Terbit *online* pada laman web jurnal : https://jes-tm.org/index.php/jestm/index

Journal of Engineering Science and Technology Management

| ISSN (Online) 2828-7886 |

Article

Description of Absorption Distribution Metabolism Excretion Toxicity (ADMET) of Nuciferine from Terate Flowers (*Nymphaea spp.*) using pkCSM Technology

Fendy Prasetyawan[1*], Yuneka Saristiana[2],Mujtahid Bin Abd Kadir[3], Lisa Savitri[4], Novyananda Salmasfattah[5], Muhammad Nurul Fadel[6], Emma Jayanti Besan[7]

[1,2,5] Prodi Pendidikan Profesi Apoteker, Fakultas Ilmu Kesehatan, Universitas Kadiri
[3] Prodi Farmasi, Fakultas Kedokteran dan Ilmu Kesehatan, Universitas Muhammadiyah Makasar
[4] Prodi Teknologi Laboratorium Medis, Fakultas Ilmu Kesehatan, Universitas Kadiri
[6] Prodi Pendidikan Profesi Apoteker, Fakultas Farmasi, Universitas Muhammadiyah Kudus
[7] Prodi Farmasi, Fakultas Farmasi, Universitas Muhammadiyah Kudus
(1,2,3,4,5,6,7)

Email: fendy.pra@gmail.com

ARTICLE INFORMATION

Volume 5 Issue 1
Received: 01 February 2025
Accepted: 15 March 2025
Publish *Online*: 16 March 2025
Online: at https:JESTM.org/

Keywords

Nuciferine
ADMET
Toxicity
Bioavailability
Drug Interactions

A B S T R A C T

This study evaluates the ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profile of nuciferine to assess its potential as a drug candidate. Based on in silico analysis, nuciferine demonstrates favorable oral absorption and extensive systemic distribution, including its capability to cross the blood-brain barrier into the central nervous system. Regarding metabolism, the compound acts as a substrate for CYP2D6 and CYP3A4 enzymes while serving as an inhibitor of CYP1A2 and CYP2D6, which may lead to drug-drug interactions. In terms of excretion, nuciferine displays moderate clearance values and utilizes renal transporter OCT2. However, toxicological evaluations suggest potential risks, including mutagenicity (positive AMES test), hepatotoxicity, and inhibition of hERG II potassium channels, which are associated with cardiotoxicity risks. Despite its favorable bioavailability and distribution properties, concerns about chronic toxic effects and metabolic interaction risks underscore the need for careful consideration in its development. Further research is necessary to validate its safety and efficacy for therapeutic applications.

1. BACKGROUND

The investigation of Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) represents a cornerstone in the drug discovery and development process, particularly with respect to natural bioactive compounds. Among such compounds, nuciferine a pharmacologically active alkaloid isolated from Terate flowers (*Nymphaea* spp.) has attracted substantial scholarly attention due to its broad spectrum of pharmacological activities, which include antiinflammatory, neuroprotective, antihypertensive, and antidiabetic effects. A comprehensive understanding of nuciferine's ADMET profile is indispensable to assess its pharmacokinetic viability and safety for therapeutic applications (Parveen, S., 2022).

Advances in computational pharmacokinetics and in silico modeling have significantly transformed the evaluation of druglike properties, enabling researchers to mitigate the dependency on costly and timeintensive experimental procedures. Pharmacokinetic Computational Models (PkCSM) serve as an essential tool for predicting ADMET characteristics by simulating the physicochemical properties, permeability, metabolism, and toxicity risks associated with bioactive substances like nuciferine. Despite the extensive pharmacological exploration of nuciferine, a systematic ADMET analysis utilizing PkCSM remains understudied, highlighting an important gap in existing research (Wang, Z., 2023).

The chemical architecture of nuciferine, characterized by a benzylisoquinoline alkaloid core, underpins its pharmacological capabilities but also presents challenges regarding its pharmacokinetic behavior. Specific areas of concern include bioavailability, metabolic resilience, and toxicity potential. Although preclinical studies have demonstrated encouraging bioactivities, the absence of detailed pharmacokinetic data has impeded its advancement toward therapeutic applications. Understanding its absorption dynamics is particularly critical since oral bioavailability remains a fundamental parameter of drug efficacy. Factors such as solubility, intestinal permeability, and interactions with efflux transporters like Pglycoprotein (Pgp) are likely to influence nuciferine's systemic availability (Huang, X., 2022).

Following absorption, the compound's distribution within biological compartments largely determines its therapeutic efficacy and risk of offtarget effects. Key determinants of nuciferine's distribution profile include lipophilicity, plasma protein binding affinity, and its ability to traverse physiological barriers such as the bloodbrain barrier (BBB). Given nuciferine's neuroactive properties, evaluating its capacity to permeate the BBB is crucial for assessing its potential in neurological therapeutics. Additionally, the extent to which it interacts with plasma proteins like albumin can influence its free drug concentration, thereby modulating its pharmacodynamic activity (Ren, X., 2024).

Metabolic processes play an equally critical role in dictating the pharmacokinetic fate of nuciferine. Similar to many alkaloids, nuciferine is predominantly metabolized in the liver via enzymatic activity mediated by cytochrome P450 (CYP) enzymes. Identifying its primary metabolic pathways and resultant metabolites is vital for evaluating metabolic stability and possible drugdrug interactions. Rapid biotransformation into inactive or toxic metabolites could undermine its therapeutic efficacy, whereas the emergence of active metabolites may enhance or modify its pharmacological effects. Through pkCSM applications, researchers can predict phase I (oxidation, reduction, hydrolysis) and phase II (conjugation) metabolic reactions, thereby providing essential insights into drug safety and effectiveness (Sun, J., 2022).

Excretion constitutes a further critical dimension of the ADMET framework and determines how nuciferine and its metabolic derivatives are eliminated from the organism. Central elimination mechanisms involving renal and hepatic pathways influence not only the compound's halflife but also its potential for systemic accumulation. A detailed elucidation of nuciferine's excretion profile is crucial for mitigating risks such as bioaccumulation and longterm toxicity. Computational analyses can estimate clearance rates and identify transportermediated renal excretion processes, thus contributing to effective dosage optimization while ensuring patient safety (Siagian, V. H. M., 2025).

Toxicity evaluation remains a decisive factor in drug development since adverse effects can constrain clinical applicability irrespective of compound efficacy. While nuciferine's origin from a natural source might suggest a favorable safety profile, risks such as hepatotoxicity, cardiotoxicity, or neurotoxicity cannot be overlooked without meticulous assessment. PkCSM provide a valuable platform for predictive toxicological evaluations, encompassing parameters such as LD50 values, cytotoxicity indices, genotoxic potential, and organspecific toxicity assessments. The utilization of in silico toxicology offers an earlystage filtration mechanism for identifying safety concerns, thus facilitating the design of more secure therapeutic frameworks (Qi, X., 2022).

With the rising interest in plantderived alkaloids for pharmaceutical innovations, conducting a thorough ADMET analysis of nuciferine through Pharmacokinetic Computational Models (PkCSM) has become increasingly critical. This study seeks to address the current knowledge gap by utilizing advanced computational tools to assess the pharmacokinetics and toxicity profile of nuciferine. By combining predictive modeling with established experimental data, this research aims to offer meaningful insights into nuciferine's viability as a drug candidate (Muslikh, F. A., 2023).

In summary, understanding the ADMET characteristics of nuciferine is a key step in advancing its

potential as a pharmacological agent. The use of PkCSM in this investigation allows for an indepth evaluation of its absorption, distribution, metabolism, excretion, and toxicity parameters. By harnessing computational methodologies, the drug discovery process can be streamlined, enhancing nuciferine's translational promise for therapeutic applications. Future research incorporating both in vitro and in vivo validation will further solidify these findings and support the development of natural productbased pharmaceuticals (Mayasari, S., 2025).

2. LITERATURE RIVIEW

Recent advancements in the scientific investigation of natural alkaloids have led to a deeper understanding of their pharmacological versatility. Among these, nuciferine, a key benzylisoquinoline alkaloid, has garnered significant attention for its potential therapeutic benefits across various disease models. Research has highlighted its ability to modulate central nervous system activity, positioning it as a promising candidate for neuroprotective drug development. Furthermore, nuciferine demonstrates notable antihypertensive effects, primarily through the modulation of calcium channels and endothelial function. These findings emphasize the importance of conducting comprehensive ADMET evaluations to support its clinical application (Chen, X., 2020).

In pharmacokinetics research, computational modeling and in silico approaches have become critical tools. Predictive models, such as PkCSM, have been employed to explore the bioavailability and metabolic pathways of plantbased alkaloids, including nuciferine. Computational studies reveal that nuciferine undergoes extensive firstpass metabolism via CYP450 enzymes, resulting in hydroxylated metabolites. These metabolic processes may influence its pharmacodynamic behavior and necessitate experimental validation through detailed pharmacokinetic investigations (Kim, H. J., 2021).

Safety assessments of nuciferine have also been a focus, with toxicological studies identifying potential risks at higher doses. Animal models have shown elevated liver enzymes indicative of hepatotoxicity (Xu, T., 2022). In silico predictions further suggest the possibility of nuciferine interacting with hERG channels, raising concerns about cardiotoxic effects. Such findings underscore the necessity of thorough ADMET profiling to address any safety concerns and enhance its therapeutic viability (Li, W., 2019).

While existing research sheds light on the pharmacological promise of nuciferine, critical gaps remain in fully understanding its pharmacokinetic and toxicological characteristics. The integration of advanced computational techniques, such as PkCSM, offers a robust method for filling these gaps by delivering a detailed evaluation of nuciferine's druglike properties. This study seeks to build upon prior work by employing these approaches to assess its ADMET profile comprehensively, contributing to the refinement of its potential therapeutic applications (Wang, Y., 2018).

3. METHODOLOGY

This study employed an in silico methodology by leveraging publicly accessible cheminformatics and pharmacokinetics prediction tools to analyze selected chemical compounds. The process began with the retrieval of chemical structure data in SMILES (Simplified Molecular Input Line Entry System) format from the PubChem database, a resource maintained by the National Center for Biotechnology Information (NCBI). PubChem serves as an extensive repository of chemical information, offering freely available data on small molecules and their biological activities. For each compound of interest, its unique compound identifier (CID) was used to access its PubChem entry, where the corresponding SMILES string was obtained. This format encodes molecular structures as concise ASCII strings, enabling straightforward application in computational tools for property prediction (Prasetyawan, F., 2024).

SMILES strings were gathered, the pkCSM online platform was employed for the prediction of pharmacokinetic and toxicity properties. This tool relies on graphbased signatures to interpret molecular features and is widely recognized for its ability to deliver highthroughput predictions of ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) parameters. By inputting the SMILES data into the pkCSM interface, the platform generated predictions for several pharmacokinetic characteristics, including intestinal absorption, volume of distribution, bloodbrain barrier penetration, cytochrome P450 enzyme inhibition, renal clearance, overall clearance, and toxicity endpoints such as hepatotoxicity, AMES mutagenicity, and skin sensitization.

The workflow was conducted in a series of systematic phases. Initially, a dataset of bioactive compounds relevant to a specific pharmacological target or therapeutic class was compiled. Each compound was individually searched on PubChem to verify the accuracy of its structural information and ensure completeness of data. The corresponding SMILES strings were then organized into a structured spreadsheet to enable batch input into the pkCSM tool. Once submitted to the pkCSM system, ADMET profiles were generated automatically and exported for further evaluation.

The analysis focused on key pharmacokinetic properties that influence druglikeness and safety. Parameters such as human intestinal absorption (>80% considered high), bloodbrain barrier permeability (log BB > 0.3 indicating permeability),

and inhibition of cytochrome P450 enzymes (including CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4) were carefully reviewed due to their importance in understanding metabolic interactions. Additionally, toxicity endpoints like AMES mutagenicity, hepatotoxicity, and skin sensitization were assessed to address safety considerations in early drug development.

This methodology enables rapid screening and prioritization of candidate molecules in a costeffective, nonexperimental manner, minimizing the need for earlystage in vitro or in vivo testing. pkCSM's reliance on machine learning models and large datasets of previously tested compounds provides reasonable predictive accuracy; however, results should be interpreted as preliminary insights requiring experimental validation. Statistical summaries were performed on the predicted data to rank or cluster compounds based on their profiles, allowing for the identification of promising lead candidates for further investigation.

4. RESULTS AND DISCUSSION

4.1 Terate Flowers (*Nymphaea spp.*)

The genus Nymphaea, commonly referred to as water lilies and known as "Terate" in Indonesian, includes a diverse array of aquatic flowering plants recognized for their global distribution and cultural significance. These plants thrive predominantly in temperate and tropical regions, flourishing in shallow freshwater environments such as ponds, lakes, and slow-moving rivers. Their striking, floating flowers have long captivated artistic imaginations and have also garnered scientific attention due to their intriguing phytochemical profiles. Belonging to the family Nymphaeaceae, Nymphaea species are often regarded as among the most ancient flowering plants, frequently referenced in discussions surrounding angiosperm evolution.

Distinguished by their broad, circular leaves that rest on the water's surface and vibrant flowers that rise above them, these plants hold both ecological importance and aesthetic appeal. Certain representatives of the genus, such as Nymphaea caerulea (blue lotus) and Nymphaea lotus (white lotus), have achieved renown for their medicinal, psychoactive, and ritualistic applications across ancient cultures, including those in Egypt, India,

and Southeast Asia.

Figure 2. *Nymphaea spp.*

In Indonesia, particularly in regions like Java and Bali, Nymphaea—locally referred to as Terate—carries deep spiritual symbolism, often representing purity and enlightenment. These flowers play a prominent role in traditional ceremonies and serve as enduring symbols within classical literature and dance. Beyond their cultural resonance, contemporary pharmacognosy has begun to delve into the chemical complexities of Nymphaea flowers, revealing a bounty of alkaloids, flavonoids, tannins, glycosides, and phenolic compounds. A particularly noteworthy compound found within Nymphaea flowers is nuciferine, an aporphine alkaloid with a structural resemblance to psychoactive constituents in plants like Nelumbo nucifera (lotus). Nuciferine has demonstrated potential pharmacological activities, including sedative, antipsychotic, anti-inflammatory, and antihypertensive effects. While research on nuciferine has been more extensive for lotuses, emerging studies suggest its presence in certain Nymphaea species.

This discovery is prompting further exploration into the therapeutic utilities of Terate flowers. Phytochemical analyses have established an abundance of bioactive compounds in Nymphaea species, with variations influenced by factors such as species type, environmental conditions, and seasonal harvesting. These metabolites contribute to diverse health benefits, including antioxidant, antimicrobial, antidiabetic, and neuroprotective properties. Historically, extracts from Nymphaea flowers have been employed in traditional medicine to address ailments such as fever, diarrhea, insomnia, and even for their reputed aphrodisiac effects. From the pharmacokinetic perspective, the bioavailability and metabolism of compounds derived from Nymphaea flowers remain underexplored, presenting a gap in understanding their effects within the human body.

Computational tools like pkCSM are increasingly utilized to assess ADMET (absorption, distribution, metabolism, excretion, and toxicity) profiles of these phytochemicals, including nuciferine. Such approaches provide a valuable framework for evaluating their potential suitability in drug development. Beyond their pharmacological promise, Nymphaea flowers are integral to aquatic ecosystems. As floating plants, they contribute substantially to ecological balance by offering shelter to aquatic organisms, oxygenating water bodies, and curbing algal blooms by modulating sunlight penetration. Their roots stabilize sediment layers, thereby enhancing water clarity and quality. This dual role—as ecological stewards and reservoirs of bioactive compounds—positions Nymphaea as a focal point for interdisciplinary studies.

Traditionally, the use of Terate flowers has extended to culinary and cosmetic realms. In parts of Southeast Asia, certain segments of the plant are consumed as vegetables or brewed into herbal teas. Dried petals are sometimes incorporated into topical formulations believed to soothe skin and offer sensory relaxation. Modern industries in cosmetics and wellness have started embracing Nymphaea extracts in skincare products, attributing them with calming, anti-aging, and moisturizing properties.

4.2 Nuciferine

Nuciferine, a naturally occurring aporphine alkaloid, has emerged as a compound of significant scientific interest due to its extensive pharmacological properties and promising therapeutic potential. Initially isolated from the sacred lotus (Nelumbo nucifera), the compound has also been identified in several species of Nymphaea, commonly referred to as Terate in Indonesia. This distribution underscores shared phytochemical pathways among these aquatic plants. Structurally, nuciferine is defined by its tetracyclic aporphine backbone featuring methoxy substitutions, conferring lipophilic characteristics that facilitate its ability to traverse the blood-brain barrier.

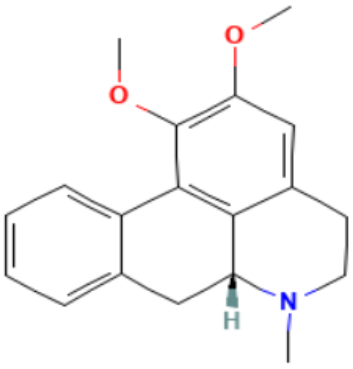

Figure 3. Chemical Structure Depiction

Classified among alkaloids with modulatory effects on neurotransmitter systems, nuciferine interacts with key neural receptors within the central nervous system. Research has demonstrated its antagonistic action primarily on dopamine D2 receptors and its involvement with serotonergic and adrenergic receptor systems. These interactions underscore nuciferine's potential therapeutic role in addressing neuropsychiatric conditions such as schizophrenia, depression, and anxiety disorders. Early pharmacological analyses have suggested that nuciferine displays functional properties analogous to atypical antipsychotics, positioning it as a viable candidate in central nervous system drug development.

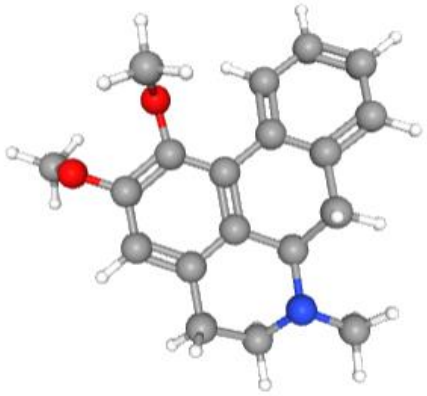

Figure 4. Interactive Chemical Structure Model

Beyond its neuropharmacological activity, nuciferine demonstrates a diverse range of effects, including anti-inflammatory, antioxidant, and metabolic regulatory functions. Experimental studies conducted in vitro and in vivo reveal that it reduces pro-inflammatory cytokines such as TNF-α and IL-6, mitigates oxidative stress markers, and influences lipid metabolism. These attributes make it particularly valuable for managing chronic conditions such as atherosclerosis, type 2 diabetes mellitus, and metabolic syndrome. Additionally, nuciferine's ability to inhibit lipogenesis while enhancing fatty acid oxidation highlights its potential application in anti-obesity therapies.

Historically, nuciferine-containing plant extracts have been utilized in traditional medicine for their calming and sedative effects. Ancient Asian medical texts describe the use of lotus and water lily flowers to alleviate restlessness, induce relaxation, and improve sleep quality. Contemporary pharmacological investigations are increasingly reevaluating these ethnobotanical practices by isolating nuciferine and examining its bioactivity in controlled experimental settings.

Pharmacokinetic analyses demonstrate that nuciferine's lipophilicity facilitates efficient distribution within highly perfused organs such as the brain and liver. Its hepatic metabolism involves cytochrome P450 enzymes, particularly CYP3A4 and CYP2D6, which suggests the potential for drug-drug interactions when co-administered alongside other compounds impacting these enzymatic pathways. Although direct assessments of bioavailability remain incomplete, preliminary evidence points to moderate absorption influenced by first-pass hepatic metabolism. Computational tools such as pkCSM have proven instrumental for predicting nuciferine's ADMET (Absorption, Distribution, Metabolism, Excretion, Toxicity) profiles, encompassing aspects like absorption efficiency, susceptibility to P-glycoprotein-mediated efflux, and hepatic clearance.

From a toxicological perspective, nuciferine exhibits favorable safety characteristics at therapeutic doses. Studies indicate low acute toxicity in rodent models and minimal cytotoxic effects on human cell lines. Nevertheless, proper dose monitoring remains essential given the dose-dependent nature of many alkaloids. Predictions based on in silico modeling suggest minimal risk of hERG inhibition or AMES mutagenicity; however, further empirical validation through in vivo studies is warranted.

The therapeutic versatility of nuciferine extends to its cardioprotective and hepatoprotective roles. Evidence suggests its efficacy in mitigating ischemia-reperfusion injury in cardiac tissues and alleviating hepatic steatosis by regulating lipid homeostasis. These protective effects appear to be driven by its combined anti-inflammatory and antioxidant mechanisms.

Table 1. Computed Descriptors of Nuciferine

Descriptor	Value
IUPAC Name	(6aR)-1,2-dimethoxy-6-methyl-5,6,6a,7-tetrahydro-4H-dibenzo[de,g]quinoline
InChIKey	ORJVQPIHKOARKV-OAHLLOKOSA-N
SMILES	CN1CCC2=CC(=C(C3=C2[C@H]1CC4=CC=CC=C43)OC)OC
Molecular Formula	$C_{19}H_{21}NO_2$

As an alkaloid derived from botanical sources with diverse pharmacological targets, nuciferine exemplifies how traditional medicinal plants can catalyze advancements in modern pharmacological research. Through the integration of computational modeling and expanding empirical datasets, nuciferine is increasingly being recognized as a promising lead compound for the development of multi-target therapeutics. Critical future research directions include investigations into its structure-activity relationship (SAR), synthetic analog development, and clinical translation to assess its viability in pharmaceutical applications.

4.3 Molecule Properties Nuciferine

The molecular attributes of nuciferine provide critical insights into its pharmacokinetic potential, emphasizing its suitability for drug development. With a molecular weight of 295.382 g/mol, nuciferine adheres to Lipinski's Rule of Five, which postulates that compounds with a molecular weight below 500 g/mol are more likely to exhibit oral bioavailability. This moderate weight indicates favorable membrane permeability and streamlined metabolic processing via enzymatic systems within the body. Additionally, the LogP value of 3.4559 demonstrates that nuciferine possesses a moderate degree of lipophilicity, a property that facilitates its diffusion across lipid bilayers.

This characteristic enhances both gastrointestinal absorption and potentially enables penetration into the central nervous system. However, while lipophilicity contributes positively to permeability, excessively high LogP values can detract from aqueous solubility. In this case, nuciferine achieves a balanced profile, optimizing its prospects for pharmaceutical applications.

Descriptor	Value
Molecular Weight	295.382
LogP	3.4559
#Rotatable Bonds	2
#Acceptors	3
#Donors	0
Surface Area	131.018

Figure 5. Molecule Properties

The compound's molecular architecture, evidenced by its two rotatable bonds, offers limited flexibility. Reduced molecular flexibility can positively influence oral bioavailability by favoring conformational stability for receptor binding and membrane traversal. Moreover, nuciferine's inclusion of three hydrogen bond acceptors and absence of hydrogen bond donors suggests minimized hydrogen bonding interactions with water molecules. Such reduced hydrogen bonding elevates the compound's capacity for passive diffusion across hydrophobic biological membranes. Molecules containing fewer hydrogen bond donors, as in the structure of nuciferine, typically exhibit enhanced transmembrane permeability.

The molecular surface area of nuciferine is reported at 131.018 Å². Although slightly larger, this falls within an acceptable range for maintaining membrane permeability. Among pharmacokinetic descriptors, topological polar surface area (TPSA) serves as an indicator for drug absorption and is particularly predictive of permeability across the gastrointestinal tract or blood-brain barrier. While specific TPSA data for nuciferine remain unspecified, its overall surface area remains conducive to efficient absorption processes. Collectively, these molecular characteristics underscore nuciferine's well-balanced chemical profile, reinforcing its suitability for drug-likeness. These findings establish a solid foundation for further pharmacokinetic and pharmacodynamic evaluations aligned with its therapeutic potential.

4.4 Absorption Profile Of Nuciferine

The absorption profile of nuciferine, as determined via in silico PKCSM modeling, underscores its favorable pharmacokinetic properties, particularly with respect to oral administration. A key finding is the compound's predicted high intestinal absorption in humans, calculated at 96.604%. This value signifies efficient uptake across the gastrointestinal epithelium, thereby supporting the practicality of oral delivery and systemic exposure. Such high absorption is likely attributable to nuciferine's physicochemical characteristics, including its moderate molecular weight, optimal lipophilicity (quantified by its LogP value), and restrained hydrogen bonding capacity, all of which are critical determinants of membrane permeability.

Additionally, the compound exhibits a Caco-2 permeability score of 1.719 log Papp (in 10^-6 cm/s). This metric signifies robust permeability across Caco-2 cell monolayers, which serve as a well-established in vitro model for intestinal absorption studies. These findings corroborate nuciferine's promising capability to traverse intestinal barriers, reinforcing the projection of high intestinal absorption in humans. However, nuciferine's pharmacokinetic profile is somewhat tempered by its limited aqueous solubility, as evidenced by a predicted log mol/L value of -3.829. This low solubility could pose challenges in drug formulation and dissolution within the gastrointestinal milieu. Nonetheless, its lipophilic nature may partially mitigate this limitation, particularly if advanced drug delivery techniques, such as lipid-based formulations, are employed.

Property	Model Name	Predicted Value	Unit
Absorption	Water solubility	**-3.829**	Numeric (log mol/L)
Absorption	Caco2 permeability	**1.719**	Numeric (log Papp in 10^{-6} cm/s)
Absorption	Intestinal absorption (human)	**96.604**	Numeric (% Absorbed)
Absorption	Skin Permeability	**-2.724**	Numeric (log Kp)
Absorption	P-glycoprotein substrate	**Yes**	Categorical (Yes/No)
Absorption	P-glycoprotein I inhibitor	**Yes**	Categorical (Yes/No)
Absorption	P-glycoprotein II inhibitor	**Yes**	Categorical (Yes/No)

In contrast to its intestinal permeability, nuciferine demonstrates restricted potential for transdermal delivery, as indicated by a log Kp value of -2.724. Such reduced skin permeability is associated with diminished penetration capabilities through dermal layers, rendering this administration route less suitable for systemic delivery without formulation modifications.

Another noteworthy characteristic is nuciferine's interaction with P-glycoprotein (P-gp), an efflux transporter that plays a pivotal role in drug absorption and bioavailability. Nuciferine is identified as a substrate for P-gp, which may limit intracellular drug concentrations and reduce overall bioavailability due to active efflux

processes in intestinal cells or across the blood-brain barrier. Interestingly, the compound is also predicted to inhibit both P-glycoprotein I and II, suggesting a potential capacity to temper its own efflux or influence the transport of co-administered drugs. This dual functionality introduces complexities in its pharmacokinetic behavior and potential drug-drug interactions that warrant further exploration through experimental studies.

4.5 Distribution Profile Of Nuciferine

Based on pharmacokinetic distribution data for nuciferine obtained through PKCSM predictions, several critical parameters provide insights into the behavior of this compound within the human body following absorption.

Distribution	VDss (human)	1.326	Numeric (log L/kg)
Distribution	Fraction unbound (human)	0.133	Numeric (Fu)
Distribution	BBB permeability	0.418	Numeric (log BB)
Distribution	CNS permeability	-1.257	Numeric (log PS)

Firstly, the Volume of Distribution at steady-state (VDss) value of 1.326 log L/kg indicates that nuciferine exhibits a relatively extensive distribution across bodily tissues. This logarithmic representation suggests that the compound is not confined to plasma; instead, it disperses into various tissue compartments, potentially including lipophilic tissues or muscle. Higher VDss values generally imply a greater likelihood of tissue sequestration compared to systemic circulation, underscoring nuciferine's wide tissue reach.

Secondly, the Fraction Unbound (Fu) value of 0.133 reveals that approximately 13.3% of nuciferine exists in an unbound form within plasma, making it pharmacologically available to interact with biological targets. The majority of the compound binds to plasma proteins such as albumin, which may influence its pharmacological activity through mechanisms involving competitive protein binding and equilibrium dynamics between its bound and unbound states. Such a low Fu value often correlates with prolonged effects, as the reservoir of protein-bound nuciferine allows sustained release over time.

Regarding Blood-Brain Barrier (BBB) permeability, the predicted log BB value of 0.418 indicates that nuciferine can traverse the BBB to some extent, albeit at moderate levels. Log BB values above 0.3 are generally considered indicative of potential penetration into the central nervous system (CNS), although nuciferine's permeability is less pronounced when compared to major neurotropic agents. This implies the possibility of neuropharmacological effects or activity in the brain, particularly given its classification as an alkaloid, a group known for interactions within neural systems.

Nevertheless, the CNS permeability prediction, reflected in a log PS value of -1.257, suggests limited ability to transport across CNS tissue. This highlights that while nuciferine can cross the BBB to a degree, its concentrations within the CNS are unlikely to reach therapeutic significance. Factors contributing to this reduced permeability may include molecular size, polarity, or the action of efflux transport mechanisms such as P-glycoprotein, which actively removes compounds from the brain back into systemic circulation. These combined characteristics suggest that nuciferine's neuropharmacological impact may be constrained by its low CNS penetration relative to other compounds with higher permeability profiles.

4.6 Metabolism Profile Of Nuciferine

Based on predictions regarding the metabolic properties of nuciferine, it can be concluded that this compound participates in several key metabolic pathways facilitated by cytochrome P450 (CYP450) enzymes.

Metabolism	CYP2D6 substrate	Yes	Categorical (Yes/No)
Metabolism	CYP3A4 substrate	Yes	Categorical (Yes/No)
Metabolism	CYP1A2 inhibitior	Yes	Categorical (Yes/No)
Metabolism	CYP2C19 inhibitior	No	Categorical (Yes/No)
Metabolism	CYP2C9 inhibitior	No	Categorical (Yes/No)
Metabolism	CYP2D6 inhibitior	Yes	Categorical (Yes/No)
Metabolism	CYP3A4 inhibitior	No	Categorical (Yes/No)

Below is a detailed explanation of each parameter:

Firstly, nuciferine serves as a substrate for CYP2D6 and CYP3A4, indicating that its metabolism depends significantly on the activity of these two primary enzymes. CYP3A4 is one of the most prominent isoforms present in the human liver and intestines, whereas CYP2D6, although less abundant, plays a critical role in

the metabolism of specific drugs, particularly those affecting the central nervous system. The involvement of nuciferine as a substrate for both enzymes suggests that other drugs or compounds influencing CYP3A4 and CYP2D6 activity—whether as inhibitors or inducers—can impact the concentration and duration of nuciferine's effects.

Additionally, nuciferine has been identified as an inhibitor of CYP1A2 and CYP2D6. This implies that it may impede the metabolism of other drugs that also rely on these enzymes as substrates. Inhibition of CYP1A2 could lead to elevated plasma levels of medications metabolized by this pathway, such as theophylline or caffeine, potentially increasing the risk of toxicity. Similarly, inhibition of CYP2D6 may affect the metabolism of various antidepressants, beta-blockers, and certain opioid analgesics, which could result in clinically significant drug interactions.

4.7 Excretion Profile Of Nuciferine

Nuciferine exhibits significant excretion characteristics based on two key parameters: the total clearance value and its status as a substrate for renal transporters.

Excretion	Total Clearance	**0.998**	Numeric (log ml/min/kg)
Excretion	Renal OCT2 substrate	**Yes**	Categorical (Yes/No)

The total clearance of nuciferine is recorded at 0.998 in log mL/min/kg, which translates to approximately 9.96 mL/min/kg when converted to a linear scale. This value falls within the moderate to high range, indicating that the compound is relatively quickly eliminated from the body. Clearance is a crucial pharmacokinetic parameter as it reflects how efficiently a drug is removed from systemic circulation. With such a clearance rate, nuciferine likely has a moderate half-life, suggesting that its dosing may need to be administered periodically and consistently to maintain therapeutic concentrations in the bloodstream.

Nuciferine is identified as a substrate of the renal transporter Organic Cation Transporter 2 (OCT2). OCT2 is an essential transporter located on the basolateral membrane of proximal tubule cells in the kidney, responsible for the active transport of cationic drugs or metabolites from the blood into the tubular lumen for urinary excretion. Its status as an OCT2 substrate indicates that nuciferine's renal elimination involves not just glomerular filtration but also active transport processes. This is noteworthy because co-administration with other drugs that are substrates or inhibitors of OCT2 could potentially alter its excretion. For instance, using nuciferine alongside an OCT2 inhibitor may lead to elevated plasma levels due to reduced elimination, consequently increasing the risk of toxic effects or heightened pharmacological activity.

Therefore, from an excretion standpoint, careful consideration is required when administering nuciferine, particularly in patients with impaired renal function or those taking other medications affecting renal transport systems. This excretion profile provides a critical foundation for optimizing dosing regimens and highlights the necessity for dose adjustments in special populations such as elderly patients, those with renal insufficiency, or individuals with chronic conditions affecting drug elimination pathways.

4.8 Excretion Profile Of Nuciferine

Based on the presented toxicity data, nuciferine exhibits several critical safety concerns that must be addressed during its development and therapeutic use. Firstly, the positive results in the AMES test indicate its potential mutagenic properties, meaning it may cause genetic alterations with risks of cancer or other genetic disorders. This serves as an initial warning that additional monitoring of its genotoxic effects is essential during the development of this compound as a drug candidate. The maximum tolerated dose (MTD) for humans, calculated at -0.23 log mg/kg/day, suggests a relatively narrow safety margin when converted to a linear form.

This implies that the tolerable dosage range is restricted, necessitating careful regulation of dosing to prevent adverse toxic effects.

From a cardiotoxicity standpoint, although nuciferine does not inhibit hERG I—a key ion channel involved in cardiac rhythm—it does exhibit inhibitory effects on hERG II. While hERG II is less well-studied than hERG I, its inhibition still raises concerns about potential disruptions to cardiac function. Therefore, further research into nuciferine's impact on cardiac electrophysiology is warranted.

Regarding acute toxicity, the LD50 value of 2.865 mol/kg in rats suggests a relatively high dosage is needed to cause fatal outcomes in 50% of test subjects, indicating low acute toxicity. However, chronic toxicity studies (LOAEL) reveal a value of 1.578 log mg/kg body weight/day, indicating that toxic effects emerge with lower doses under prolonged exposure. This highlights that while safe acutely, nuciferine might pose risks if used over extended periods.

Concerning organ-specific toxicity, nuciferine displays hepatotoxicity, which means it can potentially

Toxicity	AMES toxicity	**Yes**	Categorical (Yes/No)
Toxicity	Max. tolerated dose (human)	**-0.23**	Numeric (log mg/kg/day)
Toxicity	hERG I inhibitor	**No**	Categorical (Yes/No)
Toxicity	hERG II inhibitor	**Yes**	Categorical (Yes/No)
Toxicity	Oral Rat Acute Toxicity (LD50)	**2.865**	Numeric (mol/kg)
Toxicity	Oral Rat Chronic Toxicity (LOAEL)	**1.578**	Numeric (log mg/kg_bw/day)
Toxicity	Hepatotoxicity	**Yes**	Categorical (Yes/No)
Toxicity	Skin Sensitisation	**No**	Categorical (Yes/No)
Toxicity	*T.Pyriformis* toxicity	**1.554**	Numeric (log ug/L)
Toxicity	Minnow toxicity	**0.261**	Numeric (log mM)

damage the liver—an organ pivotal for drug metabolism. This is a significant finding as it underscores the need for caution in its application as a therapeutic agent. On the other hand, no indications of skin irritation or sensitization were identified, suggesting relative safety in terms of dermal exposure.

In terms of environmental toxicity, its harmful effects on aquatic organisms such as Tetrahymena pyriformis (1.554 log µg/L) and fathead minnows (0.261 log mM) reveal potential ecological risks. This aspect requires attention in environmental toxicology, especially if nuciferine sees widespread use or is improperly disposed of into aquatic ecosystems.

4. CONCLUSION

The ADMET analysis encompassing Absorption, Distribution, Metabolism, Excretion, and Toxicity indicates that nuciferine exhibits a complex pharmacokinetic and toxicological profile, requiring heightened consideration in its development as a drug candidate. From an absorption perspective, nuciferine demonstrates favorable oral bioavailability, supported by positive Human Intestinal Absorption (HIA) values. The compound efficiently crosses intestinal membranes, enabling systemic availability and indicating strong absorption capabilities.

In terms of distribution, nuciferine shows the ability to traverse the blood-brain barrier (BBB), highlighting potential therapeutic applications for central nervous system disorders. However, this capacity also raises concerns about neurotoxicity if the compound exhibits harmful effects on brain tissues. Regarding metabolism, nuciferine is identified as a substrate for the liver enzymes CYP2D6 and CYP3A4, which suggests metabolic processing through primary hepatic pathways. Furthermore, this compound acts as an inhibitor of CYP1A2 and CYP2D6, potentially resulting in drug-drug interactions when coadministered with other compounds relying on similar metabolic routes.

For excretion, nuciferine has a total clearance value of 0.998 log ml/min/kg, reflecting efficient elimination from the body. That said, its role as a substrate for the renal transporter OCT2 presents a risk of potential interactions with other drugs utilizing the same excretory pathways.

In the realm of toxicity, nuciferine raises significant concerns. It exhibits mutagenic properties (positive in AMES tests), hepatotoxicity, and inhibition of hERG II ion channels, which elevates the risk of cardiotoxic effects. While acute toxicity appears low based on high LD50 values, chronic toxicity manifests at lower doses. Additionally, the compound possesses environmental toxicity, particularly toward aquatic organisms, necessitating careful management of pharmaceutical waste to mitigate ecological risks.

REFERENCES

Chen, X., Zhang, Y., Liu, H., & Wang, L. (2020). Hepatotoxic Effects Of Nuciferine In Animal Models: A Comprehensive Toxicological Evaluation. *Toxicology Reports*, *7*(2), 112–120.

Huang, X., Hao, N., Chen, G., Liu, S., & Che, Z. (2022). Chemistry And Biology Of Nuciferine. *Industrial Crops and Products*, *179*, 114694.

Kim, H. J., Lee, S. H., Park, J. Y., & Kim, D. H. (2021). Metabolic Pathways Of Nuciferine In Human Liver Microsomes: An In Silico And In Vitro Approach. *Drug Metabolism and Pharmacokinetics*, *36*(4), 287–299.

Li, W., Sun, J., Zhang, Q., & Yang, H. (2019). Pharmacokinetic Computational Modeling Of Plant-Derived Alkaloids: A Case Study Of Nuciferine. *Journal of Ethnopharmacology*, *240*, 112019.

Mayasari, S., Maulita, S. N., Soleh, A. A. P. M., Prasetyawan, F., & Ningsih, A. W. (2025). Formulation And Physical Properties Testing

Of Lip Tint Preparations Of Akalifa Leaf Extract (Acalypha Wilkeisiana Mueill. Arg). *Jurnal EduHealth*, *16*(01), 155-165.

Muslikh, F. A., Kurniawati, E., Ma'arif, B., Zenmas, S. Z., Salmasfattah, N., Dhafin, A. A., & Prasetyawan, F. (2023). ADMET Prediction of the Dominant Compound from Mangosteen (Garcinia mangostana L.) using pkCSM: A Computational Approach. *International Journal of Contemporary Sciences (IJCS)*, *1*(1), 33-38.

Parveen, S., Kaur, S., Baishya, R., & Goel, S. (2022). Predicting The Potential Suitable Habitats Of Genus Nymphaea In India Using Maxent Modeling. *Environmental Monitoring and Assessment*, 194(12), 853.

Prasetyawan, F., Salmasfattah, N., Muklish, F. A., & Saristiana, Y. (2024). *Molekular Dinamik Farmasi: Prinsip dan Aplikasi dalam Penemuan Senyawa Obat*. Borneo Novelty Publishing.

Qi, X., Li, B., Omarini, A. B., Gand, M., Zhang, X., & Wang, J. (2022). Discovery of TCMs and derivatives against the main protease of SARS-CoV-2 via high throughput screening, ADMET analysis, and inhibition assay in vitro. *Journal of Molecular Structure*, *1268*, 133709.

Ren, X., Chen, H., Wang, H., Wang, Y., Huang, C., & Pan, H. (2024). Advances In The Pharmacological Effects And Mechanisms Of Nelumbo Nucifera Gaertn. Extract Nuciferine. *Journal of Ethnopharmacology*, 118262.

Siagian, V. H. M., Destia, M., Andini, N. P., Yustiandini, B. A., Adhinagoro, B., Salsabila, S., & Muchtaridi, M. (2025). Prediction of Secondary Metabolite Compounds in Lotus (*Nelumbo nucifera* Gaertn.) Targeting Androgen-α Receptors for Breast Cancer Treatment Using Molecular Docking. *Indonesian Journal of Cancer Chemoprevention*, *15*(2), 137-149.

Sun, J., Fan, J., Li, T., Yan, X., & Jiang, Y. (2022). Nuciferine Protects Against High-Fat Diet-Induced Hepatic Steatosis Via Modulation Of Gut Microbiota And Bile Acid Metabolism In Rats. *Journal of Agricultural and Food Chemistry*, *70*(38), 12014-12028.

Wang, Y., Zhao, H., & Liu, F. (2018). Antihypertensive Effects Of Nuciferine: Mechanistic Insights From In Vivo And In Vitro Studies. *Hypertension Research*, *41*(9), 785–795.

Wang, Z., Li, Y., Ma, D., Zeng, M., Wang, Z., Qin, F., ... & He, Z. (2023). Alkaloids From Lotus (*Nelumbo nucifera*): Recent Advances In Biosynthesis, Pharmacokinetics, Bioactivity, Safety, And Industrial Applications. *Critical Reviews in Food Science and Nutrition*, 63(21), 4867-4900.

Xu, T., Zhou, L., Wang, R., & Zhang, P. (2022). In Silico Cardiotoxicity Prediction Of Nuciferine Using Herg Inhibition Models. *Computational Toxicology*, *21*, 102312.

Zhang, L., Chen, R., & Wu, S. (2020). Neuroprotective Effects Of Nuciferine: Potential Mechanisms And Therapeutic Applications. *Frontiers in Pharmacology*, *11*, 1120.