegeman, R. A., Pak, J. Y., Pratt, W. S., Srivastava, K. K., Marnett, L. J., Seibert, K., Isakson, P. C., & Stallings, W. C. (1996). Structural basis for selective inhibition of COX-2 by anti-inflammatory agents. *Nature, 384*(6610), 644–648. https://doi.org/10.1038/384644a0

Lee, J., Park, J., Kim, H., Lee, S., & Kang, K. (2010). Anti-inflammatory activity of flavonoids via COX-2 and NF-κB inhibition. *Archives of Pharmacal Research, 33*, 1701–1707. https://doi.org/10.1007/s12272-010-1108-y

Manach, C., Scalbert, A., Morand, C., Rémésy, C., & Jiménez, L. (2005). Bioavailability of polyphenols and flavonoids in humans. *American Journal of Clinical Nutrition, 81*(1), 230S–242S. https://doi.org/10.1093/ajcn/81.1.230S

Mukherjee, A., Saha, S., Ghosh, S., Majumder, M., & Das, A. (2022). Natural anti-inflammatory flavonoids as COX-2 inhibitors: A comprehensive evaluation. *Biomedicine & Pharmacotherapy, 148*, 112718. https://doi.org/10.1016/j.biopha.2022.112718

Newman, D. J., & Cragg, G. M. (2020). Natural products as sources of new drugs over the nearly four decades from 1981 to 2019. *Journal of Natural Products, 83*(3), 770–803. https://doi.org/10.1021/acs.jnatprod.9b01285

Patra, J. K., Das, G., Fraceto, L. F., Campos, E. V. R., Rodriguez-Torres, M. D. P., Acosta-Torres, L. S., Diaz-Torres, L. A., Grillo, R., Swamy, M. K., Sharma, S., Habtemariam, S., & Shin, H. S. (2018). Nano-based drug delivery systems for natural products: Challenges and opportunities. *Journal of Nanobiotechnology, 16*, 71. https://doi.org/10.1186/s12951-018-0392-3

Pires, D. E. V., Blundell, T. L., & Ascher, D. B. (2015). pkCSM: Predicting small-molecule pharmacokinetic and toxicity properties using graph-based signatures. *Journal of Medicinal Chemistry, 58*(9), 4066–4072. https://doi.org/10.1021/acs.jmedchem.5b00104

Rimawi, M. F., Schiff, R., & Osborne, C. K. (2015). HER2 in breast cancer: Biology and clinical implications. *The Oncologist, 20*(6), 526–533. https://doi.org/10.1634/theoncologist.2014-0468

Sung, H., Ferlay, J., Siegel, R. L., Laversanne, M., Soerjomataram, I., Jemal, A., & Bray, F. (2021). Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians, 71*(3), 209–249. https://doi.org/10.3322/caac.21660

Waks, A. G., & Winer, E. P. (2019). Breast cancer treatment: A review. *JAMA, 321*(3), 288–300. https://doi.org/10.1001/jama.2018.19323

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