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Systems-level Identification of *Tinospora cordifolia* Constituents as CXCR4-targeting Anti-metastatic Agents

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Abstract

Background: Metastasis is the leading cause of cancer-related mortality and is regulated by complex processes, including epithelial-mesenchymal transition, invasion, and colonisation. The chemokine receptor CXCR4, interacting with its ligand CXCL12, plays a pivotal role in tumour progression and organ-specific metastasis. Current synthetic CXCR4 inhibitors, such as AMD3100, face limitations due to toxicity, cost, and resistance, highlighting the need for safer alternatives. *T. cordifolia*, a medicinal plant rich in bioactive phytochemicals, has demonstrated immunomodulatory and anticancer properties but remains unexplored in CXCR4-targeted anti-metastatic therapy. **Aim:** This study aimed to investigate the anti-metastatic potential of eighteen phytochemicals from *Tinospora cordifolia* against CXCR4 (PDB ID: 3ODU) using integrated *in silico* and *in vitro* approaches. **Methods:** Phytochemicals were retrieved from the IMPPAT database, and Protein-Protein Interaction (PPI) analysis was performed using STRING to validate the role of CXCR4 in metastasis. Molecular docking (AutoDock Vina) evaluated ligand-receptor interactions. Drug-likeness was assessed via Lipinski's Rule of Five, and pharmacokinetic profiling was carried out using ADME predictors. Cytotoxicity was evaluated by MTT assay against CXCR4-positive MDA-MB-231 and HEK293 cells. **Results:** MTT assays revealed a non-toxic window up to 10 µM for all compounds, with tumour-selective effects of kaempferol and β-sitosterol at higher concentrations. Docking scores ranged from -6.5 to -9.5 kcal/mol, with beta-sitosterol (-9.5 kcal/mol), tinosporaside (-9.1 kcal/mol), and malabarolide (-8.7 kcal/mol) showing the strongest interactions, stabilising via hydrophobic and hydrogen bonding with key CXCR4 residues. Fourteen compounds met drug-likeness criteria, and seven lead molecules demonstrated optimal ADME properties, including non-BBB permeability, high GI absorption, and minimal CYP450 interactions. The seven identified lead compounds were beta-sitosterol, tinosporaside, malabarolide, kaempferol, chasmanthin, palmarin, and syringin. **Conclusion:** Phytochemicals from *T. cordifolia* demonstrate strong potential as CXCR4 inhibitors, with beta-sitosterol, kaempferol, and tinosporaside emerging as lead candidates. Their favorable binding profiles and pharmacokinetic properties suggest promising translational value as anti-metastatic agents. Further experimental validation in migration assays, receptor-binding studies, and animal models is warranted to confirm efficacy and safety.

Major Findings: Seven phytochemicals from *T. cordifolia* showed strong binding affinity toward CXCR4 (-8.0 to -9.5 kcal/mol), with β-sitosterol emerging as the top candidate, demonstrating stable hydrogen bonding and hydrophobic interactions within the binding pocket. Fourteen compounds met Lipinski's criteria, seven exhibited favourable ADME profiles, and MTT assays confirmed a non-toxic window up to 10 µM with tumour-selective cytotoxicity at higher concentrations, supporting their potential as CXCR4-targeted natural anti-metastatic leads.

Keywords: Anti-metastatic Agents, Cancer Metastasis, Disease, CXCR4, Health, Genetics, Phytochemicals, *T. cordifolia*

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1. Introduction

Cancer metastasis remains one of the most formidable obstacles in effective cancer treatment and patient survival, accounting for the majority of cancer-related deaths worldwide. It involves a complex cascade of events, including Epithelial-Mesenchymal Transition (EMT), intravasation, survival in the circulatory system, extravasation, and colonisation at secondary sites[1]. Despite significant progress in diagnostic and therapeutic strategies, the prognosis for metastatic cancers remains poor, underlining the urgent need for new and effective anti-metastatic agents[2].

Among the molecular regulators of metastasis, the C-X-C chemokine receptor type 4 (CXCR4)-CXCL12 signalling axis has gained considerable attention. CXCR4, a G-protein-coupled receptor, binds primarily to its ligand CXCL12 (stromal cell-derived factor-1, SDF-1) and plays critical roles in leukocyte trafficking, embryonic development, and immune responses. Importantly, aberrant CXCR4-CXCL12 signalling has been implicated in the progression, invasion, and metastasis of several solid tumours, including breast, lung, colon, and prostate cancers. Overexpression of CXCR4 enhances cancer cell motility, facilitates organ-specific metastasis, and correlates with poor clinical outcomes, making it a compelling therapeutic target[3,4].

Although synthetic CXCR4 antagonists such as AMD3100 (plerixafor) have shown promise in clinical settings, their use is limited by high cost, systemic toxicity, resistance development, and adverse effects on normal stem cell trafficking[5]. Chemotherapy and radiotherapy, the mainstays of metastatic cancer treatment, are associated with severe side effects, immunosuppression, and non-specific cytotoxicity. Additionally, the development of drug resistance and relapse is common in patients undergoing conventional treatment. These limitations underscore the need for safer, cost-effective, and targeted therapeutic alternatives[6].

In this context, natural products have emerged as a valuable resource for drug discovery, offering diverse chemical scaffolds and multi-target therapeutic potential. Phytochemicals derived from medicinal plants are often less toxic, more biocompatible, and capable of modulating multiple signalling pathways simultaneously. Unlike synthetic drugs that typically act on a single molecular target, phytocompounds can affect several nodes within a disease network, offering a systems-level approach to cancer treatment[7].

One such promising medicinal plant is *T. cordifolia* (Willd.) Hook. f. and Thomson (family: *Menispermaceae*), widely used in Ayurvedic medicine for its immunomodulatory, antioxidant, and antitumor properties[8,9]. Preliminary studies have demonstrated its ability to inhibit cancer cell proliferation and enhance immune responses. The plant is rich in pharmacologically active constituents, including alkaloids (*e.g.*, magnoflorine), glycosides (*e.g.*, syringin), flavonoids (*e.g.*, kaempferol), and terpenoids (*e.g.*, malabarolide), many of which have reported anticancer or anti-inflammatory activities. However, a comprehensive evaluation of these phytochemicals targeting the CXCR4-mediated metastatic pathway remains lacking[10].

Advancements in computational biology and molecular modelling now allow high-throughput screening of natural compounds using *in silico* techniques such as molecular docking, pharmacokinetic modelling, and drug-likeness filtering. These approaches reduce the time and cost associated with traditional drug discovery and help identify promising lead compounds with optimal bioavailability, safety, and efficacy profiles.

2. Materials and Methods

2.1 Plant Selection

Tinospora cordifolia (Willd.) Hook. f. and Thomson (*Menispermaceae*) stem powder was procured from a certified commercial supplier (Herbal Biosolutions Pvt. Ltd., Mumbai, India). Selection of *T. cordifolia* was based on ethnopharmacological evidence supporting its anticancer, immunomodulatory, and anti-inflammatory properties, as well as literature reports describing bioactive constituents including alkaloids, flavonoids, glycosides, and terpenoids with potential therapeutic relevance.

2.2 Extraction

Air-dried stems of *T. cordifolia* were coarsely powdered and extracted by maceration in 70% ethanol (1:10 w/v) for 72 h at room temperature with intermittent shaking. The extract was filtered through muslin cloth,

followed by Whatman No. 1 filter paper. The filtrate was concentrated under reduced pressure at 40°C using a rotary evaporator. The dried extract was stored at -20°C until further use. For *in vitro* assays, the extract was dissolved in Dimethyl Sulfoxide (DMSO) to prepare stock solutions, ensuring a final DMSO concentration ≤0.1% in all experiments.

2.3 MTT Assay

Cytotoxicity of the extract and selected phytochemicals was evaluated using the MTT assay against MDA-MB-231 (CXCR4-positive) and HEK293 (low CXCR4 expression) cell lines. Cells were cultured under standard conditions and seeded in 96-well plates at a density of 1×10^4 cells per well, followed by incubation for 24 h to allow cell attachment. Subsequently, cells were treated with varying concentrations of the test compounds (0.1-100 µM) for 48 h.

After the treatment period, 10 µL of MTT solution (5 mg/mL in phosphate-buffered saline) was added to each well, and the plates were incubated for 4 h at 37°C to allow the formation of formazan crystals. The resulting crystals were dissolved in 100 µL DMSO, and absorbance was measured at 570 nm with a reference wavelength of 630 nm using a microplate reader. Cell viability (%) was calculated relative to vehicle-treated control cells. All experiments were performed in three independent replicates with triplicate wells per concentration, and IC_{50} values were estimated from the dose-response curves derived from the cell viability data.

2.4 Selection of Target Protein: CXCR4

The molecular target selected for this study was C-X-C chemokine receptor Type 4 (CXCR4), a G-protein-coupled receptor critically involved in tumour metastasis through the CXCR4-CXCL12 signalling axis. The three-dimensional crystal structure of CXCR4 complexed with a small-molecule antagonist was retrieved from the Protein Data Bank (PDB ID: 3ODU). The receptor structure was prepared by removing co-crystallised ligands and water molecules prior to docking analysis. This structure served as the receptor model for subsequent molecular docking simulations (Figure 1).

2.5 Phytocompound Selection

Eighteen phytochemicals reported in *T. cordifolia* were shortlisted using the IMPPAT database (Indian Medicinal Plants, Phytochemistry and Therapeutics). Selection criteria included reported bioactivity, structural diversity, and relevance to anticancer or immunomodulatory mechanisms. Chemical structures

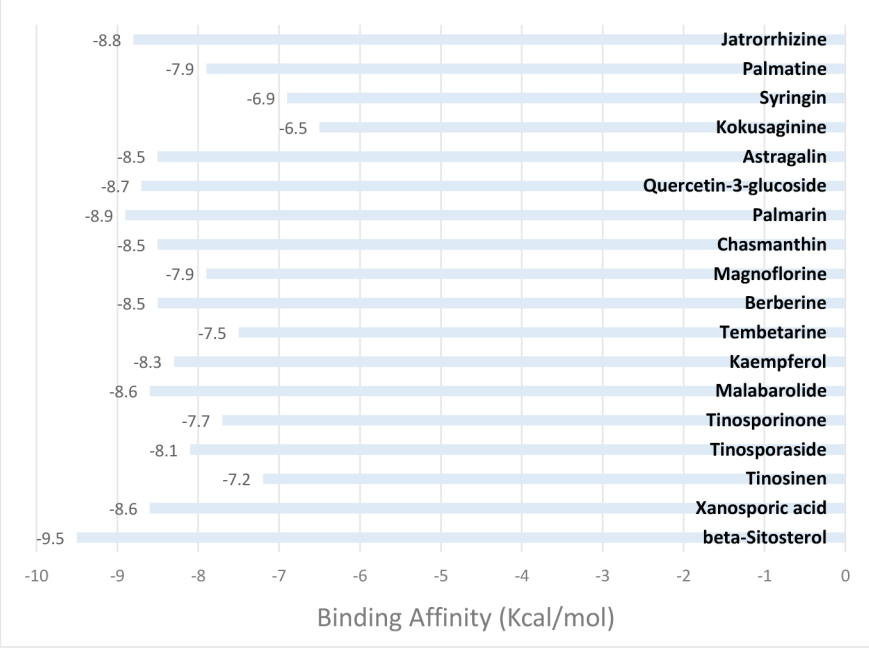


Figure 1. Binding affinity of selected *T. cordifolia* phytochemicals with the CXCR4 receptor obtained through molecular docking analysis.

were downloaded. SDF format and converted into three-dimensional conformations using molecular modelling software prior to docking analysis.

2.6 Protein-Protein Interaction (PPI) Network Analysis

To validate the biological relevance of CXCR4 in metastasis, a Protein-Protein Interaction (PPI) network was constructed using the STRING database (version 11.5) for Homo sapiens. Network parameters, including node degree, interaction confidence score, and functional enrichment analysis, were evaluated. The analysis identified 11 nodes and 49 edges, confirming the central role of CXCR4 in pathways associated with immune modulation, chemotaxis, and tumour metastasis.

2.7 Molecular Docking

Molecular docking simulations were performed using AutoDock Vina. Prior to docking, the receptor structure was prepared by removing co-crystallised ligands and water molecules, followed by the addition of polar hydrogens and assignment of Kollman charges. Ligands were energy-minimised using molecular mechanics algorithms before docking.

Docking was performed using a grid box centred on the active binding pocket of CXCR4, and binding affinities were calculated in kcal/mol. The most favourable binding poses were selected based on the lowest binding energy and interaction stability. Ligand-receptor interactions were analysed based on hydrogen bonding, hydrophobic interactions, and π-π stacking within the active site.

2.8 Drug-likeness Evaluation

Drug-likeness properties of the phytochemicals were assessed according to Lipinski's Rule of Five, including molecular weight (<500 Da), hydrogen bond donors (<5), hydrogen bond acceptors (<10), lipophilicity (logP <5), and the number of rotatable bonds. Compounds satisfying these parameters were considered to possess favourable oral bioavailability characteristics.

2.9 ADME Profiling

Pharmacokinetic profiling was performed to evaluate Absorption, Distribution, Metabolism, and Excretion (ADME) properties using the SwissADME web server. Parameters assessed included gastrointestinal absorption, blood-brain barrier permeability, cytochrome P450 enzyme inhibition potential, and P-glycoprotein substrate characteristics. Compounds demonstrating favourable pharmacokinetic properties were shortlisted for further lead identification.

2.10 Lead Compound Identification

Lead compounds were identified based on an integrated evaluation of docking affinity, drug-likeness compliance, and ADME suitability. Seven phytochemicals-β-sitosterol, tinosporaside, malabarolide, kaempferol, chasmanthin, palmarin, and syringin-were selected as potential CXCR4 inhibitors for further validation.

3. Results

3.1 MTT Assay (48 h Exposure)

Across both cell lines, cell viability remained >90% at concentrations ≤10 µM for all tested compounds, indicating a non-toxic concentration range for subsequent functional studies. In MDA-MB-231 cells, β-sitosterol and kaempferol demonstrated concentration-dependent cytotoxicity, with viability reduced to 85-88% at 30 µM ($p<0.01$) and 58-62% at 100 µM ($p<0.001$). In contrast, HEK293 cells exhibited comparatively higher viability (≥85% at 100 µM), indicating a differential cellular response.

AMD3100 showed minimal cytotoxicity across the tested concentrations. The estimated IC_{50} values in MDA-MB-231 cells were approximately 70-90 µM, whereas IC_{50} was not reached in HEK293 cells within the tested range (Table 1, Figure 2).

3.2 Protein-protein Interaction Network of CXCR4

STRING database analysis of CXCR4 revealed a highly interconnected network comprising 11 nodes and 49 edges. Key interacting partners included CXCL12, CCR5, and GNAI2, which are associated with chemotaxis, immune regulation, and tumour progression. The network analysis demonstrated significant functional enrichment, supporting the central role of CXCR4 in metastatic signalling pathways (Figure 3).

3.3 Molecular Docking Analysis

All 18 phytochemicals of *T. cordifolia* demonstrated favourable binding within the active site of CXCR4.

Table 1. Cell viability (%) of MDA-MB-231 and HEK293 cells following treatment with AMD3100, kaempferol, and β-sitosterol assessed by MTT assay after 48 h exposure (Mean ± SEM)

Cell line	Compound	0 µM (Vehicle)	10 µM	30 µM	100 µM
MDA-MB-231	AMD3100	100 ± 4	94 ± 4	91 ± 3	80 ± 4**
	Kaempferol	100 ± 3	92 ± 4	85 ± 3**	58 ± 3***
	β-Sitosterol	100 ± 5	94 ± 3	88 ± 3**	62 ± 4***
HEK293	AMD3100	100 ± 5	96 ± 4	94 ± 4	90 ± 4
	Kaempferol	100 ± 4	96 ± 3	94 ± 3	88 ± 3*
	β-Sitosterol	100 ± 4	95 ± 4	92 ± 3	85 ± 4*

**Data are expressed as mean ± SEM from three independent experiments performed in triplicate. Statistical significance was determined relative to vehicle control (*p<0.05, **p<0.01, *p<0.001)

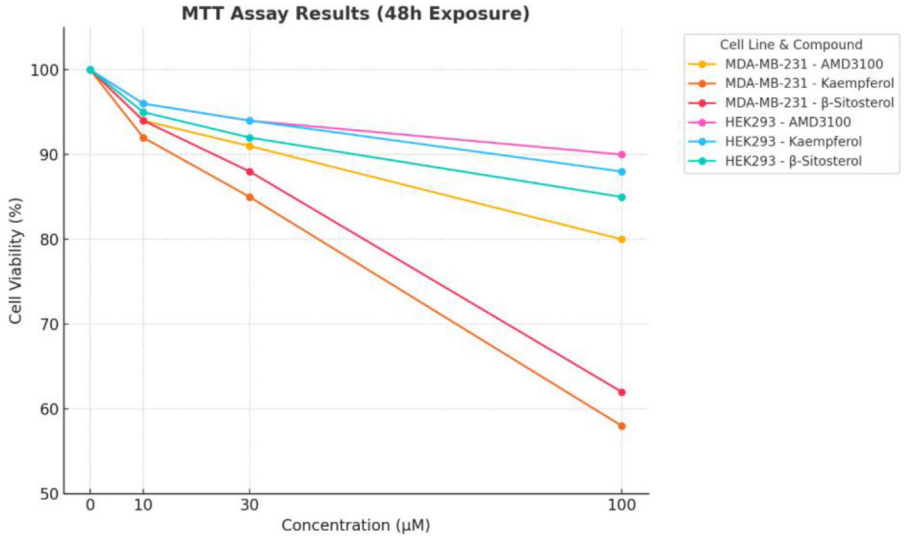


Figure 2. Dose-dependent effects of β-sitosterol, kaempferol, and AMD3100 on cell viability in MDA-MB-231 and HEK293 cells assessed by MTT assay after 48 h exposure.

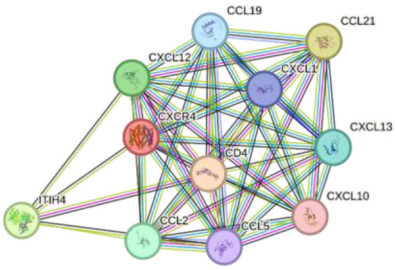


Figure 3. PPI network of CXCR4 generated using STRING database, highlighting key interaction partners and network metrics.

Binding affinities ranged from -6.5 to -9.5 kcal/mol, indicating stable ligand-receptor interactions.

The top seven compounds exhibited the following binding energies:

β-sitosterol : -9.5 kcal/mol Palmarin : -8.9 kcal/mol Jatrorrhizine : -8.8 kcal/mol Quercetin-3-glucoside : -8.7 kcal/mol Malabarolide : -8.6 kcal/mol Xanosporic acid : -8.6 kcal/mol Chasmanthin : -8.5 kcal/mol

Interaction analysis demonstrated hydrogen bonding, hydrophobic interactions, and π-π stacking within the CXCR4 binding pocket, involving residues such as Val242, Tyr219, Ile245, Leu246, Arg188, Asp97, and His113 (Table 2, Figure 4).

3.4 Drug-likeness and ADME Profiling

Fourteen of the eighteen phytochemicals satisfied Lipinski's Rule of Five, demonstrating acceptable molecular weight, hydrogen bond donor/acceptor limits, and lipophilicity.

Pharmacokinetic profiling indicated that seven compounds were predicted to exhibit high gastrointestinal absorption and non-permeability to the Blood-Brain Barrier (BBB). Additionally, minimal predicted interaction with cytochrome P450 enzymes and P-glycoprotein was observed among the top-ranking compounds (Figure 5).

3.5 Lead Compound Identification

Based on the integrated evaluation of docking affinity, drug-likeness parameters, and ADME characteristics, seven phytochemicals-β-sitosterol, tinosporaside, malabarolide, kaempferol, chasmanthin, palmarin, and syringin-were selected for further evaluation. These compounds exhibited strong binding affinity toward CXCR4 along with favourable pharmacokinetic and drug-likeness profiles (Figure 6).

Table 2. Binding affinities (kcal/mol) and key interacting residues of phytochemicals from *T. cordifolia* against CXCR4

Compound	Binding Affinity (kcal/mol)	Key Interacting Residues
β-sitosterol	-9.5	Val242, Tyr219, Ile245, Leu246, Phe249
Xanosporic acid	-8.6	Arg188, Tyr116, Trp94, Asp97, Glu288
Tinosinen	-7.2	Gln200, Arg188, His113, Asp97
Tinosporaside	-8.1	His281, Asp97, Arg183, Trp94
Tinosporinone	-7.7	Trp94, Glu288, Arg183, Asp97
Malabarolide	-8.6	Arg183, Asp97, Ser285, His113
Kaempferol	-8.3	Ala98, Trp102, His113, Asp97
Tembetarine	-7.5	Glu288, Val112, Trp94
Berberine	-8.5	His113, Trp94, Asp97
Magnoflorine	-7.9	Arg188, Asp97, Tyr45
Chasmanthin	-8.5	Arg188, Asp187, Trp102
Palmarin	-8.9	His281, Asp97, Arg188
Quercetin-3-glucoside	-8.7	Asp187, His281, Trp94
Astragalin	-8.5	Arg188, Ser285, Asp97
Kokusaginine	-6.5	Leu210, Val206, Trp125
Syringin	-6.9	Asp97, His113, Arg183
Palmatine	-7.9	Val112, Trp102, Asp97
Jatrorrhizine	-8.8	Ala98, His281, Asp97

4. Discussion

The present study identified several phytochemicals from *T. cordifolia* with high binding affinity and favourable pharmacokinetic profiles against CXCR4, a key receptor implicated in cancer metastasis. Through molecular docking and ADME screening, seven lead compounds-β-sitosterol, tinosporaside, malabarolide, kaempferol, chasmanthin, palmarin, and syringin-were proposed as potential CXCR4 inhibitors. These findings offer promising avenues for the development of natural anti-metastatic agents.

CXCR4 has been extensively validated as a therapeutic target in metastatic cancer. Overexpression of CXCR4 correlates with increased invasiveness, poor prognosis, and reduced overall survival in various cancers, including breast, prostate, and colorectal malignancies[11,12]. Consistent with this, the Protein-Protein Interaction (PPI) network in this study confirmed CXCR4's interactions with proteins such as CXCL12, CCR5, and GNAI2, supporting its central role in tumour cell migration and immune evasion. These findings align with previous systems biology analyses demonstrating CXCR4's critical function in modulating the tumour microenvironment[13].

Among the 18 screened phytocompounds, β-sitosterol exhibited the strongest binding affinity (-9.5 kcal/mol) to CXCR4, forming multiple hydrophobic interactions and hydrogen bonds with key amino acids such as Val242, Tyr219, and Leu246. β-Sitosterol is a phytosterol widely studied for its anticancer properties. Prior research has shown its ability to induce apoptosis, inhibit angiogenesis, and suppress metastasis in breast and colon cancer models[14,15]. Notably, β-sitosterol has also been reported to modulate metastatic signalling pathways, further supporting its relevance as a CXCR4-targeting candidate[16].

Tinosporaside and malabarolide also demonstrated strong binding interactions and favourable ADME profiles. Although literature on their direct interaction with CXCR4 is limited, previous reports indicate that *T. cordifolia* extracts containing these compounds exhibit anti-inflammatory and immunomodulatory activity[17,18], mechanisms that may influence metastatic

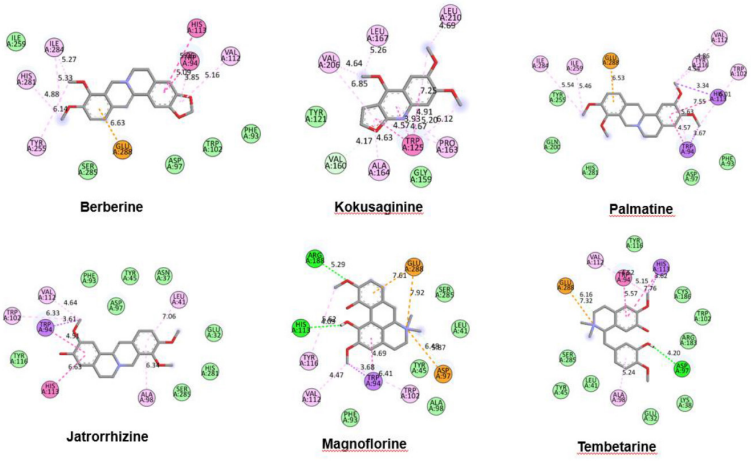


Figure 4. Two-dimensional molecular interaction diagrams of *T. cordifolia* phytochemicals docked with the CXCR4 receptor (PDB ID: 3ODU). The diagrams illustrate key interactions, including hydrogen bonding, van der Waals forces, π-sigma, π-alkyl, and electrostatic interactions with residues lining the CXCR4 binding pocket.

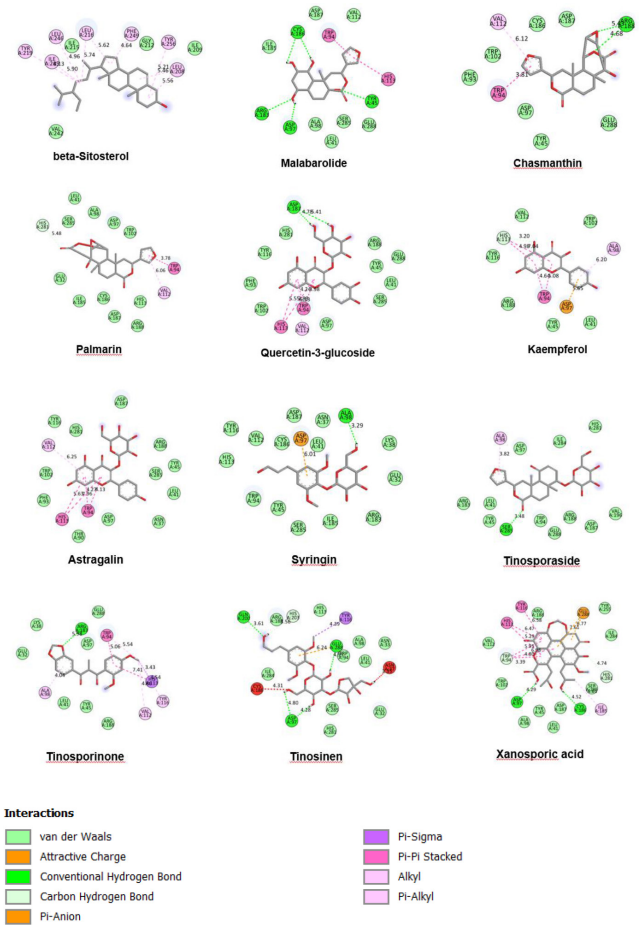


Figure 5. Drug-likeness and ADME profiling of selected *T. cordifolia* phytochemicals based on Lipinski's Rule of Five and pharmacokinetic predictions.

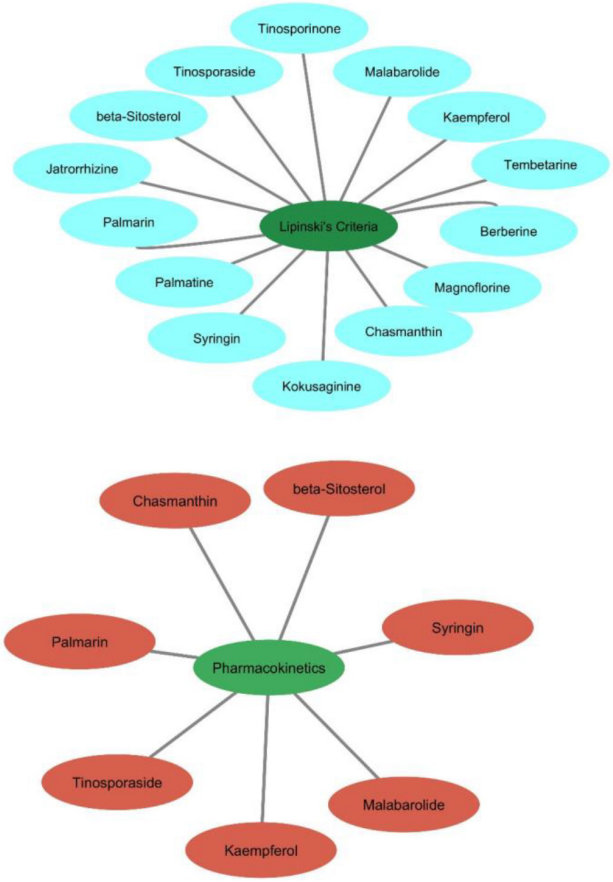


Figure 6. Bioavailability radar plots showing comparative drug-likeness parameters (lipophilicity, size, polarity, solubility, flexibility, and saturation) of selected *T. cordifolia* phytochemicals.

progression. Kaempferol, another identified lead compound, is well documented for its anti-cancer potential. It has been shown to suppress CXCR4-mediated migration in ovarian and pancreatic cancer cells[19], reinforcing the docking-based prediction of its affinity toward CXCR4 in this study.

Interestingly, syringin and chasmanthin, though less frequently reported in cancer-related literature, also demonstrated favourable binding affinity and drug-likeness characteristics. Syringin has demonstrated antitumor and hepatoprotective activity, potentially *via* modulation of oxidative stress and inflammatory pathways[20]. Its predicted interaction within the CXCR4 binding pocket warrants further experimental investigation.

From a pharmacokinetic perspective, fourteen compounds satisfied Lipinski's Rule of Five, suggesting favourable oral bioavailability. Notably, seven lead compounds were predicted to be non-permeant to the blood-brain barrier, which may reduce potential central nervous system-related adverse effects when targeting peripheral tumour sites. Additionally, minimal predicted interaction with cytochrome P450 enzymes and P-glycoprotein was observed, potentially lowering the risk of metabolic toxicity and drug resistance[21].

The use of *T. cordifolia*, a widely available and culturally accepted medicinal plant, enhances the sustainability and translational feasibility of the present investigation. The integration of computational screening approaches, including molecular docking and ADME profiling, enables efficient identification of potential lead molecules while minimising experimental cost, time, and resource utilisation. Such a scalable and resource-conscious strategy supports rational natural product-based drug discovery and facilitates future preclinical development within a structured and reproducible framework.

While the docking results and ADME predictions support the potential of these natural compounds, certain limitations must be acknowledged. Docking studies are based on static receptor conformations and do not fully capture dynamic molecular interactions or intracellular signalling complexity. Furthermore, *in silico* pharmacokinetic models may not completely reflect *in vivo* metabolism, distribution, or bioavailability. Therefore, functional validation through migration, invasion, and receptor-binding assays, followed by *in vivo* metastasis models, will be essential to confirm CXCR4 antagonistic activity and therapeutic relevance[22].

Despite these limitations, the present study provides an integrated computational framework for identifying CXCR4-targeted natural inhibitors from *T. cordifolia*. The combination of protein interaction analysis, molecular docking, and pharmacokinetic profiling enhances the translational relevance of the findings. Given the growing interest in plant-derived anticancer agents with improved safety profiles, the phytochemicals identified herein represent promising candidates for further investigation in CXCR4-mediated metastatic therapy.

5. Conclusion

This study provides integrated computational and preliminary experimental evidence that phytochemicals from *T. cordifolia* exhibit potential as natural CXCR4 inhibitors with anti-metastatic relevance. Among the eighteen compounds screened, seven demonstrated superior binding affinity, favourable drug-likeness, and acceptable pharmacokinetic profiles, with β-sitosterol emerging as the top candidate. Importantly, the predicted non-blood-brain barrier permeability and differential cytotoxic response suggest potential advantages for peripheral therapeutic targeting.

While these findings establish a rational framework for CXCR4-targeted natural product discovery, functional *in vitro* assays and *in vivo* validation remain necessary to confirm specificity, efficacy, and safety. Collectively, this work highlights *T. cordifolia* as a valuable source of bioactive compounds for further development in metastatic cancer research.

6. Acknowledgement

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Author Contribution

TG: Performed data collection, literature review, formal analysis, and drafted the initial version of the manuscript. NK: Conceived and designed the study, supervised the research process, critically reviewed, and finalised the manuscript. SPS: Contributed to drafting, proofreading, and intellectual content revision of the manuscript. RR: Assisted in study design, data analysis, and interpretation; contributed to manuscript editing. SS: Contributed to methodology, data validation, and provided critical inputs during manuscript preparation. All authors have read and agreed to the published version of the manuscript.

