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Review Article

Synergistic integration of bioinformatics and Ayurveda in obesity and cancer management: Advancements, challenges and future directions

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Abstract

Obesity is a global health concern linked not only to metabolic disorders but also to several types of cancers. Ayurvedic medicine, an ancient Indian healthcare tradition, presents a wealth of phytoconstituents with potential therapeutic benefits for obesity and related cancers. Recent advances in bioinformatics provide powerful methods for identifying and validating these natural molecules. This review emphasizes the synergistic integration of Ayurveda and bioinformatics, focusing on phytoconstituents such as flavonoids and coumarins, computationally validated as potent pancreatic lipase inhibitors. Virtual screening, molecular docking, QSAR modelling, pharmacophore mapping, and molecular dynamics simulations were employed to predict, validate, and optimise these candidates. Network pharmacology further revealed multitarget potential against obesity-linked cancer pathways involving genes like CXCL12 and LEP. Despite these promising advancements, significant challenges remain, including the chemical complexity of Ayurvedic formulations, limited bioavailability, insufficient translation from computational predictions to experimental validation, and interdisciplinary communication gaps. Addressing these issues through improved databases, refined computational methods, and collaborative frameworks can fully unlock the therapeutic potential of Ayurveda, redefined through the lens of bioinformatics.

Keywords: Ayurvedic, Bioinformatics, Cancer, MD simulation, Obesity.

Introduction

Obesity arises from an imbalance of energy, and currently, it is recognised as a serious worldwide health threat by the World Health Organization (WHO). It is linked to various health issues like fatty liver disease, osteoarthritis, oesophageal adenocarcinoma, cancers of the gastric cardia, gallbladder, liver, kidney, pancreas, postmenopausal breast, endometrium, and thyroid, as well as multiple myeloma, non-Hodgkin lymphoma, dyslipidaemia, diabetes mellitus, hypertension, asthma and most likely, ovarian cancer and high-grade prostate cancer. According to a WHO survey in 2022, over 2.5 billion (43%) adults aged 18 years or older were overweight, and 890 million (16%) among these were obese (Islam *et al*., 2024). The number of people suffering from obesity is increasing day by day. There is an excessive deposition of fat in adipose tissue due to an imbalance in energy (Veeramachaneni *et al*., 2015). The development of inhibitors of nutrient digestion and absorption is a key goal for the treatment of obesity. Inhibition of pancreatic lipase (PL), resulting in a decrease in dietary fat absorption, was one of the potential strategies for controlling obesity. For women, the average body fat percentage is 25 to 30%, whereas for men, it is 18 to 23%. Women are deemed obese if their body fat percentage exceeds 30%, while men are deemed obese if their body fat percentage exceeds 25% (Buchholz *et al*., 2015). The only authorised anti-obesity drug in Europe is Orlistat, which shows effective inhibition of pancreatic lipase (PL). Orlistat is a saturated derivative of lipstatin (McClendon *et al*., 2009). Lipstatin, the essential enzyme for the digestion of intestinal fat yielded from *Streptomyces toxytricini*, is a novel and highly effective inhibitor of pancreatic lipase (Weibel *et al*., 1987). Despite having strong anti-obesity effects, orlistat can also cause non-negligible gastrointestinal side effects such as flatus with discharge, faecal incontinence, oily spotting, and abdominal cramping. Thus, for clinical usage, more PL inhibitors that have significant PL inhibitory activity and an enhanced safety profile are required (Hou *et al*., 2018). A variety of plant, fungal, bacterial, and marine species have been searched for new compounds having PL inhibitory properties for anti-obesity medicines. Among them, the compounds extracted from common foods, including tea, ginseng, peanut, soybean, yerba mate, grape, or apple vine, have been reported. A few of

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these, such as saponins and polyphenols, can suppress pancreatic lipase activity, which could be used to control the obesity epidemic (Garza *et al*., 2011). Moreover, obesity has lately been implicated in the promotion of breast cancer (in postmenopausal women) as well as cancers of the colon/rectum, kidney, endometrial, esophagus, liver, prostate, pancreas, and gallbladder (Seyedan *et al*., 2015). Plant products with anti-obesity qualities include flavonoids, alkaloids, saponins, and phenols. Compared to treatments that frequently use a single component, the presence of various phytochemical combinations in plant medications may have an enhanced impact by acting on several molecular targets (Sharma *et al*., 2018). The advantage of developing new medicine by the action of lipase inhibitors on the peripheral elements is that they do not affect the human blood vessels or the nervous system and bone circulation, making the lipase inhibitors relatively safe (Liu *et al*., 2020). Several metabolic disorders, such as glucose intolerance, high blood pressure, insulin resistance, and dyslipidaemia, are related to obesity, which is a complex illness. Together, these disorders are called metabolic X syndrome. According to recent research, there is a high connection between pancreatic cancer and obesity. For example, one of the major risks for pancreatic cancer in both men and women is a body mass index higher than 35 (Pothuraju *et al*., 2018). In comparison to the lean people, the people with abdominal adiposity have a 50% higher risk of developing pancreatic cancer (Incio *et al*., 2016).

One of the most important issues of the human population in recent decades is cancer, which can impact a person's life in a variety of ways, including lung, breast, colorectal, prostate, and other cancers. Colorectal cancer is the second most common cancer among women and the third most common cancer among men around the world (Noorolyai *et al*., 2019). Colorectal cancer (CRC) is the third most commonly diagnosed cancer across the world and is the second most deadly cancer globally (Hossain *et al*., 2022). The colorectal cancer's prevalence and mortality have increased dramatically over the last few decades, with metastasis or tumor recurrence generally being the cause of death (Zhang *et al*., 2014). Regional lymph node metastasis is frequent in early-stage metastasis and plays a crucial role in the progression of colorectal cancer tumors. They also affect prognosis (Sasaki *et al*., 2008). Cancer is a significant global public health concern and is the second major cause of death in the United States. During 2012-2016, the mortality rates for male liver and lung cancers were 40% higher in the poor counties and twice as high for cervical cancer as compared to the most prosperous counties (Siegel *et al*., 2019). In the United States, breast cancer is the most frequently detected cancer in women and the second leading cause of cancer-related deaths in women after lung cancer (DeSantis *et al*., 2019). The fourth most common fatal tumor is gastric cancer, and if it is not found at an early stage, it is difficult to cure. The postoperative recurrence and metastasis of gastric cancer in already been operated 40 to 60% patients affect the long-term survival. According to recent studies, PFTK1 (also known as PFTAIRE protein Kinase 1, Cyclin-Dependent Kinase 14) (CDK14) is significantly expressed in various tumors, including breast cancer, oesophageal cancer, and hepatocellular carcinoma, and it also regulates the cell cycle, migration, tumor proliferation, and invasion, which further affects the prognosis of tumors (Yang *et al*., 2015).

Ayurveda is one of the oldest still-relevant medical traditions that originated in India. Ayurveda is frequently referred to as 'science of life' since Ayu means 'life' and Veda means 'science' or 'knowledge' in Sanskrit (Patwardhan *et al*., 2014). In India, modern medicine coexists with traditional knowledge systems like Ayurveda. An emerging discipline called Ayurgenomics examines the principles and methods of Ayurveda in conjunction with genomic methods for mainstream integration. Globally, healthcare has experienced a significant transition from a reactive to a proactive approach, emphasizing precision and Preventive, Personalized, Predictive, and Participatory (P4) medicine (Mukerji *et al*., 2023). The principles of Ayurveda, which have been followed for thousands of years and are still widely used today, comply with P4 medicine. Maintaining health in those people who are healthy and reducing disorders in those people who are ill are the primary goals of Ayurveda. According to Ayurveda, the subject matter is divided into three main categories called 'trisutra', which correspond to the three interconnected characteristics of causes (hetu), therapeutics (aushadha), and features (linga), both for healthy and unhealthy people (Prasher *et al*., 2016). Flavonoids are a group of bioactive compounds found in foods such as berries, grapes, apples, red wine, citrus fruit, and green tea, and it is used in diet, lowering the risk of many diseases, including obesity, cancer, and cardiovascular disease (Bustos *et al*., 2020).

Bioinformatics has become a valuable technique for contributing to the development of new drugs due to its introduction into modern research. It involves collecting unprocessed biological data from many sources, such as protein structure databases, gene expression datasets, and DNA sequencing. Computational models are created to illustrate the biological process at the molecular level based on the knowledge gained. This method of working with big datasets and running computer-based simulations is called *in-silico* studies (Goel *et al*., 2024). The field of Ayur-informatics is expected to advance one's comprehension of the fundamental concepts of traditional medicine and in the creation of more effective treatment approaches by fusing bioinformatics with Ayurvedic concepts. This interdisciplinary approach is

required to successfully integrate modern technologies with traditional wisdom (Rath, 2025). Several kinds of computer-aided techniques have been proposed and used to develop and design lead drugs because they are more affordable and produce results faster. The computational techniques, such as pharmacophore-based, 3D-QSAR methods, and machine learning methods, have been extensively used in the identification of novel chemicals that bind to specific targets (Zhang *et al*., 2021).

Literature Review of Methodology

Molecular docking

The molecular docking was performed using Maestro 12.9, and the molecular dynamics simulation was performed using the GROMACS version 2018.2 software packages. The root mean square fluctuation (RMSF), root mean standard deviation (RMSD), solvent accessible surface area (SASA), radius of gyration (Rg), hydrogen bonds, short-range Coulombic forces, and short-range Lenard-Jones potential analysis were done on MDS output.

The pancreatic lipase 3D structure (PDB ID: 1LPB) was retrieved from the Protein Data Bank (PDB) with a resolution of 2.46 Å. We used the Protein Preparation Wizard in Maestro 12.9 (Schrödinger) to prepare our target for docking studies. First, bond orders were assigned, and all hydrogen atoms were added. Any zero-order bonds to metal ions were created, and missing side-chain atoms were modeled in. The resulting structure was then subjected to optimization and energy minimization with the OPLS2005 force field to relieve steric clashes and optimize hydrogen-bonding networks prior to docking.

The 2D structures of all phytochemical ligands—including ellagic acid, ferulic acid, kaempferol, luteolin, p-coumaric acid, quercetin, rutin, syringic acid, vanillic acid, (–)-epicatechin, (+)-catechin hydrate, apigenin, chlorogenic acid, and our series of coumarin derivatives—were downloaded from the PubChem database in SDF format. These files were imported into the LigPrep module of Maestro 12.9, which generated all relevant tautomers, stereoisomers, and ring conformations at physiological pH (7.0 ± 2.0), ensuring correct protonation states. Subsequently, each resultant 3D structure underwent energy minimization using the OPLS2005 force field (Jorgensen *et al*., 1988) to relieve steric hindrance and optimize geometries. The prepared ligand set was then used for molecular docking with the target protein.

The prepared ligand library and the pancreatic lipase (PL) structure were submitted to the Glide docking workflow of Maestro 12.9. A receptor grid was defined around the PL active site using the Receptor Grid Generation tool. The grid box was generated by selecting the co-crystalized ligand. All ligands, along with standard drug orlistat, and 3GG and NAG (co-crystalized ligand), were docked using the Glide Extra Precision (XP) (Friesner *et al*., 2006) mode to predict their optimal binding poses and estimate binding affinities.

Molecular dynamics simulation

During the molecular dynamics simulation portion of our investigation, we confirmed the stability of the protein-ligand complex that was docked using Groningen Machine for Chemical Simulation (GROMACS) (Spoel *et al*., 2005) version 2018.2, a well-established software for simulating the dynamics of biomolecules. The simulation was carried out for 100 nanoseconds, allowing for a thorough examination of the stability and interactions within the protein-ligand complex. The top molecule was simulated with the CHARMM36 (Klauda *et al*., 2010) all-atom force field. After that, ligand topology was generated with the help of the online web server SwissParam (Bugnon *et al*., 2023). Before commencing the simulation, we prepared the GROMACS-compatible files, i.e., merging the topological files of proteins and ligands while ensuring that these complexes were hydrated, minimized, and stabilized. The water model employed for solvation purposes was TIP3P (Boonstra *et al*., 2016). To maintain ion balance in the grid box, Na+ and Cl- ions were utilized. The subsequent stage involved the energy minimization step using the Steepest Descent algorithm. A reliable minimization procedure ensured that the maximal force did not exceed 10 KJ/mol. We used the NVT and NPT ensembles for 100 ps each to achieve system equilibration, maintaining a constant temperature of 300K and a continuous pressure of 1 bar, respectively. Following the equilibration stage, the system performed a production run lasting 100 ns. The time step was 2 fs, and a trajectory was recorded.

Network construction and topological analysis

We used the STRING database (v11.0; https://string-db.org) (Szklarczyk *et al*., 2019) to find protein–protein interactions (PPIs) between differentially expressed genes. We used *Homo sapiens* as the reference organism and set a high-confidence score threshold of 0.700. We used Cytoscape (v3.8.2) (Shannon *et al*., 2003) to look at the interaction dataset we got back, which included 1,136 nodes and 6,137 edges. We cut out any nodes that weren't related to the main network component. Using Cytoscape's NetworkAnalyzer module, we generated topological metrics including degree, betweenness centrality, and closeness centrality. The degree of a node, which shows how many direct connections it has, was the main factor we used to choose hubs. JUN had the greatest degree among the top choices; the canonical human JUN protein is 331 amino acids, as annotated in UniProt (P05412). JUN was not included in the downstream analysis because it is a transcription factor, and transcription factors are widely considered poorly

druggable: they lack canonical small-molecule binding pockets, which are structurally challenging to target (Groner *et al*., 2012).

So, CXCL12 and LEP were kept as the main hub genes. Finally, we used Database for Annotation, Visualization, and Integrated Discovery (DAVID v6.8) (Dennis *et al*., 2003) to do gene ontology (GO) biological process and Kyoto Encyclopedia of Genes and Genomes (KEGG) (Kanehisa & Goto, 2000) pathway enrichment analyses with a Benjamini–Hochberg–adjusted *p-value* < 0.05.

Experimental validation

All reagents were purchased from Sigma-Aldrich (St. Louis, MO). Porcine pancreatic lipase was dissolved to 0.1 mg/mL in 0.1 M Tris–HCl buffer (pH 8.0). Test compounds (at final concentrations of 10, 20, 30, 50, 70, 100, 250, and 500 μM) were each pre-incubated with 100 μL of the enzyme solution (adjusted to 150 μL with buffer) for 15 minutes at 37°C. The enzymatic reaction was initiated by adding 20 μL of 10 mM p-nitrophenyl butyrate and allowed to proceed for an additional 15 minutes at 37°C (Jo *et al*., 2017). Hydrolysis of the substrate to p-nitrophenol was quantified by measuring absorbance at 415 nm on a 96-well plate reader. Percent inhibition was calculated against enzyme-only controls, with orlistat serving as the positive reference. All assays were performed in triplicate, and IC_{50} values were determined by nonlinear regression.

Outcome of review (in-silico)

Identification and computational screening of Ayurvedic phytoconstituents as potent anti-obesity and anti-cancer applications

Obesity is no longer seen only as a lifestyle issue. It is increasingly acknowledged as a multifaceted, systemic disorder intimately associated with the onset of other chronic illnesses, including cancer. Recent bioinformatics research has shown common genetic pathways linking obesity to malignancies, including breast, pancreatic, gastric, and colorectal cancers. This overlap underscores the need to identify multitarget therapy, with nature, especially Ayurveda, as a formidable resource for this endeavour.

In the previous study, a systematic virtual screening and molecular docking approach was employed to identify plant-derived compounds that can inhibit pancreatic lipase (PL) (Sun *et al*., 2016), a critical enzyme involved in dietary fat digestion. Using Maestro 12.9 (Schrödinger Suite), a library of phytoconstituents, primarily flavonoids, was docked against the active site of pancreatic lipase (PDB ID: 1LPB), and coumarins were docked against the C-X-C Motif Chemokine Ligand 12 and Leptin receptor, as shown in Table 1. In the table, 3GG is a co-crystalized ligand of C-X-C Motif Chemokine Ligand 12, and NAG is a co-crystalized ligand of Leptin receptor; both proteins were identified as common in obesity and cancer.

The docking results reveal several standout candidates:

- Among flavonoids, epigallocatechin 3,5-di-O-gallate emerged as the most potent candidate with a docking score of -10.93 kcal/mol, followed closely by -epicatechin 3-O-gallate and isoquercitrin, both demonstrating strong inhibitory potential as compared to a standard drug molecule, i.e., orlistat demonstrates -3.8 kcal/mol of docking score. The 2D interaction of the complex is shown in Figure 1.
- Isoorientin, another flavonoid derivative, also exhibited a promising binding affinity with a docking score of -9.98 kcal/mol.
- Coumarin derivatives, analysed specifically for their interaction with common genes between obesity and cancer, such as CXCL12 and LEP, exhibited high binding affinities, highlighting their potential as multitarget agents.

These results were not limited to docking scores. To ensure these compounds could serve as practical therapeutic candidates, ADME/T (Jaiswal *et al*., 2021) (Absorption, Distribution, Metabolism, Excretion, and Toxicity) profiling was conducted using the QikProp module (Schrödinger, 2018). Most of the top-ranked compounds exhibited favourable oral absorption, ideal molecular weights, acceptable solubility, and low predicted toxicity — crucial properties for oral drug development

The significance of these results is amplified by their integration of old Ayurvedic knowledge with contemporary computational confirmation. For ages, Ayurveda has promoted the use of flavonoid-rich botanicals, including green tea, amla, turmeric, and grapes, for comprehensive health practices that are now receiving molecular-level validation.

The combined use of virtual screening, docking, and ADME/T prediction illustrates the potential for revitalising Ayurveda with modern bioinformatics technologies. This collaboration facilitates the rapid detection of effective, multi-functional natural compounds that not only obstruct critical targets such as pancreatic lipase but may also influence obesity-related carcinogenic pathways.

QSAR and pharmacophore modelling in Ayurveda-based drug discovery

The rapid discovery of effective anti-obesity drugs from an extensive phytochemical reservoir necessitates tactics that extend beyond mere docking methodologies. quantitative structure-activity relationship (QSAR) modelling (Arthur *et al*., 2020; Patel *et al*., 2014) and pharmacophore modelling (Engles *et al*., 2017) provide robust computational frameworks for predicting and improving the biological activity of natural compounds, facilitating more intelligent drug design.

Our study included the development of QSAR models using multiple linear regression (MLR) and atom-

Table 1: Docking result with flavonoids, coumarins, standard drug, and the co-crystalized ligand with respective proteins

Protein	*Phytoconstituent/ Plant derivatives*	*Compound name*	*IUPAC name*	*Docking Score*	*Reference*
Pancreatic lipase	Flavonoids	Epigallocatechin 3, 5,-di-O-gallate	[(2R,3R)-7-hydroxy-5-(3,4,5-trihydroxybenzoyl)oxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2Hchromen-3-yl] 3,4,5-trihydroxybenzoate	-10.93 kcal/ mol	(Modanwal *et al*., 2023)
		-Epicatechin 3-O-gallate	[(2R,3R)-2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-8-[(2R,3R,4R)-3,5,7-trihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2Hchromen-4-yl]-3,4-dihydro-2Hchromen-3-yl] 3,4,5-trihydroxybenzoate	-10.93 kcal/ mol	(Modanwal *et al*., 2023)
		Isoquercitrin	2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-3-[(2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]oxychromen-4-one	-10.2 kcal/ mol	(Modanwal *et al*., 2023)
		Isoorientin	2-(3,4-dihydroxyphenyl)-5,7-dihydroxy-6-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]chromen-4-one	-9.98 kcal/ mol	(Modanwal *et al*., 2023)
		(+)- Catechin Hydrate	(2R,3S)-2-(3,4-dihydroxyphenyl)-3,4-dihydro-2H-chromene-3,5,7-triol;hydrate	-6.96 kcal/ mol	(Modanwal *et al*., 2024)
		Quercetin	2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one	-6.92 kcal/ mol	(Modanwal *et al*., 2024)
		Luteolin	2-(3,4-dihydroxyphenyl)-5,7-dihydroxychromen-4-one	-6.91 kcal/ mol	(Modanwal *et al*., 2024)
		Kaempferol	3,5,7-trihydroxy-2-(4-hydroxyphenyl) chromen-4-one	-6.82 kcal/ mol	(Modanwal *et al*., 2024)
		-	3,4,5-trihydroxy-2-methyl-2,3-dihydropyran-6-one	-5.75 kcal/ mol	(Modanwal *et al*., 2020)
		-	(2R)-2-[(1S)-1,2-dihydroxyethyl]-4-fluoro-3-hydroxy-2H-furan-5-one	-5.33 kcal/ mol	(Modanwal *et al*., 2020)
		-	(2R)-2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-3-methoxy-2H-furan-5-one	-5.20 kcal/ mol	(Modanwal *et al*., 2020)
		-	2-[(1S)-1,2-dihydroxyethyl]-4-hydroxy-3-methoxy-2H-furan-5-one	-5.19 kcal/ mol	(Modanwal *et al*., 2020)
	Standard	Orlistat	[(2S)-1-[(2S,3S)-3-hexyl-4-oxooxetan-2-yl]tridecan-2-yl] (2S)-2-formamido-4-methylpentanoate	-3.80 kcal/ mol	(Modanwal *et al*., 2023)
C-X-C Motif Chemokine Ligand 12	Coumarin derivatives	-	4-Methyl-7,8-Bis(Phosphonooxy)Coumarin	-8.04 kcal/ mol	(Modanwal *et al*., 2023)
			[4-Methyl-Coumarin-7-Yl] Glycamine	-5.65 kcal/ mol	
Leptin receptor			4-(2-Methoxy-3,4-Dihydroxyphenylthio) Coumarin	-6.74 kcal/ mol	
		-	4-(3,4,5-Trihydroxybenzoyloxy)Coumarin	-6.38 kcal/ mol	(Modanwal *et al*., 2023)
C-X-C Motif Chemokine Ligand 12	Co-crystalized ligand	3GG	1-phenyl-3-[4-(2H-tetrazol-5-yl)phenyl]urea	-3.82 kcal/ mol	(Modanwal *et al*., 2023)
Leptin receptor		NAG	N-[(2R,3R,4R,5S,6R)-2,4,5-trihydroxy-6-(hydroxymethyl)oxan-3-yl]acetamide	-4.95 kcal/ mol	(Modanwal *et al*., 2023)

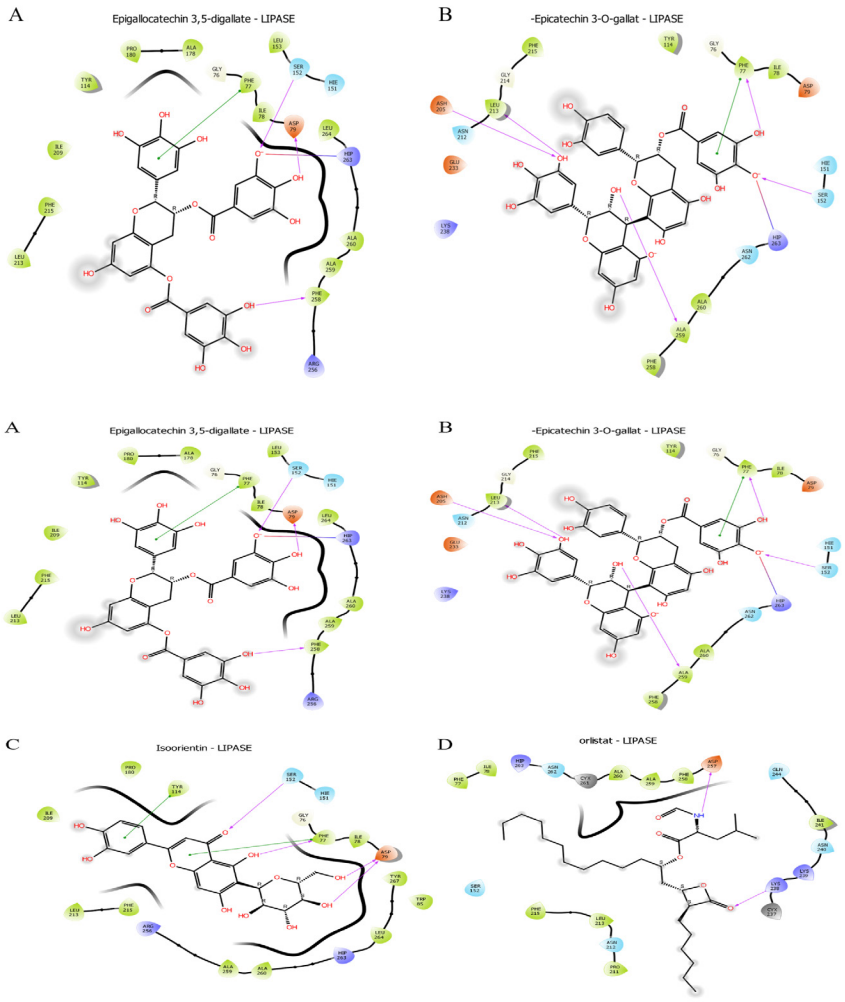

Figure 1: (A-C) 2D interaction of phytoconstituent interacting with pancreatic lipase, and (D) 2D interaction of orlistat with lipase

based 3D-QSAR methodologies (Misra *et al*., 2017) to examine the relationship between the chemical structure of flavonoids and other plant derivatives and their inhibitory effect against pancreatic lipase.

The generated models exhibited strong predictive performance:

- A well-validated QSAR model for flavonoid derivatives achieved an r^2 value of 0.8649, indicating a high correlation between predicted and observed biological activity
- Important molecular descriptors contributing to activity included hydrogen bond acceptors/ donors, topological surface area, and hydrophobic interactions — all consistent with key features for effective lipase inhibition.

To deepen the understanding of structural requirements for pancreatic lipase inhibition, ligand-based pharmacophore modelling was conducted using the PHASE module of Maestro 12.9

The pharmacophore model generated highlighted critical features essential for high inhibitory activity:

- Hydrogen bond donors,
- Hydrogen bond acceptors,
- Hydrophobic/aromatic regions.

Interestingly, these pharmacophoric features align strongly with known bioactive flavonoids like epigallocatechin, kaempferol, and quercetin, validating traditional Ayurvedic formulations at the molecular level. Moreover, the pharmacophore model served as a filter for designing new virtual molecules by modifying key scaffolds, thus improving the binding affinity and drug-likeness while preserving the natural backbone structure.

Validation through molecular dynamics simulation

Although docking and QSAR provide significant insights into the static interactions between ligands and their target proteins, biological systems are fundamentally dynamic. Molecules are always in motion, and a high docking score alone does not ensure that a ligand will

sustain stable binding over time. Molecular dynamics simulations (MDS) were used to elucidate the stability, flexibility, and conformational alterations of the protein–ligand complexes.

In this investigation, the most promising phytoconstituents found using virtual screening and QSAR modelling—specifically epigallocatechin 3,5-di-O-gallate, kaempferol, and several coumarin derivatives—were analysed using 100 nanoseconds of molecular dynamics simulations with GROMACS version 2018.2.

Multiple structural parameters were evaluated to validate the interaction stability:

- *Root mean square deviation (RMSD)*

The RMSD profiles of top complexes, such as epigallocatechin–PL and kaempferol-PL, revealed stabilisation after initial minor fluctuations, as shown in Figure 2(A). For example, the epigallocatechin–PL complex showed stabilisation around 0.20 to 0.35 nm, indicating a strong and sustained binding throughout the simulation timeframe.

- *Root mean square fluctuation (RMSF)*

RMSF analysis revealed only minor local fluctuations in the protein backbone, mainly at the flexible loop regions, while key active site residues remained remarkably stable, as shown in Figure 2(B). This suggests that ligand binding did not destabilise the protein's crucial functional domains.

- *Radius of gyration (Rg)*

The compactness of the protein-ligand complexes was maintained over the simulation period. In Figure 2 (C), the Rg plots indicated minimal expansion, reflecting that ligand binding did not induce major structural unfolding.

- *Solvent accessible surface area (SASA)*

From Figure 2 (D), the SASA values of the protein-ligand complexes slightly increased upon ligand binding, supporting the notion that ligand interaction caused moderate but stable expansion of the protein surface, without compromising core stability.

Binding free energy calculations: MM-GBSA/MM-PBSA

To complement the dynamic behaviour analysis, binding free energy calculations were performed using molecular mechanics generalized born surface area (MM-GBSA) and molecular mechanics poisson–boltzmann surface area (MM-PBSA) approaches (Genheden *et al*., 2015). For MM-PBSA analysis, frames were extracted from the entire 100 ns production trajectory. In addition, the analysis also incorporated in hydrogen- bond counts in Figure 3(A), short-range Coulombic and Lennard - Jones potentials in Figure 3(B), MM-PBSA binding free-energy calculations and interaction-energy profiles shows in Figure 3(C and D).

These energy decomposition analyses highlighted that electrostatic and Van der Waals interactions predominantly stabilised the complexes (Durai *et al*., 2023), providing a strong energetic basis for the observed docking and MDS results.

Multitarget approach: Network pharmacology and Ayurveda

Molecular dynamics simulations confirm the dynamic stability of individual phytoconstituents with their principal targets; nonetheless, the complexity of disorders such as obesity, especially when associated with malignancies, necessitates a more comprehensive

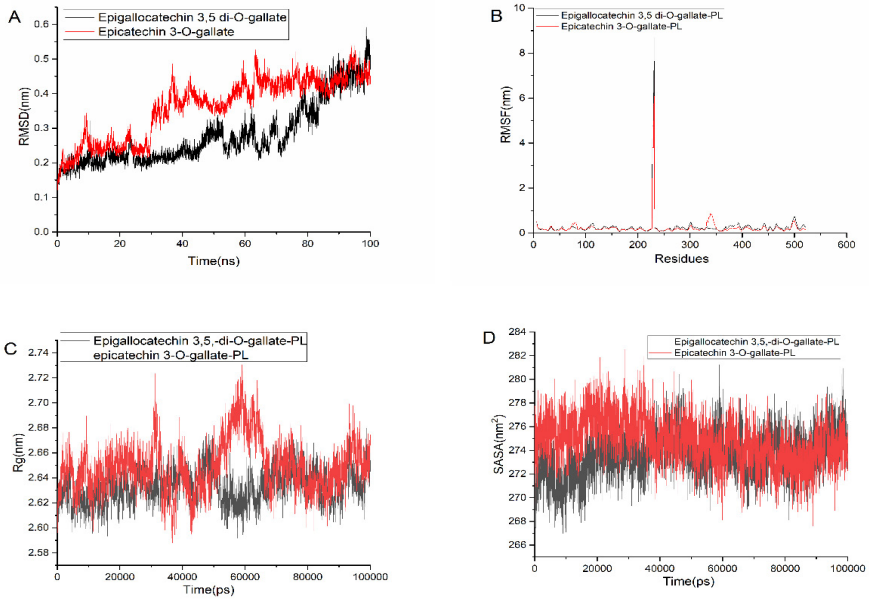

Figure 2: MDS plots of (A) RMSD, (B) RMSF, (C) Rg, and (D) SASA

treatment approach. Inhibition targeting a single entity is often inadequate. Contemporary research is progressively adopting a multitarget strategy, whereby therapies concurrently influence numerous interrelated pathways – a concept fundamentally grounded in Ayurvedic principles of holistic healing.

Network pharmacology, a computational framework that delineates the relationships between bioactive chemicals and many disease-associated genes and proteins, provides a robust approach for combining Ayurveda with contemporary multitarget drug development.

In our study, gene expression datasets from obesity and various cancers (breast, gastric, pancreatic, and colorectal) were analysed using bioinformatics pipelines. Differentially expressed genes (DEGS) were identified and subjected to protein-protein interaction (PPI) network construction using the STRING database (Szklarczyk *et al*., 2023) and Cytoscape visualisation (Smoot *et al*., 2011). The analysis uncovered critical hub genes, including:

- CXCL12 (C-X-C motif chemokine ligand 12),
- LEP (Leptin),
- JUN (a proto-oncogene transcription factor).

These genes exhibited high degrees of connectivity within the disease network, suggesting that they play pivotal roles in both obesity pathophysiology and tumorigenesis.

To explore the Ayurvedic phytoconstituent as a potential therapeutic agent, 3300 coumarin derivatives were screened against the CXCL12 and LEP using virtual screening workflow (VSW) of Maestro 12.6. The result shows that coumarin derivatives like 4-methyl-7,8-bis (Phosphonooxy) coumarin, 4-(2-Methoxy-3,4-Dihydroxyphenylthio) coumarin, and 4-(3,4,5-Trihydroxybenzoyloxy) coumarin exhibit strong binding affinities compared to the co-crystalized ligand, which are 3GG and NAG.

Importantly, the top-scoring ligand's ADME and drug likeness profile was evaluated using the QIKPROP module. This proposed compound satisfies the pharmacokinetic criteria, including molecular weight, hydrogen bond donors/acceptors, solubility (QlogS), and membrane permeability (QPlogPo/w). These properties confirmed the druggability of the coumarins and supported further development.

This study successfully implemented a comprehensive network pharmacology pipeline- encompassing transcriptomic data integration, hub gene identification, molecular docking, and simulation validation -to repurpose phytoconstituents for therapeutic applications rationally. By targeting the hub genes CXCL12 and LEP, this approach embraces the multitarget strategy that addresses the systemic complexity of obesity related malignancies. This approach gives traditional phytochemicals in a modern therapeutic framework and shows how network pharmacology can guide multitarget drug discovery for multiple pathways in complex diseases.

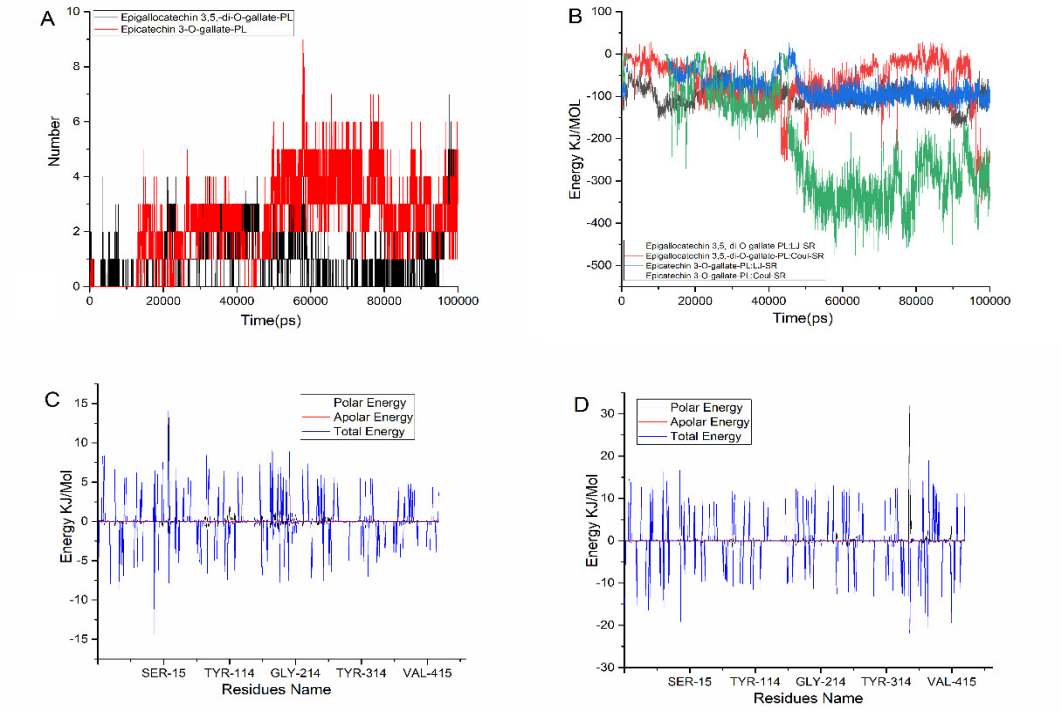

Figure 3: MDS and MM-PBSA: H-bond numbers (A), short-range Coulombic potential and short-range Lennard-Jones potential (B), MM-PBSA of epigallocatechin 3,5,-di-O-gallate (C), MM-PBSA of epicatechin 3-O-gallate (D)

Table 2: IC_{50} value of tested compounds

S. No.	*Compound Name*	*Inhibitory concentration (IC_{50} in μM)*
1	(+)- Catechin Hydrate	>500
2	Quercetin	95.1 ± 0.9
3	Luteolin	84.8 ± 4.2
4	Kaempferol	72.7 ± 3
5	Orlistat	46.3 ± 3

Experimental validation outcome (in-vitro)

The transition from computational prediction to experimental validation represents a critical validation phase that helps in the identification of the therapeutically potential phytoconstituent *via* a bioinformatics approach. The pancreatic lipase (PL) inhibition assays were implemented to serve as a bridge between the *in-silico* prediction and the *in-vitro* study. The anti-obesity potential of computationally filtered compounds is validated by this experiment.

The phytoconstituents were systematically evaluated for PL inhibition activity with a standard enzyme inhibition assay, with orlistat used as a standard drug. This experiment's results remarkably demonstrate the predicted flavonoid derivatives, which show better results as compared to the standard drug as shown in Table 2.

The most potent natural flavonoid inhibitor of pancreatic lipase was kaempferol (IC_{50} = 72.7 ± 3.0 μM), followed by luteolin (IC_{50} = 84.8 ± 4.2 μM) and quercetin (IC_{50} = 95.1 ± 0.9 μM). In contrast, (+)-catechin hydrate exhibited negligible inhibition (IC_{50} > 500 μM). While the standard drug orlistat remains the most effective (IC_{50} = 46.3 ± 3.0 μM). The relatively close IC_{50} value of kaempferol and orlistat suggests that the flavonoid shows substantial therapeutic potential as a pancreatic lipase inhibitor. The IC_{50} curves of all the tested flavonoids are shown in Figure 4. All the experiments were performed in triplicates and the average standard deviation is 3.25.

These experimental findings not only validate the computational prediction but also demonstrate the practical feasibility of translating ancient Ayurvedic wisdom into evidence-based therapeutic intervention. The successful identification and validation of a potent natural pancreatic lipase inhibitor through this integrated approach exemplifies the transformative potential of combining traditional knowledge systems with modern bioinformatics and experimental methodologies in addressing health challenges such as obesity and other related metabolic disorders.

Advancements: Success stories and recent findings

Integrating Ayurvedic phytoconstituent research with advanced bioinformatics methods has initiated a new phase in medication development, where traditional knowledge and contemporary science converge. Recent data indicate that this integrated strategy is both theoretically promising and practically useful in discovering powerful, safe, and multi-targeted options for obesity control.

One of the most significant discoveries was the recognition of flavonoid derivatives as very effective inhibitors of pancreatic lipase, an essential enzyme involved in the digestion of dietary fats. Utilizing virtual screening and molecular docking methodologies, epigallocatechin 3,5-di-O-gallate was identified as the prominent molecule, attaining a docking score of -10.93 kcal/mol, surpassing the efficacy of the standard synthetic medication, Orlistat. Additional natural chemicals, such as kaempferol, quercetin, and isoquercitrin, had significant binding affinities and exhibited substantial stability during molecular dynamics simulations, confirming their therapeutic potential. These results provide molecular-level knowledge supporting the conventional Ayurvedic use of flavonoid-rich plants. In addition to identifying existing molecules, substantial progress was achieved in the design of new, optimized candidates through computational intelligence. Utilizing robust QSAR modelling, which attained a substantial r^2 value of 0.8649, with pharmacophore analysis, researchers successfully predicted essential structural properties for activity and developed enhanced derivatives. By this, we predict the structure from the existing parent compound and attained a docking score of -6.094 kcal/mol, which exceeds traditional inhibitors and illustrates the potential of Ayurvedic scaffolds to be optimized through contemporary cheminformatics methodologies.

The vision extended beyond single-target inhibition. Understanding that obesity is intricately linked to several malignancies, network pharmacology methods were used to pinpoint shared hub genes, including CXCL12 and LEP. The Ayurvedic coumarin derivatives effectively targeted these genes, which are crucial in obesity and cancer, during virtual screening. Their capacity to engage

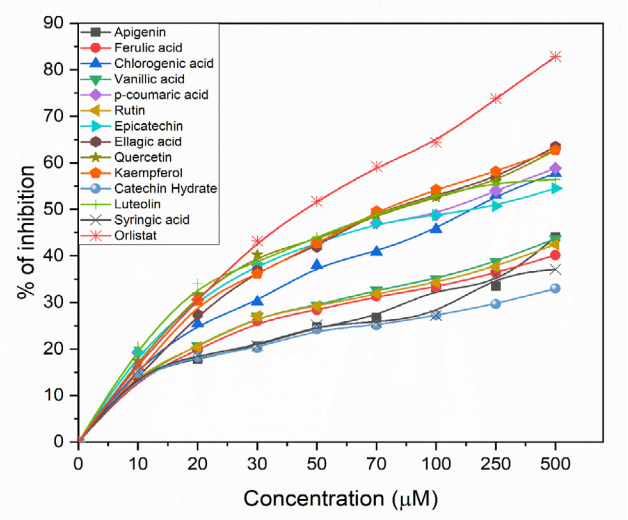

Figure 4: IC_{50} value on pancreatic lipase

with several disease pathways underscores the essentially pharmacological characteristics of numerous Ayurvedic medicines, whereby a single plant or preparation concurrently affects multiple biological systems.

These computational results were confirmed dynamically by molecular dynamics simulations and binding free energy estimates. Consistent RMSD trajectories, low structural variations, maintained compactness in radius of gyration plots, and advantageous MM-GBSA and MM-PBSA binding energies all validated the accuracy of the docking predictions. This comprehensive validation pipeline guaranteed that only the most promising candidates, based on binding affinity and physiological stability, progressed in the discovery phase.

Collectively, these improvements provide a persuasive success narrative: one in which Ayurvedic phytoconstituents are recognized not as ambiguous, primitive cures, but as scientifically substantiated, computationally refined, and pharmacologically effective choices for contemporary medicine. The integration of Ayurveda and bioinformatics transcends simple preservation of tradition; it redefines it, forging a future where ancestral knowledge and advanced technology together tackle significant health concerns of our day.

Challenges and integration

Though promising, the combination of Ayurvedic phytochemistry with bioinformatics has some major challenges. Ayurvedic formulations are fundamentally complicated, including many mixes of bioactive compounds that remain poorly known and underrepresented in ordinary chemical libraries. This variation restricts pharmacophore mapping, compromises the accuracy of QSAR models, and complicates virtual screening. One of the most pressing concerns is that the unfavourable pharmacokinetics behaviour of many phytoconstituents is low oral bioavailability, rapid metabolic degradation, poor aqueous solubility, and unpredictable tissue distribution, which often deviates from *in-silico* ADME/T prediction. These limitations emphasize the need for more accurate computational models, early-stage in vitro absorption studies, and experimental calibration of predicted properties.

To mitigate these issues, various formulation-based strategies have been proposed and gaining traction. Nanoformulations such as liposome, nanoemulsion, and solid lipid nanoparticle can significantly enhance solubility, cellular uptake, and targeted delivery. Phytosome technology, which complexes phytochemicals with phospholipids, improves the membrane permeability and absorption. Additionally, co-administration with bioenhancers like piperine may inhibit the drug metabolizing enzymes and enhance systemic availability. This modern delivery system, when applied thoughtfully, can bridge the gap between the traditional herbal potency and modern pharmacology, helping convert promising *in-silico* leads into viable therapeutics.

Moreover, the progression from computational hits to rigorous *in-vitro* and *in-vivo* validation remains in its early stages. Few *in-silico* leads progress to thorough *in-vitro* or *in-vivo* testing, partly due to the absence of standardized procedures and well-defined regulatory paths for natural-product-derived medicinal candidates. At last, real integration calls for close multidisciplinary cooperation between computer scientists and Ayurvedic practitioners to cross variations in language, technique, and research goals. Overcoming these challenges and realizing the full potential of Ayurveda–bioinformatics synergy will depend on establishing phytochemical databases, improving pharmacokinetic models, simplifying validation processes, and designing joint training programs.

Conclusion

Integrating Ayurveda with modern bioinformatics represents a transformative advancement in drug discovery, moving beyond merely preserving ancient traditions toward redefining them with scientific rigor and computational precision. Ayurvedic phytoconstituents, particularly flavonoids and coumarins, have emerged as promising multitarget inhibitors against obesity and associated cancers, validated through robust computational pipelines involving docking, QSAR, pharmacophore modelling, and molecular dynamics simulations. Despite the remarkable progress, substantial challenges remain, notably the complexity of natural formulations, bioavailability issues, limited experimental validation of computational leads, and interdisciplinary barriers. Future research must focus on establishing comprehensive phytochemical databases, enhancing predictive pharmacokinetic models, and fostering deeper interdisciplinary collaboration. By effectively addressing these challenges, Ayurveda's profound wisdom and modern bioinformatics can unite to offer safe, effective, and holistic therapeutic solutions for pressing global health issues.

Author Contributions

SVJ and KKU contributed to the comprehensive literature review and manuscript preparation. SM designed the study and conducted the experiments. NM supervised the project and critically reviewed the overall study.

Conflict of Interest

The authors have no conflict of interest.

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