Drug Design, Development and Therapy Dovepress

Open Access Full Text Article REVIEW

Updating the Pharmacological Effects of α-Mangostin Compound and Unraveling Its Mechanism of Action: A Computational Study Review

Cecep Suhandi[1,*], Gofarana Wilar[2,*], Angga Cipta Narsa[3,*], Ahmed Fouad Abdelwahab Mohammed[4,*], Ali El-Rayyes[5,*], Muchtaridi Muchtaridi[6,*], Shaharum Shamsuddin[7,*], Sabreena Safuan[8,*], Nasrul Wathoni[1,*]

[1]Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Universitas Padjadjaran, Jatinangor, 45363, Indonesia; [2]Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Jatinangor, 45363, Indonesia; [3]Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Mulawarman University, Samarinda, 71157, Indonesia; [4]Department of Pharmaceutics, Faculty of Pharmacy, Minia University, Minia, 61519, Egypt; [5]Department of Chemistry, College of Science, Northern Border University, Arar, Saudi Arabia; [6]Department of Analytical Pharmacy and Medicinal Chemistry, Faculty of Pharmacy, Universitas Padjadjaran, Jatinangor, 45363, Indonesia; [7]School of Health Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, 16150, Malaysia; [8]Department of Biomedicine, School of Health Sciences, Universiti Sains Malaysia, Kubang Kerian, Kelantan, 16150, Malaysia

*These authors contributed equally to this work

Correspondence: Nasrul Wathoni, Department of Pharmaceutics and Pharmaceutical Technology, Faculty of Pharmacy, Universitas Padjadjaran, Jatinangor, 45363, Indonesia, Tel +62-22-842-888-888, Email nasrul@unpad.ac.id

Abstract: α-Mangostin, initially identified in 1855, is a xanthone derivative compound predominantly located in the pericarp of the mangosteen fruit (*Garcinia mangostana* L). This compound is known for its beneficial properties as an antioxidant and anti-inflammatory agent, still holding promise for potential benefits in other related pathologies. In the investigative process, computational studies have proven highly valuable in providing evidence and initial screening before progressing to preclinical and clinical studies. This review aims to present the pharmacological findings and mechanisms of action of α-mangostin based on computational studies. The compilation of this review is founded on the analysis of relevant articles obtained from PubMed, Scopus, and ScienceDirect databases. The study commences with an elucidation of the physicochemical characteristics, drug-likeness, pharmacokinetics, and toxicity profile of α-mangostin, which demonstrates that α-mangostin complies with the Lipinski's Rule of Five, exhibits favorable profiles of absorption, distribution, metabolism, and excretion, and presents low toxicity. Subsequent investigations have revealed that computational studies employing various software tools including ArgusLab, AutoDock, AutoDock Vina, Glide, HEX, and MOE, have been pivotal to comprehend the pharmacology of α-mangostin. Beyond its well established roles as an antioxidant and anti-inflammatory agent, α-mangostin is now recognized for its pharmacological effects in Alzheimer's disease, diabetes, cancer, chronic kidney disease, chronic periodontitis, infectious diseases, and rheumatoid arthritis. Moreover, α-mangostin is projected to have applications in pain management and as a potent mosquito larvicide. All of these findings are based on the attainment of adequate binding affinity to specific target receptors associated with each respective pathological condition. Consequently, it is anticipated that these findings will serve as a foundation for future scientific endeavours, encompassing both in vitro and in vivo studies, as well as clinical investigations, to better understand the pharmacological effects of α-mangostin.

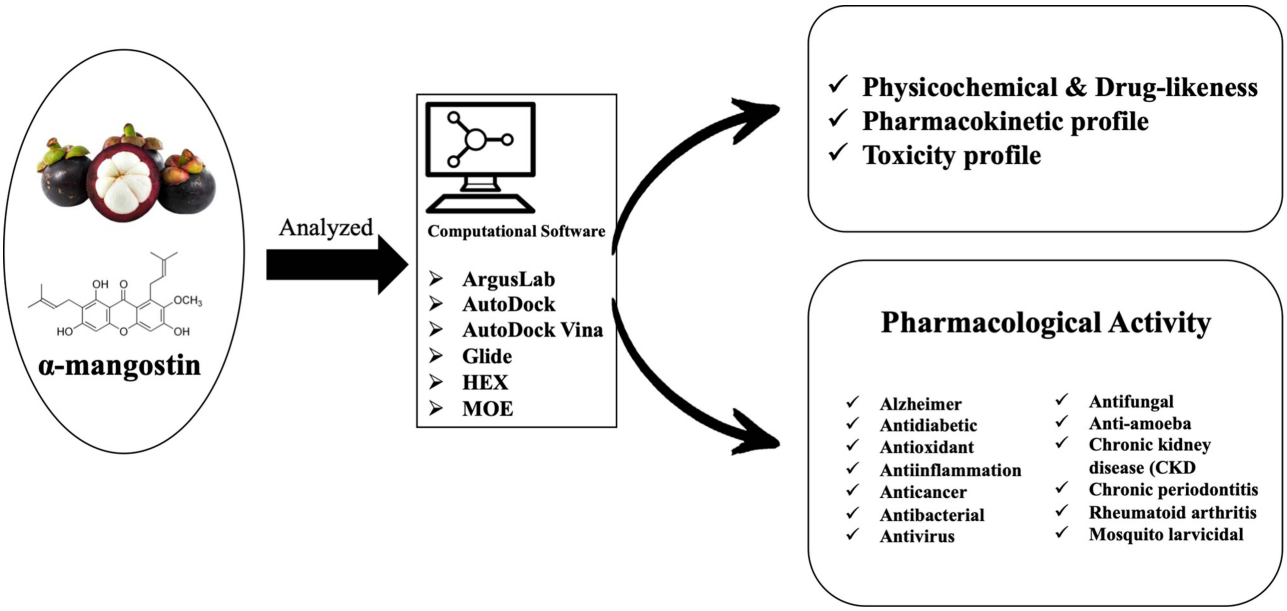
Keywords: α-mangostin, computational study, molecular docking, pharmacological activity

Introduction

The increased progress in scientific knowledge, particularly in the realm of health, opens up extensive opportunities for delving into novel drug development. The prevalence of diverse physiological and pathological disorders in the body that cannot be effectively addressed, enlarges the demand for the discovery of more effective and safe medications. The strategy in the pursuit of drug discovery has now shifted towards the utilization of secondary metabolite compounds from natural sources.[1–3] Currently, over 50% of available marketed drugs originate from compounds found in natural

Received: 15 May 2024
Accepted: 7 October 2024
Published: 24 October 2024

Graphical Abstract



materials. This approach not only enables researchers to explore the biodiversity of our planet, but also offers a promising alternative for the development of more effective medicines.[4–7] With the continued growth of research in this field, it is expected that more innovative drugs will be discovered from these diverse natural sources, furthering the enhancement of human health.

Amidst numerous potential secondary metabolite compounds, α-mangostin stands out with remarkable promise.[8–10] α-mangostin is a xanthone derivative compound commonly found in the pericarp of the mangosteen fruit (*Garcinia mangostana* L).[11,12] This plant is abundant and readily available, particularly in the Asian regions including Thailand, Indonesia, Malaysia, Vietnam, and India.[13,14] Not only does it have high potential as a natural resource, but α-mangostin also possesses versatile and promising pharmacological properties. Its primary efficacy is attributed to its robust antioxidant activity, which holds implications for improving various physiological conditions related to oxidative stress.[15–19] In various in vitro and in vivo studies, α-mangostin has demonstrated significant potential in the treatment of various types of cancer.[20] One of the most noteworthy findings is its efficacy in breast cancer cell line testing, where α-mangostin has been shown to induce apoptosis by inhibiting ER autophagy.[21] This finding has also been confirmed in in vivo tests using HT-29 xenograft tumor-BALB/c mice, which revealed that α-mangostin contributes to the reduction of Bcl-2 and β-catenin in tumors.[22] However, ongoing exploration of the pharmacological effects of α-mangostin is essential to establish its clinical efficacy.

In the relentless pursuit of uncovering the various therapeutic potential of α-mangostin, computational studies—mainly in the field of structural bioinformatics and computational biology—emerge as a strategic cornerstone, providing numerous advantages. Harnessing the power of computer-based research in the initial phases enables the prediction of the most potent pharmacologically active compounds based on their molecular mechanisms against target receptors in related pathologies.[23–25] This approach not only expedites the research timeline, potentially reducing it from 10 to 15 years, but also yields a substantial cost reduction of nearly 50%, as it allows the early elimination of compounds with low predicted potential.[26–28] Several marketed drugs, such as captopril, dorzolamide, saquinavir, indinavir, ritonavir, and tirofiban, provide evidence of the benefits of using computational studies in drug development.[29–32] Moreover, the use of computational tools has proven effective in optimizing natural product drug development, as exemplified by the case of artemisinin. Computational studies have successfully guided research efforts to obtain artemisinin derivatives with

enhanced efficacy and improved pharmacokinetic profiles, such as dihydroartemisinin and artesunate.[33] In addition, the emergence of regulations minimizing or even eliminating the use of animal testing in research opens the door to the utilization and optimization of computer-aided drug design (CADD) in drug design and discovery.[34–37]

Based on the presented facts, it is crucial to understand the progress in the discovery and development of candidate drug compounds based on in silico studies. Similarly, computational studies have significantly contributed to research on α-mangostin. In the search for transthyretin inhibitors for the treatment of amyloidosis, molecular docking analysis has shown that α-mangostin possesses potential, as demonstrated by its interaction with the crystal structure stored in the Protein Data Bank (PDB), under the code 4Y9C (Figure 1).[38] The exploration of the pharmacological potential of α-mangostin can still be further developed with the aid of computational tools. This review aims to summarize and interpret the various properties of α-mangostin based on research that utilizes computational methods. Thus, this literature review is expected to serve as a computational guide and evidence for researchers in developing α-mangostin as a drug for advanced-phase trials until it obtains the label of a marketed drug.

Method

The compilation of this review was conducted based on a thorough examination of research articles obtained from various databases, including PubMed, Scopus, and ScienceDirect. Article searches were carried out using the keywords: "(Mangostin OR α-mangostin) AND (Docking OR "In Silico" OR Computational OR Modelling)". The obtained articles were subsequently managed based on the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline, starting with the removal of duplicate articles, screening for article relevance based on titles and abstracts, screening of full-text articles, and eligibility screening based on data conformity with inclusion criteria. The inclusion criteria encompassed articles in the English language, computational studies in whole or in part of the research, as well as providing detailed information on the execution of molecular docking studies, such as the software used and binding energy outcomes (binding affinity). The workflow for the search and inclusion screening process is depicted in Figure 2. Based on the information obtained from each included article, the pharmacological activities of alpha-mangostin and its molecular mechanisms, as revealed by computational studies, are discussed in detail.

α-Mangostin as Potential Drug Candidate

α-Mangostin is a xanthone derivative compound and one of the significant phytochemical constituents found in the tropical fruit *Garcinia mangostana* L.[11] It has also been found in other Garcinia species, including *Garcinia dulcis, Garcinia staudtii, Garcinia merguensis*, and *Garcinia cowa*.[40,41] In *Garcinia mangostana*, α-mangostin is predominantly

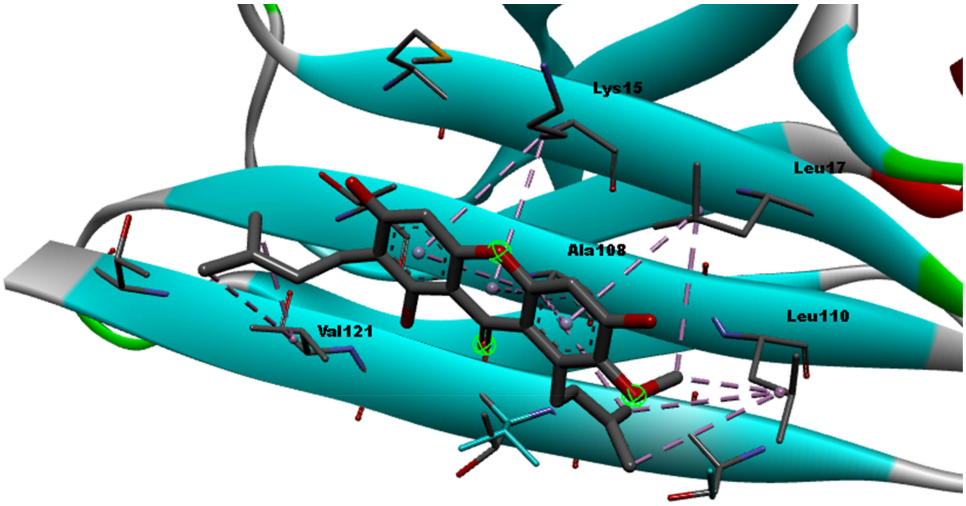


Figure 1 3D molecular interaction between α-mangostin and the active residue amino acids in transthyretin, visualized using Biovia Discovery Studio based on the complex crystal structure with PDB ID 4Y9C.

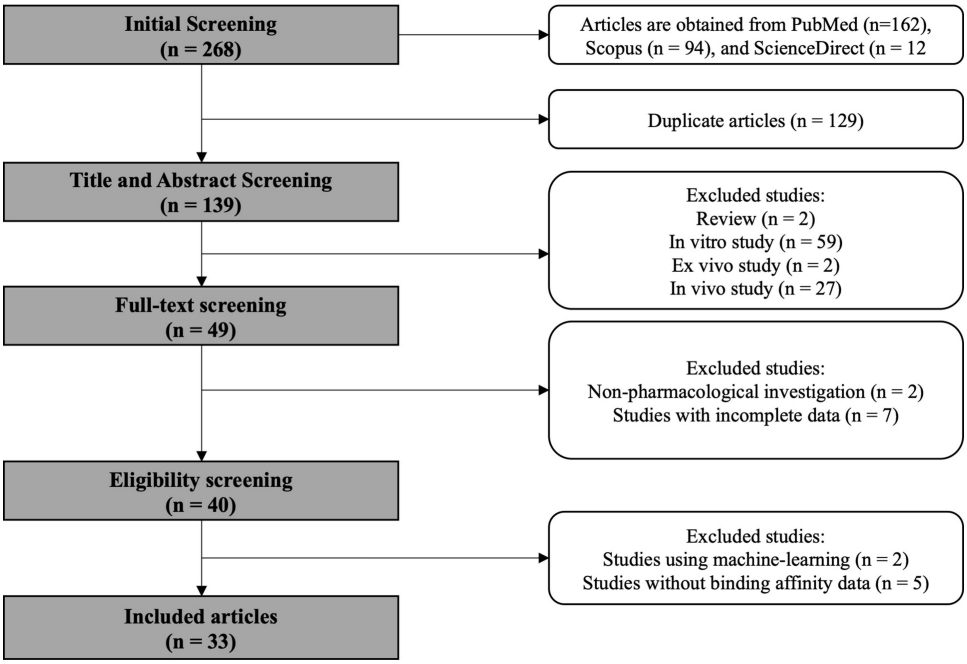


Figure 2 Flowchart of literature screening based on PRISMA guideline.
Notes: PRISMA figure adapted from Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ*. 2021;372:n71. Creative Commons.[39]

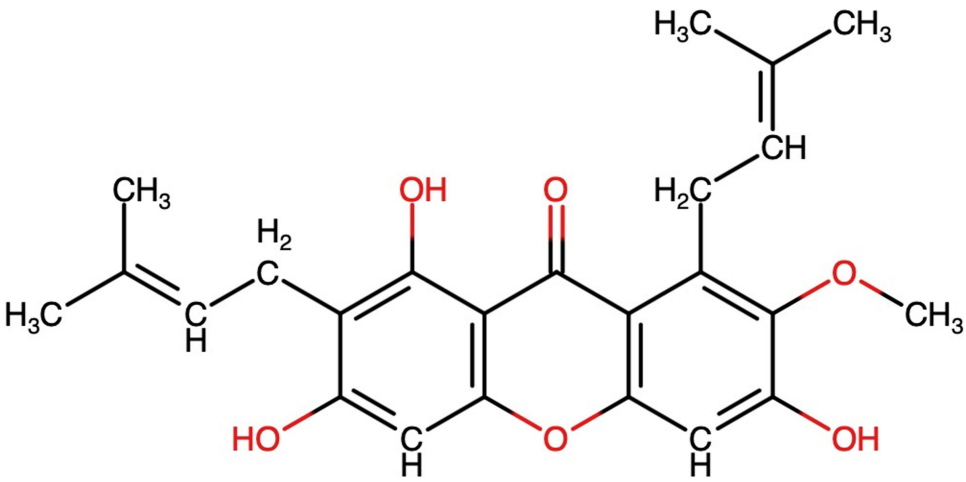


Figure 3 Chemical structure of α-mangostin. Re-drawn using Marvin JS by Chemaxon from PubChem database.

located in the fruit pericarp.[42] Chemically, α-mangostin has been identified as 3,6,8-trihydroxy-2-methoxy-1,7-bis(3-methyl but-2-enyl) xanthan-9-one.[43,44] The chemical structure of α-mangostin is shown in Figure 3. This discussion will focus on the physicochemical properties, drug-likeness properties, pharmacokinetics, and toxicity profile of α-mangostin, as predicted by computational studies.

Physicochemical and Drug-Likeness Properties

Table 1 shows the physicochemical properties of α-mangostin as determined through computational studies. Several physicochemical characteristics play a crucial role in transforming a molecule into one with drug-like properties: 1) the molecule should possess a size conducive for systemic distribution, 2) be hydrophilic enough for solubility in the bloodstream, 3) exhibit sufficient lipophilicity to traverse lipid barriers within the body, and 4) contain an adequate number of polar groups for receptor binding, but not an excessive amount that would prompt rapid elimination through

Table 1 Physicochemical and Drug-Likeness Properties and Pharmacokinetic and Toxicity Profile of α-Mangostin

Physicochemical and drug-likeness properties	
Molecular weight (g/mol)	418.530[47]
Log P value	3.71[47]
Hydrogen bond donor	3[47]
Hydrogen bond acceptor	6[47]
Pharmacokinetic profile	
Human intestinal absorption (%)	91.81[47]
Caco2 cell permeability	20.69[47]
Steady-state volume distribution (VDss) (log L/kg)	−0.23[48]
Protein plasma binding (PPB) (%)	96.62[47]
Blood-brain barrier (BBB)	3.94[47]
CYP2D6 substrate	Negative[46,48]
CYP2D6 inhibitor	Negative[46,48]
Total clearance	0.48[48]
Toxicity profile	
LD_{50} (mol/kg)	1.86[48]
Hepatotoxicity	Negative[46,48]
Mutagenicity	Negative[46,47]
Carcinogenicity	Negative[47]

urinary excretion, thereby hindering its therapeutic effect.[45] Evaluating drug-like properties, in accordance with Lipinski's Rule of Five, entails an assessment of molecular weight, the count of hydrogen bond donors and acceptors, and the log P value. As per Lipinski's Rule of Five, any compound deemed drug-like should possess a molecular weight under 500 Da, a partition coefficient (log P) value below 5, fewer than 5 hydrogen bond donors, and fewer than 10 hydrogen bond acceptors.[46]

Adherence to Lipinski's Rule of Five provides a pragmatic framework for identifying potential drug-like compounds, as those satisfying these criteria are likely to exhibit improved folding, polarity, and molecular size.[49] It is crucial to note that the rule should not be regarded as an inflexible standalone screening criterion in isolation but rather as a dependable indicator of the potential for successful oral exposure to enhanced chemical compounds.[50] In summary, α-mangostin appears to align with all of Lipinski's criteria for drug-likeness. These findings collectively underscore its potential as a promising therapeutic agent for a range of disorders.

Pharmacokinetic Profile

The pharmacokinetic properties of α-mangostin were predicted using the pre-ADMET and pkSCM webserver,[46–48] and the results are summarized in Table 1. These properties encompass aspects of absorption, distribution, metabolism, and excretion. In terms of absorption, α-mangostin is anticipated to exhibit high absorption levels, as indicated by the percentage of human intestinal absorption (%HIA) prediction (falling within the range of 70–100%)[51] and moderate absorption according to the Caco2 cell permeability model (within the range of 4–70%).[52] α-mangostin is associated with a relatively low volume of distribution, characterized by a score below −0.15.[46,48] Furthermore, its distribution process involves a high degree of plasma

protein binding (>90%).[47] Additionally, α-mangostin is projected to breach the blood-brain barrier (BBB) with a penetration value exceeding 2.0, affirming its potential to reach the central nervous system.[53] This supports the notion that α-mangostin has the potential to exert positive effects on pathologies within the central nervous system.

Furthermore, α-mangostin is anticipated to undergo metabolism by CYP450 enzymes, as it is not deemed eligible as a CYP2D6 substrate.[46] Additionally, the incompatibility profile of α-mangostin as a CYP2D6 inhibitor suggests that it is not likely to negatively interact with drugs metabolized by CYP2D6 that might be co-administered.[48] Importantly, the molecule is expected to be excreted moderately, resulting in a circulating concentration in the circulation that is neither too low nor excessively high.[48] In summary, the pharmacokinetic profile of α-mangostin indicates its potential suitability as a therapeutic agent, whether administered orally or through other routes.

Toxicity Profile

The toxicity profile of α-mangostin was predicted using the same software as employed for the pharmacokinetic profile prediction. Overall, α-mangostin exhibits a favorable toxicity profile. Notably, it does not exhibit hepatotoxic, carcinogenic, or mutagenic properties. Furthermore, α-mangostin also demonstrates a relatively low predicted LD_{50} value.[46–48] This LD_{50} prediction aligns with findings from preclinical studies indicating that α-mangostin is non-toxic, with LD_{50} values ranging from 500 to 5000 mg/kg body weight.[54]

Molecular Docking Software Used in Investigating Pharmacological Activities of α-Mangostin

The application of computational studies in both investigating and evaluating the pharmacological effects of α-mangostin encompasses various software tools, each with diverse types and principles. Each software tool possesses its own advantages and limitations when compared to others. In this review, a variety of software tools utilized in α-mangostin research, along with their respective characteristics and interpretations, are summarized and presented in Table 2.

ArgusLab

ArgusLab is a widely used software in molecular docking studies. Initially, ArgusLab was developed for molecular modelling and molecular structure analysis. However, with the evolution of computer-based research, ArgusLab has incorporated molecular docking features. This innovation was driven by the need to address the challenges encountered in computer-aided drug discovery, particularly in the domain of protein-ligand docking.[55]

One of the significant challenges faced by scientists in the application of computational studies is the cost associated with proprietary software. Addressing this financial hurdle, ArgusLab emerged as a free software solution for computational research, specifically in molecular docking. Beyond its cost-effectiveness, ArgusLab boasts advantages over other tools in terms of user-friendliness. It is highly user-friendly and can be operated even by individuals new to computational studies.[61]

Table 2 Molecular Docking Software Used in Investigating α-Mangostin's Pharmacological Activities

Software	Type	Access	Scoring Function	Reference
ArgusLab	Rigid	Free	Binding affinity	[55]
AutoDock	Rigid	Free	Binding affinity	[56]
AutoDock Vina	Rigid	Free	Binding affinity	[57]
Glide	Flexible	License	Glide score	[58]
HEX	Flexible	Free	Binding affinity	[59]
MOE	Rigid	License	S-score	[60]

To date, numerous studies have utilized ArgusLab in the pursuit for new drug candidates based on computational assistance. Most recently, Eawsakul et al employed this application in the exploration and optimization of astilbin, a compound found in *Bauhinia strychnifolia* Craib stems, as a candidate for an alpha-glucosidase inhibitor.[62] In their investigation, the binding free energy emerged as the primary scoring function, offering a basis for comparing the activity of the tested compounds against standard compounds.[63] Eawsakul et al demonstrated a strong correlation between computational and in vitro studies. The findings indicate that astilbin exhibits superior alpha-glucosidase inhibitory activity (binding free energy: −7.24823 kcal/mol and IC_{50}: 22.51±0.70 μg/mL) compared to acarbose (binding free energy: −7.58662 kcal/mol and IC_{50}: 190 ± 6.97 μg/mL).[62]

AutoDock

In parallel to ArgusLab, AutoDock stands out as a widely embraced and freely accessible software tool that has become the most popular choice for molecular docking studies. AutoDock employs the calculation of binding free energy values (in kcal/mol) as a scoring function.[64] What sets AutoDock apart from its counterparts is its distinctive edge in terms of more advanced parameterization, elevating its precision and versatility in unraveling intricate molecular interactions.[65]

Before commencing docking, the binding location of the ligand to the receptor can be validated using re-docking procedures or AutoLigand.[66,67] Re-docking involves re-docking a natural compound within a complex to obtain an ideal scoring function and root-mean-square deviation (RMSD) value (considered ideal if the RMSD value is below 3.0).[66] AutoLigand is an additional feature that allows operators to instruct the software to locate the active site of the desired target receptor. Indirectly, the use of AutoLigand also enables the analysis of the active site of the target receptor.[67] However, it is worth noting that the application of AutoDock has limitations in that it can only be used for docking small molecules up to 32 rotatable bonds.[64]

Recent research utilizing AutoDock was conducted by Jiang et al to investigate the molecular mechanisms of *Danzhi tiaochi* decoction, a traditional Chinese medicine (TCM), in the context of metabolic-associated fatty liver disease (MAFLD).[68] Since traditional medicine comprises a matrix of varying active compounds, the mechanisms of action of TCMs can be diverse, including eliminative, additive, or synergistic effects. Through the application of AutoDock, the study yielded guidance that identified five potential active compounds with optimal binding free energies to the Jun protein. In vitro and in vivo tests demonstrated a strong correlation with the results of the molecular docking study, where these five potential compounds exhibited the potential to ameliorate MAFLD via the JNK/Akt pathway. This was evident from the increased phosphorylation of c-Jun N-terminal kinase (JNK) in the MAFLD animal model.[68]

AutoDock Vina

AutoDock Vina emerges as an alternative to AutoDock, offering a more user-friendly interface.[69] AutoDock Vina is designed with default system operations, simplifying the process for users and eliminating the need for complex molecular parameterization and docking configurations.[57] While this design choice places limitations on the customization of docking simulations, AutoDock Vina still provides substantial value in drug design and discovery.[64] As evidence of its efficacy, AutoDock Vina has been successfully utilized to guide the search for potential compounds within *Laurus nobilis* essential oil for their neuroprotective and anti-amnesic effects on memory deficits.[70]

In this study, the strategic utilization of AutoDock Vina played a pivotal role in steering the discovery process, pinpointing 1.8 cineol and α-terpinyl acetate as standout compounds showcasing significant potential in inhibiting the activity of the acetylcholinesterase (AChE) enzyme. Among these, α-terpinyl acetate emerged as the most promising compound, with a binding free energy of −7.2 kcal/mol, surpassing both 1.8 cineol and donepezil, which exhibited similar binding free energies of −3.1 kcal/mol.[70]

Glide

Grid-based ligand docking with energetics (Glide) represents a more advanced tool in molecular docking. As its name suggests, unlike the three previously discussed tools, Glide is predominantly used for molecular docking with a flexible docking program. Glide employs a grid-based approach to screen conformations between ligands and target proteins.[58] In general, the screening mechanism performed by Glide proceeds through several stages, beginning with site-point

screening, followed by diameter screening, subset analysis, grid scoring, and refinement.[58,71] The best pose is then subjected to further analysis through grid minimization combined with Monte Carlo sampling. Finally, the output of the analysis is represented as the Glide score, a scoring function. Generally, a Glide score of −10 or lower signifies an optimal binding interaction between the ligand and its receptor.[72] Due to its complex screening stages, the results obtained using Glide are typically more representative compared to those obtained with rigid docking programs. Nevertheless, the use of Glide is highly restricted due to its proprietary nature and the requirement for relatively high hardware specifications.[71]

Nonetheless, the application of Glide has proven to play a significant role in the advancement of Computer-Aided Drug Design (CADD). Most recently, Glide was utilized to confirm the activity of novel morpholino-1,3,5-triazine-pyrimidine hybrid compounds as alternatives to gliptin compounds in the management of type 2 diabetes mellitus (T2DM) by inhibiting dipeptidyl peptidase-4 (DPP-4), an ubiquitous enzyme in glucose homeostasis.[73] The analysis results indicated alignment between in vitro and in silico analyses. Both approaches demonstrated that one of the tested hybrid compounds exhibited superior inhibitory effects compared to Alogliptin. Through molecular docking studies, the favorable outcomes with the hybrid compounds were symbolized by their lower Glide energy values compared to the standard compounds.[73]

Hex

In contrast to the other previously described docking tools, Hybrid Energy Exchange (HEX) is a web-based application. Its usage is relatively straightforward and user-friendly, requiring less hardware specifications.[74] HEX employs a non-3D grid-based searching system, performing searches using the Fast Fourier Transform (FFT) correlation approach.[59] Consequently, HEX offers a simpler user experience, as it does not necessitate pre-parameterization of grid coordinates. Additionally, HEX has the advantage of facilitating docking between protein-protein interactions.[75]

In a study conducted by Raissa et al, HEX was effectively utilized to predict the compound most responsible for inducing apoptosis through the death receptor-5 (DR-5) induction mechanism from *Azadirachta indica* Juss.[76] The investigation results indicated that nimbolide exhibited superior potential compared to gedunin in inducing DR-5. This is evidenced by its lower binding energy (−247.7 vs −237.12 kcal/mol). A lower binding energy suggests a more stable interaction between the ligand and the target receptor, leading to a stronger induction effect.[76]

Moe

Molecular operating environment (MOE) is a software designed for structure-based docking, sharing several similarities with AutoDock and ArgusLab in terms of its operation. However, MOE utilizes two primary parameters as scoring functions. The first, S-score, represents the docking score and can be used to predict binding affinity. The second, energy of conformation, is employed to predict the spontaneity of the reaction between the ligand and receptor in forming a stable conformation. Unlike AutoDock and ArgusLab, MOE can only be used with a registered paid license.[60]

In its application, MOE has been leveraged to expedite the search for potential compounds as candidates against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). In their research, Senobari et al identified chromone-embedded peptidomimetics and furopyrimidines as potential anti-SARS-CoV-2 agents. These findings were based on the acquisition of negative S-scores, indicating strong binding affinity with the main protease and spike protein of SARS-CoV-2.[77]

Various Pharmacological Activities of α-Mangostin Based on in silico Study

The search results indicate a noteworthy development in the application of computational studies to unraveling the pharmacological properties of α-mangostin. A summary of the pharmacological properties, target actions, molecular docking software, and binding affinity of α-mangostin to related target actions is presented in Table 3. Here is a detailed explanation of the pharmacological properties of α-mangostin based on the analysis of included articles.

Table 3 Pharmacological Activities and Its Mechanism of Action of α-Mangostin Based on Computational Studies

Pharmacological Activity		Software	Target	Standard	α-Mangostin's Score (kcal/mol)	Standard's Score (kcal/mol)	Ref
Alzheimer		AutoDock	Choline esterase	N/A	−12.69	N/A	[78]
			SIRT1	Memantine	−9.31	−7.49	[79]
		MOE	β-amyloid (Aβ)	N/A	−68.76	N/A	[80]
Antidiabetic		AutoDock	Aldose reductase	Zopolrestat	−8.15	−12.59	[81]
			HDAC-2	N-(2-aminophenyl) benzamide	−7.15	−10.27	[82]
			Maltase-glucoamylase (α-glucosidase)	Miglitol	−7.84	−9.14	[48]
			α-amylase	N/A	−7.56	N/A	[18]
			α-glucosidase	N/A	−7.90	N/A	
		AutoDock Vina	α-glucosidase	Acarbose	−7.3	−7.1	[83]
Infectious Disease	Antibacteria (*Staphylococcus aureus*)	AutoDock	Beta lactamase	N/A	−6.02	N/A	[84]
	Anti-*Acanthamoeba keratitis*	Arguslab	Beta Tubulin	N/A	−11.22	N/A	[85]
		AutoDock	Beta Tubulin	N/A	−10.18	N/A	
	Antifungal		GlcN-6-P synthase	Terbinafine	−7.04	−8.58	[86]
	Coronavirus disease 2019 (Covid-19)		ACE2	Chloroquine	−4.27	−4.10	[11]
		AutoDock Vina	Main protease	Lopinavir	−7.4	−7.4	[87]
		AutoDock	Main protease	Remdesivir	−8.31	−6.50	[11]
			Main protease	Nelfinavir	−8.58	−9.74	[47]
	Human immunodeficiency virus (HIV)		HIV reverse transcriptase	Etravirine	−10.51	−8.82	[88]

(*Continued*)

https://doi.org/10.2147/DDDT.S478388 DovePress

Table 3 (Continued).

Pharmacological Activity	Software	Target	Standard	α-Mangostin's Score (kcal/mol)	Standard's Score (kcal/mol)	Ref
Antioxidant	AutoDock Vina	MMP1	N/A	−8.9	N/A	[89]
		NEP	N/A	−7.4	N/A	
		PPO3	N/A	−6.5	N/A	
Breast Cancer	AutoDock Vina	EGFR	Gefitinib	−9	−9.0	[90]
	AutoDock	GSK3β	3-amino-6-(4-{[2-(dimethylamino)ethyl]sulfamoyl}phenyl)-N-pyridin-3-ylpyrazine-2-carboxamide	−8.92	−8.22	[91]
		hERα	Estradiol	−9.05	−10.12	[92,93]
		hERα	4-OHT	−8.82	−11.49	[94]
	AutoDock Vina	hERα	Estradiol	−7.1	−9.0	[95]
		HER2	Lapatinib	−5.8	−6.6	[90]
		IGF1R	BI 885578 (Inhibitor)	−7.9	−8.2	
		β-ketoacyl part of fatty acid synthase	4-[4-(1-benzofuran-5-yl)phenyl]-5-{[(3S)-1-(cyclopropylcarbonyl) pyrrolidin-3-yl]methyl}-2,4-dihydro-3H-1,2,4-triazol-3-one	−9.6	−12.4	[95]
Cancer	AutoDock Vina	MARK4	N/A	−9.2	N/A	[96]
		USP45	N/A	−8.4	N/A	[97]
		p53	Nutlin-3a	−6.8	−7.4	[98]
Chronic Kidney Disease	Glide	IP3R	N/A	−3.357	N/A	[99]
		JNK	N/A	−6.707	N/A	
		KEAP-1	N/A	−5.63	N/A	
		NF-kB	N/A	−7.187	N/A	
		P38 kinase	N/A	−4.569	N/A	

Chronic Periodontitis	AutoDock Vina	ALP	N/A	−6.9	N/A	[100]
		Osteocalcin	N/A	−5.4	N/A	
		Osteonectin	N/A	−7.1	N/A	
		Rank-Rankl	N/A	−7.2	N/A	
		Sclerotin	N/A	−6.8	N/A	
		TRAP	N/A	−6.1	N/A	
Inflammation	AutoDock	COX-1	N/A	−3.81	N/A	[101]
		COX-2	N/A	−8.26	N/A	
		NF-kB	N/A	−9.64	N/A	
	HEX 8.0	RAGE	Imidazole	−260.42	−97.22	[102]
Mosquito Larvicidal	AutoDock	AeSCP-2	Panthenol	−13.65	−9.23	[103]
Oral Cancer	AutoDock	ARRB1	N/A	−4.46	N/A	[104]
		CALM3	N/A	−6.36	N/A	
		FLNA	N/A	−3.32	N/A	
		HTT	N/A	−3.93	N/A	
Pain Management	AutoDock Vina	$Na_V1.7$	TTX	−7.7	−7.8	[105]
		TREK-1	Norfluoxetine	−7.6	−6.4	
		TREK-2	Norfluoxetine	−7.2	−6.5	
		TRPV1	Capsaicin	−7.7	−8.0	
Rheumatoid Arthritis	AutoDock Vina	PPAR-γ	N/A	−6.7	N/A	[106]

https://doi.org/10.2147/DDDT.S478388

Alzheimer's Disease

Figure 4 visually represent the role of α-mangostin in addressing Alzheimer's disease. In the context of Alzheimer's disease, a neurodegenerative disorder characterized by neuronal dysfunction in the brain, α-mangostin demonstrates the ability to intervene in the aggregation of β-amyloid (Aβ). α-mangostin binds strongly to Aβ with a binding affinity of −68.76 kcal/mol.[78,80] This strong binding enhances the stability of the Aβ conformation, preventing Aβ from interacting with each other.[107,108]

In addition to its primary mechanism in Alzheimer's pathophysiology, α-mangostin also exhibits strong interactions with cholinesterase.[78] In Alzheimer's conditions, cholinesterase enzyme activity leads to the degradation of acetylcholine, an essential neurotransmitter for brain function.[109] The interaction with the enzyme's substrate site results in the inhibition of acetylcholine breakdown.[110] Furthermore, through computational studies, α-mangostin is found to have a strong binding affinity for the activator site of sirtuin 1 (SIRT-1).[79] The binding strength (−9.31 kcal/mol) is significantly higher than that of resveratrol (−7.57 kcal/mol), a compound known for its ability to activate SIRT-1, and memantine (−7.49 kcal/mol), an Alzheimer's marketed drug. Activation of SIRT-1 plays a pivotal role in Alzheimer's condition as it possesses a remarkable capability to disrupt cross-linkages within tau proteins ensnared in neurofibrillary tangle (NFT), possibly through protein deacetylation.[111,112]

Antidiabetic

In the pathology of diabetes mellitus, α-mangostin demonstrates significant potential as anti-diabetic agent through various mechanisms (Figure 5), including the inhibition of polysaccharide and disaccharide breakdown.[18,48,83]

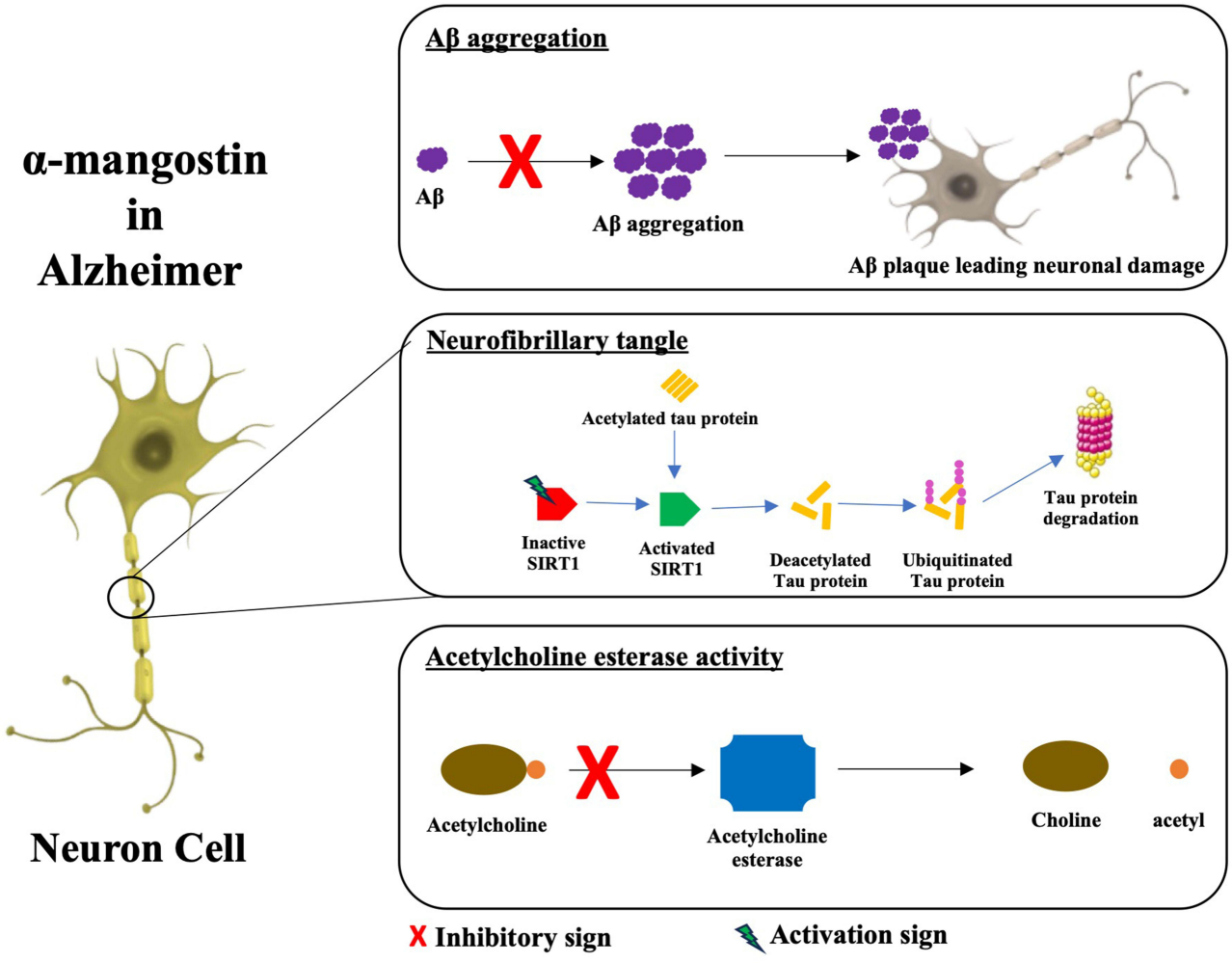


Figure 4 Mechanism of action of α-mangostin in treating Alzheimer disease based on computational studies.

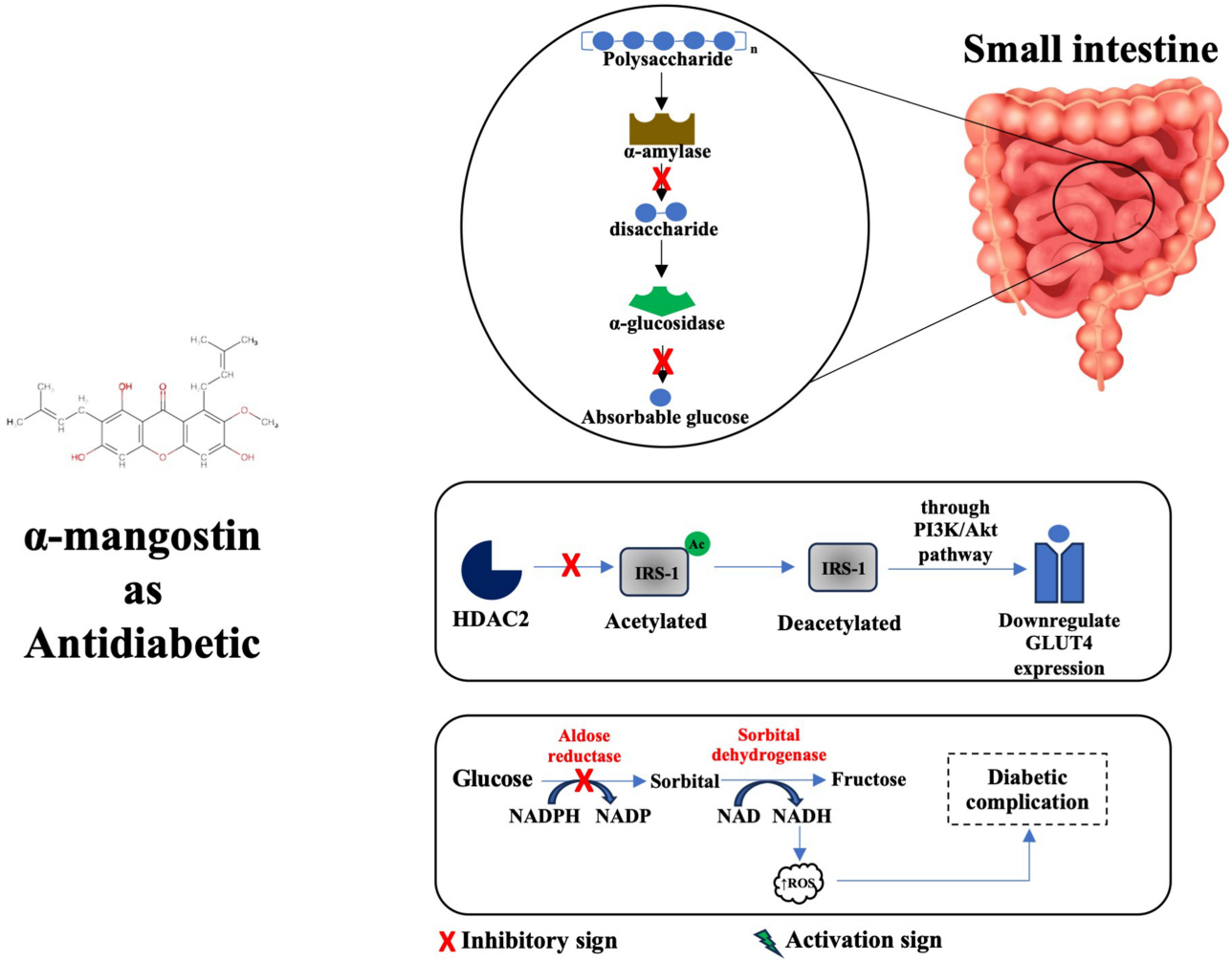


Figure 5 Mechanism of action of α-mangostin as antidiabetic agent predicted using computational studies.

Polysaccharide breakdown is inhibited through the inhibition of the α-amylase enzyme, preventing the cleavage of α-1,4-glycosidic bonds in the polysaccharide chain.[113] Disaccharide breakdown inhibition is achieved by inhibiting the α-glucosidase enzyme, which plays a role in the final breakdown of glucose in the small intestine.[114] This finding shows that α-mangostin can inhibit the glucose breakdown process from early to late stages.

Furthermore, α-mangostin's role is seen from another etiological perspective of diabetes mellitus. Histone deacetylase 2 (HDAC2) plays a crucial role in the epigenetic aspects of diabetes mellitus. HDAC2 catalyzes the deacetylation of histone proteins on the DNA sequence, which are then transcribed and translated into glucose metabolism inhibitory factors.[115,116] α-mangostin has the potential to be an HDAC2 inhibitor candidate with a binding affinity of −7.15 kcal/mol.[82]

On the other hand, α-mangostin also has the potential to address complications that may arise from diabetes. Excessive blood glucose levels in diabetes can lead to a shift in glucose metabolism activation to sorbitol by aldose reductase.[117] This metabolic process involves the excessive utilization of NADPH, leading to a decrease in glutathione (GSH) and the production of reactive oxygen species (ROS), resulting in a hyperoxidative condition.[118] α-Mangostin is recognized for its potent activity by robustly engaging with the active site of aldose reductase, with a binding affinity of −8.15 kcal/mol.[81] This binding strength is comparable to the marketed drug Zopolrestat which exhibits a binding affinity of −12.59 kcal/mol.

Antioxidant

The paramount quality of α-mangostin often underscored by researchers is its noteworthy antioxidant properties. However, there is a limited number of computational studies that directly investigate α-mangostin's role in pro-oxidant markers. Only one study conducted by Widowati et al suggests that α-mangostin may act as an antioxidant by inhibiting matrix metalloproteinase 1 (MMP-1), nuclear export protein (NEP), and prophenoloxidase (PPO3).[89] The highest binding affinity of α-mangostin is observed in its interaction with MMP-1 (−8.9 kcal/mol). NEP and PPO3 display binding affinities of −7.4 and −6.5 kcal/mol, respectively. Inhibition of MMP-1 has the secondary effect of reducing oxidative imbalance by impeding the degradation of interstitial collagen.[119,120]

Breast Cancer, Oral Cancer, and Other Types of Cancer

In the case of cancer, α-mangostin has been extensively studied as an anti-breast cancer agent. However, computational studies open up the possibility of α-mangostin being used in the treatment of various other types of cancer. In the treatment of breast cancer, α-mangostin is known to actively inhibit epidermal growth factor receptor (EGFR),[90] glycogen synthase kinase 3β (GSK3β),[91] insulin-like growth factor 1 receptor (IGF1R),[90] human estrogen receptor alpha (hERα),[92–94] and the β-ketoacyl part of fatty acid synthase (FAS) as depicted in Figure 6.[95] α-mangostin exhibits strong molecular interactions (binding affinity below −5.50 kcal/mol) with all of these targets.[121] Although α-mangostin has a wide range of targets, the strongest predicted interaction occurs with FAS. This aligns with several findings indicating that α-mangostin is effective in reducing breast cancer malignancy through alterations in the FAS cell signaling pathway.[122]

For oral cancer, α-mangostin has been simulated to dock with four main targets in oral cancer: calmodulin 3 (CALM3), beta arrestin 1 (ARRB1), huntingtin (HTT), and filamin A (FLNA).[104] α-mangostin exhibits negative binding affinity, indicating

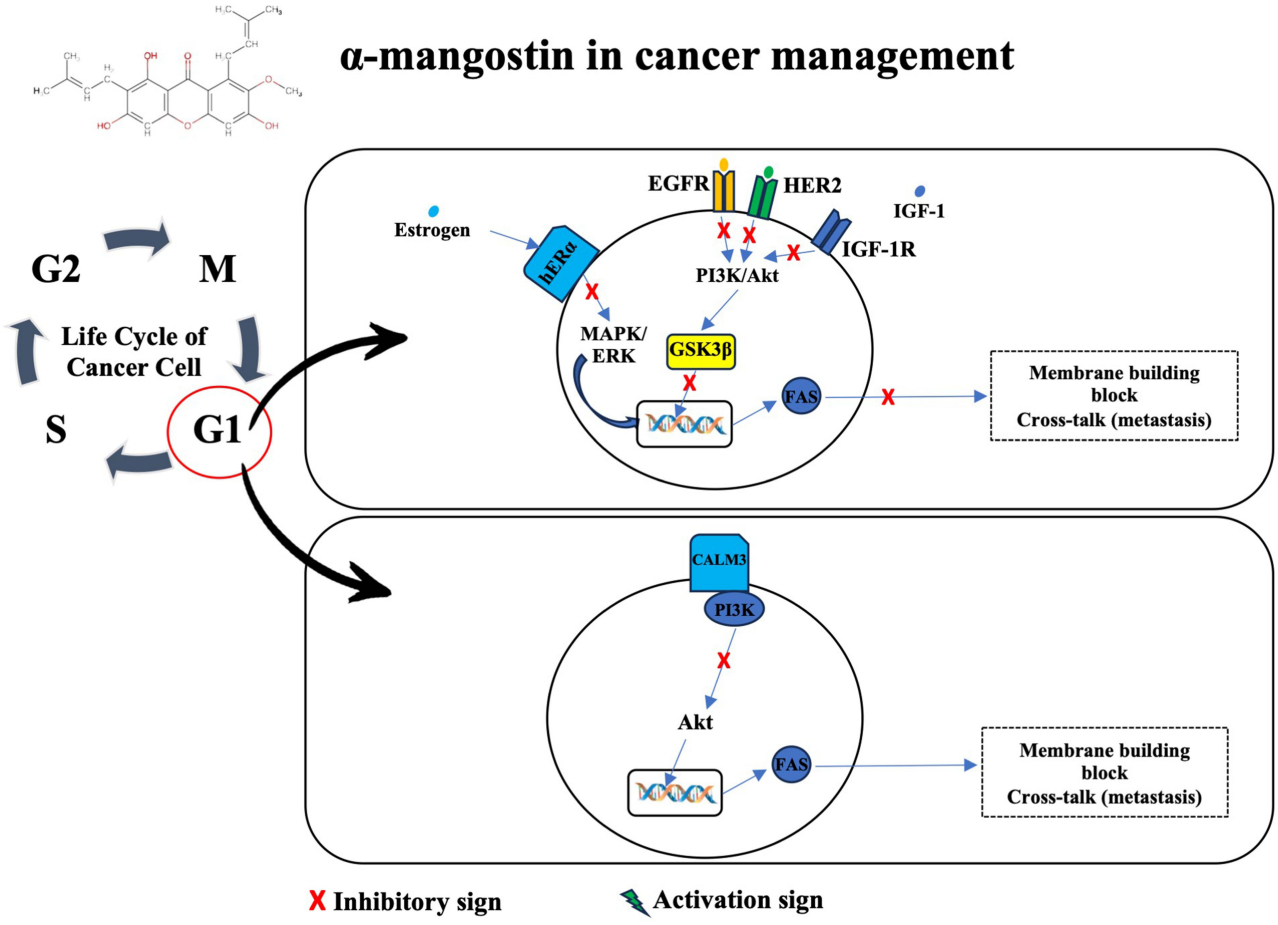


Figure 6 Computational studies reveal mechanism of action of α-mangostin in cancer treatment.

spontaneous interactions. However, it only achieves a binding affinity below −5.50 kcal/mol in the case of CALM3 (Figure 6). CALM3 binds to phosphoinositide 3-kinase α (PI3Kα), leading to the hyperactivation of the PI3Kα/Akt/mammalian target of rapamycin signalling pathway, affecting cell proliferation, differentiation, motility, and development.[123] The interaction between α-mangostin and CALM3 leads to downregulation of cell signalling, thereby reducing cancer cell growth progression.[124]

Furthermore, in various types of cancer, overexpression of certain kinase enzymes, such as microtubule-affinity-regulating kinase 4 (MARK4) and ubiquitin-specific protease 45 (USP45), has been observed. MARK4 plays a crucial role in phosphorylating tau proteins, resulting in increased cell migration and polarity, potentially leading to metastasis.-[125] Inhibition of MARK4 activity can prevent cancer cell metastasis. Additionally, inhibiting USP45 leads to the failure of cell migration by blocking the deubiquitination of SPDL1 protein and downregulating its protein expression level.[126] Both MARK4 and USP45 are highly promising as general cancer treatment targets. Interestingly, studies conducted by Khan et al[96] and Tu et al[97] demonstrate that α-mangostin strongly interacts with both of these targets. α-mangostin exhibits strong binding affinity with MARK4 and USP45, with binding affinities of −9.2 and −8.4 kcal/mol, respectively.

Chronic Kidney Disease

Indications arising from the various protective and pharmacological effects of α-mangostin suggest its capability to shield and induce recovery from organ damage, particularly in the case of chronic kidney disease (CKD). The antioxidant and anti-inflammatory effects of α-mangostin are likely the primary factors contributing to its performance in improving CKD conditions. Through an in silico study conducted by Rana et al, it is ultimately revealed that α-mangostin is predicted to play a role in ameliorating CKD conditions by altering inositol 1,4,5-trisphosphate (IP3) receptor (IP3R), kelch-like ECH-associated protein-1 (KEAP-1), c-Jun N-terminal kinase (JNK), p38 kinase, and nuclear factor kappa beta (NF-kB), as illustrated in Figure 7.[99] The

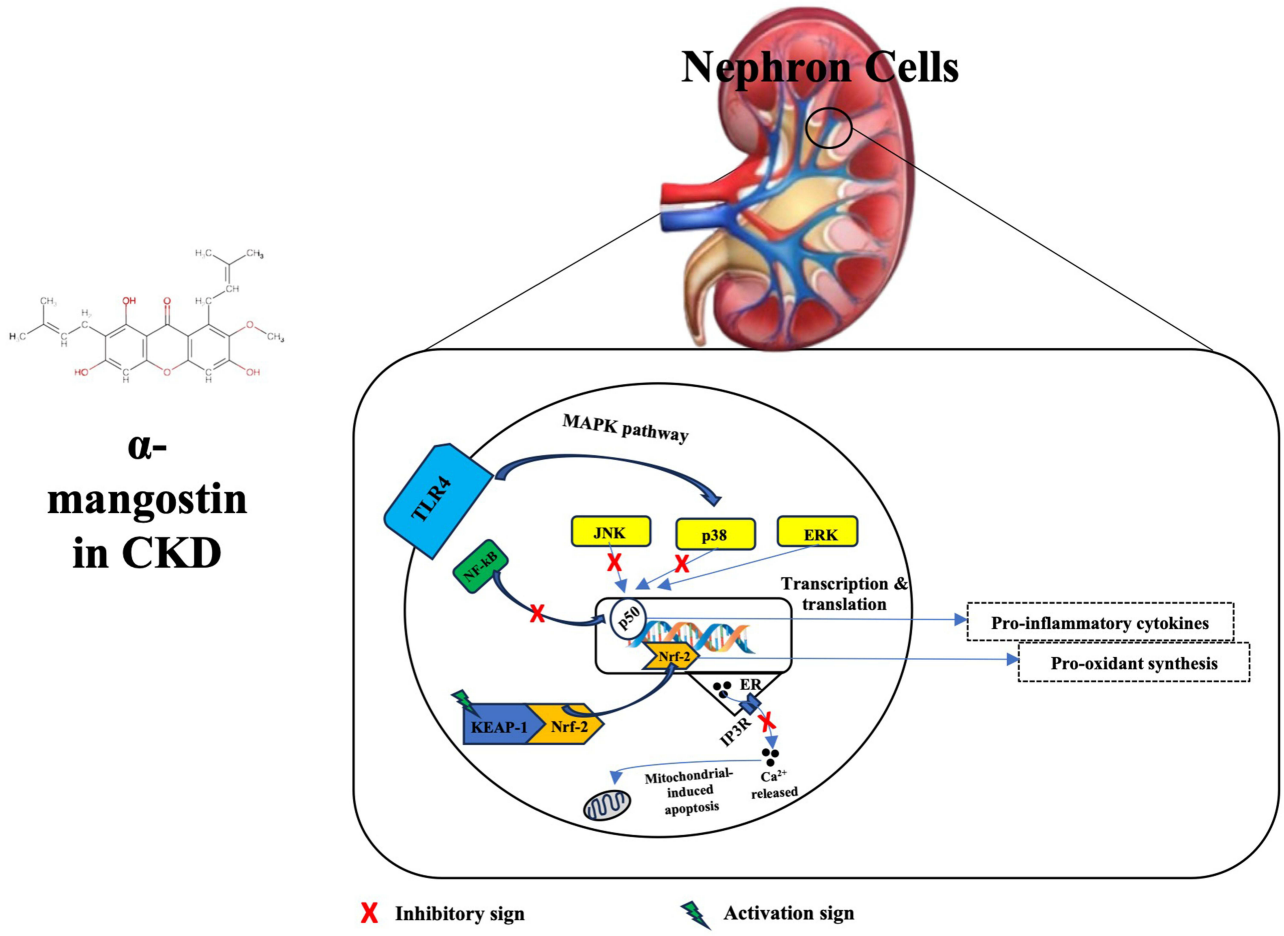


Figure 7 α-mangostin are predicted to be involved in chronic kidney disease amelioration.

study demonstrates strong binding affinities for each receptor, measuring at −3.357 kcal/mol, −5.63 kcal/mol, −6.707 kcal/mol, −4.569 kcal/mol, and −7.187 kcal/mol, respectively.

Inhibition of IP3R leads to the hindrance of calcium ion (Ca^{2+}) release from the endoplasmic reticulum (ER), thereby impeding apoptosis and mitochondrial damage in nephron cells.[127] Subsequently, the protective mechanism against inflammatory effects on kidney nephron cells occurs through the inhibition of the MAPK pathway (JNK and p38 kinase) and NF-kB.[128] Moreover, through its antioxidant mechanism, α-mangostin enhances the activity of endogenous anti-oxidant enzymes, such as sodium dismutase (SOD) and catalase (CAT). The improvement of the pro-oxidant profile is achieved indirectly due to KEAP-1 activation, which leads to the release of Nrf-2, indirectly increasing the expression of pro-oxidant enzymes.[129]

Chronic Periodontitis

With its recognized anti-inflammatory properties, the prospect of utilizing α-mangostin in the treatment of chronic periodontitis emerges as a feasible avenue. However, there is limited evidence regarding the use of α-mangostin for this condition, whether in preclinical or clinical studies. Therefore, the use of computational studies is highly beneficial for predicting the efficacy and potential mechanisms of α-mangostin in the treatment of chronic periodontitis.

A study conducted by Saputra et al suggests that α-mangostin shows significant alterations with good binding affinities (below −5.50 kcal/mol) with alkaline phosphatase (ALP), osteonectin, receptor activator nuclear kappa beta (RANK) and ligand (RANKL), sclerostin, and tartrate-resistant acid phosphatase (TRAP).[100] Of these six targets, RANKL appears to be the most optimal target for α-mangostin in the management of chronic periodontitis, primarily due to its greater binding affinity compared to other receptors, amounting to −7.2 kcal/mol.

Infectious Disease

Based on the in silico study evidence concerning infectious diseases, α-mangostin exhibits a broad spectrum of antimicrobial effects, spanning from antibacterial, antifungal, anti-amoeba, to antiviral actions (Figure 8). As an antibacterial agent, α-mangostin is known to possess effective inhibitory activity against β-lactamase in *Staphylococcus aureus* bacteria.[84] The interactions involved are strong, displaying a binding affinity of −6.02 kcal/mol. Additionally, α-mangostin also demonstrates robust interactions with β-tubulin in *Acanthamoeba keratitis*, an amoeba species targeting the cornea, with a binding affinity of −11.22 kcal/mol.[85] Inhibition of β-tubulin's performance obstructs the movement of essential organelles critical for the growth and replication of eukaryotic cells such as amoebas.[130]

Beyond single-celled organisms, α-mangostin is predicted to act as an antifungal agent by inhibiting glucosamine-6-phosphate (GlcN-6-P) synthase performance.[86] Inhibition of GlcN-6-P synthase prevents fungal cells from producing N-glycosylated mannoproteins crucial for maintaining fungal cell wall integrity.[131,132] Although the interaction strength between α-mangostin and GlcN-6-P synthase is not as robust as that exhibited by terbinafine, a marketed antifungal drug (−7.04 vs −8.58 kcal/mol), it is suggested that α-mangostin may serve as an alternative antifungal treatment, especially for patients resistant to terbinafine.

Lastly, it is worth noting that α-mangostin has demonstrated antiviral properties, particularly in combating severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and human immunodeficiency virus (HIV). The emergence of the coronavirus disease 2019 (COVID-19) pandemic has prompted researchers to identify suitable antivirals to inhibit the spread of SARS-CoV-2. In silico studies on various phytoconstituents indicate that α-mangostin has significant potential as an anti-SARS-CoV-2 agent by inhibiting the main protease (MPro) and angiotensin-converting enzyme 2 (ACE2).[133–136] Molecular docking results reveal that α-mangostin has binding affinities of −8.58 and −4.27 kcal/mol for each receptor, respectively.[11,47,87] These binding affinities are stronger compared to some off-label drugs like lopinavir, nelfinavir, remdesivir, and chloroquine. Regarding HIV, α-mangostin inhibits HIV reverse transcriptase with a binding affinity of −10.51 kcal/mol,[88] leading to the virus's failure to convert its RNA genetic material into DNA within host cells.[137,138]

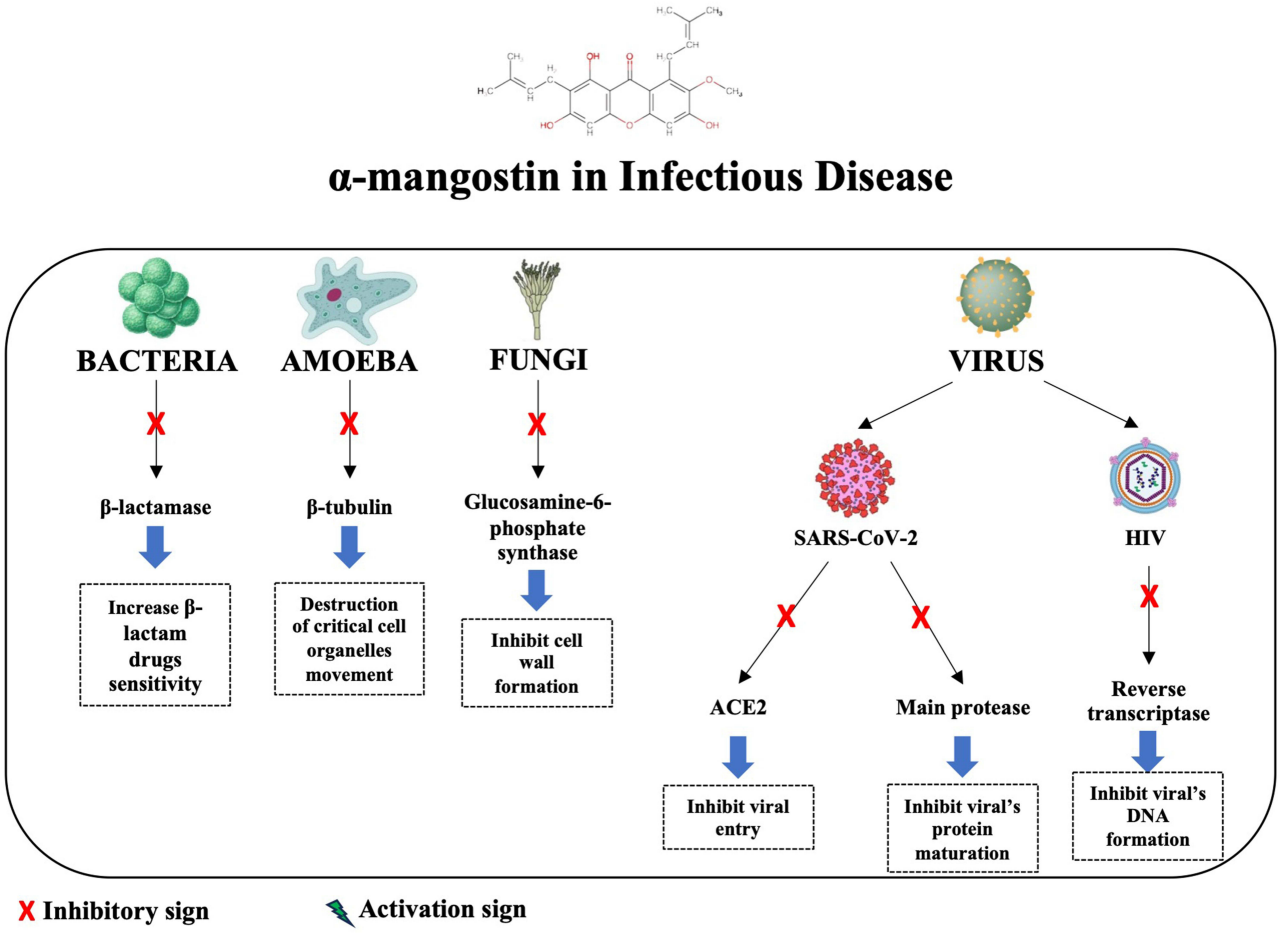


Figure 8 α-mangostin as antimicrobial agent in treating infectious diseases based on computational studies.

Inflammation

In addition to being a potent antioxidant, α-mangostin is increasingly associated with its notable anti-inflammatory properties. In silico studies suggest that α-mangostin effectively inhibits pro-inflammatory enzymes, such as cyclooxygenase I (COX-I) and cyclooxygenase II (COX-II), nuclear factor kappa beta (NF-kB), and AGE-RAGE interaction (Figure 9). In a study conducted by Mohan et al, α-mangostin demonstrated binding affinities of −3.81 and −8.26 kcal/mol towards COX-I and COX-II, respectively.[101] The binding affinity of α-mangostin towards COX-I, above −5.50 kcal/mol, indicates a weak binding affinity, implying that α-mangostin likely provides selective inhibition of COX-II only. This finding addresses the issue of non-selective non-steroidal anti-inflammatory drugs (NSAIDs) which often exhibit increased side effects.[139,140]

Furthermore, α-mangostin is predicted to have anti-inflammatory properties by inhibiting cell signalling within the immune system. α-mangostin interacts with the p50 subunit of nuclear factor kappa beta (NF-kB) with a binding affinity of −9.64 kcal/mol.[101] Deactivation of NF-kB leads to the downregulation of immune system-related cytokine transcription and macrophage stimulation.[141] In other findings, a study conducted by Faisal et al also discovered that α-mangostin can intervene in the interaction between advanced glycation end-products (AGE) and their receptor, the advanced glycation end-products receptor (RAGE).[102,142] RAGE is a member of the immunoglobulin superfamily, encoded in the Class III region of the major histocompatibility complex (MHC Class III).[143] Inhibiting the AGE-RAGE interaction can prevent the transmission of inflammatory signals through the MHC Class III pathway.[142,143] α-mangostin competes with AGE for binding at the active site of RAGE, resulting in a binding affinity of −260.42 kcal/mol.[102]

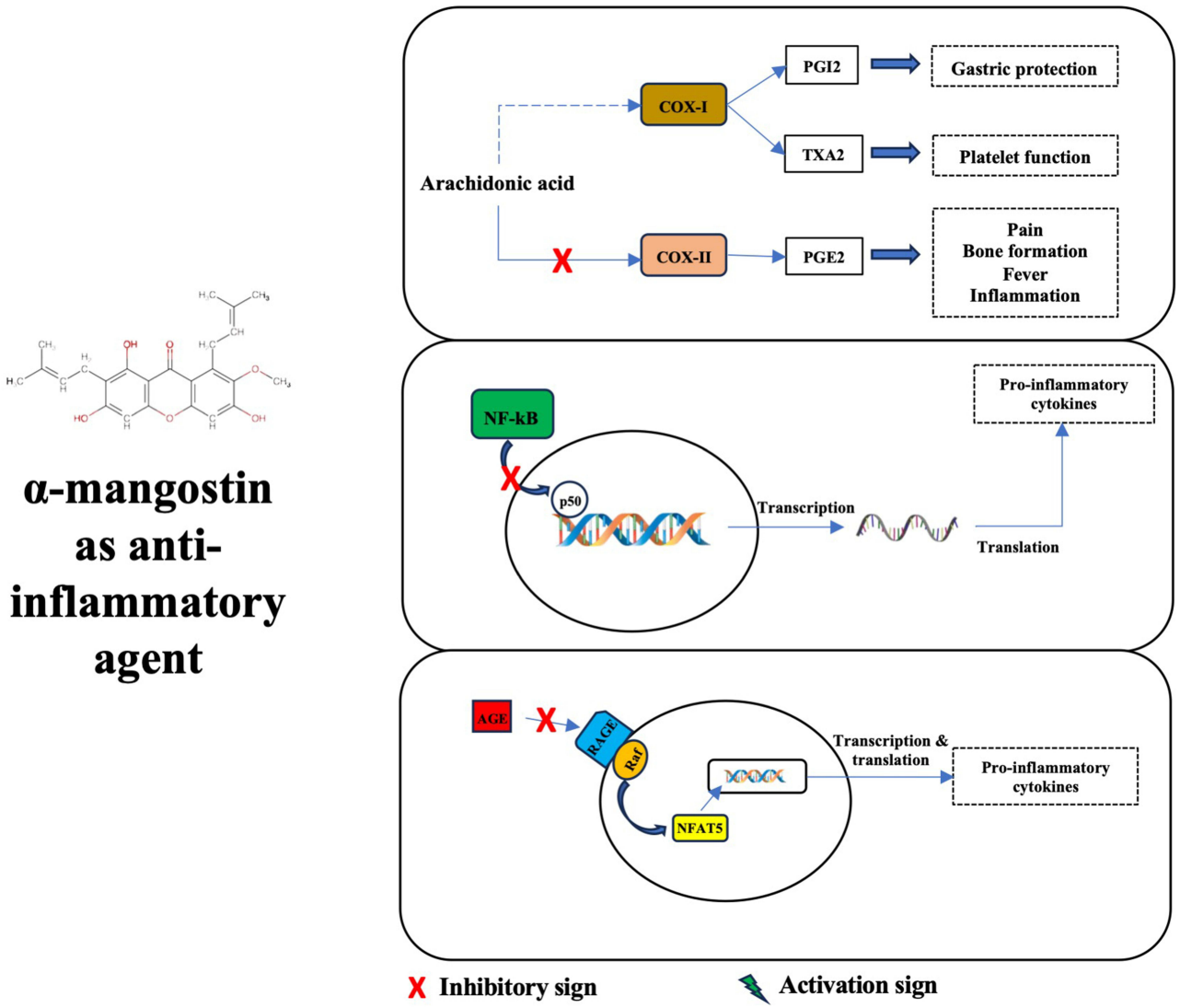


Figure 9 Mechanism of action of α-mangostin as anti-inflammatory predicted using computational studies.

Mosquito Larvicidal

In addition to its direct application for human treatment, α-mangostin also exhibits significant potential as a mosquito larvicide. Particularly, in the case of dangerous mosquitoes like *Aedes aegypti*, carrier proteins responsible for cholesterol become essential factors in the process of larval development into adult mosquitoes.[144] Among sterol carrier proteins (SCPs), the type SCP-2 in *Aedes aegypti* mosquitoes (AeSCP-2) plays the most significant role in mosquito cholesterol metabolism.[145] Therefore, targeting inhibition in AeSCP-2 presents a viable option for finding larvicidal solutions for Aedes aegypti mosquitoes. A study by Kumar et al demonstrates that α-mangostin can compete with cholesterol to bind with AeSCP-2.[103] The bond formed is robust, with a binding affinity of −13.65 kcal/mol. This value is significantly higher than that of other larvicidal candidates like panthenol, which exhibits a binding affinity of −9.23 kcal/mol for AeSCP-2.

Pain Management

Surprisingly, α-mangostin is known to function as an analgesic. This is indicated in studies by Sani et al and Cui et al, showing that α-mangostin effectively alleviates pain and inflammatory symptoms in rodent models induced by a hot plate and formalin injection.[146,147] While α-mangostin is recognized for its anti-inflammatory properties that contribute to pain relief, the exact mechanism behind α-mangostin's analgesic effects remains uncertain. Through computational studies

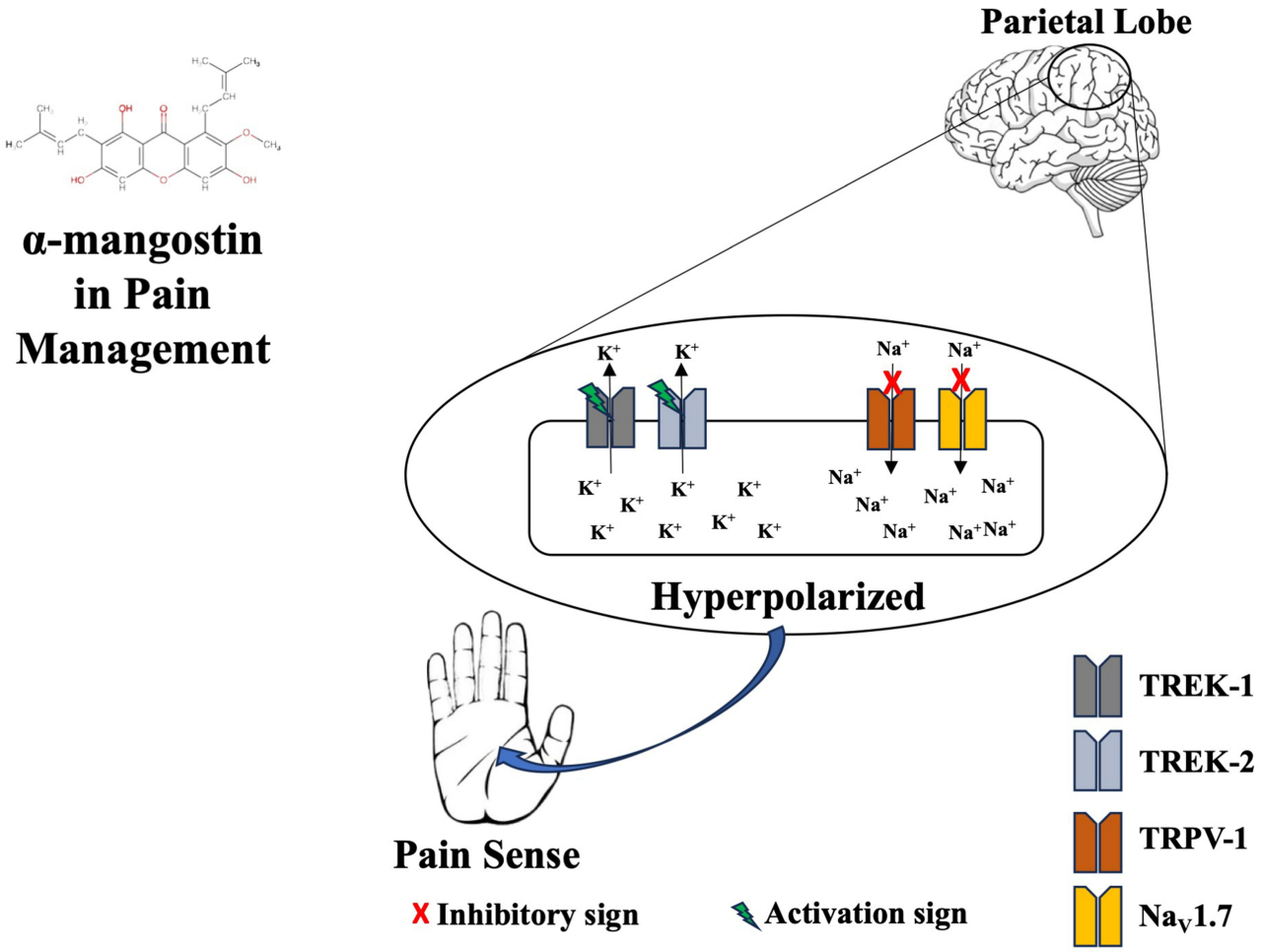


Figure 10 Role of α-mangostin in pain management based on computational study.

conducted by Kim et al, it is predicted that α-mangostin imparts its analgesic effects by activating tandem pore domains in a weak inward-rectifying K^+ channel (TWIK)-related K^+ channels (TREK), specifically TREK-1 and TREK-2, and TWIK-related arachidonic acid-activated K^+ channels (TRAAK). This action inhibits transient receptor potential vanilloid 1 (TRPV1) and reduces tetrodotoxin (TTX)-sensitive Na_V ($Na_V1.7$), as visualized in Figure 10.[105]

TRPV1 plays a vital role as a membrane channel in T cells, regulating the influx of calcium ions. In addition to body temperature regulation, TRPV1 also senses scalding heat and pain (nociception). Inhibiting TRPV1 suggests the suppression of receptor potentials.[148,149] TREK-1, TREK-2, and TRAAK are key K^+ channels at the nodes of Ranvier for rapid action potential conduction in mammalian myelinated afferent nerves.[150–152] On the other hand, $Na_V1.7$ belongs to the family of voltage-gated sodium channels, facilitating sodium influx under physiological conditions when the nerve membrane is depolarized.[153,154] The activation of TREK/TRAAK and the inhibition of $Na_V1.7$ indicate membrane stabilization and the suppression of action potential firing in dorsal root ganglion (DRG) neurons.

Rheumatoid Arthritis

In the context of rheumatoid arthritis (RA), the crucial role of immune system regulation is paramount. One of the factors that can alleviate hyperimmunity in RA is peroxisome proliferator-activated receptor γ (PPAR-γ).[155] The activation of PPAR-γ is known to actively contribute to the overexpression of sirtuin 1 (SIRT-1) through an unknown cross-talk mechanism. This overexpressed SIRT-1 subsequently leads to the final suppression of immune system activity by preventing macrophage/monocyte polarization.[156] Interestingly, the pharmacological targeting potential of PPAR-γ in

RA is substantial, given that upregulation of PPAR-γ is observed in RA conditions.[157] α-mangostin is known to interact strongly with PPAR-γ, exhibiting a binding affinity of −6.7 kcal/mol.[106] This finding is reinforced by in *vivo* testing conducted by Wu et al, showing that the group administered with α-mangostin demonstrates overexpression of SIRT-1, aligning with the expected mechanism for RA inflammation management.

Future Perspective

The utilization of computational studies continues to evolve over time, offering extensive opportunities for investigating the therapeutic potential of α-mangostin. This review highlights the software tools employed to predict α-mangostin's efficacy, including ArgusLab, AutoDock, AutoDock Vina, Glide, HEX, and MOE. However, there is still a plethora of software yet to be maximized for evaluating α-mangostin's mechanisms in specific clinical pathologies. Offline software such as GOLD,[158] FlexX,[159] rDOCK,[160] and UCSF Dock,[161] along with web server-based software like PatchDock,[162] HADDOCK,[163] ClusPro,[164] and FireDOCK,[165] provide promising avenues for exploring the best-suited software in terms of validity and compatibility for α-mangostin's applications. In its development, the correlation between computational study results and wet lab studies has also continually improved. One significant advancement is in the enhancement of QSAR (Quantitative Structure-Activity Relationship) validation, a method that constructs predictive models of molecular structures based on activity in wet lab studies. Initially, QSAR relied solely on molecular descriptors (2D QSAR); however, it has now transitioned to 3D QSAR, which also incorporates spatial factors that influence molecular interactions.[166]

Furthermore, beyond the vast possibilities in software exploration, investigating α-mangostin's efficacy for various other pathological conditions is imperative. This is underscored by the high likelihood of in vitro and in vivo findings demonstrating the exceptional antioxidant and anti-inflammatory properties of α-mangostin. As known, hyperoxidative and inflammatory conditions can correlate with secondary diseases such as cancer and other metabolic disorders.[167–170] Hence, the continued utilization of computational studies for α-mangostin's role in pathologies related to oxidative stress and inflammation remains highly necessary. Ultimately, it is expected that a comprehensive database regarding the therapeutic efficacy and mechanisms of α-mangostin will be established based on the overall pharmacological activity predictions from computational studies.

Similarly to the success of computational studies in identifying more effective derivatives of artemisinin, various computational research efforts have also been directed towards finding more effective derivatives of α-mangostin with improved pharmacokinetic profiles.[171] For instance, studies conducted by Maulana et al and Mardianingrum et al have sought to discover α-mangostin derivatives with enhanced efficacy in anti-diabetic and anti-breast cancer applications.-[83,94] Thus, a potential strategy for drug development from natural sources encompasses not only the discovery of existing compounds but also the search for more optimal derivatives.

Conclusion

α-Mangostin exhibits a wide range of therapeutic potentials, as evidenced by computational studies. The predicted benefits include antioxidant, anti-inflammatory, Alzheimer's disease treatment, antidiabetic, antimicrobial agent, anticancer, chronic periodontitis management, pain relief, chronic kidney disease treatment, and rheumatoid arthritis. Additionally, intriguing findings suggest that α-mangostin functions as a larvicide against Aedes aegypti mosquito larvae. Each pharmacological activity of α-mangostin is associated with specific target mechanisms, validated by its binding affinity to target receptors. However, it is important to emphasize that this review does not intend to present α-mangostin as a "panacea" or a universal cure for all health conditions. Rather, it aims to guide researchers towards further investigations to substantiate the clinical applications of α-mangostin. It is important to recognize that in silico studies are a crucial component of the early stages in drug design and development. Further clinical research is necessary to elucidate the effectiveness of this compound before it can be translated into clinical practice.

Acknowledgments

We thank the Rector of Universitas Padjadjaran for the APC. The figures and graphical abstract in this manuscript were created with Microsoft PowerPoint Version 16.77.1. The authors would like also to extend their appreciation to the

Deanship of Scientific Research at Northern Border University, Arar, KSA for funding this research work through the project number "NBU-FFR-2024-2985-11".

Funding

This research was funded by the Deanship of Scientific Research at Northern Border University, Arar, KSA.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Gorlenko CL, Kiselev HY, Budanova EV, Zamyatnin AA, Ikryannikova LN. Plant secondary metabolites in the battle of drugs and drug-resistant bacteria: new heroes or worse clones of antibiotics? *Antibiotics*. 2020;9(4). doi:10.3390/antibiotics9040170
2. Kabera JN, Semana E, Mussa AR, et al. Plant Secondary Metabolites: biosynthesis, Classification, Function and Pharmacological Properties. *J Pharm Pharmacol*. 2014;2(January).
3. Altmann KH. Drugs from the oceans: marine natural products as leads for drug discovery. *Chimia*. 2017;71(10). doi:10.2533/chimia.2017.646
4. Tresina PS, Selvam MS, Rajesh A, Doss A, Mohan VR. Natural Products in Drug Discovery: approaches and Development. *J Pharm Res Int*. doi:10.9734/jpri/2021/v33i35a31879
5. Mathur S, Hoskins C. Drug development: lessons from nature. *Biomed Rep*. 2017;6(6). doi:10.3892/br.2017.909
6. Veeresham C. Natural products derived from plants as a source of drugs. *J Adv Pharm Technol Res*. 2012;3(4). doi:10.4103/2231-4040.104709
7. Wathoni N, Suhandi C, Purnama MFG, et al. Alginate and Chitosan-Based Hydrogel Enhance Antibacterial Agent Activity on Topical Application. *Infect Drug Resist*. 2024:17. doi:10.2147/IDR.S456403
8. Pomalingo DR, Suhandi C, Megantara S, Muchtaridi M. The optimization of α-mangostin as a new drug candidate through molecular docking and dynamic simulations. *Rasayan J Chemi*. 2021;14(2). doi:10.31788/RJC.2021.1425770
9. Megantara S, Wathoni N, Mohammed AFA, Suhandi C, Ishmatullah MH, MFFD P. In Silico Study: combination of α-Mangostin and Chitosan Conjugated with Trastuzumab against Human Epidermal Growth Factor Receptor 2. *Polymers*. 2022;14(13). doi:10.3390/polym14132747
10. Suhandi C, Wilar G, Lesmana R, et al. Propolis-Based Nanostructured Lipid Carriers for α-Mangostin Delivery: formulation, Characterization, and In Vitro Antioxidant Activity Evaluation. *Molecules*. 2023;28(16). doi:10.3390/molecules28166057
11. Suhandi C, Alfathonah SS, Hasanah AN. Potency of Xanthone Derivatives from Garcinia mangostana L. for COVID-19 Treatment through Angiotensin-Converting Enzyme 2 and Main Protease Blockade: a Computational Study. *Molecules*. 2023;28(13). doi:10.3390/molecules28135187
12. Suharyani I, Suhandi C, Rizkiyan Y, et al. Molecular docking in prediction of α-mangostin/cyclodextrin inclusion complex formation. In: *AIP Conference Proceedings*. Vol 2706.; 2023. doi:10.1063/5.0120782.
13. Suharyani I, Muchtaridi M, Mohammed AFA, Elamin KM, Wathoni N, Abdassah M. α-Mangostin/γ-Cyclodextrin Inclusion Complex: formation and Thermodynamic Study. *Polymers*. 2021;13(17). doi:10.3390/polym13172890
14. Milanda T, Cindana Mo'o FR, Mohammed AFA, et al. Alginate/Chitosan-Based Hydrogel Film Containing α-Mangostin for Recurrent Aphthous Stomatitis Therapy in Rats. *Pharmaceutics*. 2022;14(8). doi:10.3390/pharmaceutics14081709
15. Dang TH, Kim JY, Kim HJ, et al. Alpha-Mangostin: a Potent Inhibitor of TRPV3 and Pro-Inflammatory Cytokine Secretion in Keratinocytes. *Int J Mol Sci*. 2023;24(16). doi:10.3390/ijms241612930
16. Li D, Liu Q, Lu X, et al. α-Mangostin remodels visceral adipose tissue inflammation to ameliorate age-related metabolic disorders in mice. *Aging*. 2019;11(23). doi:10.18632/aging.102512
17. Vien LC, Chinnappan S, Mogana R. Antioxidant activity of Garcinia mangostana l and alpha mangostin: a review. *Res J Pharm Technol*. 2021;14(8). doi:10.52711/0974-360X.2021.00776
18. Wang Q, Li R, Li N, et al. The antioxidant activities, inhibitory effects, kinetics, and mechanisms of artocarpin and α-mangostin on α-glucosidase and α-amylase. *Int J Biol Macromol*. 2022:213. doi:10.1016/j.ijbiomac.2022.06.017
19. Herrera-Aco DR, Medina-Campos ON, Pedraza-Chaverri J, Sciutto-Conde E, Rosas-Salgado G, Alpha-mangostin F-G-G. Anti-inflammatory and antioxidant effects on established collagen-induced arthritis in DBA/1J mice. *Food Chemical Toxic*. 2019;124. doi:10.1016/j.fct.2018.12.018
20. Alam M, Rashid S, Fatima K, et al. Biochemical features and therapeutic potential of α-Mangostin: mechanism of action, medicinal values, and health benefits. *Biomed Pharmaco*. 2023:163. doi:10.1016/j.biopha.2023.114710
21. Huang W, Liang Y, Ma X. Alpha-mangostin induces endoplasmic reticulum stress and autophagy which count against fatty acid synthase inhibition mediated apoptosis in human breast cancer cells. *Cancer Cell Int*. 2019;19(1). doi:10.1186/s12935-019-0869-z
22. Chitchumroonchokchai C, Thomas-Ahner JM, Li J, et al. Anti-tumorigenicity of dietary α-mangostin in an HT-29 colon cell xenograft model and the tissue distribution of xanthones and their Phase II metabolites. *Mol Nutr Food Res*. 2013;57(2). doi:10.1002/mnfr.201200539
23. Kaur P, Khatik G. An Overview of Computer-aided Drug Design Tools and Recent Applications in Designing of Anti-diabetic Agents. *Curr Drug Targets*. 2020;22(10). doi:10.2174/1389450121666201119141525
24. Wang G, Xu L, Chen H, Liu Y, Pan P, Hou T. Recent advances in computational studies on voltage-gated sodium channels: drug design and mechanism studies. *Wiley Interdiscip Rev Comput Mol Sci*. 2023;13(2). doi:10.1002/wcms.1641
25. Hu JP, Wu ZX, Xie T, et al. Applications of Molecular Simulation in the Discovery of Antituberculosis Drugs: a Review. *Protein Pept Lett*. 2019;26(9). doi:10.2174/0929866526666190620145919
26. Dorahy G, Chen JZ, Balle T. Computer-Aided Drug Design towards New Psychotropic and Neurological Drugs. *Molecules*. 2023;28(3). doi:10.3390/molecules28031324

27. Vemula D, Jayasurya P, Sushmitha V, Kumar YN, CADD BV. AI and ML in drug discovery: a comprehensive review. *Eur J Pharm Sci*. 2023;181. doi:10.1016/j.ejps.2022.106324
28. Yasuo N, Ishida T, Sekijima M. Computer aided drug discovery review for infectious diseases with case study of anti-Chagas project. *Parasitol Int*. 2021;83. doi:10.1016/j.parint.2021.102366
29. Leelananda SP, Lindert S. Computational methods in drug discovery. *Beilstein J. Org. Chem*. 2016;12. doi:10.3762/bjoc.12.267
30. Drie JH. Computer-aided drug design: the next 20 years. *J Comput Aided Mol Des*. 2007;21(10–11). doi:10.1007/s10822-007-9142-y
31. Talele T, Khedkar S, Rigby A. Successful Applications of Computer Aided Drug Discovery: moving Drugs from Concept to the Clinic. *Curr Top Med Chem*. 2010;10(1). doi:10.2174/156802610790232251
32. Vijayakrishnan R. Structure-based drug design and modern medicine. *J Postgrad Med*. 2009;55(4). doi:10.4103/0022-3859.58943
33. Wen L, Chan BCL, Qiu MH, Leung PC, Wong CK. Artemisinin and Its Derivatives as Potential Anticancer Agents. *Molecules*. 2024;29(16). doi:10.3390/molecules29163886
34. Kiani AK, Pheby D, Henehan G, et al. Ethical considerations regarding animal experimentation. *J Prev Med Hyg*. 2022;63(2). doi:10.15167/2421-4248/jpmh2022.63.2S3.2768
35. Aerts L, Miccoli B, Delahanty A, et al. Do we still need animals? Surveying the role of animal-free models in Alzheimer's and Parkinson's disease research. *EMBO J*. 2022;41(6). doi:10.15252/embj.2021110002
36. Kabene S, Baadel S. Bioethics: a look at animal testing in medicine and cosmetics in the UK. *J Med Ethics Hist Med*. 2019;12. doi:10.18502/jmehm.v12i15.1875
37. Naderi MM, Sarvari A, Milanifar A, Boroujeni SB, Akhondi MM. Regulations and ethical considerations in animal experiments: international laws and Islamic perspectives. *Avicenna J Med Biotechnol*. 2012;4(3).
38. Yokoyama T, Ueda M, Ando Y, Mizuguchi M. Discovery of γ-Mangostin as an Amyloidogenesis Inhibitor. *Sci Rep*. 2015;5. doi:10.1038/srep13570
39. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;n71 372
40. Khamthong N, Hutadilok-Towatana N. Phytoconstituents and biological activities of Garcinia dulcis (Clusiaceae): a review. *Nat Prod Commun*. 2017;12(3). doi:10.1177/1934578x1701200337
41. Wahyuni FS, Ali DAI, Lajis NH. Anti-inflammatory activity of isolated compounds from the Stem Bark of Garcinia cowa Roxb. *Pharmacogn J*. 2017;9(1). doi:10.5530/pj.2017.1.10
42. John OD, Mushunje AT, Surugau N, Guad RM. The metabolic and molecular mechanisms of α-mangostin in cardiometabolic disorders (Review). *Int J Mol Med*. 2022;50(3). doi:10.3892/ijmm.2022.5176
43. Sultan OS, Kantilal HK, Khoo SP, et al. The Potential of α-Mangostin from Garcinia mangostana as an Effective Antimicrobial Agent—A Systematic Review and Meta-Analysis. *Antibiotics*. 2022;11(6). doi:10.3390/antibiotics11060717
44. Narasimhan S, Maheshwaran S, Abu-Yousef IA, et al. Anti-bacterial and anti-fungal activity of xanthones obtained via semi-synthetic modification of α-mangostin from Garcinia mangostana. *Molecules*. 2017;22(2). doi:10.3390/molecules22020275
45. Lipinski CA, Lombardo F, Dominy BW, Feeney PJ. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev*. 2012;64. doi:10.1016/j.addr.2012.09.019
46. Saputro AH, Amelia T, Mahardhika AB, et al. Alpha-mangostin, piperine and beta-sitosterol as hepatitis C antivirus (HCV): in silico and in vitro studies. *Heliyon*. doi:10.1016/j.heliyon.2023.e20141
47. Hidayat S, Ibrahim F, Pratama K, Muchtaridi M. The interaction of alpha-mangostin and its derivatives against main protease enzyme in COVID-19 using in silico methods. *J Adv Pharm Technol Res*. 2021;12(3). doi:10.4103/japtr.JAPTR_299_20
48. Prasetyanti IK, Sukardiman S. Admet prediction and in silico analysis of mangostin derivatives and sinensetin on maltase-glucoamylase target for searching anti-diabetes drug candidates. *Pharmacogn J*. 2021;13(4). doi:10.5530/pj.2021.13.113
49. Lipinski CA. Lead- and drug-like compounds: the rule-of-five revolution. *Drug Discov Today Technol*. 2004;1(4). doi:10.1016/j.ddtec.2004.11.007
50. Lipinski CA. Rule of five in 2015 and beyond: target and ligand structural limitations, ligand chemistry structure and drug discovery project decisions. *Adv Drug Deliv Rev*. 2016;101. doi:10.1016/j.addr.2016.04.029
51. Cheng F, Li W, Liu G, Tang Y. In Silico ADMET Prediction: recent Advances, Current Challenges and Future Trends. *Curr Top Med Chem*. 2013;13(11). doi:10.2174/15680266113139990033
52. Yazdanian M, Glynn SL, Wright JL, Hawi A. Correlating partitioning and Caco-2 cell permeability of structurally diverse small molecular weight compounds. *Pharm Res*. 1998;15(9). doi:10.1023/A:1011930411574
53. Ma XL, Chen C, Yang J. Predictive model of blood-brain barrier penetration of organic compounds. *Acta Pharmacol Sin*. 2005;26(4). doi:10.1111/j.1745-7254.2005.00068.x
54. Setyawati LU, Nurhidayah W, Khairul Ikram NK, Mohd Fuad WE, Muchtaridi M. General toxicity studies of alpha mangostin from Garcinia mangostana: a systematic review. *Heliyon*. 2023;9(5). doi:10.1016/j.heliyon.2023.e16045
55. Bitencourt-Ferreira G, de Azevedo WF. Molecular docking simulations with ArgusLab. *Meth Molecular Biolo*. 2019. doi:10.1007/978-1-4939-9752-7_13
56. Steffen C, Thomas K, Huniar U, Hellweg A, Rubner O, Schroer A. AutoDock4 and AutoDockTools4: automated Docking with Selective Receptor Flexibility. *J Comput Chem*. 2010;31(16).
57. Trott O, Olson AJ. AutoDock Vina: improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *J Comput Chem*. doi:10.1002/jcc.21334
58. Friesner RA, Banks JL, Murphy RB, et al. Glide: a New Approach for Rapid, Accurate Docking and Scoring. 1. Method and Assessment of Docking Accuracy. *J Med Chem*. 2004;47(7). doi:10.1021/jm0306430
59. Macindoe G, Mavridis L, Venkatraman V, Devignes MD, Ritchie DW. HexServer: an FFT-based protein docking server powered by graphics processors. *Nucleic Acids Res*. 2010;38(SUPPL. 2). doi:10.1093/nar/gkq311
60. Corbeil CR, Williams CI, Labute P. Variability in docking success rates due to dataset preparation. *J Comput Aided Mol Des*. 2012;26(6). doi:10.1007/s10822-012-9570-1

61. Joy S, Nair PS, Hariharan R, Pillai MR. Detailed comparison of the protein-ligand docking efficiencies of GOLD, a commercial package and arguslab, a licensable freeware. *Silico Biol*. 2006;6(6).
62. Eawsakul K, Ongtanasup T, Ngamdokmai N, Bunluepuech K. Alpha-glucosidase inhibitory activities of astilbin contained in Bauhinia strychnifolia Craib. stems: an investigation by in silico and in vitro studies. *BMC Complement Med Ther*. 2023;23(1). doi:10.1186/s12906-023-03857-5
63. Oda A, Takahashi O. Validation of ArgusLab Efficiencies for Binding Free Energy Calculations. *Chem-Bio Inf J*. 2009;9. doi:10.1273/cbij.9.52
64. Forli S, Huey R, Pique ME, Sanner MF, Goodsell DS, Olson AJ. Computational protein-ligand docking and virtual drug screening with the AutoDock suite. *Nat Protoc*. 2016;11(5). doi:10.1038/nprot.2016.051
65. Morris GM, Goodsell DS, Halliday RS, et al. Automated docking using a Lamarckian genetic algorithm and an empirical binding free energy function. *J Comput Chem*. 1998;19(14). doi:10.1002/(SICI)1096-987X(19981115)19:14
66. Jain AN, Nicholls A. Recommendations for evaluation of computational methods. *J Comput Aided Mol Des*. 2008;22(3–4). doi:10.1007/s10822-008-9196-5
67. Harris R, Olson AJ, Goodsell DS. Automated prediction of ligand-binding sites in proteins. *Proteins*. 2008;70(4). doi:10.1002/prot.21645
68. Jiang X, Tang N, Liu Y, et al. Integrating network analysis and pharmacokinetics to investigate the mechanisms of Danzhi Tiaozhi Decoction in metabolic-associated fatty liver disease (MAFLD). *J Ethnopharmacol*. 2024:318. doi:10.1016/j.jep.2023.117008
69. Cosconati S, Forli S, Perryman AL, Harris R, Goodsell DS, Olson AJ. Virtual screening with AutoDock: theory and practice. *Expert Opin Drug Discov*. 2010;5(6). doi:10.1517/17460441.2010.484460
70. ali SM, Hafsa J, Ben Abdallah J, Charfeddine B, Limem K. Neuroprotective and anti-amnesic effects of Laurus Nobilis essential oil against scopolamine-induced memory deficits in mice brain. *J Ethnopharmacol*. 2024;319. doi:10.1016/j.jep.2023.117151
71. Adeniyi AA, Ajibade PA. Comparing the suitability of autodock, gold and glide for the docking and predicting the possible targets of Ru(II)-based complexes as anticancer agents. *Molecules*. 2013;18(4). doi:10.3390/molecules18043760
72. Deng W, CLMJ V. Evaluation of different virtual screening programs for docking in a charged binding pocket. *J Chem Inf Model*. 2008;48(10). doi:10.1021/ci800154w
73. Gupta A, Bhat HR, Singh UP. Discovery of novel hybrids of Morpholino-1,3,5-triazine-pyrimidine as an anti-diabetic agent in High-fat, Low-dose Streptozotocin-induced diabetes in Wistar rats: an in-vitro, in-silico and in-vivo study. *J Mol Struct*. 2023;1294. doi:10.1016/j.molstruc.2023.136478
74. Ritchie DW. Evaluation of protein docking predictions using Hex 3.1 in CAPRI rounds 1 and 2. *Proteins*. 2003;52(1). doi:10.1002/prot.10379
75. Pagadala NS, Syed K, Tuszynski J. Software for molecular docking: a review. *Biophys Rev*. 2017;9(2). doi:10.1007/s12551-016-0247-1
76. Raissa R, Safitri A, Masruri M, Beltran MAG, Aulanni'am A. An In Silico Study of Examining Bioactive Compounds from Azadirachta indica Juss. (Neem) as Potential Death Receptor 5 Inductor in Hepatoma Cells. *Pharmacogn J*. 2022;14(2). doi:10.5530/pj.2022.14.44
77. Shakibay Senobari Z, Masoumian Hosseini M, Teimouri MB, Rezayan AH, Samarghandian S, Hekmat A. Chromone-embedded peptidomimetics and furopyrimidines as highly potent SARS-CoV-2 infection inhibitors: docking and MD simulation study. *BMC Res Notes*. 2023;16(1). doi:10.1186/s13104-023-06508-7
78. Khaw KY, Choi SB, Tan SC, Wahab HA, Chan KL, Murugaiyah V. Prenylated xanthones from mangosteen as promising cholinesterase inhibitors and their molecular docking studies. *Phytomedicine*. 2014;21(11). doi:10.1016/j.phymed.2014.06.017
79. Ruankham W, Suwanjang W, Phopin K, Songtawee N, Prachayasittikul V, Prachayasittikul S. Modulatory Effects of Alpha-Mangostin Mediated by SIRT1/3-FOXO3a Pathway in Oxidative Stress-Induced Neuronal Cells. *Front Nutr*. 2022;8. doi:10.3389/fnut.2021.714463
80. Wang Y, Xia Z, Xu JR, et al. α-Mangostin, a polyphenolic xanthone derivative from mangosteen, attenuates β-amyloid oligomers-induced neurotoxicity by inhibiting amyloid aggregation. *Neuropharmacology*. 2012;62(2). doi:10.1016/j.neuropharm.2011.09.016
81. Mahmudah R, Adnyana I, Sukandar E. Molecular docking studies of α-mangostin, γ-mangostin, and xanthone on peroxisome proliferator-activated receptor gamma diphenyl peptidase-4 enzyme, and aldose reductase enzyme as an antidiabetic drug candidate. *J Adv Pharm Technol Res*. 2021;12(2). doi:10.4103/japtr.JAPTR_255_20
82. Setiawan MT, Yanuar A. Virtual screening and molecular dynamics simulation of compounds from the herbal database of Indonesia against histone deacetylase 2. *Int J Appl Pharm*. 2018;10(Special Issue 1). doi:10.22159/ijap.2018.v10s1.52
83. Maulana AF, Sriwidodo S, Rukayadi Y, Maksum IP. In Silico Study of Mangostin Compounds and Its Derivatives as Inhibitors of α-Glucosidase Enzymes for Anti-Diabetic Studies. *Biology*. 2022;11(12). doi:10.3390/biology11121837
84. Lakshmi PTV, Radhika S, Annamalai A. Molecular docking analysis of phyto-ligands with multi drug resistant β-lactamases of Staphylococcus aureus. *Trends in Bioinformatics*. 2011;4(1). doi:10.3923/tb.2011.23.34
85. Ongtanasup T, Mazumder A, Dwivedi A, Eawsakul K. Homology Modeling, Molecular Docking, Molecular Dynamic Simulation, and Drug-Likeness of the Modified Alpha-Mangostin against the β-Tubulin Protein of Acanthamoeba Keratitis. *Molecules*. 2022;27(19). doi:10.3390/molecules27196338
86. Kalpana A, Vinodhini T. Insilico validation and comparison of antifungal competence and druglikeness of some natural xanthones – a step towards antimycotic therapeutics. *J Indian Chem Soc*. 2022;99(8). doi:10.1016/j.jics.2022.100577
87. Sumaryada T, Pramudita CA. Molecular docking evaluation of some indonesian's popular herbals for a possible covid-19 treatment. *Biointerface Res Appl Chem*. 2021;11(3). doi:10.33263/BRIAC113.98279835
88. Syahdi RR, Mun'im A, Suhartanto H, Yanuar A. Virtual screening of Indonesian herbal database as HIV-1 reverse transcriptase inhibitor. *Bioinformation*. 2012;8(24):1206–1210. doi:10.6026/97320630081206
89. Widowati W, Ginting CN, Lister INE, et al. Anti-aging effects of mangosteen peel extract and its phytochemical compounds: antioxidant activity, enzyme inhibition and molecular docking simulation. *Trop Life Sci Res*. 2020;31(3). doi:10.21315/tlsr2020.31.3.9
90. Vania L, Widyananda MH, Kharisma VD, et al. Anticancer activity prediction of Garcinia mangostana l. against her2-positive breast cancer through inhibiting egfr, her2 and igf1r protein: A bioinformatics study. *Biochem Cell Arch*. 2021;21(2).
91. Dewi C, Fristiohady A, Amalia R, Bunggulawa EJ, Muchtaridi M. Alpha-mangostin as an inhibitor of GSK3β in triple-negative breast cancer. *J Biomol Struct Dyn*. 2023;41(10). doi:10.1080/07391102.2022.2068074
92. Muchtaridi M, Dermawan D, Yusuf M. Molecular docking, 3D structure-based pharmacophore modeling, and ADME prediction of alpha mangostin and its derivatives against estrogen receptor alpha. *J Young Pharm*. 2018;10(3). doi:10.5530/jyp.2018.10.58

93. Muchtaridi M, Megantara S, Dermawan D, Yusuf M. Antagonistic mechanism of α-mangostin derivatives against human estrogen receptor α of breast cancer using molecular dynamics simulation. *Rasayan J Chemi*. 2019;12(4). doi:10.31788/RJC.2019.1245391
94. Mardianingrum R, Yusuf M, Hariono M, Mohd Gazzali A, Muchtaridi M. α-Mangostin and its derivatives against estrogen receptor alpha. *J Biomol Struct Dyn*. 2022;40(6). doi:10.1080/07391102.2020.1841031
95. See I, Ee GCL, Jong VYM, Teh SS, Acuña CLC, Mah SH. Cytotoxic activity of phytochemicals from Garcinia mangostana L. and G. benthamiana (Planch. & Triana) Pipoly against breast cancer cells. *Nat Prod Res*. 2021;35(24). doi:10.1080/14786419.2020.1836629
96. Khan P, Queen A, Mohammad T, et al. Identification of α-Mangostin as a Potential Inhibitor of Microtubule Affinity Regulating Kinase 4. *J Nat Prod*. 2019;82(8). doi:10.1021/acs.jnatprod.9b00372
97. Tu X, Li C, Sun W, et al. Suppression of Cancer Cell Stemness and Drug Resistance via MYC Destabilization by Deubiquitinase USP45 Inhibition with a Natural Small Molecule. *Cancers*. 2023;15(3). doi:10.3390/cancers15030930
98. Leão M, Gomes S, Pedraza-Chaverri J, et al. α-mangostin and gambogic acid as potential inhibitors of the p53-MDM2 interaction revealed by a yeast approach. *J Nat Prod*. 2013;76(4). doi:10.1021/np400049j
99. Rana MN, Tangpong J, Rahman MA. Xanthones protects lead-induced chronic kidney disease (CKD) via activating Nrf-2 and modulating NF-kB, MAPK pathway. *Biochem Biophys Rep*. 2020;21. doi:10.1016/j.bbrep.2019.100718
100. Saputra D, Ridwan RD. Exploration of Mangosteen Rind Extract (Garcinia Mangostana Linn.) as an Inhibitor of Cytokine from Chronic Periodontitis: a Bioinformatic Approach. *J Int Dental Med Res*. 2023;16(2).
101. Mohan S, Syam S, Abdelwahab SI, Thangavel N. An anti-inflammatory molecular mechanism of action of α-mangostin, the major xanthone from the pericarp of Garcinia mangostana: an in silico, in vitro and in vivo approach. *Food Funct*. 2018;9(7). doi:10.1039/c8fo00439k
102. Faisal MA, Oktaviyanti IK, Sujuti H, Rudijanto A. Virtual screening of the active components of Garcinia mangostana Linn. Potentially inhibiting the interaction of advanced glycation end-products and their receptor. *Open Access Maced J Med Sci*. 2020;8(A). doi:10.3889/oamjms.2020.5505
103. Kumar RB, Shanmugapriya B, Thiyagesan K, Kumar SR, Xavier SM. A search for mosquito larvicidal compounds by blocking the sterol carrying protein, AeSCP-2, through computational screening and docking strategies. *Pharmacogn Res*. 2010;2(4). doi:10.4103/0974-8490.69126
104. Sunitha J. Molecular docking studies of α-mangostin with oral cancer targets ARRB1, FLNA, CALM3 and HTT. *Bioinformation*. 2020;16(8):625–630. doi:10.6026/97320630016625
105. Kim SE, Yin MZ, Roh JW, et al. Multi-target modulation of ion channels underlying the analgesic effects of α-mangostin in dorsal root ganglion neurons. *Phytomedicine*. 2023:115. doi:10.1016/j.phymed.2023.154791
106. Wu YJ, Zhang SS, Yin Q, et al. α-Mangostin Inhibited M1 Polarization of Macrophages/Monocytes in Antigen-Induced Arthritis Mice by Up-Regulating Silent Information Regulator 1 and Peroxisome Proliferators-Activated Receptor γ Simultaneously. *Drug Des Devel Ther*. 2023:17. doi:10.2147/DDDT.S397914
107. Zaman M, Khan AN, Wahiduzzaman ZSM, Khan RH. Protein misfolding, aggregation and mechanism of amyloid cytotoxicity: an overview and therapeutic strategies to inhibit aggregation. *Int J Biol Macromol*. 2019;134. doi:10.1016/j.ijbiomac.2019.05.109
108. Giorgetti S, Greco C, Tortora P, Aprile FA. Targeting amyloid aggregation: an overview of strategies and mechanisms. *Int J Mol Sci*. 2018;19(9). doi:10.3390/ijms19092677
109. Marucci G, Buccioni M, Ben DD, Lambertucci C, Volpini R, Amenta F. Efficacy of acetylcholinesterase inhibitors in Alzheimer's disease. *Neuropharmacology*. 2021;190. doi:10.1016/j.neuropharm.2020.108352
110. Moreta MPG, Burgos-Alonso N, Torrecilla M, Marco-Contelles J, Bruzos-Cidón C. Efficacy of acetylcholinesterase inhibitors on cognitive function in Alzheimer's disease. Review of reviews. *Biomedicines*. 2021;9(11). doi:10.3390/biomedicines9111689
111. Julien C, Tremblay C, Émond V, et al. SIRT1 decrease parallels the accumulation of tau in Alzheimer disease. *J Neuropathol Exp Neurol*. 2009;68(1).
112. Qin W, Yang T, Ho L, et al. Neuronal SIRT1 activation as a novel mechanism underlying the prevention of Alzheimer disease amyloid neuropathology by calorie restriction. *J Biol Chem*. 2006;281(31). doi:10.1074/jbc.M602909200
113. Agarwal P, Gupta R. Alpha-amylase inhibition can treat diabetes mellitus. *Res Revi J Med Health Sci*. 2016;5(4).
114. Promyos N, Temviriyanukul P, Suttisansanee U. Investigation of anthocyanidins and anthocyanins for targeting α-glucosidase in diabetes mellitus. *Prev Nutr Food Sci*. 2020;25(3). doi:10.3746/pnf.2020.25.3.263
115. Gediya P, Parikh PK, Vyas VK, Ghate MD. Histone deacetylase 2: a potential therapeutic target for cancer and neurodegenerative disorders. *Eur J Med Chem*. 2021;216. doi:10.1016/j.ejmech.2021.113332
116. Hou Q, Hu K, Liu X, Quan J, Liu Z. HADC regulates the diabetic vascular endothelial dysfunction by targetting MnSOD. *Biosci Rep*. 2018;38(5). doi:10.1042/BSR20181042
117. Chang KC, Shieh B, Petrash JM. Role of aldose reductase in diabetes-induced retinal microglia activation. *Chem Biol Interact*. 2019;302. doi:10.1016/j.cbi.2019.01.020
118. Oyebamiji AK, Akintayo ET, Akintayo CO, Aworinde HO, Adekunle OD, Akintelu SA. Biochemical Study on Bioactive Peptides: potential Anti-aldose Reductase Targeting Diabetes mellitus. *Lett Applied NanoBioScie*. 2024;13(1). doi:10.33263/LIANBS131.036
119. Gabasa M, Radisky ES, Ikemori R, et al. MMP1 drives tumor progression in large cell carcinoma of the lung through fibroblast senescence. *Cancer Lett*. 2021:507. doi:10.1016/j.canlet.2021.01.028
120. Wang F, Murrell GAC, Wang MX. Oxidative stress-induced C-jun N-terminal kinase (JNK) activation in tendon cells upregulates MMP1 mRNA and protein expression. *J Orthop Res*. 2007;25(3). doi:10.1002/jor.20294
121. Hidayat S, Ibrahim FM, Suhandi C, Muchtaridi M. A systematic review: molecular docking simulation of small molecules as anticancer non-small cell lung carcinoma drug candidates. *J Adv Pharm Technol Res*. 2022;13(3). doi:10.4103/japtr.japtr_311_21
122. Liu Q, Tan Q, Zheng Y, et al. Blockade of fas signaling in breast cancer cells suppresses tumor growth and metastasis via disruption of fas signaling-initiated cancer-related inflammation. *J Biol Chem*. 2014;289(16). doi:10.1074/jbc.M113.525014
123. Peyvandi H, Peyvandi AA, Safaei A, Azodi MZ, Rezaei-Tavirani M. Introducing potential key proteins and pathways in human laryngeal cancer: a system biology approach. *Iran J Pharm Res World*. 2018;17(1).
124. Anticariogenic And Anticarcinogenic Effects Of Garcinia Mangostana Pericarp Extracts On Cariogenic Bacteria And On Cancer Cell Lines With Molecular Docking Study. *Int J PharmRes*. 2021;13(02). doi:10.31838/ijpr/2021.13.02.040

125. Naz F, Khan FI, Mohammad T, et al. Investigation of molecular mechanism of recognition between citral and MARK4: a newer therapeutic approach to attenuate cancer cell progression. *Int J Biol Macromol*. 2018:107. doi:10.1016/j.ijbiomac.2017.10.143
126. Li K, Wang Q, Bian H, et al. Comprehensive Analysis Reveals USP45 as a Novel Putative Oncogene in Pan-Cancer. *Front Mol Biosci*. 2022:9. doi:10.3389/fmolb.2022.886904
127. Burlaka I, Nilsson LM, Scott L, et al. Prevention of apoptosis averts glomerular tubular disconnection and podocyte loss in proteinuric kidney disease. *Kidney Int*. 2016;90(1). doi:10.1016/j.kint.2016.03.026
128. Wang M, Xu H, Chong Lee Shin OLS, et al. Compound α-keto acid tablet supplementation alleviates chronic kidney disease progression via inhibition of the NF-kB and MAPK pathways. *J Transl Med*. 2019;17(1). doi:10.1186/s12967-019-1856-9
129. Nezu M, Suzuki N, Yamamoto M. Targeting the KEAP1-NRF2 System to Prevent Kidney Disease Progression. *Am J Nephrol*. 2017;45(6). doi:10.1159/000475890
130. Rodríguez-Expósito RL, Nicolás-Hernández DS, Sifaoui I, et al. Gongolarones as antiamoeboid chemical scaffold. *Biomed Pharmaco*. 2023:158. doi:10.1016/j.biopha.2022.114185
131. Miszkiel A, Wojciechowski M, Milewski S. Long range molecular dynamics study of regulation of eukaryotic glucosamine-6-phosphate synthase activity by UDP-GlcNAc. *J Mol Model*. 2011;17(12). doi:10.1007/s00894-011-1003-x
132. Ortiz-Ramírez JA, Cuéllar-Cruz M, López-Romero E. Cell compensatory responses of fungi to damage of the cell wall induced by Calcofluor White and Congo Red with emphasis on Sporothrix schenckii and Sporothrix globosa. A review. *Front Cell Infect Microbiol*. 2022;12. doi:10.3389/fcimb.2022.976924
133. Steuten K, Kim H, Widen JC, et al. Challenges for Targeting SARS-CoV-2 Proteases as a Therapeutic Strategy for COVID-19. *ACS Infect Dis*. 2021;7(6). doi:10.1021/acsinfecdis.0c00815
134. Abhinand CS, Nair AS, Krishnamurthy A, Oommen OV, Sudhakaran PR. Potential protease inhibitors and their combinations to block SARS-CoV-2. *J Biomol Struct Dyn*. 2022;40(2). doi:10.1080/07391102.2020.1819881
135. Bourgonje AR, Abdulle AE, Timens W, et al. Angiotensin-converting enzyme 2 (ACE2), SARS-CoV-2 and the pathophysiology of coronavirus disease 2019 (COVID-19). *J Pathol*. 2020;251(3). doi:10.1002/path.5471
136. Beyerstedt S, Casaro EB, Éb R. COVID-19: angiotensin-converting enzyme 2 (ACE2) expression and tissue susceptibility to SARS-CoV-2 infection. *Eur J Clin Microbiol Infec. Dis*. 2021;40(5). doi:10.1007/s10096-020-04138-6
137. Cilento ME, Kirby KA, Sarafianos SG. Avoiding Drug Resistance in HIV Reverse Transcriptase. *Chem Rev*. 2021;121(6). doi:10.1021/acs.chemrev.0c00967
138. Singh AK, Das K. Insights into HIV-1 Reverse Transcriptase (RT) Inhibition and Drug Resistance from Thirty Years of Structural Studies. *Viruses*. 2022;14(5). doi:10.3390/v14051027
139. Sahu A, Raza K, Pradhan D, Jain AK, Verma S. Cyclooxygenase-2 as a therapeutic target against human breast cancer: a comprehensive review. *WIREs Mech Dise*. 2023;15(3). doi:10.1002/wsbm.1596
140. Narasimha A, Watanabe J, Lin JA, et al. A novel anti-atherogenic role for COX-2-potential mechanism for the cardiovascular side effects of COX-2 inhibitors. *Prostaglandins Other Lipid Mediat*. 2007;84(1–2). doi:10.1016/j.prostaglandins.2007.03.004
141. Chang JE, Choi MS. A molecular perspective on the potential benefits of metformin for the treatment of inflammatory skin disorders. *Int J Mol Sci*. 2020;21(23). doi:10.3390/ijms21238960
142. Brenner T, Fleming TH, Spranz D, et al. Reactive metabolites and AGE-RAGE-mediated inflammation in patients following liver transplantation. *Mediators Inflamm*. 2013;2013. doi:10.1155/2013/501430
143. Chen J, Peng H, Chen C, et al. NAG-1/GDF15 inhibits diabetic nephropathy via inhibiting AGE/RAGE-mediated inflammation signaling pathways in C57BL/6 mice and HK-2 cells. *Life Sci*. 2022:311. doi:10.1016/j.lfs.2022.121142
144. Suresh Kumar P, Chezhian A, Senthil Raja P, Sathiyapriya J. Computational selections of terpenes present in the plant Calotropis gigantea as mosquito larvicide's by blocking the sterol carrying protein, AeSCP-2. *Bangladesh J Pharmacol*. 2012;7(1). doi:10.3329/bjp.v7i1.8414
145. Da Silva JBP, DMDAF N, Da Silva AG, et al. Thiosemicarbazones as Aedes aegypti larvicidal. *Eur J Med Chem*. 2015:100. doi:10.1016/j.ejmech.2015.04.061
146. Cui J, Hu W, Cai Z, et al. New medicinal properties of mangostins: analgesic activity and pharmacological characterization of active ingredients from the fruit hull of Garcinia mangostana L. *Pharmacol Biochem Behav*. 2010;95(2). doi:10.1016/j.pbb.2009.12.021
147. Mohd SMH, Taher M, Susanti D, Kek TL, Salleh MZ, Zakaria ZA. Mechanisms of α-Mangostin-Induced Antinociception in a Rodent Model. *Biol Res Nurs*. 2015;17(1). doi:10.1177/1099800414529648
148. Hagenacker T, Ledwig D, Büsselberg D. Feedback mechanisms in the regulation of intracellular calcium ([Ca2+]i) in the peripheral nociceptive system: role of TRPV-1 and pain related receptors. *Cell Calcium*. 2008;43(3). doi:10.1016/j.ceca.2007.05.019
149. Evangelista S. Novel therapeutics in the field of capsaicin and pain. *Expert Rev Clin Pharmacol*. 2015;8(4). doi:10.1586/17512433.2015.1044438
150. Han HJ, Lee SW, Kim GT, et al. Enhanced expression of TREK-1 is related with chronic constriction injury of neuropathic pain mouse model in dorsal root ganglion. *Biomol Ther*. 2016;24(3). doi:10.4062/biomolther.2016.038
151. Walsh Y, Leach M, Veale EL, Mathie A. Block of TREK and TRESK K2P channels by lamotrigine and two derivatives sipatrigine and CEN-092. *Biochem Biophys Rep*. 2021;26. doi:10.1016/j.bbrep.2021.101021
152. Dadi PK, Vierra NC, Days E, et al. Selective Small Molecule Activators of TREK-2 Channels Stimulate Dorsal Root Ganglion c-Fiber Nociceptor Two-Pore-Domain Potassium Channel Currents and Limit Calcium Influx. *ACS Chem Neurosci*. 2017;8(3). doi:10.1021/acschemneuro.6b00301
153. Minett MS, Falk S, Santana-Varela S, et al. Pain without nociceptors? Nav1.7-independent pain mechanisms. *Cell Rep*. 2014;6(2). doi:10.1016/j.celrep.2013.12.033
154. Kingwell K. Nav1.7 withholds its pain potential. *Nat Rev Drug Discov*. doi:10.1038/d41573-019-00065-0
155. Li XF, Sun YY, Bao J, et al. Functional role of PPAR-γ on the proliferation and migration of fibroblast-like synoviocytes in rheumatoid arthritis. *Sci Rep*. 2017;7(1). doi:10.1038/s41598-017-12570-6
156. feng LX, qin YS, Li H, et al. PPAR-γ alleviates the inflammatory response in TNF-α-induced fibroblast-like synoviocytes by binding to p53 in rheumatoid arthritis. *Acta Pharmacol Sin*. 2023;44(2). doi:10.1038/s41401-022-00957-9

157. Jalil SF, Ahmed I, Gauhar Z, et al. Association of Pro12Ala (rs1801282) variant of PPAR gamma with Rheumatoid Arthritis in a Pakistani population. *Rheumatol Int*. 2014;34(5). doi:10.1007/s00296-013-2768-2
158. Verdonk ML, Cole JC, Hartshorn MJ, Murray CW, Taylor RD. Improved protein-ligand docking using GOLD. *Proteins*. 2003;52(4). doi:10.1002/prot.10465
159. Schellhammer I, Rarey M. FlexX-Scan: fast, structure-based virtual screening. *Proteins*. 2004;57(3). doi:10.1002/prot.20217
160. Ruiz-Carmona S, Alvarez-Garcia D, Foloppe N, et al. rDock: a Fast, Versatile and Open Source Program for Docking Ligands to Proteins and Nucleic Acids. *PLoS Comput Biol*. 2014;10(4). doi:10.1371/journal.pcbi.1003571
161. Ermel UH, Arghittu SM, Frangakis AS. ArtiaX: an electron tomography toolbox for the interactive handling of sub-tomograms in UCSF ChimeraX. *Protein Sci*. 2022;31(12). doi:10.1002/pro.4472
162. Schneidman-Duhovny D, Inbar Y, Nussinov R, et al. PatchDock and SymmDock: servers for rigid and symmetric docking. *Nucleic Acids Res*. 2005;33(SUPPL. 2). doi:10.1093/nar/gki481
163. Spiliotopoulos D, Kastritis PL, Melquiond ASJ, et al. dMM-PBSA: a new HADDOCK scoring function for protein-peptide docking. *Front Mol Biosci*. 2016;3(AUG). doi:10.3389/fmolb.2016.00046
164. Kozakov D, Hall DR, Xia B, et al. The ClusPro web server for protein-protein docking. *Nat Protoc*. 2017;12(2). doi:10.1038/nprot.2016.169
165. Mashiach E, Schneidman-Duhovny D, Andrusier N, Nussinov R, Wolfson HJ. FireDock: a web server for fast interaction refinement in molecular docking. *Nucleic Acids Res*. 2008;36(Web Server issue). doi:10.1093/nar/gkn186
166. Rasulev B. Recent developments in 3D QSAR and molecular docking studies of organic and nanostructures. In: *Handbook of Computational Chemistry*. 2017. doi:10.1007/978-3-319-27282-5_54
167. Nyawo TA, Pheiffer C, Mazibuko-Mbeje SE, et al. Physical exercise potentially targets epicardial adipose tissue to reduce cardiovascular disease risk in patients with metabolic diseases: oxidative stress and inflammation emerge as major therapeutic targets. *Antioxidants*. 2021;10(11). doi:10.3390/antiox10111758
168. Li S, Hong M, Tan HY, Wang N, Feng Y. Insights into the Role and Interdependence of Oxidative Stress and Inflammation in Liver Diseases. *Oxid Med Cell Longev*. 2016;2016. doi:10.1155/2016/4234061
169. Ito F, Sono Y, Ito T. Measurement and clinical significance of lipid peroxidation as a biomarker of oxidative stress: oxidative stress in diabetes, atherosclerosis, and chronic inflammation. *Antioxidants*. 2019;8(3). doi:10.3390/antiox8030072
170. Suhandi C, Mohammed AFA, Wilar G, El-Rayyes A, Wathoni N. Effectiveness of Mesenchymal Stem Cell Secretome on Wound Healing: a Systematic Review and Meta-analysis. *Tissue Eng Regen Med*. doi:10.1007/s13770-023-00570-9
171. WANG MH, ZHANG KJ, GU QL, BI XL, WANG JX. Pharmacology of mangostins and their derivatives: a comprehensive review. *Chinese J Nat Med*. 2017;15(2). doi:10.1016/S1875-5364(17)30024-9