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Original Article

An Amalgamated *in silico* Approach to Screen Lipid Lowering Herbs towards Developing Antilipidemic Polyherbal Formulation

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ABSTRACT

Background: Atherosclerotic Cardiovascular Disease (ASCVD) is largely caused by hyperlipidemia, characterized by high cholesterol and triglyceride levels. Standard treatments like statins face limitations such as intolerance and poor adherence. This study uses amalgamated *in silico* techniques to screen and identify potential lipid-lowering phytoconstituents from traditional medicinal herbs to develop safe polyherbal formulations. **Materials and Methods:** A multi-tiered virtual screening narrowed 708 antilipidemic plants to 64 Indian species. *Allium cepa* was selected for detailed screening, and a library of 52 phytoconstituents was evaluated for drug-likeness, ADMET, and molecular docking against prominent lipid-lowering targets (PPAR-Ɣ, Squalene synthase, and HMG-CoA reductase). **Results:** Fourteen safe candidates were identified through toxicity evaluation. IMPHY012524 was identified as a potential lead with a substantial binding affinity to PPAR-Ɣ (-6.717 kcal/mol), comparable to Pravastatin (-6.76 kcal/mol). IMPHY015116 also emerged as a multi-target candidate. **Conclusion:** The findings highlight multi-target potential constituents that may be optimized further for safe antilipidemic medicine development.

Keywords: Antilipidemic, *In silico*, Molecular Docking, Phytoconstituents, Polyherbal.

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INTRODUCTION

The main metabolic cause of Atherosclerotic Cardiovascular Disease (ASCVD) is still hyperlipidemia, which is defined by abnormal increases in serum lipids such as Triglycerides (TG), Total Cholesterol (TC), and Low-Density Lipoprotein Cholesterol (LDL-C). The increasing frequency of lipid diseases is taking center stage in the worldwide cardiovascular health landscape. Global dyslipidemia profiles have undergone a notable epidemiological shift, according to recent systematic reviews and meta-analyses that include data through 2025. Currently, 28.8% of adults worldwide have hypertriglyceridemia, while 24.1% have hypercholesterolemia. According to global health metrics from the Global Burden of Disease (GBD) study, elevated LDL-C caused about 4.51 million deaths in 2021. This represents a significant increase over the previous three decades due to aging populations and the rapid Westernization of dietary habits in developing regions. The Age-Standardized Mortality Rate (ASMR) linked to high LDL-C has sharply increased in countries like China, and projections indicate that it will rise by an additional 55% by 2050 (Li *et al*., 2025).

High-income nations are no longer the only places where dyslipidemia is common. Nearly two out of three persons may be overweight or obese by 2050, according to data from the World Heart Report 2025 (Chong *et al*., 2025). These illnesses are closely related to metabolic dysregulation and lipid abnormalities. Due to medical expenses and lost productivity, this systemic increase in lipid diseases results in a significant financial burden, estimated at 2.2% of the world's GDP. Real-world treatment gaps still exist despite increased public health awareness. For example, only a small percentage of patients in high-risk populations sometimes as low as 5.5% receive appropriate lipid-lowering therapy (Zhang *et al*., 2026).

Dyslipidemia has more clinical ramifications than just elevated cholesterol. Chronic subclinical inflammation, oxidative stress, and endothelial dysfunction are all brought on by persistent hyperlipidemia. The management of dyslipidemia has been greatly aided by statins, which dramatically lower the risk of cardiovascular events by lowering LDL-C (Sabatine *et al*., 2017). But there are still three main issues: poor adherence, residual risk, and statin intolerance. Approximately 9.1% of people suffer from statin intolerance; real-world data indicate rates as high as 17% (Reijnders *et al*., 2023).

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Statin-associated muscle symptoms are the most prevalent problem, which may deter patients from continuing their medication (Gavina *et al.*, 2026). Adherence is further complicated by variables including age, female sex, diabetes, and hypothyroidism. Furthermore, due in part to compensatory mechanisms that restrict statin efficacy, more than 70% of very-high-risk patients fail to meet LDL-C goals on statins alone. High triglycerides and low HDL-C, which also raise the risk of cardiovascular disease, are not sufficiently addressed by statins, which mainly reduce LDL-C (Eyadiel and Modarressi, 2026).

Patients with poor long-term adherence are more likely to die and experience unfavorable cardiovascular events. Additionally, many people have been discouraged from beginning treatment due to rising skepticism regarding statins that has been encouraged by social media. Due to these difficulties, there is growing interest in alternative therapies, such as polyherbal formulations and ethnopharmacology, which may offer enhanced safety and synergistic effects (Rosenberg *et al.*, 2025).

For complicated disorders like hyperlipidemia, which include several processes like lipid absorption and production, the conventional "one-drug, one-target" strategy in pharmacology is inadequate. Polyherbal treatments, which use a variety of herbs to obtain higher therapeutic benefits with lower doses and less toxicity, have seen a resurgence of interest as a result. Four primary processes underlie polyherbalism: anti-resistance tactics, improved pharmacokinetics, neutralization of negative effects, and multi-target effects. Polyherbal formulations, in contrast to synthetic statins, include a variety of substances that target different metabolic pathways, such as alkaloids and flavonoids (Vasantrao and Bhambar, 2025). For instance, some can prevent intestinal absorption or increase the expression of LDL receptors, while others can prevent the creation of cholesterol. According to research, entire plant extracts frequently work better than isolated chemicals because of their synergistic effects, which increase bioavailability. The inhibition of PCSK9 and the activation of AMPK demonstrate this synergy. These combinations were traditionally developed using ethnopharmacological techniques, while contemporary drug discovery uses *in silico* ADMET profiling to improve conventional formulas. Researchers may evaluate the safety and effectiveness of polyherbal ingredients by screening huge phytochemical libraries. This allows them to combine evidence-based science with traditional methods to develop standardized antilipidemic formulations (Tan *et al.*, 2025).

A significant advancement in the validation of traditional medicine is the use of bioinformatics into ethnopharmacological research. The complicated chemistry of plants, which include a large number of secondary metabolites, has made the shift from "botanical extract" to "molecular drug" difficult. By simulating interactions between phytoconstituents and human protein targets, *in silico* techniques like HTVS, molecular docking, and ADMET profiling efficiently handle this complexity and allow lead compounds with desirable pharmacokinetic profiles to be prioritized before more resource-intensive assays (Sliwoski *et al.*, 2014). The "black box" of polyherbal compositions is also made clear by computational methods. Particularly in lipid management, systems biology approaches forecast synergistic effects that are difficult to measure using conventional techniques. This "Reverse Pharmacology" promotes the regulatory acceptability of herbal remedies and speeds up medication research. The objective of this research is to develop an efficient antilipidemic polyherbal formulation by methodically evaluating lipid-lowering herbs (Atanasov *et al.*, 2021).

To screen the antilipidemic plants and buildup the extensive library of phytoconstituents we have selected three important databases for an inspired phytochemical library. The first is IMPPAT, which includes more than 1,700 medicinal plants that connect contemporary chemistry with Ayurveda (Mohanraj *et al.*, 2018). The second is the enormous collection of plant chemicals and their biological activity found in Dr. Duke's Phytochemical and Ethnobotanical Databases (Ben, 2001). Lastly, the KNApSAcK Core System highlights the geographical significance of the herbs under study by providing a thorough understanding of secondary metabolites across several taxonomies. Our approach places a strong emphasis on thorough data mining and focused molecular investigation of important lipid homeostasis-related enzymes and receptors, such as PPAR-alpha, PCSK9, and HMG-CoA Reductase. We explored a synergistic combination that overcomes the drawbacks of existing monotherapy by screening phytoconstituents against this multi-target panel. This will provide the groundwork for a novel and safe polyherbal antilipidemic drug.

MATERIALS AND METHODS

Database Screening and Plant Selection

Potential antilipidemic plants were identified using a multi-tiered virtual screening method that included three core specialist databases. This methodical mining promises that the chosen herbs have both a known chemical profile and a proven history of traditional medicinal usage.

IMPPAT (Indian Medicinal Plants, Phytochemistry, and Therapeutics) is an extensive registry that contains information on the chemical contents and therapeutic applications of more than 1,700 Indian medicinal plants used in traditional medicine. It attempts to integrate ancient Ayurvedic techniques with current phytochemistry, hence facilitating medication development from natural ingredients. The portal provides information about phytochemicals, such as their structures, characteristics, drug similarity, therapeutic associations, and molecular scaffolds (Vivek-Ananth *et al.*, 2023).

Dr. Duke's Phytochemical and Ethnobotanical Databases (USDA) is an online resource created by James A. Duke of the United States Department of Agriculture (Duke, 2020). It allows researchers to investigate the interaction between plants, their chemical contents, and biological activities, with a particular emphasis on qualities such as "hypolipidemic," "anticholesterolemic," and "antiobesity." The database has a straightforward interface for searching plants, chemicals, ethnobotany, biological activities, and syndromes. It provides simple data export, public access, and thousands of species including over 50,000 biomolecules (Lans and van Asseldonk, 2020).

The KNApSAcK Core System is a comprehensive metabolomics database that finds metabolic pathways and secondary metabolites shared by species from the same botanical families. It contributes to research in plant studies, drug discovery, and traditional medicine by recording over 100,000 species-metabolite correlations across 20,000 species and 50,000 metabolites (Afendi *et al.*, 2012). Users can look up information by species name, metabolite name, molecular weight, or chemical formula. It also connects to other specialized databases, such as WorldMap DB, Biological Activity DB, and KAMPO/JAMU DB, acting as a centralized repository for relevant information (Wijaya *et al.*, 2016).

Library Preparation

A prioritized selection of "Plants of Interest" was chosen based on historic use in local ethnomedical systems (e.g., Ayurveda) for illnesses such as "Sthaulya" (obesity) and "Raktagata Vata" (hyperlipidemia), as well as proven local availability. This technique promotes standardized extract preparation and long-term pharmacognosy. The chemical structures of the necessary phytoconstituents were developed with ChemDraw Ultra 8.0 and then translated to 3D models with Chem3D Ultra. Following geometry optimization with the MM2 force field, the finished 3D structures were exported in standard formats (.mol, and .sdf) for ADMET and molecular docking procedures.

ADMET and Drug-likeness Profiling

In order to assure both safety and oral bioavailability, a rigorous sorting procedure is necessary when going from a chemical library to a potential lead molecule in the drug discovery process. This technique section describes the "drug-likeness" filter, which is used to identify active phytochemicals that meet pharmacokinetic and toxicity requirements. Lipinski's Rule of Five was used to screen for molecules with a molecular weight of less than 500 Da, lipophilicity (Log p<5), hydrogen bond donors (≤5), and acceptors (≤10). Phytoconstituents tested positive for membrane permeability and gastrointestinal absorption, with just one infraction. The SwissADME web server was used to forecast each molecule's ADME profile, which took into account parameters including skin permeability, blood-brain barrier penetration, and gastrointestinal absorption using the BOILED-Egg model (Daina *et al.*, 2017).

In an attempt to forecast metabolic stability and potential herb-drug interactions, metabolism was evaluated by analyzing interactions with major Cytochrome P450 isoforms. The ProTox-II online server, which forecasts toxicity endpoints including acute toxicity (LD_{50}), organ toxicity, and possible problems like hepatotoxicity and carcinogenicity as well as Tox21 signaling pathways, was used to assess the phytoconstituents' safety profile (Banerjee *et al.*, 2024). Phytoconstituents with good drug-like scores, Lipinski criteria compliance, and a safe ADMET profile (non-mutagenic, non-hepatotoxic, and high GI absorption) were shortlisted. This selection was then prepared for molecular docking to determine its affinity for certain antilipidemic targets.

Molecular Docking Studies

Ligand Preparation

Ligand preparation is a crucial stage in molecular docking, ensuring that compounds are modeled in biologically relevant chemical states with minimal energy. All the phytoconstituents satisfying to Lipinski's Rule of Five and Veber's parameters to confirm drug-likeness and oral bioavailability were saved in SDF format for the molecular docking study. The LigPrep module in Maestro (version 12.5) was then used to generate optimized 3D structures. This process included enumeration of all possible stereoisomers and tautomers to capture chemical diversity, while ionization states at physiological pH (7.4) were predicted using Epik to ensure realistic protonation patterns. Geometry optimization was subsequently performed using the OPLS4 force field to obtain energetically stable ligand conformations. These systematically refined structures provided a reliable basis for accurate receptor-ligand docking simulations (Biharee *et al.*, 2023).

Protein Preparation

The crystal structure of the HMG-CoA reductase (PDB ID: 1HW8) with resolution 2.33Å, Squalene synthase (PDB ID: 3ASX) with resolution 2.00 Å, and Peroxisome proliferator-activated receptor gamma (PPAR-Y) (PDB ID: 7AWC) with resolution 1.74 Å, were retrieved from the Protein Data Bank (https://www.rcsb.org/) and processed using the Protein Preparation Wizard in Maestro 12.5 to obtain an energetically and biologically reliable model for docking studies. During preparation, non-essential heteroatoms such as ions and solvents were removed, while crystallographic water molecules within 3 Å of the binding site were retained to preserve critical water-mediated interactions. Missing loops, side chains, and residues were reconstructed to ensure structural completeness (Biharee *et al.*, 2024). Protonation states of ionizable groups were adjusted, and hydrogen-bonding networks were optimized to represent physiological pH conditions accurately. Finally, the structure was energy-minimized using the OPLS4 force field to relieve steric strain and achieve a stable, native-like conformation. This refined receptor model provided a structurally

consistent and functionally accurate framework for subsequent molecular docking analyses (Gupta *et al*., 2024).

Receptor grid generation and docking

Receptor grid generation was carried out using the Glide Grid Generation module to define the docking search space around the established rosiglitazone binding site of PPAR-Ɣ (X: 41.47, Y: 5.25, Z: 83.31), Mevastatin binding site of HMG-CoA reductase (X: 19.04, Y: -23.68, Z: 15.11), and co-crystalize ligand binding site of Squalene synthase (X: 17.70, Y: -2.83, Z: 57.18) with a radius of 20 Å to accommodate ligands of diverse sizes and conformational flexibility. This configuration ensured comprehensive coverage of the active pocket, encompassing key residues essential for PPAR-Ɣ, squalene synthase, and HMG-CoA reductase activity and enabling precise modeling of ligand receptor interactions during docking studies (Kulkarni *et al*., 2023).

Statistical Analysis

Defined filtering criteria such Lipinski's Rule of Five (MW< 500 Da, Log *p*< 5, HBD< 5, HBA<10) and Veber's standards for drug-likeness were used for all data processing, including phytochemical library curation from IMPPAT, Dr. Duke's, and KNApSAcK databases. To top rank phytoconstituents, docking scores from Maestro 12.5 (Glide module) were directly compared to reference ligands (e.g., Rosuvastatin for HMG-CoA reductase, TAK-475 for squalene synthase) using raw binding affinities (kcal/mol). While toxicity predictions from ProTox-II and pkCSM/Deep-PK used binary classifiers (e.g., non-toxic vs. hepatotoxic) based on machine learning models trained on large datasets (e.g., >40,000 compounds for LD_{50}), shortlisting thresholds were established empirically.

RESULTS AND DISCUSSION

Database screening and plant selection

Three specialized databases IMPPAT, USDA phytochemical resources, and KNApSAcK as well as literature-supported ethnobotanical evidence were integrated into a multi-tiered data-mining approach to find potential lipid-lowering medicinal plants. This process made it possible to filter plants sequentially from a large worldwide pool to Indian medicinal species that are geographically relevant, have proven traditional uses, and have chemical annotations. A wide yet extremely diverse phytochemical landscape for antihyperlipidemic research was revealed by the first database search, which produced 708 plants claimed to have lipid-lowering activities in various areas of the world. The list was narrowed to 64 plant species after these widely dispersed candidates were evaluated in the IMPPAT database to limit the dataset to plants recorded in Indian subregions.

To guarantee practical translational value and congruence with indigenous medical knowledge, these 64 Indian herbs were then thoroughly assessed for availability, traditional usage, and ethnobotanical significance. Only four plants *Allium cepa, Gymnema sylvestre* (Rachh *et al*., 2010), *Murraya koenigii* (Hendre, 2019), and *Terminalia chebula* (Reddy *et al*., 2015) met the combined requirements of geographical accessibility, ethnomedicinal significance, and interest for lipid-lowering research.

Allium cepa was chosen for the current study's in-depth phytochemical analysis out of these four nominated species because its bulb portion is readily available in India and has a carefully chosen repertoire of bioactive components appropriate for *in silico* screening (Baragob *et al*., 2015). In order to determine their potential as lipid-lowering options, the phytochemical profile of *Allium cepa* was created, and the chosen bulb phytoconstituents were selected for further ADMET, toxicity assessment and molecular docking study (Airaodion *et al*., 2020).

ADMET and Drug-likeness Profiling

The pkCSM website, which forecasts ADMET behaviour using molecular graph-based signatures and associated structural descriptors, was used for pharmacokinetic profiling. The Deep-PK upgrades and the original pkCSM framework are described on the platform's current theory page. The platform was created as a quick *in silico* filter to predict important drug-likeness qualities prior to experimental testing. Compounds with estimated absorption below 30% are regarded as poorly absorbed in this method, which primarily interprets absorption through human intestine absorption. Steady-state Volume of Distribution (VDss) is frequently used to evaluate distribution; low VDss is defined as log VDss<-0.15 and high VDss as log VDss>0.45; a reasonable range between these cutoffs is typically thought to be advantageous for balanced tissue distribution. Inhibition of the major CYP450 isoforms is used to assess metabolic liability; substances expected to be non-inhibitors are favoured since they are less likely to result in metabolic drug-drug interactions. AMES mutagenicity, hepatotoxicity, hERG inhibition, and skin sensitisation are examples of toxicity screening, whereas renal OCT2 interaction is frequently used to assess excretion. Only a smaller portion of the 52 *Allium cepa* bulb phytoconstituents maintained favourable behaviour across distribution and metabolism, and only one molecule passed all toxicity safety criteria, according to the pkCSM/Deep-PK ADMET profiling. IMPHY007084 was the only completely non-toxic component in the final integrated screening, however a number of other compounds had acceptable ADME characteristics and could still be valuable as lead-like candidates. The results of the absorption investigation revealed that 45 of the 52 phytoconstituents were expected to be absorbed in the human gut, suggesting that most of the metabolites of *Allium cepa* had potentially sufficient oral absorption. This high percentage indicates that the majority of components have physicochemical characteristics that are consistent with early systemic exposure following oral administration and gastrointestinal absorption.

Table 1: Prediction data of Pharmacokinetic (ADME) behavior of selected phytoconstituents of *Allium cepa* using pKCSM webserver.

IMPPAT Phytochemical identifier	[Absorption/ Caco-2 (logPaap)] Predictions	[Absorption/ Human Oral Bioavailability 20%] Probability	Distribution/ BBB Predictions	[Metabolism/ CYP 2C19_ substrate] Predictions	[Excretion/ Half-Life of Drug] Predictions
IMPHY000308	-4.75	0.217	-2.42	Non-Substrate	Half-Life >= 3hs
IMPHY001268	-6.63	0.205	-4.36	Non-Substrate	Half-Life < 3hs
IMPHY001886	-4.3	0.861	-0.88	Substrate	Half-Life < 3hs
IMPHY001915	-4.9	0.159	-2.33	Non-Substrate	Half-Life >= 3hs
IMPHY002736	-4.42	0.682	-2.77	Non-Substrate	Half-Life < 3hs
IMPHY002983	-4.92	0.183	-2	Non-Substrate	Half-Life >= 3hs
IMPHY003016	-4.74	0.366	-2.43	Non-Substrate	Half-Life >= 3hs
IMPHY003377	-4.47	0.585	-2.59	Non-Substrate	Half-Life < 3hs
IMPHY003681	-4.73	0.821	-2.71	Substrate	Half-Life < 3hs
IMPHY003710	-4.62	0.829	-2.6	Non-Substrate	Half-Life < 3hs
IMPHY003919	-4.74	0.69	-1.83	Non-Substrate	Half-Life < 3hs
IMPHY004079	-4.27	0.774	-1.75	Non-Substrate	Half-Life < 3hs
IMPHY004187	-4.95	0.672	-3.77	Non-Substrate	Half-Life < 3hs
IMPHY004328	-6.41	0.088	-4.71	Non-Substrate	Half-Life < 3hs
IMPHY004388	-5.26	0.507	-2.75	Non-Substrate	Half-Life < 3hs
IMPHY004619	-5.8	0.419	-3.12	Non-Substrate	Half-Life < 3hs
IMPHY005471	-6.32	0.316	-3.33	Non-Substrate	Half-Life < 3hs
IMPHY005896	-4.42	0.84	-3.03	Non-Substrate	Half-Life >= 3hs
IMPHY006310	-6.22	0.492	-3.72	Non-Substrate	Half-Life < 3hs
IMPHY007006	-4.79	0.834	-2.25	Non-Substrate	Half-Life < 3hs
IMPHY007041	-4.27	0.85	-2.2	Non-Substrate	Half-Life < 3hs
IMPHY007084	-4.88	0.629	-3.98	Non-Substrate	Half-Life < 3hs
IMPHY007134	-3.98	0.737	-2.59	Substrate	Half-Life >= 3hs
IMPHY008688	-5.87	0.779	-4.29	Non-Substrate	Half-Life >= 3hs
IMPHY009368	-4.83	0.186	-2.36	Non-Substrate	Half-Life >= 3hs
IMPHY009369	-4.97	0.134	-2.29	Non-Substrate	Half-Life >= 3hs
IMPHY009593	-4.11	0.705	-2.86	Non-Substrate	Half-Life >= 3hs
IMPHY009908	-6.89	0.083	-4.26	Non-Substrate	Half-Life < 3hs
IMPHY009927	-6.62	0.077	-4.6	Non-Substrate	Half-Life < 3hs
IMPHY010083	-5.18	0.718	-2.69	Non-Substrate	Half-Life < 3hs
IMPHY010631	-4.28	0.821	-2.64	Non-Substrate	Half-Life >= 3hs
IMPHY011561	-6.43	0.219	-4.24	Non-Substrate	Half-Life < 3hs
IMPHY011572	-5.49	0.826	-2.03	Non-Substrate	Half-Life < 3hs
IMPHY011802	-4.94	0.676	-2.71	Non-Substrate	Half-Life < 3hs
IMPHY011883	-5.18	0.644	-2.9	Non-Substrate	Half-Life >= 3hs
IMPHY011933	-4.95	0.615	-2.12	Non-Substrate	Half-Life >= 3hs
IMPHY011974	-4.87	0.712	-1.77	Non-Substrate	Half-Life < 3hs
IMPHY012133	-4.75	0.274	-2.22	Non-Substrate	Half-Life >= 3hs

IMPPAT Phytochemical identifier	[Absorption/ Caco-2 (logPaap)] Predictions	[Absorption/ Human Oral Bioavailability 20%] Probability	Distribution/ BBB Predictions	[Metabolism/ CYP 2C19_ substrate] Predictions	[Excretion/ Half-Life of Drug] Predictions
IMPHY012223	-4.78	0.864	-1.88	Substrate	Half-Life < 3hs
IMPHY012263	-5.9	0.697	-4.15	Non-Substrate	Half-Life >= 3hs
IMPHY012524	-6.54	0.079	-4.71	Non-Substrate	Half-Life < 3hs
IMPHY013109	-4.53	0.797	-2.88	Substrate	Half-Life >= 3hs
IMPHY014836	-4.84	0.79	-2.11	Substrate	Half-Life < 3hs
IMPHY015003	-4.62	0.877	-2.6	Non-Substrate	Half-Life < 3hs
IMPHY015056	-5.17	0.679	-4.09	Non-Substrate	Half-Life >= 3hs
IMPHY015057	-5.13	0.707	-3.51	Non-Substrate	Half-Life >= 3hs
IMPHY015116	-5.15	0.733	-3.55	Non-Substrate	Half-Life >= 3hs
IMPHY015256	-4.15	0.794	-2.68	Non-Substrate	Half-Life < 3hs
IMPHY015595	-4.34	0.763	-3.22	Non-Substrate	Half-Life < 3hs
IMPHY017518	-5.14	0.84	-3.16	Non-Substrate	Half-Life < 3hs
IMPHY017892	-5.14	0.59	-3.18	Non-Substrate	Half-Life < 3hs

Only 16 compounds came inside the moderate VDss window in terms of distribution, indicating that a smaller portion of the sample could be able to attain a balanced plasma-tissue distribution profile. Thirty substances were found by metabolic screening to be non-inhibitors of the five main CYP450 enzymes: CYP1A2, CYP2C19, CYP2C9, CYP2D6, and CYP3A4. This is a helpful discovery since substances that escape widespread CYP inhibition are less likely to induce significant pharmacokinetic interactions or interfere with xenobiotic metabolism. Since all 52 phytoconstituents were anticipated to be non-inhibitors of OCT2, excretion profiling was the least restrictive stage (Table 1). This full pass rate indicates that renal cation transport-mediated elimination is unlikely to be significantly hampered by the entire set, which is advantageous for avoiding one typical pathway of transporter-based interaction.

TEST 5.1.2 software was used to predict the toxicological behaviour and bioconcentration potential of the chosen *Allium cepa* phytoconstituents (Table 2). Several toxicity endpoints, such as mutagenicity, developmental toxicity, oral rat acute toxicity (LD_{50}), aquatic toxicity toward fathead minnow and *Daphnia magna*, and bioconcentration factor, are estimated by the system using QSAR-based consensus models. With just a small number of compounds exhibiting mutagenic liability and the remainder anticipated to be non-mutagenic, the resulting predictions showed that the phytochemical library exhibited diverse toxicity behaviour. In a similar vein, the acute and developmental toxicity outputs showed that while certain components were within safer prediction limits, others had quantifiable toxicological risk. The majority of chemicals exhibited low to moderate accumulation potential, according to the bio-concentration study, suggesting a restricted tendency for bioaccumulation.

Toxicity prediction served as the primary criterion in the workflow, employing ProTox 3.0 to assess the toxicity profiles of *Allium cepa* bulb phytoconstituents. This *in silico* technology offers insights into acute toxicity, organ toxicity, and toxicological pathways by combining molecular similarity with machine-learning models for quick screening. With the acute toxicity model trained on over 40,000 chemicals with LD_{50} values, the ProTox-3.0 workbook functions as a prioritisation filter instead of a final endpoint screen. Only a small number of chemicals satisfied the stringent toxicity requirements, according to the research, suggesting that the majority of constituents still pose safety risks. Toxicity analysis of *Allium cepa* bulb phytoconstituents found that several chemicals have potential toxicological risks. Among the 52 chemicals analysed (Table 3) in this approach, two, IMPHY003919 and IMPHY011572, were shown to be hepatotoxic, while eight constituents showed neurotoxicity. In addition, 18 compounds were found to be nephrotoxic, 21 to be respiratory toxic, 8 to be cardiotoxic, 11 to be carcinogenic, and 11 to be immunotoxic (Figure 1).

Furthermore, just one chemical, IMPHY001268, was anticipated to be cytotoxic, whereas three compounds were found to be mutagenic: IMPHY004619, IMPHY007041, and IMPHY005471. With the exception of three substances that failed to breach the blood-brain barrier, the majority of compounds were able to do so, suggesting possible neuropharmacological effects. Only 14 of the 38 chemicals that were found to have at least one toxicity class were free from these risks. All of these findings point to a

Table 2: Prediction data of toxicological behavior and bioconcentration potential of selected phytoconstituents of *Allium cepa* using TEST 5.1.2 software.

Phytochemical name	IMPPAT Phytochemical identifier	Bioconcentration Factor	*Daphnia magna* LC_{50} (48hr): mg/L	Oral rat LD_{50}: mg/kg	Developmental Toxicity	Mutagenicity
Hexadecane	IMPHY000308	349.77	0.58	9996.80	NON-toxicant	Negative
Peonidin-3-glucoside	IMPHY001268	N/A	N/A	N/A	N/A	N/A
Diphenylamine	IMPHY001886	72.32	5.40	1742.58	Toxicant	Negative
Octadecane	IMPHY001915	432.39	0.44	5686.06	NON-toxicant	Negative
Tsibulin 2	IMPHY002736	10.59	134.10	2426.64	Toxicant	Negative
1-Hexadecanol	IMPHY002983	160.22	2.62	6539.32	NON-toxicant	Negative
Lauric acid	IMPHY003016	24.16	5.80	8479.65	Toxicant	Negative
4-Octylcyclopentane-1,3-dione	IMPHY003377	7.96	79.99	2510.82	NON-toxicant	Negative
Diosgenin	IMPHY003681	227.34	1.86	109.42	Toxicant	Negative
(-)-Isopulegol	IMPHY003710	12.45	6.78	2411.63	Toxicant	Negative
2-Hydroxycinnamic acid	IMPHY003919	1.65	13.92	2658.13	Toxicant	Negative
Catechol	IMPHY004079	5.05	11.58	199.57	Toxicant	Negative
L-(+)-Arabinose	IMPHY004187	N/A	2430.95	15259.78	NON-toxicant	Negative
Quercetin 3,4'-diglucoside	IMPHY004328	N/A	147.92	6694.80	Toxicant	Negative
Kaempferol	IMPHY004388	8.03	3.62	2017.98	Toxicant	Positive
Quercetin	IMPHY004619	3.53	3.59	1738.18	Toxicant	Positive
Myricetin	IMPHY005471	5.96	2.92	1632.87	Toxicant	Positive
2,4,6-Triethyl-1,3,5-dithiazinane	IMPHY005896	68.91	2.79	191.46	NON-toxicant	Negative
Folic	IMPHY006310	3.34E-02	300.52	2964.90	Toxicant	Negative
Furfuryl alcohol	IMPHY007006	4.62	149.76	242.87	Toxicant	Positive
Furfural	IMPHY007041	N/A	39.69	362.17	NON-toxicant	Positive
Vanillic acid	IMPHY007084	1.37	91.22	958.07	Toxicant	Negative
Allicin	IMPHY007134	6.30	38.68	N/A	Toxicant	N/A
S-Methyl-L-cysteine sulfoxide	IMPHY008688	0.19	307.06	1152.04	Toxicant	N/A
Heptadecane	IMPHY009368	423.24	0.53	6281.16	NON-toxicant	Negative
Nonadecane	IMPHY009369	439.85	0.35	4298.82	NON-toxicant	Negative
Dipropyl disulfide	IMPHY009593	41.49	1.23	462.64	Toxicant	Negative
Cyanidin 3-malonylglucoside	IMPHY009908	N/A	N/A	N/A	N/A	N/A
Cyanidin 3-laminaribioside	IMPHY009927	N/A	N/A	N/A	N/A	N/A
4-Hydroxybenzoic acid	IMPHY010083	1.54	55.72	1713.62	NON-toxicant	Negative
(E)-1-Propene-1-sulfenic acid	IMPHY010631	6.69	N/A	N/A	NON-toxicant	Positive
Spiraeoside	IMPHY011561	7.37	62.49	3403.00	Toxicant	Negative
(4aR,6aR,6aS,6bR,8aR,10S,12aR,14bS)-10-hydroxy-2,2,6a,6b,9,9,12a-heptamethyl-1,3,4,5,6,6a,7,8,8a,10,11,12,13,14b-tetradecahydropicene-4a-carboxylic acid	IMPHY011572	81.75	0.32	4815.74	Toxicant	Negative
Ferulic acid	IMPHY011802	1.14	21.11	4634.30	Toxicant	Negative
3,4-Dihydroxybenzoic acid	IMPHY011883	1.05	50.41	2109.38	NON-toxicant	Negative

Phytochemical name	IMPPAT Phytochemical identifier	Bioconcentration Factor	*Daphnia magna* LC_{50} (48hr): mg/L	Oral rat LD_{50}: mg/kg	Developmental Toxicity	Mutagenicity
Caffeic acid	IMPHY011933	0.52	6.84	3484.34	NON-toxicant	Negative
4-Hydroxycinnamic acid	IMPHY011974	1.11	9.57	2806.93	Toxicant	Negative
1-Hexadecene	IMPHY012133	248.62	0.58	9323.26	Toxicant	Negative
beta-Amyrin	IMPHY012223	892.46	8.99E-02	2149.35	Toxicant	Negative
3-(Allylsulphinyl)-L-alanine	IMPHY012263	0.27	290.32	N/A	Toxicant	N/A
Cyanin	IMPHY012524	N/A	N/A	N/A	N/A	N/A
2,4,6-Triethyl-1,3,5-trithiane	IMPHY013109	154.13	1.48	27.55	N/A	Negative
beta-Sitosterol	IMPHY014836	784.71	0.38	895.24	Toxicant	Negative
Cyanidin 3-glucoside	IMPHY014890	N/A	N/A	N/A	N/A	N/A
Menthol	IMPHY015003	19.25	29.43	2355.15	Toxicant	Negative
L-Rhamnose	IMPHY015056	0.24	5734.71	13891.54	NON-toxicant	Negative
D-Ribose	IMPHY015057	0.26	8549.77	12540.81	NON-toxicant	Negative
D-Xylose	IMPHY015116	0.26	8549.77	12540.81	NON-toxicant	Negative
2-Ethylbutanal	IMPHY015256	N/A	31.23	3851.70	Toxicant	Negative
Cyclopentadecanone	IMPHY015595	65.83	13.64	2877.20	NON-toxicant	Negative
5-Methoxypyrimidin-4-ol	IMPHY017518	2.74	56.57	N/A	Toxicant	Negative
2,6-Dihydroxybenzoic acid	IMPHY017892	0.48	92.27	1082.86	NON-toxicant	Negative

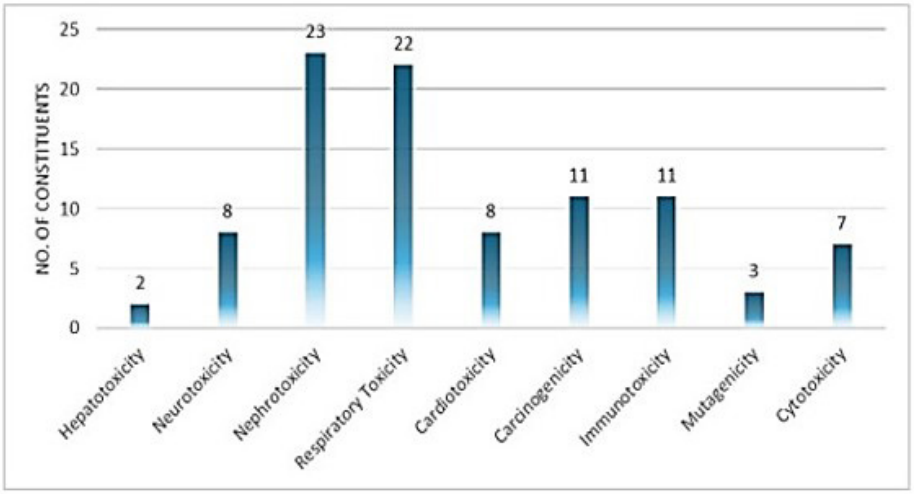

Figure 1: Representation of number of constituents found positive while screening for specific toxicity.

small fraction of safer options in the bulb-derived phytochemical library, but most compounds may need further safety screening and experimental toxicological confirmation before moving on to further pharmacological research. In order to determine the lipid-lowering effects of *Allium cepa* based on receptor interaction scores, the 14 compounds were then chosen for molecular docking studies against a designated target for hypolipidemic activity.

Molecular Docking Study

The antilipidemic potential of the chosen *Allium cepa* phytoconstituents was assessed using molecular docking in Maestro 12.8 against three validated targets: squalene synthase,

Table 3: Toxicity prediction of Phytoconstituents from bulb part of *Allium cepa*.

Phytoconstituents	Toxicity prediction and probability	Organ toxicity/ Toxicity end points									
		Hepatotoxicity	Neurotoxicity	Nephrotoxicity	Respiratory toxicity	Cardiotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity	BBB-barrier
IMPHY000308	Prediction	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes
	Probability	0.74	0.66	0.87	1	0.83	0.58	0.98	1	0.78	0.99
IMPHY001268	Prediction	NA	NA	Yes	Yes	NA	NA	Yes	NA	Yes	NA
	Probability	0.82	0.88	0.73	0.60	0.57	0.87	0.89	0.65	0.50	0.69
IMPHY001886	Prediction	NA	Yes	NA	NA	NA	NA	NA	NA	NA	Yes
	Probability	0.56	0.70	0.88	0.96	0.85	0.69	0.99	0.76	0.86	0.95
IMPHY001915	Prediction	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes
	Probability	0.74	0.66	0.87	1	0.83	0.58	0.98	1	0.78	0.99
IMPHY002736	Prediction	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes
	Probability	0.76	0.65	0.78	0.86	0.85	0.62	0.57	0.85	0.69	0.92
IMPHY002983	Prediction	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes
	Probability	0.90	0.90	0.67	0.93	1	0.5	0.97	1	0.83	0.92
IMPHY003016	Prediction	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes
	Probability	0.52	0.92	0.53	0.85	0.99	0.63	0.99	1	0.74	0.90
IMPHY003377	Prediction	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes
	Probability	0.76	0.65	0.78	0.86	0.85	0.62	0.57	0.85	0.69	0.92
IMPHY003681	Prediction	NA	NA	NA	Yes	NA	NA	Yes	NA	NA	Yes
	Probability	0.69	0.78	0.61	0.74	0.85	0.55	0.99	0.96	0.99	0.76
IMPHY003710	Prediction	NA	Yes	NA	NA	NA	NA	NA	NA	NA	Yes
	Probability	0.71	0.51	0.81	0.75	0.75	0.79	0.99	0.87	0.93	0.86
IMPHY003919	Prediction	Yes	NA	Yes	NA	NA	Yes	NA	NA	NA	Yes
	Probability	0.53	0.63	0.67	0.54	0.94	0.51	0.86	0.92	0.81	0.67
IMPHY004079	Prediction	NA	NA	NA	NA	Yes	Yes	NA	NA	NA	NA
	Probability	0.82	0.63	0.63	0.87	0.68	0.84	0.99	0.9	0.87	0.50
IMPHY004187	Prediction	NA	NA	Yes	Yes	Yes	NA	NA	NA	NA	NA
	Probability	0.97	0.97	0.57	0.64	0.97	0.84	0.99	0.94	0.83	0.85
IMPHY004328	Prediction	NA	NA	Yes	Yes	NA	NA	Yes	NA	NA	NA
	Probability	0.83	0.88	0.78	0.64	0.53	0.85	0.85	0.74	0.67	0.51
IMPHY004388	Prediction	NA	NA	Yes	Yes	NA	NA	NA	NA	NA	Yes
	Probability	0.68	0.89	0.62	0.83	0.91	0.72	0.96	0.52	0.98	0.57
IMPHY004619	Prediction	NA	NA	Yes	Yes	NA	Yes	NA	Yes	NA	Yes
	Probability	0.69	0.89	0.62	0.83	0.99	0.68	0.87	0.51	0.99	0.53
IMPHY005471	Prediction	NA	NA	Yes	Yes	NA	Yes	NA	Yes	NA	Yes
	Probability	0.69	0.89	0.62	0.83	0.99	0.68	0.86	0.51	0.99	0.53
IMPHY005896	Prediction	NA	Yes	NA	Yes	NA	NA	NA	NA	NA	Yes
	Probability	0.61	0.58	0.81	0.59	0.84	0.67	0.99	0.75	0.78	0.92

Phytoconstituents	Toxicity prediction and probability	Organ toxicity/ Toxicity end points									
		Hepatotoxicity	Neurotoxicity	Nephrotoxicity	Respiratory toxicity	Cardiotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity	BBB-barrier
IMPHY006310	Prediction	NA	Yes	Yes	Yes	NA	NA	NA	NA	NA	Yes
	Probability	0.97	0.52	0.52	0.92	0.81	0.56	0.99	0.81	0.74	0.79
IMPHY007006	Prediction	NA	NA	NA	Yes	NA	Yes	NA	NA	NA	Yes
	Probability	0.86	0.77	0.58	0.66	0.78	0.56	0.99	0.75	0.81	0.92
IMPHY007041	Prediction	NA	NA	NA	NA	NA	Yes	NA	Yes	NA	Yes
	Probability	0.73	0.57	0.66	0.84	0.84	0.89	0.99	0.77	0.72	0.95
IMPHY007084	Prediction	NA	NA	Yes	NA	NA	NA	NA	NA	NA	Yes
	Probability	0.55	0.77	0.64	0.77	0.76	0.64	0.97	0.96	0.93	0.71
IMPHY007134	Prediction	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes
	Probability	0.73	0.54	0.74	0.72	0.64	0.64	0.99	0.61	0.74	0.97
IMPHY008688	Prediction	NA	NA	NA	NA	Yes	NA	NA	NA	NA	Yes
	Probability	0.76	0.75	0.65	0.56	0.64	0.69	0.99	0.78	0.62	0.63
IMPHY009368	Prediction	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes
	Probability	0.74	0.66	0.87	1	0.83	0.58	0.98	1	0.78	0.99
IMPHY009369	Prediction	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes
	Probability	0.74	0.66	0.87	1	0.83	0.58	0.98	1	0.78	0.99
IMPHY009593	Prediction	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes
	Probability	0.75	0.63	0.84	0.84	0.68	0.51	0.99	0.85	0.82	0.98
IMPHY009908	Prediction	NA	NA	Yes	Yes	NA	NA	NA	NA	NA	NA
	Probability	0.82	0.86	0.74	0.72	0.86	0.82	0.65	0.58	0.67	0.63
IMPHY009927	Prediction	NA	NA	Yes	Yes	NA	NA	Yes	NA	NA	Yes
	Probability	0.84	0.89	0.74	0.60	0.51	0.84	0.89	0.70	0.59	0.58
IMPHY010083	Prediction	NA	NA	Yes	NA	NA	NA	NA	NA	NA	Yes
	Probability	0.52	0.76	0.68	0.61	0.96	0.51	0.99	0.99	0.86	0.59
IMPHY010631	Prediction	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes
	Probability	0.89	0.69	0.67	0.63	0.76	0.64	0.99	0.52	0.76	0.97
IMPHY011561	Prediction	NA	NA	Yes	Yes	NA	NA	Yes	NA	NA	NA
	Probability	0.82	0.88	0.76	0.61	0.67	0.85	0.75	0.76	0.69	0.57
IMPHY011572	Prediction	Yes	NA	NA	Yes	Yes	Yes	Yes	NA	NA	Yes
	Probability	0.52	0.74	0.62	0.89	0.71	0.57	0.79	0.85	0.99	0.69
IMPHY011802	Prediction	NA	NA	Yes	NA	NA	NA	Yes	NA	NA	Yes
	Probability	0.51	0.74	0.62	0.77	0.85	0.61	0.91	0.96	0.88	0.70
IMPHY011883	Prediction	NA	NA	Yes	NA	NA	Yes	NA	NA	NA	Yes
	Probability	0.59	0.86	0.61	0.58	0.90	0.72	0.99	0.97	0.90	0.66
IMPHY011933	Prediction	NA	NA	Yes	NA	NA	Yes	NA	NA	NA	Yes
	Probability	0.57	0.83	0.59	0.59	0.97	0.78	0.50	0.98	0.86	0.66
IMPHY011974	Prediction	NA	NA	Yes	NA	NA	Yes	NA	NA	NA	Yes
	Probability	0.51	0.71	0.66	0.62	0.98	0.50	0.91	0.93	0.81	0.57

Phytoconstituents	Toxicity prediction and probability	Organ toxicity/ Toxicity end points									
		Hepatotoxicity	Neurotoxicity	Nephrotoxicity	Respiratory toxicity	Cardiotoxicity	Carcinogenicity	Immunotoxicity	Mutagenicity	Cytotoxicity	BBB-barrier
IMPHY012133	Prediction	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes
	Probability	0.75	0.58	0.87	0.96	0.79	0.59	0.95	1	0.77	0.99
IMPHY012223	Prediction	NA	Yes	NA	Yes	NA	NA	Yes	NA	NA	Yes
	Probability	0.75	0.57	0.94	0.81	0.82	0.63	0.93	0.92	0.95	0.89
IMPHY012263	Prediction	NA	NA	NA	Yes	Yes	NA	NA	NA	NA	Yes
	Probability	0.76	0.68	0.59	0.61	0.59	0.62	0.99	0.72	0.58	0.55
IMPHY012524	Prediction	NA	NA	Yes	Yes	NA	NA	Yes	NA	NA	Yes
	Probability	0.84	0.89	0.74	0.60	0.51	0.84	0.60	0.70	0.59	0.58
IMPHY013109	Prediction	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes
	Probability	0.75	0.57	0.79	0.52	0.82	0.53	0.99	0.79	0.85	0.97
IMPHY014836	Prediction	NA	Yes	NA	Yes	NA	NA	Yes	NA	NA	Yes
	Probability	0.87	0.54	0.89	0.82	0.85	0.60	0.99	0.98	0.94	0.91
IMPHY014890	Prediction	NA	NA	Yes	Yes	NA	NA	Yes	NA	NA	Yes
	Probability	0.76	0.88	0.77	0.64	0.59	0.86	0.72	0.72	0.59	0.61
IMPHY015003	Prediction	NA	NA	NA	Yes	NA	NA	NA	NA	NA	Yes
	Probability	0.77	0.62	0.79	0.66	0.91	0.89	0.99	0.73	0.88	0.92
IMPHY015056	Prediction	NA	NA	Yes	NA	Yes	NA	NA	NA	NA	Yes
	Probability	0.85	0.93	0.66	0.64	0.62	0.61	0.97	0.73	0.78	0.72
IMPHY015057	Prediction	NA	NA	Yes	NA	Yes	NA	NA	NA	NA	Yes
	Probability	0.93	0.94	0.70	0.92	0.92	0.76	0.99	0.80	0.83	0.68
IMPHY015116	Prediction	NA	NA	Yes	NA	Yes	NA	NA	NA	NA	Yes
	Probability	0.93	0.94	0.70	0.92	0.92	0.76	0.99	0.80	0.83	0.68
IMPHY015256	Prediction	NA	NA	NA	NA	NA	NA	NA	NA	NA	Yes
	Probability	0.85	0.57	0.79	0.75	0.65	0.51	0.99	0.91	0.81	0.99
IMPHY015595	Prediction	NA	Yes	NA	NA	NA	NA	NA	NA	NA	Yes
	Probability	0.73	0.55	0.79	0.92	0.73	0.79	0.99	0.87	0.72	0.94
IMPHY017518	Prediction	NA	Yes	NA	Yes	NA	Yes	NA	NA	NA	Yes
	Probability	0.51	0.71	0.64	0.50	0.84	0.53	0.87	0.72	0.86	0.85
IMPHY017892	Prediction	NA	NA	Yes	Yes	NA	NA	NA	NA	NA	Yes
	Probability	0.54	0.82	0.74	0.62	0.79	0.65	0.99	0.99	0.85	0.73

HMG-CoA reductase, and PPAR-γ. A prioritized subset of possibilities for additional lead optimization is highlighted by the docking results, which reveal that while a number of ligands had quantifiable affinity for one or more targets, only a small number of compounds approached or exceeded the binding performance of the reference drugs. With a docking score of -7.83 kcal/mol, TAK-475 demonstrated the greatest binding to PPAR-γ among the reference and test drugs, followed by Mevastatin (-7.082), Atorvastatin (-6.786), Pravastatin (-6.76), and Squalestatin 1 (-6.535). IMPHY12524 is one of the components of *Allium cepa* (Table 4). At -6.717 kcal/mol, had the best docking score, which was comparable to the standard ligands and indicate rather robust contact with the receptor. IMPHY010083 and IMPHY015116 (-6.386). Several ligands produced positive or almost zero docking scores, indicating poor receptor compatibility in the PPAR-γ active site, and the remainder compounds exhibited low to insignificant binding. Practically speaking, IMPHY12524 is suggested by the PPAR-γ findings. Because it combines a highest

docking score with a binding profile that approaches recognized lipid-lowering criteria, it is the most promising phytochemical for more investigation. This lends credence to the idea that some phytoconstituents of *Allium cepa* may function by modulating lipid metabolism through PPAR-γ (Figure 2).

Rosuvastatin had the greatest interaction with HMG-CoA reductase among the reference drugs (-5.168 kcal/mol), followed by Pravastatin (-4.61) and Mevastatin (-2.87). With a docking score of -3.632 kcal/mol, IMPHY015116 showed the highest affinity among the phytoconstituents of *Allium cepa*, followed by IMPHY12524 (-3.294), IMPHY010083 (-2.619), IMPHY001915 (-2.399), and IMPHY007084 (-2.172). These scores show detectable binding and imply that a portion of the onion-derived elements may interact with the cholesterol biosynthesis target, even though they were lower than those of the best statin reference. IMPHY003016, IMPHY002983, IMPHY004187, IMPHY001886, IMPHY008688, and IMPHY011974 were among the compounds that had positive or very weak scores, indicating limited compatibility with the HMG-CoA reductase active site. With IMPHY015116 and IMPHY12524, the docking pattern suggests that the *Allium cepa* library's overall HMG-CoA reductase inhibitory potency is modest (Figure 3).

TAK-475 (-10.431 kcal/mol) and the common inhibitors Mevastatin (-6.469), Pravastatin (-6.019), Rosuvastatin (-6.345), and Pioglitazone (-5.035) had the best docking scores against squalene synthase. IMPHY12524 is one of the phytoconstituents of *Allium cepa*. With a docking score of -5.948 kcal/mol, sdf once again came in first, closely followed by IMPHY015116 (-5.0), IMPHY010083 (-3.71), IMPHY009369 (-4.129), IMPHY001915 (-4.196), IMPHY007084 (-3.268), and IMPHY003016 (-3.031). According to these scores, a number of chemicals produced from onions have a modest affinity for the squalene synthase pocket and may disrupt the manufacture of cholesterol downstream of HMG-CoA reductase (Figure 4).

The research on molecular interactions involving PPAR-γ (PDB ID: 7AWC) revealed that pioglitazone and IMPHY12524 occupied a common binding pocket and exhibited hydrophobic interactions with crucial amino acid residues within the receptor cavity. Given that hydrophobic and hydrogen-bond interactions are prevalent, it is plausible that the strong chemical could exhibit receptor activation potential akin to that of pioglitazone. The interaction profile of HMG-CoA reductase (PDB ID: 1HW8) reveals that the potent compound (IMPHY004187) and the well-known medication mevastatin demonstrate similar hydrogen bonding and polar interactions within the active site. Both ligands formed hydrogen bonds and engaged in electrostatic interactions with LYS691, ARG590, and SER684/ SER661, contributing to the stabilization of ligand accommodation. Both compounds also formed water-mediated connections and engaged with adjacent hydrophilic residues, suggesting that the potent molecule could

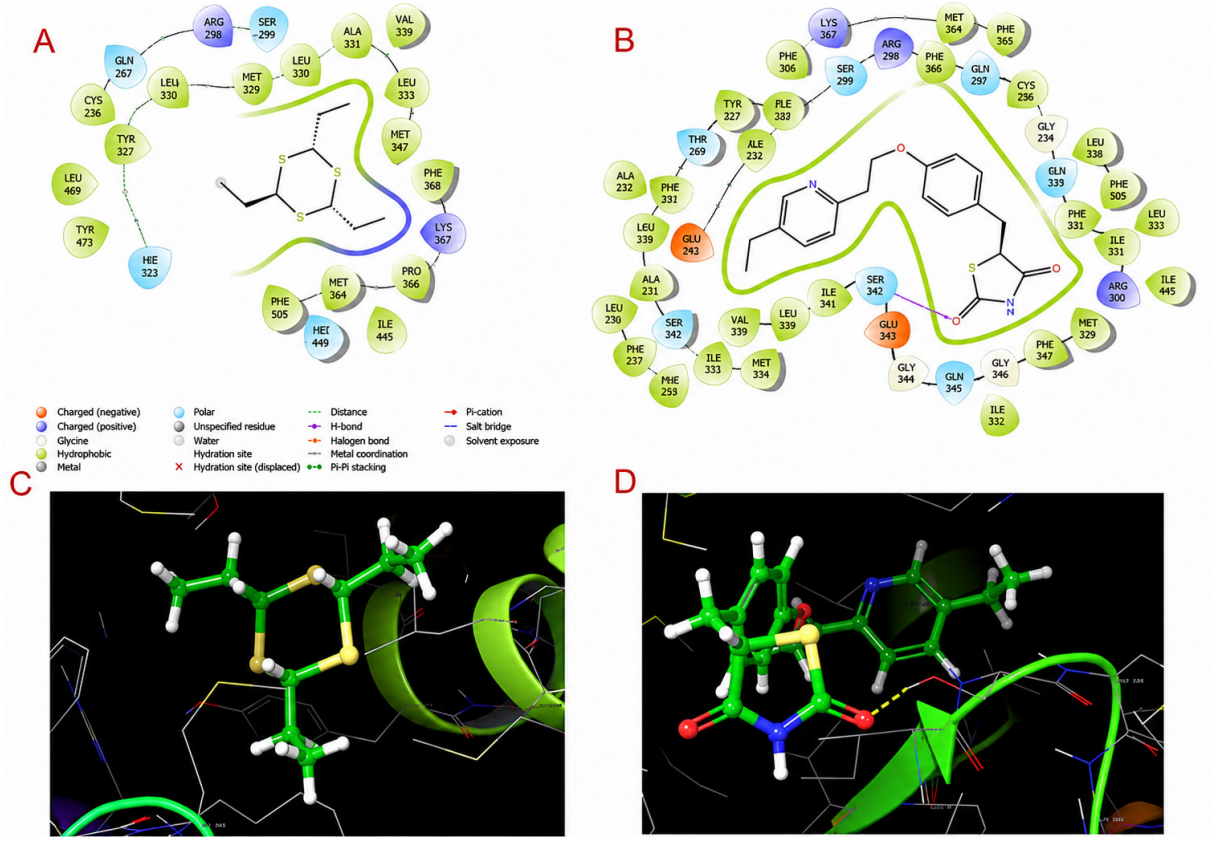

Figure 2: Representation of ligand-receptor interactions between PPAR-Ϋ (PDB ID: 7AWC) and A) Potent compound- 2D view, b) Pioglitazone- 2D view, C) Potent compound- 3D view, D) Pioglitazone- 3D view.

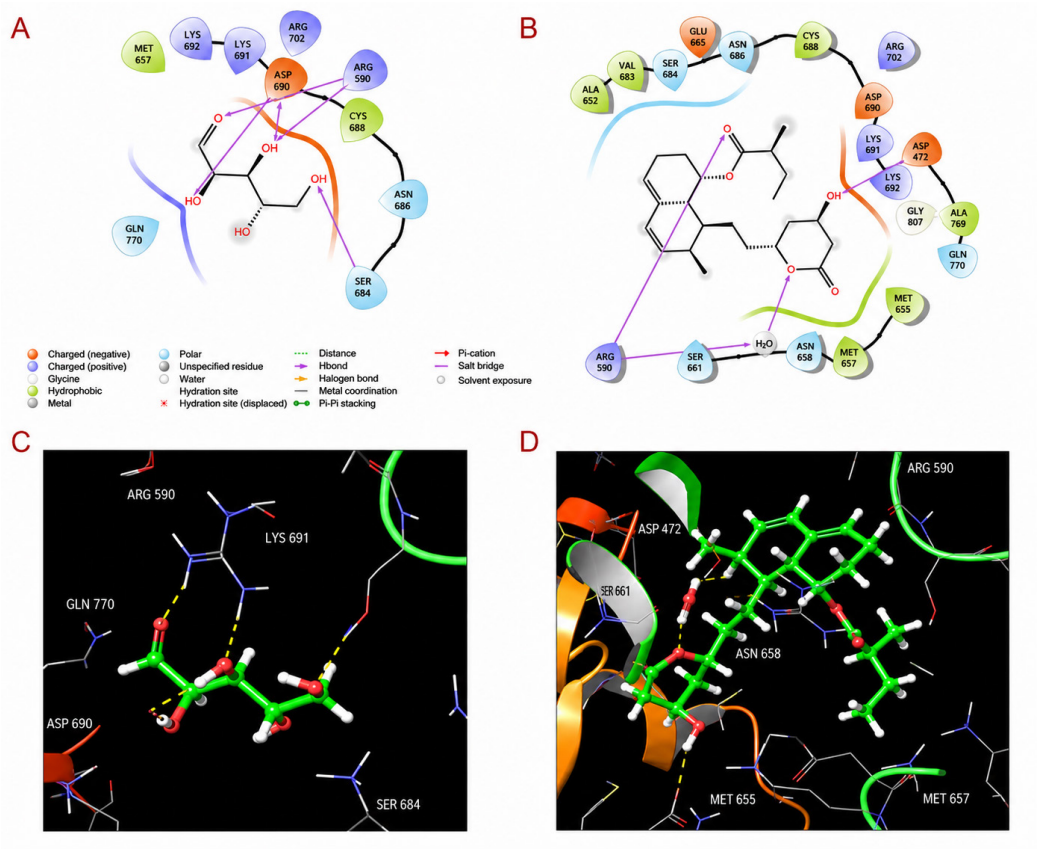

Figure 3: Representation of ligand-receptor interactions between HMG-CoA reductase (PDB ID: 1HW8) and A) Potent compound (IMPHY004187)- 2D view, b) Mevastatin- 2D view, C) Potent compound (IMPHY004187)- 3D view, D) Mevastatin- 3D view.

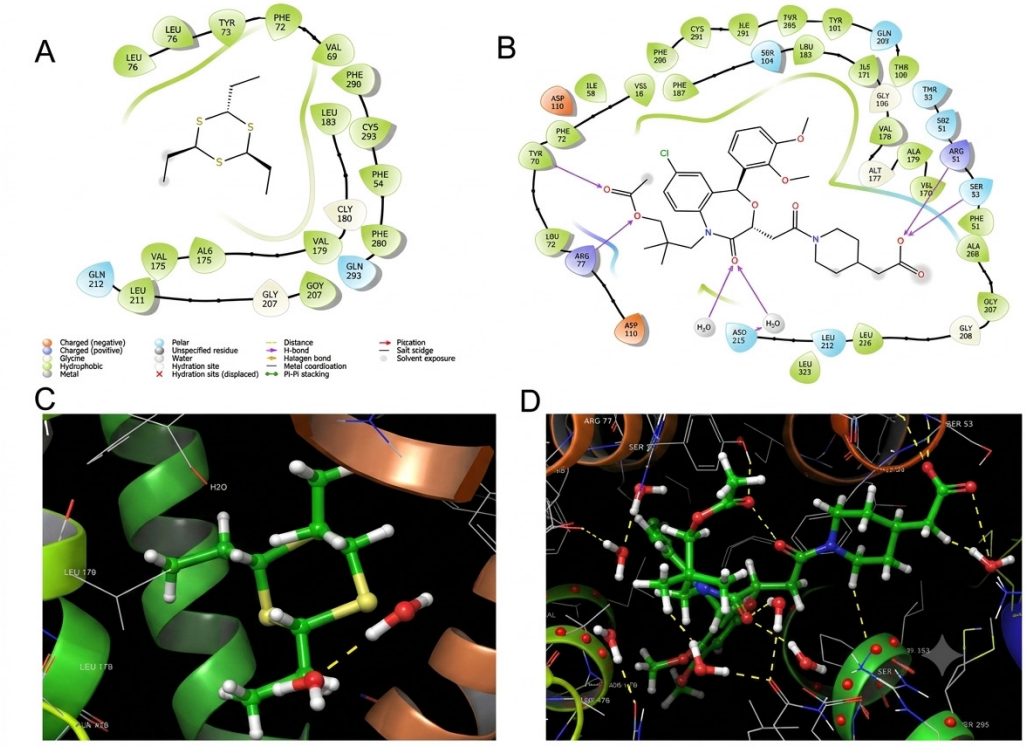

Figure 4: Representation of ligand-receptor interactions between squalene synthase (PDB ID: 3ASX) and A) Potent compound (IMPHY012524)- 2D view, b) TAK-475- 2D view, C) Potent compound (IMPHY012524)- 3D view, D) TAK-475- 3D view.

Table 4: Representation of docking score of selected phytoconstituents of *Allium cepa* against various antilipidemic targets.

Ligand	Docking Score (kcal/mol)		
	PPAR-ϒ (PDB ID: 7AWC)	HMG-CoA reductase (PDB ID: 1HW8)	Squalene synthase (PDB ID: 3ASX)
TAK-475 (9874248)	-7.83	--	-10.431
Mevastatin (64715)	-7.082	-2.87	
Atorvastatin (60823)	-6.786		-6.469
Pravastatin (54687)	-6.76	-4.61	-6.019
IMPHY012524	-6.717	-3.294	-5.948
Squalestatin 1 (6438355)	-6.535	--	-5.391
IMPHY015116	-6.386	-3.632	-5
Pioglitazone (4829)	-6.006	--	-4.544
Rosuvastatin (446157)	-5.918	-5.168	-6.345
IMPHY010083	-5.038	-2.619	-3.71
IMPHY001915	-4.923	-2.399	-4.196
IMPHY009369	-4.544	-1.255	-4.129
Pioglitazone (77999)	-3.74	--	-5.035
IMPHY007084	-3.737	-2.172	-3.268
IMPHY003016	-1.882	0.569	-3.031
IMPHY002983	-1.402	1.245	0.416
IMPHY009368	-0.475	4.335	-0.051
IMPHY002736	0.138	3.512	0.572
IMPHY004187	0.723	-3.918	0.249
IMPHY001886	0.756	3.737	-0.166
IMPHY008688	0.863	4.257	-0.113
IMPHY011974	1.561	4.81	1.844

hinder the activities of mevastatin. Docking studies of squalene synthase (PDB ID: 3ASX) revealed that the standard inhibitor TAK-475 and the potent medication IMPHY012524 demonstrate comparable hydrogen-bond and hydrophobic interactions within the catalytic region. Standard inhibitor and potent compound primarily engaged with hydrophobic residues such as PHE, LEU, VAL, and ALA, which serve to stabilize ligands within the enzyme cavity. Both ligands exhibited hydrogen-bond interactions with residues adjacent to the active site, indicating that the potent compound may inhibit squalene synthase and bind similarly to TAK-475.

CONCLUSION

This study successfully evaluated lipid-lowering botanicals using a thorough *in silico* approach, creating a strong computational foundation for creating a new antilipidemic polyherbal product. A major metabolic factor in ASCVD, which kills millions of people annually globally, is hyperlipidemia. Even while traditional statin treatments significantly lower LDL-C, clinical issues including statin intolerance (which affects around 17% of patients) and lingering cardiovascular risks call for the investigation of alternate treatment strategies. This study conducted a thorough assessment of phytochemicals against a multi-target panel essential to lipid regulation, such as PPAR-Y, HMG-CoA reductase, and squalene synthase, in order to solve these problems. We narrowed down a global selection of 708 plant species to 64 medicinal plants of Indian provenance using a multi-tiered database mining approach, finally identifying *Allium cepa* (bulb) as the best option for more research. Both contemporary chemical profiling and a long history of usage in Ayurvedic medicine for ailments like "Sthaulya" (obesity) and "Raktagata Vata" (hyperlipidemia) supported this decision. A "Reverse Pharmacology" approach was made possible by the confluence of ethnopharmacology and contemporary bioinformatics, which improved the efficiency and regulatory acceptability of herbal medicine development. The rigorous use of ADMET and toxicity filters, which revealed the complex structure of natural phytochemical libraries, was

a critical component of this study. Although human intestinal absorption of 52 phytochemicals from *Allium cepa* was generally acceptable, the toxicity evaluation posed considerable challenges. Only 14 chemicals were found to be safe for molecular docking after the study revealed a variety of toxicological characteristics, such as hepatotoxicity, nephrotoxicity, and mutagenicity. These results highlight the need for high-throughput safety screens before turning natural compounds into promising candidates for pharmaceutical investigation. The multi-target capabilities of *Allium cepa* phytoconstituents were convincingly demonstrated by molecular docking studies. With a good binding affinity for all three targets, IMPHY012524 stood out as a top lead. Its docking score against PPAR-Ɣ (-6.717 kcal/mol) is comparable to well-known reference substances such as Pravastatin (-6.76 kcal/mol), suggesting a strong potential to influence lipid metabolism. Additionally, IMPHY012524 and IMPHY015116 showed notable interactions with Squalene synthase and HMG-CoA reductase, indicating their capacity to disrupt cholesterol production at several stages. These findings support the synergistic theory of polyherbalism, in which many phytochemicals interact with several metabolic pathways to maximize therapeutic efficacy while reducing toxicity.

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ABBREVIATIONS

ADME: Absorption, Distribution, Metabolism, Excretion; **ADMET:** Absorption, Distribution, Metabolism, Excretion, Toxicity; **AMES:** Mutagenicity test; **AMPK:** AMP-activated Protein Kinase; **ASMR:** Age-Standardized Mortality Rate; **ASCVD:** Atherosclerotic Cardiovascular Disease; **BBB:** Blood-Brain Barrier; **GBD:** Global Burden of Disease; **GI:** Gastrointestinal; **HBA:** Hydrogen Bond Acceptor; **HBD:** Hydrogen Bond Donor; **HDL-C:** High-Density Lipoprotein Cholesterol; **HMG-CoA:** 3-Hydroxy-3-Methylglutaryl-Coenzyme A; **HTVS:** High-Throughput Virtual Screening; **IMPPAT:** Indian Medicinal Plants, Phytochemistry, and Therapeutics; **LD50:** Median Lethal Dose; **LDL-C:** Low-Density Lipoprotein Cholesterol; **Log P:** Logarithm of Partition Coefficient; **MW:** Molecular Weight; **NA:** Not Applicable; **OCT2:** Organic Cation Transporter 2; **OPLS:** Optimized Potentials for Liquid Simulations; **PCSK9:** Proprotein Convertase Subtilisin/Kexin Type 9; **PDB:** Protein Data Bank; **PPAR-Ɣ:** Peroxisome Proliferator-Activated Receptor Gamma; **QSAR:** Quantitative Structure-Activity Relationship; **SDF:** Structure-Data File; **TC:** Total Cholesterol; **TG:** Triglycerides; **USDA:** United States Department of Agriculture; **VDss:** Volume of Distribution at Steady State.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHORS CONTRIBUTION

Conceptualization: V.T., and P.A., **Data collection and writing of the original draft:** V.T.; **Experimentation:** V.T.; **Review and Editing:** V.T and N.A., **Supervision:** P.A.

SUMMARY

The transformation in the global epidemiological landscape regarding dyslipidemia, which reveals an alarming prevalence of 28.8% for hypertriglyceridemia and 24.1% for hypercholesterolemia as of 2025, calls for a shift from traditional "one-drug, one-target" treatments to more comprehensive, multi-target strategies. This recent computational study offers an organized, *in silico* framework for assessing the antilipidemic effects of *Allium cepa*, connecting ancient Ayurvedic wisdom with modern molecular pharmacology. The ensuing discussion evaluates the sequential results of the research, ranging from database mining to lead optimization via molecular docking. The initial stage of the study implemented a multi-layered data-mining method to refine a large global assortment of 708 lipid-lowering plants down to a culturally and geographically pertinent selection of 64 Indian medicinal species. This systematic filtering process guarantees that the resulting formulations are not only biologically effective but also accessible and rooted in local medical traditions. The final choice of *Allium cepa* (bulb) among the top four contenders, which also featured *Gymnema sylvestre, Murraya koenigii*, and *Terminalia chebula*, was influenced by its widespread availability in the Indian subcontinent and its diverse array of bioactive compounds appropriate for high-throughput screening. By concentrating on a plant historically utilized for conditions such as "Sthaulya" (obesity) and "Raktagata Vata" (hyperlipidemia), the research adopts a "Reverse Pharmacology" approach that expedites drug discovery by using traditional effectiveness as a foundational point for molecular validation.

An intriguing investigation of 52 phytonutrients from the *Allium cepa* bulb has shown an intriguing pharmacokinetic landscape while highlighting the complexity of natural extracts. Remarkably, the human gut was able to absorb 45 of the 52 substances, with absorption rates surpassing 30%. This implies that onions are a great option for the long-term treatment of dyslipidemia since most of their advantageous metabolites are prepared for oral consumption. The statistics, however, reveal a different picture when it comes to distribution. Just sixteen compounds were able to reach the VDss sweet spot. Achieving a balanced VDss is essential because it guarantees that medications are efficiently distributed between the target tissues and the circulation, preventing both quick clearance and excessive buildup. Positively, 30 substances were shown to be non-inhibitors of the major

Cytochrome P450 (CYP) isoforms, specifically CYP1A2, 2C19, 2C9, 2D6, and 3A4. Compounds that do not interfere with these enzymes reduce the possibility of negative herb-drug interactions, which makes this discovery especially encouraging for polyherbal compositions. For patients who are currently on several drugs for their cardiovascular health, this is particularly crucial. The most notable accomplishment was the excretion profile, which indicated that all 52 components would not block the renal transporter OCT2. This confirms the onion's advantageous qualities by showing a reduced likelihood of transporter-related kidney damage or interactions. A surprising range of toxicological profiles among different substances have been shown by recent investigations utilizing ProTox 3.0 and TEST 5.1.2 software. Some organ toxicities drew our attention, even though the majority had a minimal potential for bioaccumulation. IMPHY003919 and IMPHY011572, in particular, highlighted concerns for hepatotoxicity, while several additional compounds showed nephrotoxicity (18) and respiratory toxicity (21). Positively, IMPHY007084 was the only component in the comprehensive pkCSM screening that was shown to be totally non-toxic. In the end, 14 compounds were found to be sufficiently safe to proceed to molecular docking investigations. The fact that several of these substances seem to be able to pass across the Blood-Brain Barrier (BBB), suggesting potential neuropharmacological effects, is especially noteworthy.

The pharmacological study concentrated on docking 14 carefully chosen drugs with good safety profiles against three essential enzymes and receptors involved in lipid homeostasis: PPAR-Y, squalene synthase, and HMG-CoA reductase. One important regulator of glucose homeostasis and lipid metabolism is PPAR-Y. The reference medication in this investigation was TAK-475, which had the greatest binding affinity at -7.83 kcal/mol. With a docking score of -6.717 kcal/mol, IMPHY012524 (Cyanidin 3-glucoside/Cyanin) was shown to be the best candidate among the components produced from *Allium cepa*. This affinity is strikingly similar to well-known statins like atorvastatin (-6.786 kcal/mol) and pravastatin (-6.76 kcal/mol), suggesting that IMPHY012524 may successfully regulate lipid metabolism by activating PPAR-Y. In order to prevent the creation of cholesterol, statins mainly work by inhibiting HMG-CoA reductase. Compounds IMPHY015116 (D-Xylose) and IMPHY012524 showed binding affinities of -3.632 and -3.294 kcal/mol, respectively, although Rosuvastatin remained the most effective binder to this target (-5.168 kcal/mol). Significantly, squalene synthase, a downstream enzyme in the cholesterol manufacturing pathway, showed higher binding affinities for the substances. Significant interactions within the squalene synthase active site were shown by IMPHY012524 (-5.948 kcal/mol) and IMPHY015116 (-5.0 kcal/mol), indicating that compounds derived from *Allium cepa* may offer a supplementary mechanism to statin therapy, potentially inhibiting cholesterol production at multiple enzymatic stages.

REFERENCES

Afendi, F. M., Okada, T., Yamazaki, M., Hirai-Morita, A., Nakamura, Y., *et al.* (2012). KNApSAcK family databases: integrated metabolite-plant species databases for multifaceted plant research. Plant and Cell Physiology, 53(2), e1-e1.

Airaodion, A. I., Akaninyene, I. U., Ngwogu, K. O., Ekenjoku, J. A., and Ngwogu, A. C. (2020). Hypolipidaemic and antidiabetic potency of *Allium cepa* (onions) bulb in alloxan-induced diabetic rats. Acta Scientific Nutritional Health, 4(3), 1-8.

Atanasov, A. G., Zotchev, S. B., Dirsch, V. M., and Supuran, C. T. (2021). Natural products in drug discovery: advances and opportunities. Nat Rev Drug Discov, 20(3), 200-216. doi:10.1038/s41573-020-00114-z

Banerjee, P., Kemmler, E., Dunkel, M., and Preissner, R. (2024). ProTox 3.0: a webserver for the prediction of toxicity of chemicals. Nucleic acids research, 52(W1), W513-W520.

Baragob, A., Al-Wabel, N. A., Ahmed, N., Babiker, M., Abdalkarim, A. S., & Elboshra, M. (2015). Study to investigate the pancreatic regeneration and evaluation of the antidiabetic and antihyperlipidemic potential of aerial parts of *Allium cepa*. Biochem Biotechnol Res, 3, 19-29.

Ben, W. (2001). Dr. Duke's phytochemical and ethnobotanical databases. Choice Rev. Online, 38, 38-3317.

Biharee, A., Singh, Y., Kulkarni, S., Jangid, K., Kumar, V., Jain, A. K., and Thareja, S. (2024). An amalgamated molecular dynamic and Gaussian based 3D-QSAR study for the design of 2, 4-thiazolidinediones as potential PTP1B inhibitors. Journal of Molecular Graphics and Modelling, 127, 108695.

Biharee, A., Singh, Y., Kulkarni, S., Jangid, K., Kumar, V., Jain, A. K., & Thareja, S. (2024). An amalgamated molecular dynamic and Gaussian based 3D-QSAR study for the design of 2, 4-thiazolidinediones as potential PTP1B inhibitors. Journal of Molecular Graphics and Modelling, 127, 108695.

Chong, B., Jayabaskaran, J., Jauhari, S. M., Chia, J., Le Roux, C. W., *et al.* (2025). The global syndemic of modifiable cardiovascular risk factors projected from 2025 to 2050. Journal of the American College of Cardiology, 86(3), 165-177.

Daina, A., Michielin, O., and Zoete, V. (2017). SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. Scientific reports, 7(1), 42717.

Duke, J. A. (2020). Database of biologically active phytochemicals and their activity: CRC Press.

Eyadiel, L. S., and Modarressi, T. (2026). Bridging the Gap: Pragmatic Strategies to Overcome Barriers in the Implementation of Cardiometabolic Care. Journal of Cardiac Failure - Intersections, 2(2), 147-156. doi:https://doi.org/10.1016/j.yjcafi.2025.08.015

Gavina, C., Araújo, F., Luz, A. R., Jácome, C., Ruivo, J. A., *et al.* (2026). Prevalence of Statin Intolerance in a Primary Care Portuguese Population: A Retrospective Cohort Study. J Lipid Atheroscler, 15(1), 138-150. doi:10.12997/jla.2026.15.1.138

Gupta, K., Gautre, P., Biharee, A., Singh, Y., Patil, U. K., *et al.* (2024). Exploring the potential of essential oil from *Plectranthus amboinicus* leaves against breast cancer: *in vitro* and *in silico* analysis. Medical Oncology, 41(4), 81.

Rohan, S. P., Chitra, C. K., Somnath, M. M., Kailas, D. D., & Anup, S. H. (2019). Antihyperlipidemic Activity of *Murraya koenigii* Leaves Methanolic and Aqueous Extracts on Serum Lipid Profile of High Fat-Fructose Fed Rats. Pharmacognosy Journal, 11(4).

Kulkarni, S., Singh, Y., Biharee, A., Bhatia, N., Monga, V., *et al.* (2023). Molecular docking, 3D-QSAR and simulation studies for identifying pharmacophoric features of indole derivatives as 17β-hydroxysteroid dehydrogenase type 5 (17β-HSD5) inhibitors. Journal of Biomolecular Structure and Dynamics, 41(22), 12668-12685.

Lans, C., & van Asseldonk, T. (2020). Dr. Duke's phytochemical and ethnobotanical databases, a cornerstone in the validation of ethnoveterinary medicinal plants, as demonstrated by data on pets in British Columbia. In Medicinal and aromatic plants of North America (pp. 219-246). Springer.

Li, J., Gao, Y., Ren, M., Yu, Z., Ren, X., Chao, S.,…Wang, Y. (2025). Burden and trends of cardiovascular diseases attributable to high LDL-C in China, 1990-2021: an age-period-cohort analysis with projectioans to 2050. Front Cardiovasc Med, 12, 1698172. https://doi.org/10.3389/fcvm.2025.1698172

Mohanraj, K., Karthikeyan, B. S., Vivek-Ananth, R., Chand, R. B., Aparna, S., *et al.* (2018). IMPPAT: A curated database of I ndian M edicinal P lants, P hytochemistry A nd T herapeutics. Scientific reports, 8(1), 4329.

Rachh, P., Rachh, M., Ghadiya, N., Modi, D., Modi, K., *et al.* (2010). Antihyperlipidemic activity of *Gymenma sylvestre* R. Br. leaf extract on rats fed with high cholesterol diet. International journal of pharmacology, 6(2), 138-141.

Reddy, M. M., Dhas Devavaram, J., Dhas, J., Adeghate, E., and Starling Emerald, B. (2015). Anti-hyperlipidemic effect of methanol bark extract of *Terminalia chebula* in male albino Wistar rats. Pharmaceutical biology, 53(8), 1133-1140.

Reijnders, E., van der Laarse, A., Jukema, J. W., & Cobbaert, C. M. (2023). High residual cardiovascular risk after lipid-lowering: prime time for Predictive, Preventive, Personalized, Participatory, and Psycho-cognitive medicine. Front Cardiovasc Med, 10, 1264319. https://doi.org/10.3389/fcvm.2023.1264319

Rosenberg, J., Lampridou, S., Moores, A., Garfield, S., Wingfield, D., & Judah, G. (2025). A systematic review uncovering modifiable influences on statin adherence. Patient preference and adherence, 29-48.

Sabatine, M. S., Giugliano, R. P., Keech, A. C., Honarpour, N., Wiviott, S. D., *et al.* (2017). Evolocumab and Clinical Outcomes in Patients with Cardiovascular Disease. N Engl J Med, 376(18), 1713-1722. doi:10.1056/NEJMoa1615664

Sliwoski, G., Kothiwale, S., Meiler, J., and Lowe, E. W. (2014). Computational Methods in Drug Discovery. Pharmacological Reviews, 66(1), 334-395. doi:https://doi.org/10.1124/pr.112.007336

Tan, E. W., Low, L. H., Atanasov, A. G., and Goh, B. H. (2025). Bridging Traditions and Technology: The Role of Ethnopharmacology in Shaping Next-Generation Multidisciplinary Researchers. Pharmacology Research and Perspectives, 13(1), e70074. doi:https://doi.org/10.1002/prp2.70074

Vasantrao, M. B. V., & Bhambar, R. (2025). Synergistic Potential of Polyherbal Combinations: An Integrative Review of Phytochemistry, and Therapeutic Applications. MIJPLS, 01, 1-19. https://doi.org/https://mijpls.com/wp-content/uploads/2025/12/review_vrushali-bhaisane.pdf

Vivek-Ananth, R., Mohanraj, K., Sahoo, A. K., and Samal, A. (2023). IMPPAT 2.0: an enhanced and expanded phytochemical atlas of Indian medicinal plants. ACS omega, 8(9), 8827-8845.

Wijaya, S. H., Tanaka, Y., Altaf-Ul-Amin, M., Morita, A. H., Afendi, F. M., Batubara, I.,…Kanaya, S. (2016). Utilization of KNApSAcK family databases for developing herbal medicine systems. Journal of Computer Aided Chemistry, 17, 1-7.

Zhang, J., Wu, Y., Zhang, Y., Gao, L., and Hu, Y. (2026). Global burden and causal analysis of LDL-C-related cardiovascular diseases: A GBD 2021 and Mendelian randomization study. Nutrition, Metabolism and Cardiovascular Diseases, 36(6), 104622. doi:https://doi.org/10.1016/j.numecd.2026.104622

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