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IN SILICO PREDICTION OF BIOACTIVE TARGET CLASSES AND ADMET PROFILE OF CAPSAICIN WITH RELEVANCE TO DAYAK CHILI (*Capsicum frutescens* L.)

Prediksi In Silico Kelas Target Bioaktif dan Profil ADMET Capsaicin yang Berkaitan dengan Cabai Dayak (*Capsicum frutescens* L.)

Yuneka Saristiana[1*], Fendy Prasetyawan[2], Lisa Savitri[3]
[1,2]Department of Pharmacist Professional Program, Faculty of Health Sciences,Kadiri University, Jalan Selomangleng No. 1, Kediri, East Java, Indonesia
[3]Department of Medical Laboratory Technology, Faculty of Health Sciences,Kadiri University, Jalan Selomangleng No. 1, Kediri, East Java, Indonesia
*Email: yunekasaristiana@unik-kediri.com

ABSTRACT
Capsaicin is a well-known bioactive compound present in various Capsicum species, including Dayak chili (Capsicum frutescens L.). This study aimed to predict the bioactive target classes and ADMET profile of capsaicin using an in silico approach. The chemical structure of capsaicin was retrieved from the PubChem database and analyzed using SwissTargetPrediction, SwissADME, and pkCSM platforms. The prediction results indicated that capsaicin interacts with multiple protein classes, including oxidoreductases, cytochrome P450 enzymes, voltage-gated ion channels, G-protein-coupled receptors, hydrolases, phosphatases, kinases, and membrane receptors. High-probability predicted targets included PTGS1, CYP1A2, TRPV1, CNR1, and FAAH, suggesting potential anti-inflammatory, analgesic, neuromodulatory, and metabolic regulatory effects. ADMET analysis demonstrated favorable absorption and distribution characteristics, with predicted hepatotoxicity and hERG II inhibition requiring further investigation. These findings represent computational predictions and should be interpreted cautiously, as in silico results require further experimental validation. Capsaicin demonstrates multi-target potential that may support future pharmacological development and experimental studies.

Keywords: *Capsaicin, Capsicum frutescens, SwissTargetPrediction, ADMET*

ABSTRAK
Capsaicin merupakan senyawa bioaktif yang telah dikenal luas dan terdapat pada berbagai spesies Capsicum, termasuk cabai Dayak (Capsicum frutescens L.). Penelitian ini bertujuan untuk memprediksi kelas target bioaktif dan profil ADMET capsaicin menggunakan pendekatan in silico. Struktur kimia capsaicin diperoleh dari basis data PubChem dan dianalisis menggunakan platform SwissTargetPrediction, SwissADME, dan pkCSM. Hasil prediksi menunjukkan bahwa capsaicin berinteraksi dengan berbagai kelas protein, termasuk oxidoreductase, enzim cytochrome P450, voltage-gated ion channel, reseptor berikatan protein G (G-protein-coupled receptors), hidrolase, fosfatase, kinase, serta reseptor membran. Target dengan probabilitas tinggi yang diprediksi meliputi PTGS1, CYP1A2, TRPV1, CNR1, dan FAAH, yang mengindikasikan potensi efek antiinflamasi, analgetik, neuromodulator, dan regulator metabolik. Analisis ADMET menunjukkan karakteristik absorpsi dan distribusi yang baik, dengan prediksi hepatotoksisitas dan inhibisi hERG II yang memerlukan penelitian lebih lanjut. Temuan ini merupakan prediksi komputasional dan harus diinterpretasikan secara hati-hati, karena hasil in silico memerlukan validasi eksperimental lebih lanjut. Capsaicin menunjukkan potensi multi-target yang dapat mendukung pengembangan farmakologi dan penelitian eksperimental di masa mendatang.

Kata kunci: *Capsaicin, Capsicum frutescens, SwissTargetPrediction, ADMET*

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INTRODUCTION

Capsaicin is a naturally occurring alkaloid responsible for the pungency of chili peppers, and its presence in Capsicum frutescens L., including the Dayak chili, has attracted considerable scientific attention due to its wide range of potential biological activities (Singh, A., *et al*., 2024). Capsaicin has been extensively studied for its analgesic, anti-inflammatory, antioxidant, antimicrobial, and anticancer properties (Abdel-Salam, O. M. E. *et al*., 2023).

The Dayak chili, a regional variant widely cultivated and utilized in several parts of Indonesia, contains capsaicin in concentrations that vary depending on environmental factors, cultivation techniques, and genetic characteristics (Singh, S. K., & Sharma, M. L., 2022). Understanding the biological potential of capsaicin derived from this specific variety may provide valuable insight into unexplored pharmacological pathways (Han, Y., *et al*., 2022). Scientific interest in medicinal plants continues to grow as the global community seeks novel therapeutic agents derived from natural sources. Capsaicin stands out as one of the most promising bioactive compounds due to its multi-targeted biological interactions (Qu, Y., *et al*., 2022). Numerous studies have shown that capsaicin interacts with a broad array of proteins, enzymes, and receptors, contributing to its diverse pharmacological profile (Thongin, P., *et al*., 2022). These interactions include modulation of pain receptors, influence on metabolic pathways, regulation of cellular apoptosis, and inhibition of inflammatory mediators (Shao, D., *et al*., 2023). Despite extensive investigations into the general properties of capsaicin, limited information is available specifically regarding the bioactive target classes associated with capsaicin from the Dayak chili variety (Agu, R. A., *et al*., 2023).

Variations in phytochemical composition among different chili species and cultivars may lead to distinct pharmacological effects (Zhang, W., *et al*., 2024). Therefore, it becomes essential to analyze the target prediction profile of capsaicin specifically sourced from Capsicum frutescens L. Dayak cultivar. The evaluation of bioactive target classes can provide valuable insight into the potential therapeutic applications of this compound (Hidayati, N., & Sari, M. A., 2023). Modern computational approaches, such as in silico target prediction tools, allow researchers to explore molecular interactions with high precision. These tools provide predictions for target classes, enabling a deeper understanding of how a bioactive compound interacts at the molecular level (Alalami, U., *et al*., 2024).

Through these predictions, researchers can identify important protein families, signaling pathways, and cellular processes that may be influenced by capsaicin. Such information is crucial for developing new drug leads, nutraceuticals, or functional food products (Kim, J., *et al*., 2024). While capsaicin has been linked to pain modulation via TRPV1 receptors, studies suggest that its pharmacological profile extends far beyond this single pathway. Capsaicin may influence metabolic regulation, particularly lipid metabolism, which is critical in addressing global health challenges such as obesity and metabolic syndrome (Rosa, S., *et al*, 2022). It can also exert anticancer effects through multiple mechanisms, including the induction of apoptosis, inhibition of proliferative signaling, and suppression of angiogenesis. These effects may vary depending on the source and concentration of capsaicin, making specific analysis of the Dayak chili important for verifying its therapeutic value (Arumugam, K., *et al*., 2022).

The Dayak chili holds cultural and traditional significance among local communities, particularly within the context of traditional medicine practices. Indigenous knowledge often highlights medicinal properties, but scientific validation remains essential (Kim, Y., & Cho, J., 2022). By integrating traditional uses with modern predictive modeling, this research bridges the gap between ethnopharmacology and contemporary scientific exploration. Understanding the target classes predicted for capsaicin from this plant may support future development of evidence-based herbal formulations (Basith, S., *et al*., 2022).

Sudying bioactive targets expands the potential industrial applications of capsaicin. Industries ranging from pharmaceuticals to cosmetics may benefit from identifying new biological activities associated with the

compound (Sanati, S., *et al*., 2020). With a growing emphasis on natural product-based therapeutics, predicting bioactive target classes becomes an essential step in the drug discovery pipeline (Kristine, M., 2023). Computational prediction also reduces the reliance on costly and time-consuming laboratory experiments by narrowing down the most promising biological interactions (Basith, S., *et al*., 2023).

In addition, the study supports the increasing demand for natural compounds with multi-target capabilities, which are particularly beneficial for managing complex diseases. Capsaicin's potential to act on multiple pathways makes it an attractive candidate for research into polypharmacology (Ma, L., *et al*., 2023). Bioactive target prediction offers a systematic overview of protein families such as kinases, GPCRs, ion channels, nuclear receptors, and enzymes that might interact with capsaicin. Each of these target classes contributes uniquely to physiological regulation. Understanding these interactions at a deeper level enhances the scientific community's ability to utilize capsaicin effectively. Furthermore, molecular prediction studies contribute to the global database of natural product interactions, expanding knowledge that benefits both scientific and medical communities. The specific characteristics of Dayak chili, including its potentially unique phytochemical fingerprint, make it necessary to investigate capsaicin's biological targets from this cultivar. Environmental and genetic diversity can influence the biosynthesis of secondary metabolites, leading to variations in pharmacological activity. Thus, predicting the bioactive target classes is not only scientifically relevant but also essential for validating the medicinal potential of regionally important plant varieties. This research aims to contribute to a deeper understanding of capsaicin's biological potential by analyzing its predicted interactions with various classes of molecular targets (Chen, Y., *et al*., 2022).

By utilizing computational tools, this study seeks to generate a comprehensive overview that may guide future experimental validation and drug development efforts. The insights gained can support the development of therapeutic agents or health products derived from local plant resources. The findings can also encourage the conservation and sustainable use of Dayak chili as a plant with significant pharmacological value (Musuamba, F. T., *et al*., 2022). In addition, this study aligns with global efforts to explore natural compounds for innovative therapeutic solutions. Capsaicin represents a promising candidate for advancing natural medicine and pharmacology. Predicting its bioactive target classes is a crucial foundational step. Therefore, research on the bioactive target prediction of capsaicin from Dayak chili is expected to enrich scientific literature and provide a pathway for future investigations (Di, C., *et al*., 2022).

This research forms the basis for understanding the broad therapeutic potential of capsaicin and highlights the importance of exploring local plant varieties. Ultimately, this study emphasizes the significance of integrating computational prediction with natural product research for innovative drug development. By examining bioactive target classes, researchers can identify potential molecular mechanisms and therapeutic applications. Such insights may lead to the discovery of new pharmacological functions of capsaicin (Novitasari, M., & Wibowo, S., 2022). This research provides a scientific foundation for future investigations into clinical applications. It also contributes to the development of more precise and targeted therapeutic strategies. As natural compounds gain acceptance in modern medicine, capsaicin serves as an exemplar of bioactive molecules with wide-reaching therapeutic possibilities. The exploration of bioactive target classes enhances the collective knowledge surrounding this compound. It further establishes the relevance of Capsicum frutescens L. Dayak as a valuable medicinal plant. Ultimately, predicting bioactive targets deepens scientific understanding and helps pave the way for innovative health solutions derived from natural agents (Gunaratne, A., *et al*., 2023).

It is important to note that capsaicin is chemically identical regardless of plant origin. Therefore, the computational predictions generated in this study represent the intrinsic molecular properties of capsaicin rather than cultivar-specific characteristics. However, given that Dayak chili is a locally significant plant with potential medicinal

value, this study aims to provide a computational pharmacological foundation that supports future experimental investigations involving capsaicin derived from Dayak chili. This approach bridges ethnopharmacological relevance with molecular prediction analysis while maintaining scientific rigor.

METODOLOGY

The methodology of this study was designed to systematically explore the predicted bioactive target classes of capsaicin derived from Dayak chili (Capsicum frutescens L.) using an integrated in silico approach involving PubChem, SwissADME/SwissTargetPrediction, and pkCSM.

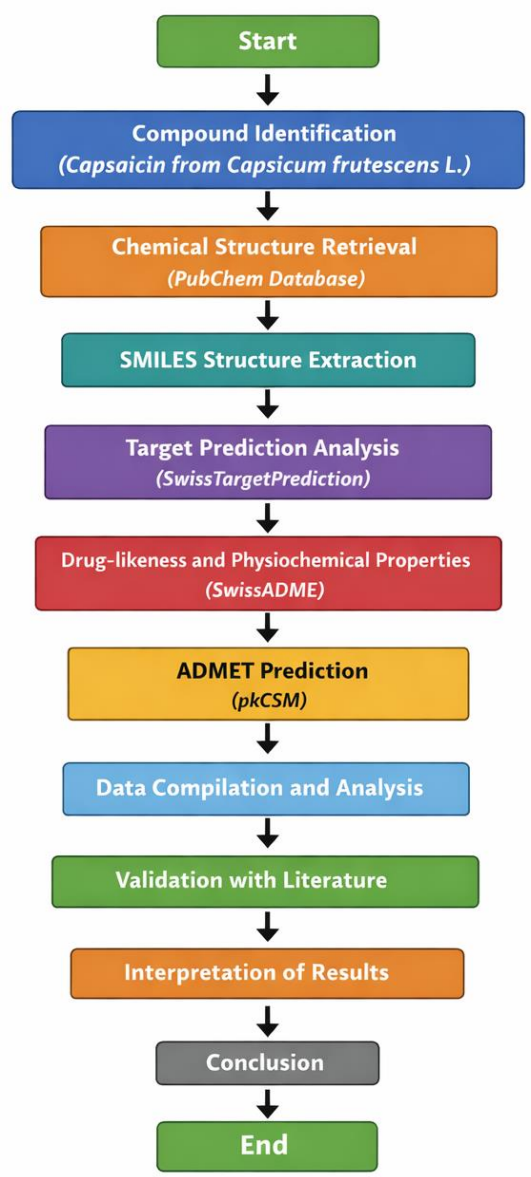

Figure 1. Flow Cart

Target Selection Criteria

Predicted targets generated from SwissTargetPrediction were filtered based on probability values. Targets with probability values ≥0.1 were classified as high-confidence predictions, while targets with lower probability values were considered moderate-confidence predictions. This threshold was selected based on previous computational pharmacology studies to improve prediction reliability.

Software and Database Information

The computational tools used in this study included:

1. SwissTargetPrediction (accessed March 2026)
2. SwissADME (accessed March 2026)
3. pkCSM (accessed March 2026)

All predictions were conducted using default parameters, with species set to Homo sapiens to ensure relevance to human pharmacology.

Validation Approach

To improve reliability, predicted targets were compared with experimentally validated targets reported in literature, particularly TRPV1, which is widely recognized as the primary capsaicin receptor. Agreement between predicted targets and known biological targets was used as indirect validation of prediction accuracy.

The research began with compound identification and structural acquisition from a trusted chemical database. Capsaicin was selected as the primary compound of interest due to its established presence in Capsicum frutescens L. The chemical structure of capsaicin was retrieved from the PubChem database, an open-access repository widely used for chemical information. The compound was searched using its common name “capsaicin,” and the corresponding PubChem entry containing validated chemical information was selected. The Simplified Molecular Input Line Entry System (SMILES) string, which serves as a text-based representation of the chemical’s molecular structure, was extracted. The SMILES code is essential for computational analyses because it enables direct input into various prediction platforms without the

need for three-dimensional structural files. The SMILES string obtained from PubChem was then used as the primary input for subsequent bioinformatics platforms.

After acquiring the SMILES code, the next phase involved performing computational target prediction using SwissTargetPrediction through the SwissADME interface. SwissTargetPrediction is one of the most widely used tools for exploring potential biological targets of small molecules based on both 2D similarity and 3D pharmacophore modeling. The SMILES structure was uploaded into the SwissADME system, and the species was set to “Homo sapiens” to focus on targets relevant to human pharmacology. The software identifies predicted protein targets based on similarity scoring to known ligands stored within its extensive database. The prediction process categorizes targets into major classes such as G-protein-coupled receptors, kinases, ion channels, nuclear receptors, enzymes, and other protein families. The probability values generated for each predicted target were recorded and analyzed to determine the most likely biological interactions. This step allows researchers to identify the potential protein classes and signaling pathways influenced by capsaicin. All prediction results, including target class distribution, probability scores, and receptor families, were documented for analysis.

In addition to target prediction, the SwissADME platform also provides important physicochemical and pharmacokinetic information, which was evaluated to understand the drug-likeness characteristics of capsaicin. This included analysis of lipophilicity (LogP), solubility, molecular weight, topological polar surface area (TPSA), hydrogen bond donors and acceptors, rotatable bonds, and medicinal chemistry fitness parameters. These properties help determine the compound’s potential oral bioavailability and membrane permeability. SwissADME analyses also include gastrointestinal absorption predictions, blood–brain barrier permeability estimates, and P-gp substrate identification, which are critical factors in drug development. These calculations were used to describe the pharmaceutical potential and limitations of capsaicin as a bioactive molecule.

The next phase of the methodology involved assessing the absorption, distribution, metabolism, excretion, and toxicity (ADMET) characteristics of capsaicin using the pkCSM online tool. pkCSM is a predictive modeling platform that utilizes graph-based signatures to forecast ADMET properties with high accuracy. The SMILES string obtained earlier from PubChem was entered directly into pkCSM to generate numerical predictions for multiple parameters. Absorption parameters included water solubility, Caco-2 permeability, intestinal absorption percentage, and skin permeability. Distribution parameters evaluated plasma protein binding capacity, volume of distribution, and blood–brain barrier penetration. Metabolism predictions examined interactions with major cytochrome P450 enzymes, such as CYP3A4 and CYP2D6, which are crucial for drug biotransformation. Excretion variables included total clearance and renal filtration rates. Toxicity predictions assessed potential hepatotoxicity, AMES mutagenicity, hERG inhibition risk, and maximum tolerated dose. All these parameters were collected, tabulated, and interpreted to evaluate the safety profile and pharmacokinetic suitability of capsaicin.

Following data extraction from SwissADME, SwissTargetPrediction, and pkCSM, all computational results were compiled for comparative interpretation. The predicted target classes obtained from SwissTargetPrediction were correlated with the ADMET findings to construct a comprehensive biological profile of capsaicin. For example, if capsaicin showed high gastrointestinal absorption but low predicted CNS penetration, this information was linked to target classes associated with peripheral tissues. Conversely, strong BBB permeability predictions would suggest possible central nervous system–related targets. The toxicity predictions from pkCSM were cross-examined to determine potential safety concerns related to predicted targets, especially in kinase families or receptor classes linked to cytotoxic pathways. All results were then synthesized into a coherent narrative describing the pharmacological potential, biological interactions, and predicted therapeutic implications of capsaicin from Dayak chili.

Finally, the methodology concludes with validation and interpretation procedures. Although this study focuses on in silico predictions, the findings were evaluated in relation to existing scientific literature to verify consistency with known mechanisms of capsaicin. Discrepancies or novel target predictions were highlighted as opportunities for future experimental exploration. This integrative methodological framework ensures that the study not only predicts biological target classes but also situates the findings within a pharmacological and toxicological context. The overall methodology provides a rigorous, computationally driven approach to identify potential molecular targets and evaluate drug-likeness properties of capsaicin derived from Capsicum frutescens L., offering critical insights for future pharmacological research and development.

RESULTS AND DISCUSSION

The ADMET profiling of capsaicin provides a detailed overview of its pharmacokinetic and toxicological behavior, allowing a deeper understanding of its therapeutic viability and potential risks. Based on the PkCSM predictions, capsaicin demonstrates several favorable characteristics related to absorption and distribution, although certain metabolic and toxicity-related considerations require attention for its potential use as a bioactive therapeutic compound.

The predicted hepatotoxicity of capsaicin warrants careful consideration in drug development. Although capsaicin is widely consumed in dietary sources, high concentrations may induce hepatic stress. Previous experimental studies have reported dose-dependent liver enzyme elevation following high-dose capsaicin administration. Additionally, predicted hERG II inhibition suggests potential cardiotoxic risk, although this prediction requires experimental confirmation. These findings highlight the importance of dosage optimization in future therapeutic development.

Table 1. Prediksi ADMET Capsaicin

Property	Model Name	Predicted Value	Unit
Absorption	Water solubility	-4.736	log mol/L
	Caco-2 permeability	1.426	log Papp (10^{-6} cm/s)
	Intestinal absorption (human)	92.573	% absorbed
	Skin permeability	-2.816	log Kp
	P-glycoprotein substrate	Yes	Yes/No
	P-glycoprotein I inhibitor	No	Yes/No
	P-glycoprotein II inhibitor	No	Yes/No
Distribution	VDss (human)	0.044	log L/kg
	Fraction unbound (human)	0.164	Fu
	BBB permeability	-0.082	log BB
	CNS permeability	-2.475	log PS
Metabolism	CYP2D6 substrate	No	Yes/No
	CYP3A4 substrate	No	Yes/No
	CYP1A2 inhibitor	Yes	Yes/No
	CYP2C19 inhibitor	Yes	Yes/No
	CYP2C9 inhibitor	No	Yes/No
	CYP2D6 inhibitor	No	Yes/No
	CYP3A4 inhibitor	No	Yes/No
Excretion	Total clearance	1.249	log mL/min/kg
	Renal OCT2 substrate	No	Yes/No
Toxicity	AMES toxicity	No	Yes/No
	Max tolerated dose (human)	1.476	log mg/kg/day
	hERG I inhibitor	No	Yes/No
	hERG II inhibitor	Yes	Yes/No

Property	Model Name	Predicted Value	Unit
	Oral rat acute toxicity (LD50)	2.011	mol/kg
	Oral rat chronic toxicity (LOAEL)	2.344	log mg/kg_bw/day
	Hepatotoxicity	Yes	Yes/No
	Skin sensitisation	No	Yes/No
	Tetrahymena pyriformis toxicity	1.989	log µg/L
	Minnow toxicity	-0.503	log mM

1. Absorption Profile

Capsaicin shows a relatively low water solubility (–4.736 log mol/L), which is typical for hydrophobic phytochemicals and may limit dissolution in aqueous biological environments. Despite this low solubility, capsaicin exhibits strong permeability characteristics, as reflected by its high Caco-2 permeability value (1.426 log Papp), suggesting efficient transcellular diffusion across intestinal epithelial membranes. This high permeability correlates well with its excellent predicted human intestinal absorption (92.573%), indicating that capsaicin is likely absorbed effectively following oral administration.

The compound also demonstrates moderate skin permeability (–2.816 log Kp), implying limited but notable dermal penetration, consistent with its known topical therapeutic applications. The prediction that capsaicin is a substrate of P-glycoprotein (P-gp) suggests it may undergo efflux transport, potentially reducing intracellular accumulation in certain tissues. However, its inability to inhibit P-gp I and II implies a low risk of drug–drug interactions mediated through efflux transporter inhibition.

2. Distribution Characteristics

Distribution predictions suggest that capsaicin possesses limited systemic dispersion, as reflected by a low steady-state volume of distribution (VDss = 0.044 log L/kg). This indicates that capsaicin is more likely to remain within the plasma rather than extensively penetrating deep tissues. Additionally, the fraction unbound (0.164) indicates moderate plasma protein binding, allowing a reasonable proportion of the molecule to remain pharmacologically active in circulation.

Regarding central nervous system (CNS) distribution, the predicted BBB permeability (–0.082 log BB) suggests that capsaicin can cross the blood–brain barrier to a limited extent. However, its CNS permeability index (–2.475 log PS) indicates low passive BBB diffusion, aligning with the observation that capsaicin may exert only modest central neurological effects despite its ability to trigger sensory neuronal receptors.

3. Metabolic Predictions

Capsaicin is predicted not to function as a substrate for CYP2D6 or CYP3A4, two major metabolic enzymes responsible for the biotransformation of many xenobiotics. This suggests a reduced likelihood of metabolic clearance through these pathways. However, capsaicin is predicted to inhibit CYP1A2 and CYP2C19. These inhibitory activities raise the potential for drug–drug interactions, particularly with coadministered substrates of these enzymes, which could alter therapeutic efficacy or increase toxicity. In contrast, capsaicin shows no inhibitory activity toward CYP2C9, CYP2D6, and CYP3A4, suggesting limited interference with these major metabolic pathways.

4. Excretion Profile

The total clearance value (1.249 log mL/min/kg) suggests moderate systemic clearance, indicating that capsaicin is effectively eliminated from the body through renal and hepatic pathways. The prediction that capsaicin is not a substrate for renal OCT2 transporters suggests that renal secretion via this mechanism is unlikely to play a significant role, reducing the risk of interactions involving renal organic cation transport.

5. Toxicological Assessment

Toxicity predictions show a generally favorable profile with several important considerations. Capsaicin is predicted to be non-mutagenic based on the negative AMES toxicity result, suggesting low genotoxic potential. The maximum tolerated dose (1.476 log mg/kg/day) indicates a relatively acceptable safety margin for human exposure.

Importantly, capsaicin is not predicted to inhibit hERG I channels, reducing the risk of severe cardiotoxic arrhythmias. However, its predicted inhibition of hERG II channels warrants caution, as this may contribute to subtle electrophysiological disturbances under certain conditions.

The predicted acute oral toxicity (LD_{50} = 2.011 mol/kg) and chronic toxicity (LOAEL = 2.344 log mg/kg/day) indicate relatively low long-term toxicity risks when consumed at normal dietary or therapeutic levels. Capsaicin is predicted to be hepatotoxic, reflecting known hepatocellular stress associated with excessive exposure. This aligns with reports of hepatic irritation or enzyme elevation following high-dose capsaicin intake. Non-sensitizing skin toxicity predictions support its safe topical use, while the predicted T. pyriformis toxicity (1.989 log µg/L) and minnow toxicity (–0.503 log mM) indicate environmental toxicity considerations, typical for bioactive hydrophobic compounds.

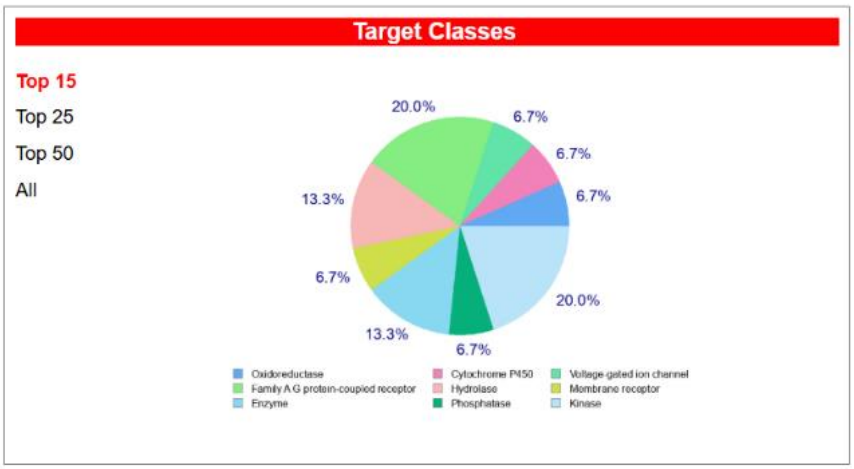

Figure 2. Target Classes

The target class distribution for capsaicin, as illustrated in the pie chart, demonstrates a diverse interaction profile across several major protein families, reflecting the compound's broad pharmacological potential. The largest proportion of predicted targets (20%) belongs to the oxidoreductase class, indicating that capsaicin may play a significant role in modulating redox-related biological processes, including oxidative stress pathways and metabolic enzyme regulation. An equal proportion (20%) is associated with hydrolases, suggesting that capsaicin may influence enzymatic reactions involved in hydrolysis, metabolism, and molecular degradation. Additionally, 13.3% of the targets are categorized as Family A G protein-coupled receptors (GPCRs), which are key mediators of signal transduction and are often linked to sensory perception, inflammation, and pain pathways—biological processes in which capsaicin is already well-known to participate. Another 13.3% are enzymes more broadly, reinforcing the compound's ability to interact with catalytic proteins involved in various biochemical pathways.

Smaller but notable percentages (6.7% each) correspond to cytochrome P450 enzymes, phosphatases, voltage-gated ion channels, membrane receptors, and kinases. The involvement of cytochrome P450 enzymes highlights potential interactions with metabolic detoxification systems, while phosphatase involvement suggests a role in regulating phosphorylation-dependent signaling. The presence of voltage-gated ion channels aligns closely with capsaicin's known action on neuronal pathways, particularly its activation of TRPV1 channels associated with nociception. Membrane receptors and kinase interactions further indicate that capsaicin may influence broader cell signaling networks, including immune responses, hormonal regulation, and cellular growth mechanisms.

Distribution of target classes reveals that capsaicin is a multi-target bioactive compound capable of interacting with a wide spectrum of biomolecular systems. This

diversity supports its potential therapeutic relevance not only in pain modulation but also in anti-inflammatory, metabolic, enzymatic, and neuromodulatory applications. The spread across multiple protein classes underscores its polypharmacological nature and highlights the importance of further experimental validation to better understand its complex mechanism of action.

Target	Common name	Uniprot ID	ChEMBL ID	Target Class
Cyclooxygenase-1	PTGS1	P23219	CHEMBL221	Oxidoreductase
Cytochrome P450 1A2	CYP1A2	P05177	CHEMBL3356	Cytochrome P450
Vanilloid receptor	TRPV1	Q8NER1	CHEMBL4794	Voltage-gated ion channel
Cannabinoid receptor 1	CNR1	P21554	CHEMBL218	Family A G protein-coupled receptor
Cannabinoid receptor 2	CNR2	P34972	CHEMBL253	Family A G protein-coupled receptor
Butyrylcholinesterase	BCHE	P06276	CHEMBL1914	Hydrolase
Acetylcholinesterase	ACHE	P22303	CHEMBL220	Hydrolase
Sigma opioid receptor	SIGMAR1	Q99720	CHEMBL287	Membrane receptor
Anandamide amidohydrolase	FAAH	O00519	CHEMBL2243	Enzyme
Protein-tyrosine phosphatase 1B	PTPN1	P18031	CHEMBL335	Phosphatase
Dopamine D2 receptor	DRD2	P14416	CHEMBL217	Family A G protein-coupled receptor
Serine/threonine-protein kinase RAF	RAF1	P04049	CHEMBL1906	Kinase

Figure 3. Probability Targets

The target prediction results indicate that capsaicin interacts with a diverse set of molecular targets across multiple protein classes, reflecting its broad mechanistic potential and polypharmacological nature. Among the highest-probability targets is Cyclooxygenase-1 (PTGS1), an oxidoreductase involved in prostaglandin synthesis, suggesting a strong mechanistic basis for capsaicin's known anti-inflammatory and analgesic actions. The interaction with Cytochrome P450 1A2 (CYP1A2) highlights a possible role in metabolic modulation and xenobiotic biotransformation, consistent with ADMET predictions that capsaicin may influence CYP-mediated pathways. Another key high-probability target is the Transient Receptor Potential Vanilloid 1 (TRPV1) channel, a voltage-gated ion channel that mediates nociception and thermosensation. This aligns with the well-established pharmacological action of capsaicin as a TRPV1 agonist responsible for its pungency and pain-modulating effects.

Capsaicin also shows moderate predicted affinity for Cannabinoid Receptors 1 and 2 (CNR1 and CNR2), both belonging to the Family A GPCR class. These interactions suggest potential neuromodulatory, anti-nociceptive, and immunoregulatory effects, given the involvement of cannabinoid receptors in pain signaling, appetite regulation, and inflammatory responses. Additionally, capsaicin demonstrates predicted interactions with Butyrylcholinesterase (BCHE) and Acetylcholinesterase (ACHE), both belonging to the hydrolase class. These interactions may indicate possible modulatory effects on the cholinergic system, which may contribute to neuroprotective or neuromodulatory actions.

The involvement of Sigma-1 receptor (SIGMAR1), a membrane-associated receptor, underscores capsaicin's potential influence on cellular stress responses, neuroprotection, and modulation of ion channels and neurotransmission. Capsaicin is also predicted to interact with Fatty Acid Amide Hydrolase (FAAH), a key enzyme regulating endocannabinoid metabolism, further supporting its interaction with the endocannabinoid system and potential impact on pain and inflammation. The predicted binding to Protein Tyrosine Phosphatase 1B (PTPN1) suggests a role in metabolic regulation and insulin signaling, indicating possible antidiabetic or metabolic-modulating effects.

The interaction with the Dopamine D2 Receptor (DRD2), another GPCR, points to potential neuromodulatory effects related to motor control, reward pathways, and mood regulation. Finally, capsaicin's predicted interaction with Serine/Threonine-Protein Kinase RAF1, a kinase involved in cell proliferation and MAPK signaling, suggests a possible influence on cellular growth pathways and may provide molecular insight into its reported anticancer properties.

Table 2. Top Predicted Targets

Target	Class	Probability	Biological Function
PTGS1	Oxidoreductase	High	Inflammation
TRPV1	Ion channel	High	Pain modulation
CYP1A2	Enzyme	High	Drug metabolism
CNR1	GPCR	Moderate	Neuromodulation
FAAH	Enzyme	Moderate	Endocannabinoid metabolism

The target prediction profile highlights capsaicin as a multi-target bioactive compound capable of modulating inflammation, pain perception, metabolic regulation, neurotransmission, cellular signaling, and enzymatic pathways. This broad interaction landscape supports the compound's extensive pharmacological potential and emphasizes the importance of further in-vitro and in-vivo validation to confirm these predicted molecular mechanisms.

The predicted targets identified in this study should be interpreted cautiously, as in silico predictions represent probabilistic estimations rather than experimentally confirmed biological interactions. Therefore, the predicted pharmacological effects require further validation using in vitro and in vivo experimental approaches. This study provides a computational overview of capsaicin pharmacology; however, further experimental validation is necessary to confirm these predicted biological interactions and therapeutic implications.

CONCLUSION

The present in silico study demonstrates that capsaicin exhibits multi-target interaction potential across diverse protein classes. However, these findings represent computational predictions and should be interpreted cautiously. The predicted interactions with PTGS1, TRPV1, and CYP1A2 suggest potential pharmacological relevance in inflammation, pain modulation, and metabolic pathways. ADMET profiling indicates favorable pharmacokinetic properties with certain toxicity considerations. Further experimental validation is required to confirm these predicted biological interactions.

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