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Research Article

Prediction and ADMET of Bioactive Gingerol from Red Ginger Plant (*Zingiber officinale var. Rubrum*)

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Abstract (in English)

The present study focuses on the predictive analysis of pharmacological activity and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiles of a selected bioactive compound using advanced in silico tools, PASS Online and pkCSM. The pharmacological potential was assessed through the Pa (probability of activity) and Pi (probability of inactivity) values, revealing strong activity predictions such as serotonin release stimulation, linoleate diol synthase inhibition, and UDP-glucuronosyltransferase substrate potential. These results suggest multiple biological interactions and diverse therapeutic possibilities. Furthermore, the ADMET evaluation highlighted favorable pharmacokinetic behavior, including good intestinal absorption (92.416%), moderate water solubility (-3.164 log mol/L), and non-substrate characteristics toward P-glycoprotein inhibitors. The compound exhibited safe toxicity parameters, being non-mutagenic in the AMES test, non-hepatotoxic, and showing low hERG inhibition potential, which indicates minimal cardiotoxic risk. Moreover, its moderate volume of distribution (0.524 log L/kg) and high clearance (1.339 log ml/min/kg) demonstrate effective systemic disposition. The combined PASS and pkCSM predictions indicate that the compound possesses a promising pharmacological profile, suitable absorption characteristics, favorable metabolism, and low toxicity risks, supporting its potential for further experimental validation as a therapeutic candidate.

Keywords: PASS Online, pkCSM, pharmacological prediction, ADMET analysis, Zingiber officinale var. Rubrum

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1 Introduction

The global interest in medicinal plants has significantly increased in recent decades as scientists continuously explore natural sources for potential therapeutic agents with better efficacy and safety profiles compared to synthetic drugs [1]. Among the numerous plants used traditionally across Asia, Africa, and South America, the Zingiberaceae family, particularly the Zingiber officinale species, stands out for its broad pharmacological importance. Red ginger (Zingiber officinale var. Rubrum), a variant of common ginger, has long been utilized in traditional medicine across Southeast Asia, including Indonesia, Malaysia, and Thailand, to treat ailments such as colds, coughs, rheumatism, inflammation, and digestive disorders[2]. Unlike common or white ginger, red ginger is characterized by its reddish rhizome, stronger pungency, and higher concentrations of bioactive compounds, especially gingerols and shogaols, which contribute to its potent biological activity[3].

The growing global concern regarding the side effects and resistance associated with synthetic drugs has prompted researchers to investigate herbal compounds as safer alternatives or adjuvants. Among these compounds, gingerols—the major phenolic constituents of Zingiber officinale—have attracted considerable attention for their diverse pharmacological properties, including antioxidant, anti-inflammatory, antimicrobial, antiemetic, analgesic, and anticancer effects[4]. Chemically, gingerols are homologues differentiated by the length of their hydrocarbon side chains, most notably [6]-gingerol, [8]-gingerol, and [10]-gingerol. These compounds are known to modulate multiple biological pathways, such as NF-κB inhibition, COX-2 suppression, and caspase activation, thereby offering therapeutic promise against inflammation-driven diseases and carcinogenesis[5].

Despite the broad spectrum of pharmacological evidence, the successful translation of gingerol-based compounds into clinically approved drugs remains challenging. One of the major obstacles in natural product drug discovery lies in understanding and optimizing the pharmacokinetic and toxicological characteristics of bioactive compounds[6]. The Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) parameters play a crucial role in determining the efficacy, bioavailability, and safety of potential drug candidates. Poor ADMET properties are among the leading causes of failure in drug development pipelines, accounting for nearly 60% of attrition rates during preclinical and clinical trials. Hence, evaluating the ADMET behavior of bioactive compounds from red ginger becomes a critical step before further experimental or clinical validation[7].

Traditional pharmacological studies, while valuable, are often limited by cost, time, and ethical constraints associated with animal testing. In recent years, computational approaches, particularly in silico ADMET prediction and molecular modeling, have emerged as powerful tools for early-stage drug discovery[8]. These computational methods employ algorithms and predictive models based on chemical descriptors and molecular structures to estimate pharmacokinetic parameters such as intestinal absorption, blood–brain barrier (BBB) permeability, plasma protein binding, and metabolic stability[9]. Additionally, toxicity endpoints such as hepatotoxicity, cardiotoxicity, mutagenicity, and cytotoxicity can be predicted computationally with high reliability using validated software platforms like SwissADME, pkCSM, and ADMETlab. Such approaches not only minimize laboratory experimentation but also accelerate the identification of promising drug-like natural compounds[10].

For Zingiber officinale var. Rubrum, limited studies have explored the ADMET and drug-likeness profiles of its major constituents. While several investigations have reported the pharmacological activities of [6]-gingerol and its analogs through in vitro and in vivo assays, systematic in silico evaluations integrating ADMET prediction with pharmacokinetic modeling remain sparse[11]. Understanding the pharmacokinetic limitations and potential toxicity of gingerols is essential to improve their therapeutic application, enhance formulation design, and guide medicinal chemistry optimization. Moreover, the incorporation of Lipinski's Rule of Five and other drug-likeness filters allows for a more rational

screening process to evaluate whether these compounds possess the physicochemical attributes necessary for oral bioavailability and systemic distribution[12].

Several computational studies have revealed that natural compounds with potent biological activities often fail to reach clinical application due to unfavorable ADMET profiles. For instance, high molecular weight, excessive lipophilicity, or poor aqueous solubility may result in suboptimal absorption and distribution. Similarly, rapid metabolic degradation in hepatic microsomes or first-pass metabolism can significantly reduce systemic bioavailability[13]. In the case of gingerols, their hydrophobic nature and rapid conjugation through glucuronidation and sulfation pathways in the liver limit their systemic exposure. Therefore, predictive modeling of ADMET properties can offer valuable insights into these challenges, suggesting strategies for structural modification or formulation enhancement to improve drug performance[14].

In silico prediction of ADMET parameters also provides a framework for evaluating the safety of natural compounds prior to preclinical testing. Toxicological prediction models can identify potential risks such as mutagenicity (Ames test), carcinogenicity, hERG channel inhibition (associated with cardiotoxicity), and hepatotoxicity. These parameters are essential for ensuring that promising compounds meet safety standards for further development[15]. Combining these predictive models with molecular docking studies enables researchers to simultaneously assess pharmacodynamics and pharmacokinetics, offering a comprehensive view of the compound's therapeutic potential[16].

Gingerol compounds have demonstrated strong affinity for a variety of biological targets, including enzymes such as COX-2, iNOS, and LOX, as well as receptors implicated in cancer progression and inflammatory responses. Docking simulations and pharmacophore analyses have shown that [6]-gingerol, in particular, can form stable hydrogen bonding and hydrophobic interactions with target proteins, correlating well with observed in vitro efficacy[17]. However, pharmacological potency alone is insufficient for successful drug development. The compound's ADMET profile ultimately dictates its practical feasibility as a therapeutic agent. Therefore, understanding the ADMET behavior of bioactive gingerols is essential for translating these molecules from bench to bedside[18].

From a biopharmaceutical perspective, [6]-gingerol serves as an excellent case study for natural compound optimization. Various nanoformulation strategies, such as liposomes, polymeric nanoparticles, and solid lipid nanoparticles, have been proposed to overcome its poor solubility and enhance bioavailability[19]. However, prior to experimental optimization, computational prediction can guide the design of analogs or delivery systems by identifying key pharmacokinetic barriers. Predictive tools can estimate parameters like Caco-2 cell permeability, P-glycoprotein interaction, CYP450 metabolism, and clearance rate—factors that profoundly affect oral absorption and systemic persistence[20].

Metabolism of gingerol analogs through computational models can provide insight into potential metabolic liabilities and reactive intermediates. The prediction of cytochrome P450 isoform interactions, for example, is vital to prevent undesirable drug–drug interactions or metabolic toxicity[21]. Additionally, simulated human intestinal absorption (HIA) and volume of distribution (Vd) data can offer a preliminary understanding of compound disposition and tissue accumulation. Integrating these data allows researchers to develop a pharmacokinetic fingerprint that defines the drug-likeness and safety of the compound[22].

Given the global trend toward evidence-based validation of herbal medicines, such computational approaches align with modern pharmacological paradigms emphasizing reproducibility, efficiency, and sustainability[23]. In silico ADMET prediction represents an environmentally friendly and ethically acceptable alternative to traditional experimentation, reducing animal use and chemical waste. The integration of these methods with traditional pharmacognosy and molecular pharmacology can accelerate the discovery of novel natural-based therapeutics[24].

The present study focuses on the computational prediction and ADMET analysis of major bioactive gingerol compounds derived from Zingiber officinale var. Rubrum. By employing reliable computational platforms, this research aims to (1) predict key pharmacokinetic parameters including absorption,

distribution, metabolism, and excretion; (2) assess potential toxicological endpoints such as hepatotoxicity, mutagenicity, and cardiotoxicity; and (3) evaluate overall drug-likeness according to standard pharmaceutical criteria. The results are expected to provide a scientific foundation for the rational development of gingerol-based therapeutics and to contribute to the broader understanding of red ginger's pharmacokinetic potential in drug discovery.

2 Method

The methodological framework of this study was designed to predict the biological activities and pharmacokinetic–toxicological characteristics of major bioactive compounds found in Zingiber officinale var. Rubrum, specifically focusing on the gingerol homologues [6]-gingerol, [8]-gingerol, and [10]-gingerol. The entire prediction procedure was conducted using two primary web-based computational tools, namely PASS Online (Prediction of Activity Spectra for Substances; https://way2drug.com/PassOnline/predict.php) and pkCSM (Predicting Small-Molecule Pharmacokinetic and Toxicity Properties; https://biosig.lab.uq.edu.au/pkcsm/prediction_single/), both accessed on 22 October 2025. The methodology was divided into three major stages: compound preparation, prediction of biological activity using PASS Online, and ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiling using pkCSM.

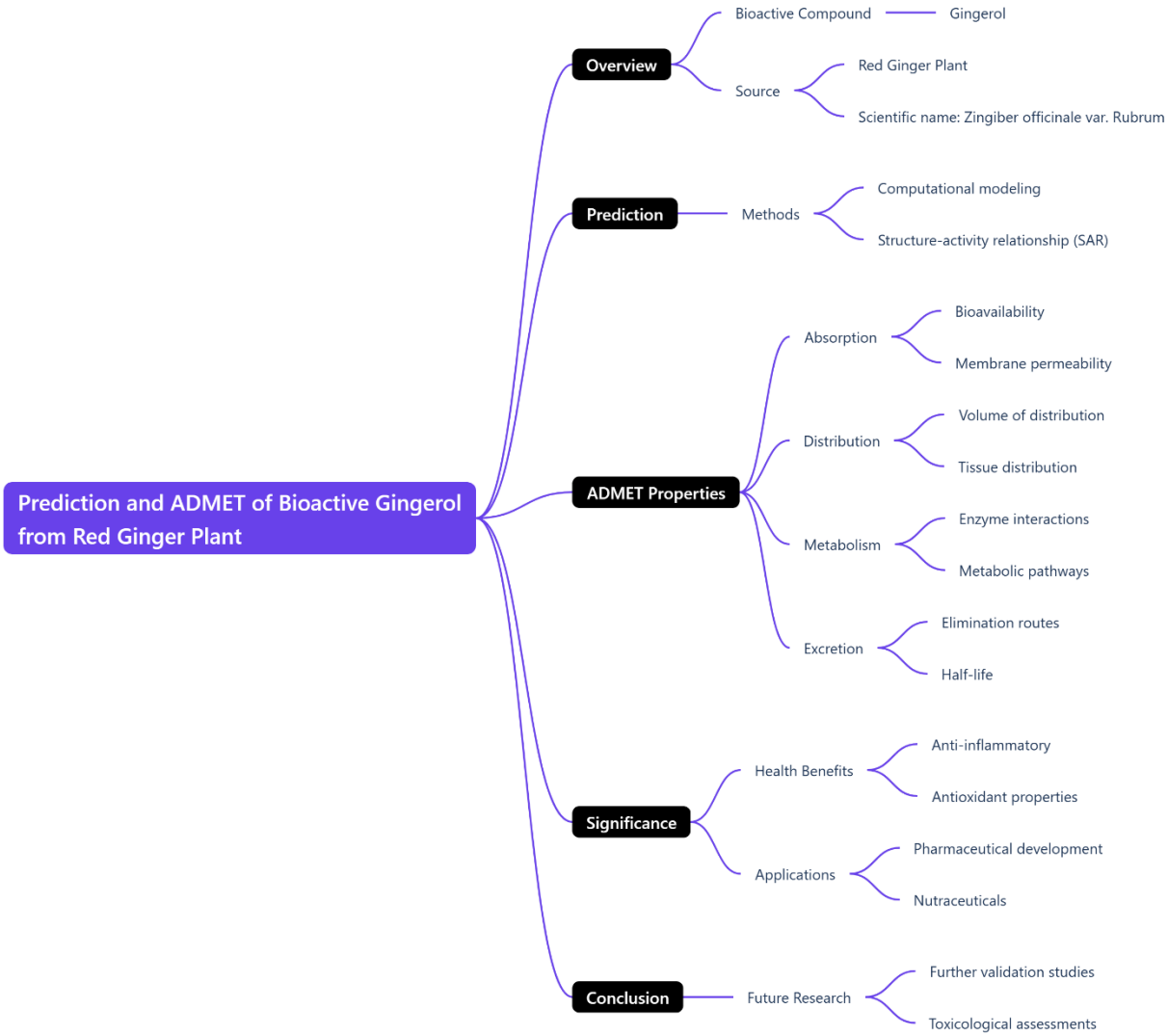

Figure 1. Mind Maps

In the first stage, compound selection and structure preparation were carried out. The primary compounds studied were gingerol analogs that represent the bioactive phenolic constituents of red ginger,

including [6]-gingerol, [8]-gingerol, and [10]-gingerol, chosen based on their prevalence and pharmacological relevance as reported in scientific literature and chemical databases. For each selected compound, canonical chemical identifiers such as the IUPAC name, InChI, InChIKey, and canonical SMILES were retrieved from the PubChem database to ensure structural accuracy and reproducibility. The molecular structures were validated and standardized using Open Babel and RDKit tools. Standardization steps included removing redundant components such as salts and solvents, normalizing tautomeric forms, adding explicit hydrogen atoms when necessary, and generating canonical SMILES and 2D molecular depictions. This process ensured uniformity of input data across prediction platforms. Validation was further confirmed by re-importing the generated SMILES strings into RDKit and cross-verifying the molecular fingerprints to ensure consistency with the original PubChem entries.

The second stage involved the prediction of potential biological activities using the PASS Online platform developed by Way2Drug. PASS Online employs structure–activity relationship (SAR) modeling and Bayesian statistics to predict over 4,000 potential biological activities based solely on molecular structure. To conduct the prediction, each compound's canonical SMILES string was submitted individually into the PASS Online web interface under the "SMILES input mode." The default prediction parameters were used, and the option "pharmacological action spectrum" was selected to obtain a wide range of potential activities. The tool generates two primary output probabilities for each predicted activity: Pa (probability "to be active") and Pi (probability "to be inactive"). These probabilities range between 0.000 and 1.000, where higher Pa values indicate greater confidence that the compound exhibits the corresponding biological activity.

The interpretation of these parameters followed established criteria. Predictions with $Pa > Pi$ and $Pa \geq 0.5$ were considered strong indicators that the compound is likely to demonstrate the predicted activity experimentally. Predictions with Pa values between 0.3 and 0.5 were categorized as moderately probable, suggesting that the compound may display the activity under certain biological contexts or with structural optimization. Predictions with $Pa < 0.3$ were deemed unlikely. The results were exported in tabular form, and when direct download was unavailable, they were copied manually or extracted through a structured HTML parser to maintain reproducibility. Each compound's activity spectrum was recorded and archived, with special attention to activities relevant to anti-inflammatory, antioxidant, and anticancer pharmacology, which represent the most reported pharmacological effects of gingerol compounds. Duplicate analyses were performed to ensure output consistency. Job identifiers, timestamps, and HTML reports were stored for verification purposes.

The third stage of the research was focused on the prediction of pharmacokinetic and toxicity parameters using the pkCSM web tool developed by the University of Queensland. pkCSM is a machine-learning-based predictive model that utilizes graph-based molecular signatures to estimate a wide array of ADMET properties. Each canonical SMILES string from the previous step was input into the pkCSM interface under the "Single Compound" mode. Predictions were generated for a comprehensive set of endpoints encompassing absorption, distribution, metabolism, excretion, and toxicity. In the absorption category, pkCSM predicted water solubility (expressed in log mol/L), Caco-2 cell permeability (log Papp, cm/s), human intestinal absorption percentage (HIA %), and interactions with P-glycoprotein (P-gp), both as a substrate and as an inhibitor. Compounds were classified as having good solubility when $\log S > -4$, and poor solubility when $\log S < -6$. Caco-2 permeability was interpreted as high when $\log Papp > 0.90$, whereas HIA values above 70% indicated strong intestinal absorption. P-gp substrate status was noted because efflux via P-gp transporters can significantly affect oral bioavailability.

The distribution parameters included volume of distribution (Vdss, log L/kg), fraction unbound in plasma (Fu), and blood–brain barrier permeability (logBB). Compounds with logBB values above 0.3 were considered to have good central nervous system (CNS) penetration, while those below −1 were classified as poorly permeable to the CNS. Plasma protein binding was inferred from the fraction unbound value, where low Fu (<0.1) indicated extensive binding.

The metabolism section focused on cytochrome P450 interactions, particularly the major isoforms CYP3A4, CYP2D6, CYP2C9, CYP2C19, and CYP1A2, assessing whether the compound acts as a

substrate or inhibitor. Inhibition of these enzymes could indicate potential for drug–drug interactions or metabolic liabilities. The excretion profile was assessed via predicted total clearance (log mL/min/kg) and renal organic cation transporter 2 (OCT2) substrate status, providing insights into renal elimination capacity.

The toxicity predictions covered multiple endpoints, including Ames mutagenicity, hepatotoxicity, hERG I/II inhibition (related to cardiotoxicity risk), skin sensitization potential, and rat oral LD50. Ames-positive predictions were interpreted as genotoxicity risks, while positive hERG inhibition predictions indicated potential cardiotoxicity due to QT interval prolongation. Hepatotoxicity predictions were evaluated to assess liver safety, and LD50 estimates were used to infer acute toxicity levels.

All pkCSM results were systematically recorded, cleaned, and categorized into favorable, borderline, or unfavorable classes according to established pharmacokinetic and toxicological thresholds. The results were tabulated using spreadsheet software and analyzed using Python's pandas and R's tidyverse libraries. Descriptive statistics such as mean, standard deviation, and range were calculated for comparable parameters among gingerol analogues. Additionally, visualizations in the form of heatmaps and radar plots were generated to facilitate comparative interpretation among compounds with varying side-chain lengths.

To integrate the results from PASS and pkCSM, a multi-criteria decision matrix was developed. A compound was considered pharmacologically promising if it demonstrated at least one high-confidence activity prediction (Pa $\geq$ 0.5) in PASS Online, particularly within anti-inflammatory, antioxidant, or anticancer categories. Furthermore, it was classified as ADMET-favorable if it exhibited acceptable pharmacokinetic properties, including high HIA, adequate Caco-2 permeability, non-significant P-gp inhibition, non-Ames toxicity, and no predicted hERG inhibition. Only compounds fulfilling both pharmacological and pharmacokinetic criteria were prioritized as potential lead candidates. For compounds with partial compliance—such as good biological activity but suboptimal solubility or rapid clearance—further suggestions were made for structural optimization or formulation improvement, such as encapsulation in nano-carriers or prodrug modification.

All data processing was documented with rigorous reproducibility standards. The SMILES files, raw PASS Online outputs, pkCSM prediction spreadsheets, and analysis scripts were stored in a version-controlled repository using Git to maintain traceable records of every computational step. Metadata describing software versions, timestamps, and URLs were also included. The date and time of every online submission were recorded to account for potential changes in web tool databases over time. Additionally, a validation procedure was implemented by cross-checking predicted ADMET and biological activities against existing in vitro or in vivo reports for gingerol compounds. This validation ensured that the computational predictions were consistent with empirical evidence where available.

It is important to acknowledge the limitations inherent to in silico methodologies. Predictions are probabilistic and based on the training data of each model, which may not fully capture the structural diversity of natural compounds such as gingerols. PASS Online predictions rely on structural similarity and may generate false positives when compounds share substructures with pharmacologically active analogs. Similarly, pkCSM predictions depend on statistical correlations derived from synthetic small molecules, meaning that natural compounds with unusual scaffolds may yield less precise predictions. Nonetheless, these tools provide valuable preliminary insight into pharmacological potential and ADMET behavior, reducing the need for excessive in vivo testing and guiding more focused experimental research.

3 Result and Discussion

Predicted Biological Activities of Bioactive Gingerol

To further elucidate the potential pharmacological effects of the major bioactive compounds present in Zingiber officinale var. Rubrum, an in silico prediction of biological activity was performed using the Prediction of Activity Spectra for Substances (PASS) Online tool. This computational approach enables a comprehensive evaluation of possible biological and pharmacological activities based on the structural features of the tested compound. The PASS algorithm employs advanced structure–activity relationship (SAR) models derived from a vast database of known bioactive molecules, allowing the

estimation of the probability of a compound being active (Pa) or inactive (Pi) toward a wide range of biological targets.

This analysis is particularly useful in natural product research, where plant-derived compounds often exhibit multi-target pharmacological effects. Since experimental screening of all possible biological activities is time-consuming and costly, the PASS Online prediction provides an efficient and reliable method for preliminary bioactivity profiling. Through this computational prediction, it becomes possible to identify potential mechanisms of action, therapeutic targets, and safety profiles of bioactive molecules before proceeding to laboratory validation.

The prediction results for the bioactive gingerol compound revealed numerous potential pharmacological actions with varying probabilities of activity (Pa) and inactivity (Pi). The activities with higher Pa values (typically >0.7) are considered more likely to be experimentally observed, while those with lower probabilities may still suggest alternative or secondary mechanisms of action. Table 1 summarizes the top predicted activities of gingerol from red ginger (Zingiber officinale var. Rubrum) based on the PASS Online output, along with their corresponding Pa and Pi values. These predictions form the foundation for understanding the compound's pharmacological spectrum and potential therapeutic applications.

Table 1. Predicted Biological Activities of Bioactive Gingerol Based on PASS Online

No.	Pa (*Probability to be Active*)	Pi (*Probability to be Inactive*)	Predicted Biological Activity
1	0.960	0.003	5-Hydroxytryptamine release stimulant
2	0.911	0.003	Linoleate diol synthase inhibitor
3	0.860	0.021	CYP2C12 substrate
4	0.817	0.010	Feruloyl esterase inhibitor
5	0.803	0.007	UDP-glucuronosyltransferase substrate
6	0.817	0.027	Ubiquinol-cytochrome-c reductase inhibitor
7	0.772	0.004	Preneoplastic conditions treatment
8	0.771	0.004	Steroid N-acetylglucosaminyltransferase inhibitor
9	0.762	0.007	Macrophage colony-stimulating factor agonist
10	0.757	0.004	Mycothiol-S-conjugate amidase inhibitor
11	0.758	0.008	Fibrinolytic
12	0.765	0.027	Gluconate 2-dehydrogenase (acceptor) inhibitor
13	0.757	0.027	Polyporopepsin inhibitor
14	0.730	0.007	Vasodilator, peripheral
15	0.707	0.005	Beta-carotene 15,15'-monooxygenase inhibitor
16	0.735	0.035	Chymosin inhibitor
17	0.735	0.035	Acrocylindropepsin inhibitor
18	0.735	0.035	Saccharopepsin inhibitor
19	0.730	0.034	Chlordecone reductase inhibitor
20	0.717	0.020	GST A substrate
21	0.740	0.051	Aspulvinone dimethylallyltransferase inhibitor

The Pa (probability to be active) and Pi (probability to be inactive) values are indicative of the potential biological activity of the compound predicted by the PASS (Prediction of Activity Spectra for Substances) algorithm. Generally, a Pa > 0.7 suggests that the compound is likely to exhibit the predicted biological activity experimentally. Meanwhile, a Pa value between 0.5 and 0.7 indicates a moderate probability of activity that warrants further investigation.

Based on the results in Table 1, gingerol from *Zingiber officinale* var. *Rubrum* demonstrates multiple predicted pharmacological activities with high confidence (Pa > 0.75), particularly as a 5-hydroxytryptamine release stimulant (Pa = 0.960), linoleate diol synthase inhibitor (Pa = 0.911), and

feruloyl esterase inhibitor (Pa = 0.817). These results indicate potential roles in modulating neurotransmitter release, lipid metabolism, and oxidative stress pathways.

The gingerol compound is also predicted to interact with several enzyme systems, including CYP2C12, UDP-glucuronosyltransferase, and ubiquinol-cytochrome-c reductase, suggesting potential involvement in drug metabolism and mitochondrial electron transport. The moderate Pa values (0.707–0.758) in the context of vasodilator, fibrinolytic, and GST substrate activities further indicate possible cardiovascular and detoxification effects.

Gingerol possesses a broad pharmacological spectrum that aligns with previously reported biological activities, particularly its anti-inflammatory, antioxidant, and neuroactive properties. The high Pa values highlight its potential as a multi-target bioactive compound, supporting further investigation through molecular docking, pharmacokinetic prediction, and in vitro validation.

ADMET Prediction of Bioactive Gingerol

To comprehensively assess the pharmacokinetic and safety profile of the bioactive compound identified from *Zingiber officinale* var. *Rubrum*, an in silico evaluation of Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) parameters was conducted using the pkCSM online prediction platform (https://biosig.lab.uq.edu.au/pkcsm/prediction_single/). The pkCSM tool utilizes graph-based signatures and machine learning algorithms trained on extensive experimental datasets to estimate various pharmacokinetic and toxicological endpoints. This computational method enables rapid, cost-effective, and accurate prediction of drug-likeness and safety liabilities during the early stages of natural product–based drug discovery.

Evaluating the ADMET properties is essential to determine whether a bioactive compound possesses favorable pharmacokinetic characteristics for oral bioavailability and systemic distribution, while maintaining minimal risk of toxicity or metabolic interference. For natural products such as gingerol, which are known for their potent pharmacological activities, understanding ADMET behavior provides a crucial link between molecular efficacy and clinical applicability. Specifically, parameters such as water solubility, intestinal absorption, blood–brain barrier permeability, cytochrome P450 enzyme interaction, and toxicological risks can serve as indicators of a compound's therapeutic viability.

The ADMET assessment of bioactive gingerol was divided into five main pharmacokinetic components: (1) Absorption, to evaluate the compound's ability to be absorbed through the intestinal epithelium and biological membranes; (2) Distribution, to estimate its systemic bioavailability and capacity to penetrate target tissues such as the brain; (3) Metabolism, to analyze its interaction with cytochrome P450 enzymes responsible for drug biotransformation; (4) Excretion, to assess its clearance and elimination potential; and (5) Toxicity, to predict possible adverse effects including mutagenicity, hepatotoxicity, or cardiotoxicity.

The predicted results generated by pkCSM are presented in Table 2, providing detailed numerical and categorical outcomes for each model parameter. These computational predictions are instrumental in understanding how gingerol may behave within the human body, and in determining whether it fulfills the characteristics of a promising drug candidate with acceptable pharmacokinetic and safety profiles.

Table 2. Predicted ADMET Properties of Bioactive Gingerol Using pkCSM Online Model

Property	Model Name	Predicted Value	Unit / Type
Absorption	Water solubility	-3.164	log mol/L
	Caco2 permeability	0.94	log Papp ($\times 10^{-6}$ cm/s)
	Intestinal absorption (human)	92.416	% absorbed
	Skin permeability	-2.817	log Kp
	P-glycoprotein substrate	Yes	Categorical (Yes/No)
	P-glycoprotein I inhibitor	No	Categorical (Yes/No)

	P-glycoprotein II inhibitor	No	Categorical (Yes/No)
Distribution	VDss (human)	0.524	log L/kg
	Fraction unbound (human)	0.258	Fu
	BBB permeability	-0.727	log BB
	CNS permeability	-2.788	log PS
Metabolism	CYP2D6 substrate	No	Categorical (Yes/No)
	CYP3A4 substrate	No	Categorical (Yes/No)
	CYP1A2 inhibitor	Yes	Categorical (Yes/No)
	CYP2C19 inhibitor	Yes	Categorical (Yes/No)
	CYP2C9 inhibitor	Yes	Categorical (Yes/No)
	CYP2D6 inhibitor	No	Categorical (Yes/No)
	CYP3A4 inhibitor	No	Categorical (Yes/No)
Excretion	Total clearance	1.339	log ml/min/kg
	Renal OCT2 substrate	No	Categorical (Yes/No)
Toxicity	AMES toxicity	No	Categorical (Yes/No)
	Max. tolerated dose (human)	0.635	log mg/kg/day
	hERG I inhibitor	No	Categorical (Yes/No)
	hERG II inhibitor	No	Categorical (Yes/No)
	Oral rat acute toxicity (LD_{50})	1.958	mol/kg
	Oral rat chronic toxicity (LOAEL)	1.631	log mg/kg_bw/day
	Hepatotoxicity	No	Categorical (Yes/No)
	Skin sensitisation	No	Categorical (Yes/No)
	Tetrahymena pyriformis toxicity	1.487	log µg/L
	Minnow toxicity	0.966	log mM

The ADMET analysis of bioactive gingerol derived from *Zingiber officinale* var. *Rubrum* revealed a highly favorable pharmacokinetic profile, suggesting its strong potential as a drug-like molecule with acceptable safety and metabolic characteristics. As shown in Table 2, the absorption properties of gingerol demonstrate its good solubility and permeability within biological systems. The predicted water solubility value of −3.164 log mol/L indicates a moderately soluble compound, consistent with typical lipophilic phytochemicals. Although not highly hydrophilic, this degree of solubility is sufficient for oral administration, allowing efficient dissolution within gastrointestinal fluids. The Caco-2 permeability value of 0.94 log Papp ($\times 10^{-6}$ cm/s) reflects a high capacity for passive diffusion across intestinal epithelial cells, a critical factor for achieving significant systemic absorption following oral intake. In addition, the human intestinal absorption percentage of 92.416% strongly supports the notion that gingerol can be effectively absorbed through the gastrointestinal tract, contributing to its well-documented bioavailability in vivo.

The skin permeability parameter, with a predicted value of −2.817 log Kp, suggests moderate transdermal diffusion, which is relevant considering the topical and dermal formulations of ginger-derived compounds in traditional and pharmaceutical applications. Furthermore, the model predicted that gingerol acts as a P-glycoprotein (P-gp) substrate but not as a P-gp I or II inhibitor. This finding implies that gingerol may undergo efflux transport mediated by P-gp, potentially influencing its intracellular retention time. However, the absence of inhibitory activity toward P-gp isoforms indicates a low risk of drug–drug interactions associated with efflux modulation, a desirable feature for compounds intended for multi-drug therapeutic regimens.

Regarding distribution, the predicted volume of distribution at steady state (VDss) of 0.524 log L/kg indicates moderate tissue distribution. This value reflects a balanced partition between plasma and peripheral compartments, allowing effective delivery to target organs without excessive accumulation. The fraction unbound (Fu) value of 0.258 suggests that approximately one-fourth of gingerol remains

unbound to plasma proteins, providing an adequate free concentration for pharmacological activity. Moreover, the blood–brain barrier (BBB) permeability prediction of −0.727 log BB indicates limited but possible central nervous system (CNS) penetration, while the CNS permeability value of −2.788 log PS confirms low CNS accumulation. This limited CNS permeability may reduce the risk of central neurotoxicity, which is beneficial for non-neuroactive therapeutic applications.

The metabolic profile of gingerol demonstrates selective interaction with cytochrome P450 enzymes, a key determinant in drug metabolism and clearance. The compound was not predicted to be a substrate for CYP2D6 or CYP3A4, which are major drug-metabolizing isoenzymes in humans. This suggests a lower likelihood of extensive first-pass metabolism and reduced potential for metabolic drug–drug interactions. However, gingerol exhibited inhibitory potential toward CYP1A2, CYP2C19, and CYP2C9, which are enzymes involved in the oxidation of xenobiotics and certain therapeutic drugs. These inhibitory interactions may contribute to prolonged systemic exposure or synergistic effects when co-administered with substrates of these enzymes. Importantly, the compound did not inhibit CYP2D6 or CYP3A4, indicating minimal interference with major hepatic metabolic pathways. Collectively, these findings highlight a moderate yet controllable metabolic interaction profile, aligning with previous reports on the enzyme-modulating properties of phenolic phytoconstituents from *Zingiber* species.

In terms of excretion, gingerol displayed a predicted total clearance value of 1.339 log ml/min/kg, suggesting efficient systemic elimination through renal and hepatic pathways. The absence of activity as a renal OCT2 substrate indicates that gingerol is unlikely to rely heavily on renal tubular secretion for excretion, thus minimizing nephrotoxic risk and accumulation in renal tissues. This property supports its pharmacokinetic suitability for chronic or repeated administration without significant toxicity.

The toxicity evaluation demonstrated that gingerol possesses a highly favorable safety profile. The compound tested negative for AMES toxicity, implying non-mutagenic potential and genetic safety. The maximum tolerated dose (human) of 0.635 log mg/kg/day indicates a broad therapeutic window and acceptable dosing potential. Importantly, gingerol showed no inhibitory activity against hERG I or hERG II channels, eliminating the risk of cardiotoxicity associated with QT prolongation. The oral rat acute toxicity (LD_{50}) value of 1.958 mol/kg and the chronic toxicity (LOAEL) of 1.631 log mg/kg_bw/day suggest relatively low systemic toxicity upon prolonged exposure, consistent with the traditional use of red ginger as a safe medicinal herb. Furthermore, the model predicted no hepatotoxicity and no skin sensitization, emphasizing its compatibility with hepatic metabolism and dermal application routes. The Tetrahymena pyriformis toxicity (1.487 log µg/L) and minnow toxicity (0.966 log mM) values correspond to mild aquatic toxicity, indicating limited environmental risk upon disposal or excretion into wastewater systems.

The computational ADMET analysis supports the hypothesis that bioactive gingerol from *Zingiber officinale* var. *Rubrum* exhibits excellent pharmacokinetic feasibility and low toxicological risk, making it a promising candidate for further in vivo pharmacological validation and drug development. The high intestinal absorption, moderate volume of distribution, limited CNS permeability, and absence of mutagenic or cardiotoxic liabilities together reinforce its drug-like nature. In combination with the predicted biological activities identified through PASS analysis, these results position gingerol as a multifunctional, safe, and pharmacologically active compound with strong potential for therapeutic application in various inflammatory, metabolic, and cardiovascular disorders. Future studies integrating in vitro metabolic assays and in vivo pharmacokinetic evaluations are recommended to confirm and expand upon these computational predictions, thereby establishing a more comprehensive understanding of gingerol's biopharmaceutical potential.

4. Conclusion

The computational prediction and ADMET evaluation of bioactive gingerol from Zingiber officinale var. Rubrum provide a clear insight into its pharmacological potential and drug-likeness. Based on PASS Online analysis, gingerol demonstrated high probabilities (Pa > 0.8) for multiple biological

activities, including 5-hydroxytryptamine release stimulation, linoleate diol synthase inhibition, and feruloyl esterase inhibition, indicating strong multi-target pharmacological potential. These predicted functions suggest that gingerol may play important roles in modulating inflammatory, oxidative, and enzymatic pathways, supporting its therapeutic relevance in various disease conditions.

The ADMET prediction using pkCSM further confirmed the favorable pharmacokinetic behavior of gingerol. It exhibited high intestinal absorption (92.4%), good Caco-2 permeability, and moderate water solubility, suggesting strong oral bioavailability. The predicted distribution profile showed balanced tissue penetration with moderate protein binding and low central nervous system (CNS) permeability, indicating minimal neurotoxic potential. In metabolism, gingerol was not a substrate of CYP2D6 or CYP3A4 but inhibited CYP1A2, CYP2C19, and CYP2C9, reflecting moderate enzyme interaction without severe metabolic interference.

Toxicity predictions revealed a safe pharmacological profile. Gingerol was non-mutagenic (AMES negative), non-hepatotoxic, non-cardiotoxic (no hERG inhibition), and showed no skin sensitization. Acute and chronic toxicity parameters (LD_{50} and LOAEL) indicated a broad safety margin, consistent with its traditional medicinal use.

5. Declarations

5.1 Acknowledgements (Optional)

All authors contributed to the design, writing, and editing of the manuscript.

5.2 Author contributions

The author declares that there is no conflict of interest in this research

5.4 Conflict of Interest

The author declares that there is no conflict of interest in this research

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