

SYSTEMATIC REVIEW

Artificial Intelligence–Driven Discovery of Plant-Derived Bioactive Compounds in Cancer Therapeutics: Computational Approaches and Molecular Target Identification

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ABSTRACT:

Objective: Artificial intelligence (AI) use and computational approaches have transformed the discovery of plant-derived bioactive chemicals for cancer treatment. This review synthesized evidence on AI-based approaches, including network pharmacology, molecular docking, and machine learning, for identifying and validating anticancer plant-derived phytochemicals, focusing on their molecular targets and signaling pathways. **Data Sources:** PRISMA 2020 guidelines were followed. PubMed, Scopus, Web of Science, and Google Scholar were searched between October 2020 and July 2025. **Study Selection:** Studies with at least one AI or computational method, investigating plant-derived phytochemicals for anticancer effects, reporting quantitative computational outcomes, and offering free full-text access in English were included. Review articles, conference abstracts, non-plant studies, and non-English publications were excluded. **Data Extraction:** Two reviewers extracted data on predefined variables. An adapted PROBAST tool was used to assess risk of bias for in silico studies and modified SYRCLE tools for in vitro and in vivo studies, with certainty of evidence evaluated using the GRADE method. **Data Synthesis:** Eighteen studies satisfied the inclusion criteria. The most frequently discovered bioactive chemical was quercetin, which targets breast cancer, hepatocellular carcinoma (HCC), and lung cancer via AKT1, EGFR, TP53, and MAPK signaling pathways. The majority of in silico studies have a high risk of bias, while in vitro and in vivo studies were rated as having some concerns. The overall certainty of evidence was low. **Conclusion:** AI-based computational techniques have become critical tools for discovering plant-derived compounds and identifying multi-target mechanisms involving AKT1, EGFR, and PI3K/Akt signaling.

Keywords: Artificial Intelligence; Computational Biology; Drug Discovery; Molecular Docking Simulation; Neoplasms; Phytochemicals; Plants; Medicinal

INTRODUCTION

Cancer was among the leading causes of morbidity and mortality, with an estimated 19.3 million new cases and about 10 million deaths reported in 2020 alone ¹. Even with significant improvements in surgery, radiotherapy, and conventional chemotherapy, plant-derived bioactive compounds offer more effective, safe, and specific anticancer agents, which provide multi-targeted pharmacological properties and also overcome the concerns related to drug resistance ^{2,3}. Nevertheless, the traditional experimental process of discovery and confirmation of such compounds was laborious, time-consuming, and resource-intensive ⁴.

The advent of machine learning (ML) and artificial intelligence (AI) has revolutionized the drug discovery and development field ⁵. Computational methods, such as deep learning, quantitative structure-activity relationship (QSAR) modelling, network pharmacology, molecular docking and molecular dynamics (MD) simulation, can screen tens of thousands of phytochemicals with respect to molecular targets and map multi-target pharmacological networks at an unprecedented speed and accuracy ⁶. The built-in databases like the Traditional Chinese Medicine Systems Pharmacology Database (TCMSP), PubChem, DrugBank, ChEMBL, and SwissTargetPrediction also assist AI-based virtual pipelines with curated chemical, biological, and clinical data ⁷.

Although the AI-assisted phytochemical studies were increasing rapidly, a comprehensive synthesis consolidating the evidence on the AI-based computational strategies to identify plant-derived anticancer bioactives, to characterize their molecular targets, and validate their interactions by in silico and in experimental systems, was still lacking ⁸. The main objective of the systematic review was to summarize the data from computational pharmacology studies, including network pharmacology, molecular docking, molecular dynamics simulations, and AI/ML, on the identification and validation of plant-derived bioactive compounds with anticancer properties to assess the range of computational methods used, index the databases and virtual screening pipelines, examine the applicability of multi-target network pharmacology to explain polypharmacological mechanisms, and critically evaluate the limitations and translation issues of in silico predictions in phytochemical oncology.

METHODOLOGY

Due to the direct retrospective design of this systematic review, which relies entirely on previously published, aggregated public data, this study was not prospectively registered in an international repository. However, to guarantee scientific rigor, the research layout, search strings, and evaluation criteria were mapped internally and strictly followed the structural framework of the PRISMA 2020 statement ⁹.

Database Search: An extensive search of electronic literature was performed in four scientific databases: PubMed, Scopus, Web of Science, and Google Scholar to find publications published from October 2020 to July 2025.

Search Strategy Used: The search strategy was developed as a structured search with the help of MeSH terms and free-text keywords, along with the Boolean operators (AND, OR). The main keywords were: "artificial intelligence ", "machine learning ", "deep learning ", "QSAR ", "network pharmacology ", "molecular docking ", "phytochemicals ", "plant-derived compounds ", "neoplasm ", "molecular target ", "protein-ligand interaction ", "signaling pathway ", "in silico ", and "computational pharmacology ". Other records were identified during manual review of reference lists of the qualified full-text articles.

Inclusion and Exclusion Criteria: The studies included were original research articles, used at least one AI or computational method, studied plant-derived phytochemicals, investigated anticancer effects or molecular targets in cancer, used known computational databases, and were published in English and provided free access to the full text. The studies were excluded if they were review article, conference abstracts, editors, or book chapters.

Study Selection Process: All database search results were imported into a reference management system, and duplicates were removed. All remaining records were then screened by two independent reviewers (ME, MA) in two distinct stages: title and abstract screening and got same results. Full-text screening of the remaining articles was done. Any disagreement between reviewers at any level was settled by discussion.

Data Extraction: The data were independently extracted by two reviewers (ME, MA), comprising study design, AI and computational methods used, database and bioinformatics tools used, source of plant and specific bioactive compound(s), type(s) of cancer investigated, molecular target, identified signaling pathways, validation methodology, and key findings. Any discrepancies among reviewers were resolved through discussion.

Primary Outcome: The main focus of the systematic review was to describe and review the AI/computational methods of identifying and verifying plant-derived bioactive compounds as anticancer agents with particular attention to the molecular targets and signaling pathways.

Quality Assessment: There is no validated method for in silico studies, the risk of bias was assessed using an adapted version of the PROBAST. PROBAST domains were organized as follows: participants (data sources/databases), predictors (compounds/features), outcomes (molecular targets/pathways), and analysis (computational methods such as docking, network pharmacology, and machine learning). For studies involving experimental validation, appropriate domains from the Joanna Briggs Institute Critical Appraisal Tools were also evaluated. The domains were graded as low (+), high (-), or unclear (?). Studies with ≥ 1 high-risk domain were categorized as overall high risk, with focus on the analysis domain and validation status ¹⁰. The risk of bias was assessed with the SYRCLE tool for in vitro and in vivo research requirements. The certainty of evidence was evaluated according to the GRADE approach.

RESULTS

The first search of electronic databases retrieved 342 records (PubMed: 128, Scopus: 94, Web of Science: 76, Google Scholar: 44). Following automated and manual elimination of duplicate records, 219 unique articles were left. An additional 98 records failed to pass title and abstract screening and were excluded due to non-conformity with inclusion criteria, mainly because they were review articles, did not deal with plant-derived compounds or did not contain any in silico computational aspect. The 121 full-text articles were evaluated, 103 were eliminated due to the following reasons: not available freely in the full-text (n = 35), not a primary AI/computational component (n = 22), review or non-original research design (n = 19), only non-cancer diseases (n = 14), not in English (n = 7), and lack of quantitative computational outcomes. Eventually, 18 studies were included in this systematic review and met all the eligibility criteria. The PRISMA flow diagram in **Figure 1**, summarize the process of study selection.

The main findings of all 18 studies incorporated into this systematic review were given in **Table I**, and all of them utilized at least one of the AI-driven or computational pharmacology methods to explore the use of plant-derived bioactive compounds in anticancer applications. Studies included in this review contain network pharmacology, molecular docking, molecular dynamics simulation, QSAR modelling, machine learning, and pharmacophore-based approaches representing a variety of cancer types. Different bioinformatics databases were used to find phytochemical targets and map pertinent disease pathways.

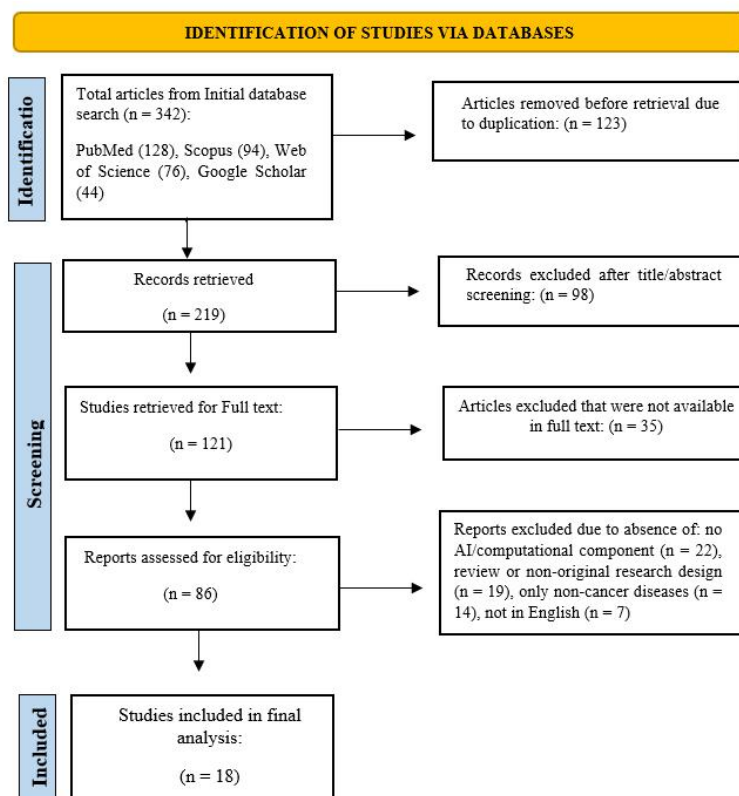


Figure 1: A PRISMA flow diagram following PRISMA guidelines 2020 outlining the study selection process of the systematic review

Table I: Summary Table Showing Characteristics and Key Findings of Studies Included in the Systematic Review

Study (Author, Year)	Study Type	AI/ Computational Method	Dataset / Database Used	Plant Source / Compound	Cancer Type	Molecular Target(s)	Validation Method	Key Findings
Country								
Sakle et al., 2020 ¹¹ India	In silico + In vitro + In vivo	Network pharmacology + Molecular docking + PPI network analysis	PubChem, GeneCards, STRING, TCMID, TCMSP, TCM, Cytoscape, GO, KEGG	<i>Caesalpinia pulcherrima</i> Catechin, Ellagic acid, Cyaniding, Quercetin	Breast cancer	ESR1, ESR2, ESRRA, MET, VEGF, FGF, PI3K, PDK-1, MAPK, NEK-2, GRK ESR1, EGFR	In vitro (MCF-7) + In vivo (MNU-induced rats) + Western blot	29 components screened; 4 actives against breast cancer.
Zhao et al., 2021 ¹² China	In silico + In vitro	Network pharmacology + Molecular docking + PPI	BATMAN TCM databases, GeneCard, OMIM, Oncodb, hcc databases, Cytoscape v3.7.1, UniProt, SwissTargetPrediction, GO, KEGG	Oxyresveratrol	Liver cancer (HCC)		Network pharmacology + In vitro validation (HepG2 cells)	ESR1 and EGFR identified as key anti-liver cancer targets an reduced ESR1 and EGFR mRNA in treated liver cancer cells. 122 shared targets identified; signalling pathways (PI3K/Akt, MAPK) predicted to underlie resveratrol's anti-endometrial cancer activity.
Zhong et al., 2022 ¹³ China	In silico	Network pharmacology + Molecular docking + PPI	TCMSP, GeneCards, STRING, UniProt	Resveratrol	Endometrial cancer (Type I)	TP53, AKT1, PIK3CA, CASP3, EGFR	Molecular docking (hydrogen bonding and hydrophobic interaction analysis)	Top 3 hub genes (AKT1, ESR1, HSP90AA1) negatively correlated with survival. Tamarixetin induced G2/M arrest/
Shaji et al., 2022 ¹⁴ India	In silico + In vitro	Reverse docking + Network pharmacology	PubChem, SwissTargetPrediction, GeneCards, TCGA	Tamarixetin	Breast cancer	AKT1, ESR1, HSP90AA1	In vitro cell-based assays (proliferation, ROS, mitochondrial membrane potential, cell-cycle, migration/invasion)	44 homo sapiens biotargets identified. Curcuminol predicted to induce apoptosis and modulate inflammatory response. Quercetin identified as primary active compound inhibiting HCC targets. In vitro results confirmed anti-cancerous activity of <i>S. surattense</i> .
Huang et al., 2022 ¹⁵ Hungary / Pakistan	In silico	Network pharmacology + Bioinformatics + molecular docking + survival analysis	TCMSP, CTD, TCGA, Human Protein Atlas, SwissTargetPrediction, SwissADME, GO/KEGG	<i>Rhizoma curcumae</i> Curcumol	Hepatocellular carcinoma (HCC)	RELA, SQSTM1	Molecular docking simulation; in silico survival analysis	
Khalid et al., 2022 ¹⁶ Pakistan	In silico + In vitro	Network pharmacology + Molecular docking + PPI network + System pharmacology	SwissTargetPrediction, OMIM, DisGeNET, CTD, GeneCard, PDB, GO, KEGG	<i>Solanum surattense</i> Quercetin	Hepatocellular carcinoma (HCC)	TNF, EGFR, mTOR, BCL2L1, ESR1, HRAS, HIF1 α , AKT1	Molecular docking validation; in vitro anti-cancerous activity on human liver cells (HepG2) and Vero cell lines	
Wu et al., 2022 ¹⁷ China	In silico + In vitro	Network pharmacology + Molecular docking + Pathway enrichment + Bioinformatics + PPI	TCMSP, (BATMAN-TCM, UALCAN, Human Protein Atlas (HPA), TCGA dataset, RCSB PDB, GO, KEGG	TCM formula (Yiqi Jianpi Jiedu) / Quercetin, Luteolin, Baicalein, Wogonin	Hepatocellular carcinoma (HCC)	MAPK3, RAC1, RHOA, β -catenin, PI3K, AKT	In vitro proliferation, migration, invasion and apoptosis assays; mRNA and protein expression verification	Key bioactive ingredients act via PI3K/Akt. In vitro results confirmed inhibition of HCC proliferation, migration and

								invasion in a concentration-dependent manner.
Bultum et al., 2022 ¹⁸ South Korea / Ethiopia	In silico	Pharmacophore-based virtual screening + ADMET profiling + Network propagation analysis	PubChem, SwissADME, admetSAR, CODA, UniProt, KEGG, GO	Ethiopian indigenous aloes	Multiple cancer types (pathway-based)	82 human targets (KEGG: steroid hormone biosynthesis, cancer pathways)	In silico target fishing; network propagation on CODA network; no experimental validation	207 KEGG pathways enriched including chemical carcinogenesis. Aloe phytochemicals exhibited polypharmacological effects on multiple genes and signalling pathways. Quercetin 3-O-β-D-glucopyranosyl-(1→2)-rhamnopyranoside as hit compound identified targeting HRAS and VEGFA inhibitor.
Bhattacharya et al., 2024 ¹⁹ India / Nepal	In silico	Network pharmacology + Molecular docking + Molecular dynamics simulation + MM-GBSA	TCMSP, TCMID PubChem, ChemDraw, MolSoft L.L.C, Prottox II, Way2Drug, DisGeNET, Ensemble, VENNY, GeneCards, STRING, KEGG, SwissTargetPrediction	<i>Drymaria cordata</i>	Cervical cancer	HRAS, VEGFA	Molecular docking (AutoDock); MD simulation; MM-GBSA analysis	14 phytochemicals prioritized; betulinic acid and stigmasterol confirmed significant anti-breast-cancer activity. In vivo experiment showed significant recovery of cancer biomarkers.
Arif et al., 2024 ²⁰ Pakistan / Saudi Arabia	In silico + In vitro + In vivo	Network pharmacology + Molecular docking + ADMET profiling	IMMPAT, SwissTargetPrediction, STITCH, GeneCards, DisGeNet, Cytoscape, STRING, DAVID database, Go, KEGG	<i>N. sativa</i> Betulinic acid, Stigmasterol	Breast cancer	EGFR, MAPK3, ESR1, MAPK1, PTGS2	In vitro (MDA-MB-231 cell line, MTT assay) + In vivo (DMBA-induced rat model)	33 bioactive molecules screened; 72 intersected with 666 lung cancer markers. 6-α-diols showed pronounced affinity for HIF1A. Purely computational; requires in vitro confirmation.
Varadharajan et al., 2024 ²¹ India / Korea / Saudi Arabia	In silico	Network pharmacology + Omics-based target identification + Molecular docking	SwissTargetPrediction, SuperPred, DIGEPred, TTD, OMIM, GeneCards IMPPAT, GO/KEGG	<i>Piper longum</i> 7-epi-eudesm-4(15)-ene-1β, demethoxyplartine, methyl 3,4,5-trimethoxycinnamate, 6-α-diols, and aristolodione	Lung cancer	CTNNB1, STAT3, HIF1A, HSP90AA1, ERBB2	Molecular docking + PPI network + GO/KEGG pathway analysis	

Saini et al., 2024 ²²	In silico	Network pharmacology + Molecular docking + Molecular dynamics simulation + MM/GBSA + Free energy landscape (FEL)	Human Protein Atlas (HPA), cBioportal, SwissADME, Cytoscape, GeneCodis4, ShinyGO 0.76, PubChem	<i>Krishnadi Churna</i> (polyherbal) / Gallic acid, Piperine, Quercetin, Resveratrol, β -sitosterol	Breast cancer	ESR1, CYP19A1, EGFR	Molecular docking (Schrödinger); MD simulation; MM/GBSA + FEL analysis; ADMET (SwissADME + ADMETlab 2.0)	134 of 135 predicted targets mutated in breast cancer patients. Phytoconstituents showed similar or better docking scores than positive controls. Computational predictions pending experimental validation.
India								
Irham et al., 2025 ²³	In silico + In vitro	Network pharmacology + Molecular docking + Molecular dynamics +PPI	KNAPSAcK, SwissTargetPrediction, GO, KEGG, cBioPortal, WebGestalt, RCSB PDB	<i>Avicennia alba</i> Avicenol B, Avicenol C, Avicequinone B, and Avicequinone C	Colorectal cancer	EGFR, PIK3CA, JAK2	MTT assay on WiDr cell lines, molecular dynamics simulations	Avicequinone C showed the strongest binding to hub genes with stable π -sigma, alkyl, and hydrogen bonds; confirmed by in vitro cytotoxic activity
Indonesia								Identified potent plant-based inhibitors of EGFR L858R with stable binding conformations and favourable pharmacokinetic profiles
Gao et al., 2024 ²⁴	In silico	High-throughput virtual screening + Network pharmacology + Molecular docking + Molecular dynamics + PPI	Swiss Target Prediction, Cytoscape3.9.1, PDB, STRING, GeneCards, OMIM	<i>Saussurea lappa</i>	Non- small cell lung cancer (NSCLC)	EGFR L858R mutant	GC–MS analysis, molecular dynamics simulations (RMSD, RMSF)	
China								
Gondoke sumo & Rasyak, 2024 ²⁵	In silico	Machine learning (ML) + Molecular docking	Dudedocking, ADME databases, PRODIGY	<i>Zingiber officinale</i> (ginger)	Breast cancer	KIT, MAPK2	ML model validation (ROC, AUC), molecular docking	ML models predicted several ginger compounds as superior to reference ligands for MAPK2; lycopene and shogaols showed low predicted toxicity
Indonesia								n-hexane, ethyl acetate, and methanol leaf extracts from <i>A. muricata</i> , <i>L. domesticum</i> and <i>M. indica</i> gave the highest growth inhibitory activity against A549 lung cancer cells
Grijaldo et al., 2023 ²⁶	In silico + In vitro	Network pharmacology + Molecular docking	PubMed NCBI, PubChem, SWISS Target Prediction, STITCH, DGIdb, RCSB PDB	<i>M. zapota</i> , <i>M. indica</i> , <i>A. muricata</i> , <i>A. heterophyllus</i> , <i>L. domesticum</i> , <i>A. buniis</i> Quercetin, Genistein, α -pinene, cyanomaclurin, kaempferol, norartocarpetin, rutin, ellagic acid	Lung cancer	EGFR, AKT1, KDR, MMP2, MMP9, ERBB2, IGF1R, MTOR, and HRAS	In vitro cytotoxicity assay on A549 cells	
Philippines								
Quintal Bojórquez et al., 2024 ²⁷	In silico	Multi- criteria decision analysis + Molecular docking	Protein fraction <1 kDa	<i>Salvia hispanica</i>	Various cancer	Cancer- related and apoptosis- related molecules	Molecular docking (binding free energy calculations)	All five PAPs exhibited strong binding interactions (< –100 kcal/mol); PAP- 3 showed the lowest binding
Mexico								

free energies
with multiple
targets

Das et al., 2024 ²⁸	In silico	Machine learning (Random Forest, k-NN, SVM, XGBoost) + Molecular docking + Molecular dynamics	NPACT database, COCONUT database (~400,000 natural products)	Natural product library	Lung cancer	EGFR (mutant)	ML model validation (accuracy, ROC), 100 ns MD simulations	Random forest with MACCS fingerprint achieved best performance; identified 205 potential inhibitors; top three compounds validated by MD as strong binders similar to staurosporine
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PPI, protein-protein interaction; *ESR1*, estrogen receptor 1; *ESR2*, estrogen receptor 2; *ESRRA*, estrogen related receptor alpha; *MET*, *MET* proto-oncogene, receptor tyrosine kinase; *VEGF*, vascular endothelial growth factor; *FGF*, fibroblast growth factor; *PI3K*, phosphoinositide 3-kinase; *PDK-1*, pyruvate dehydrogenase kinase 1; *MAPK*, mitogen-activated protein kinase; *NEK-2*, NIMA-related kinase 2; *GRK*, G protein-coupled receptor kinase; *MCF-7*, Michigan Cancer Foundation-7 (breast cancer cell line); *MNE*, N-methyl-N-nitrosourea; *UniProt*, universal protein resource; *SwissTargetPrediction*, *SIB* target prediction web server; *HCC*, hepatocellular carcinoma; *HepG2*, Hepatoblastoma G2 (liver cancer cell line); *mRNA*, messenger ribonucleic acid; *TCMSP*, traditional Chinese medicine systems pharmacology database; *TP53*, tumor protein p53; *AKT1*, AKT serine/threonine kinase 1; *PIK3CA*, phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha; *CASP3*, caspase 3; *EGFR*, epidermal growth factor receptor; *TCGA*, the cancer genome atlas; *HSP90AA1*, heat shock protein 90 alpha family class A member 1; *ROS*, reactive oxygen species; *CTD*, comparative toxicogenomics database; *SwissADME*, Swiss institute of bioinformatics ADME tool; *RELA*, *RELA* proto-oncogene, NF- κ B subunit; *SQSTM1*, sequestosome 1; *TNF*, tumor necrosis factor; *mTOR*, mechanistic target of rapamycin; *BCL2L1*, *BCL2* like 1; *HRAS*, *HRAS* proto-oncogene, *GTPase*; *HIF1A*, hypoxia-inducible factor 1 subunit alpha; *DrugBank*, drug bank database; *MAPK3*, mitogen-activated protein kinase 3; *RAC1*, Rac family small GTPase 1; *RHOA*, Ras homolog family member A; *ADMET*, absorption, distribution, metabolism, excretion, toxicity; *ChemSpider*, chemspider chemical database; *CODA*, network propagation tool; *MM-GBSA*, molecular mechanics generalized born surface area; *AutoDock*, autodock molecular docking software; *DMBA*, 7,12-dimethylbenz[a]anthracene; *MDA-MB-231*, M.D. Anderson metastatic breast cancer 231 cell line; *MTT*, 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; *PTGS2*, prostaglandin-endoperoxide synthase 2 (*COX-2*); *IMPPAT*, Indian medicinal plants, phytochemistry and therapeutics; *SuperPred*, superpred target prediction webserver; *DIGEP-Pred*, drug-induced gene expression profile predictor; *TTD*, therapeutic target database; *OMIM*, online mendelian inheritance in man; *CTNNT1*, catenin beta 1; *STAT3*, signal transducer and activator of transcription 3; *ERBB2*, ErbB-2 receptor tyrosine kinase 2 (*HER2*); *FEL*, free energy landscape; *PharmMapper*, pharmacophore mapper; *PDB*, protein data bank; *CYP19A1*, cytochrome P450 family 19 subfamily A member 1; *ADMETlab*, *ADMETlab* web server; *cBioPortal*, cBio cancer genomics portal; *JAK2*, Janus kinase 2; *WDR*, Widr colorectal cancer cell line; *GC-MS*, gas chromatography-mass spectrometry; *NSCLC*, non-small cell lung cancer; *RMSD*, root-mean-square deviation; *RMSF*, root-mean-square fluctuation; *ML*, machine learning; *ROC*, receiver operating characteristic; *AUC*, area under the curve; *KIT*, *KIT* proto-oncogene, receptor tyrosine kinase; *MAPK2*, mitogen-activated protein kinase 2; *MMP2*, matrix metalloproteinase 2; *MMP9*, matrix metalloproteinase 9; *A549*, A549 lung cancer cell line; *PAP*, peptide from *Salvia hispanica* (anticancer peptide); *kDa*, kilodalton; *k-NN*, k-nearest neighbors; *SVM*, support vector machine; *XGBoost*, extreme gradient boosting; *COCONUT*, collection of open natural products database; *MD*, molecular dynamics; *ns*, nanosecond; *MACCS*, molecular ACCess system fingerprints.

The 18 studies addressed a variety of phytochemicals of medicinal plants and a variety of cancers. The most widely used computational model was network pharmacology along with molecular docking, followed by machine learning to train predictive anticancer activity models. The most frequently identified bioactive phytochemical was quercetin, which was used against breast cancer, hepatocellular carcinoma, and lung cancer via regulation of AKT1, EGFR, TP53, and MAPK signaling pathways. Among the included studies, 10 were purely based on in silico findings and 8 were supported by some experimental validations i.e., 8 studies used in vitro cytotoxicity measurements, with 2 studies also utilizing in vivo animal models, providing multi-level mechanistic confidence to the computational findings.

The study designs ranged from pure computational pharmacology to integrative in silico, in vitro, and in vivo platforms, indicating the steadily advanced AI-aided phytochemical research. The molecular targets that were observed in multiple studies were largely biased by a small group of high-connectivity oncoproteins, in particular, EGFR, AKT1, TP53, ESR1 and MAPK3, which are repeated across cancer types and plant sources, implying that the hub targets of phytochemical intervention are the intersections. KEGG pathway enrichment analysis demonstrated that PI3K/Akt, MAPK, NF- κ B cascades were consistently enriched by plant-derived compounds. Notably, results from all studies that included in vitro or in vivo validation were consistent with in silico predictions, which indicated biological plausibility of the computational methods used.

The PROBABT-based assessment showed that the majority of research were at high risk of bias, resulting from limits in the analysis domain, such as a lack of external validation and reliance on computational predictions. Studies that included in vitro and/or in vivo validation had lower risk in outcome areas, but pure in-silico studies were consistently assessed as high risk. Applicability problems were typically minimal, while several studies had unclear applicability due to inadequate reporting of outcome definitions and predictor selection, as shown in **Table II**.

Table II: Risk of bias assessment of the included studies using adapted PROBABT (Prediction Model Risk of Bias Assessment Tool)

Study author	Risk of Bias				Applicability				
	Participants	Predictors	Outcome	Analysis	Overall	Participan ts	Predictors	Outcome	Overall
Sakle et al., 2020 ¹¹	+	+	+	—	—	+	+	+	+
Zhao et al., 2021 ¹²	—	+	+	—	—	+	+	+	+
Zhong et al., 2022 ¹³	—	+	?	—	—	+	+	?	?
Shaji et al., 2022 ¹⁴	—	+	+	—	—	+	+	+	+
Huang et al., 2022 ¹⁵	—	+	?	—	—	+	+	?	?
Khalid et al., 2022 ¹⁶	—	+	+	—	—	+	+	+	+
Wu et al., 2022 ¹⁷	+	+	+	—	—	+	+	+	+
Bultum et al., 2022 ¹⁸	—	—	?	—	—	+	—	?	—
Bhattacharya et al., 2024 ¹⁹	—	+	?	—	—	+	+	?	?
Arif et al., 2024 ²⁰	+	+	+	+	+	+	+	+	+
Varadharajan et al., 2024 ²¹	—	—	?	—	—	+	—	?	—
Saini et al., 2024 ²²	—	—	?	—	—	+	—	?	—
Irham et al., 2025 ²³	—	+	+	—	—	+	+	+	+
Gao et al., 2024 ²⁴	—	+	?	—	—	+	+	?	?
Gondokesumo & Rasyak, 2024 ²⁵	—	+	+	—	—	+	+	+	+

Grijaldo et al., 2023 ²⁶	–	+	+	–	–	+	+	+	+
Quintal Bojórquez et al., 2024 ²⁷	–	–	?	–	–	+	–	?	–
Das et al., 2024 ²⁸	–	+	+	–	–	+	+	+	+

The risk of bias assessment of the eight studies that involved in vitro experimental validation showed a similar tendency of some concerns in all the studies, as shown in **Table III**. The area of random sequence generation was homogeneously considered as Low risk because all the studies used randomized layouts and indicated cell line sources and cell culture conditions. The allocation concealment and result assessment are rated as some concerns in all eight studies, which is a well-known weakness of in vitro laboratory-based research. The unfinished outcome data and selective reporting areas were considered low risk in all situations because studies reported complete data of all biological replicates and assessed outcomes.

Table III: Risk of Bias Assessment of In Vitro Studies using Modified SYRCLE Tool

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias	Overall
Sakle et al., 2020 ¹¹	Low (randomly assigned wells)	Some concerns (not described)	Some concerns (blinding not stated)	Some concerns (assessor blinding not stated)	Low	Low	Low	Some concerns
Zhao et al., 2021 ¹²	Low (randomized plate layout)	Some concerns	Some concerns	Some concerns	Low	Low	Low	Some concerns
Shaji et al., 2022 ¹⁴	Low (randomized)	Some concerns	Some concerns	Some concerns	Low	Low	Low	Some concerns
Khalid et al., 2022 ¹⁶	Low (randomized)	Some concerns	Some concerns	Some concerns	Low	Low	Low	Some concerns
Wu et al., 2022 ¹⁷	Low (randomized)	Some concerns	Some concerns	Some concerns	Low	Low	Low	Some concerns
Arif et al., 2024 ²⁰	Low (randomized)	Some concerns	Some concerns	Some concerns	Low	Low	Low	Some concerns
Irham et al., 2025 ²³	Low (randomized)	Some concerns	Some concerns	Some concerns	Low	Low	Low	Some concerns
Das et al., 2024 ²⁸	Low (randomized)	Some concerns	Some concerns	Some concerns	Low	Low	Low	Some concerns

The risk of bias assessment of the two studies that used in vivo animal model validation has produced an overall rating of some concerns, as shown in **Table IV**. The process of random sequence generation was also low risk in both studies, with animals being randomly assigned to experimental groups with well-defined group sizes. Generally, the in vivo experiments showed that preclinical animal research has acceptable methodological standards, but some concerns rating indicated that it would be better to be clearer about how blinding and allocation procedures were carried out in subsequent in vivo phytochemical validation experiments instead of showing that the reported results were systematically biased.

Table IV: Risk of Bias assessment of In Vivo Studies using SYRCLE Tool

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias	Overall
Sakle et al., 2020 ¹¹	Low (randomly divided)	Some concerns (not described)	Low (animals housed together)	Some concerns (IHC blinding not stated)	Low	Low	Low	Some concerns
Arif et al., 2024 ²⁰	Low (56 rats, 7 groups)	Some concerns (not described)	Low	Some concerns (blinding not stated)	Low	Low	Low	Some concerns

Traffic light plot showing the risk of bias of the two in vivo preclinical animal studies were assessed using Robvis software, as shown in **Figure 2**. The small sample size of in vivo studies (n = 2) limited the generalizable conclusions on the quality of the overall preclinical evidence but the findings indicated that subsequent in vivo validation studies should incorporate and explicitly describe standardized blinding and randomization protocols to enhance the translational plausibility of computational predictions.

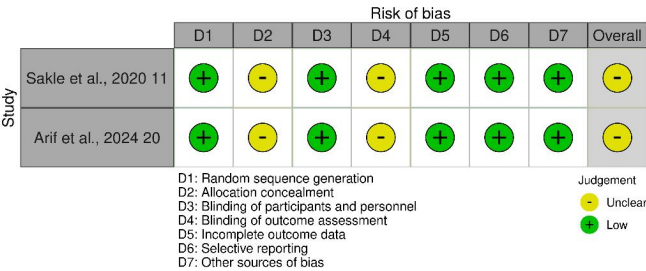


Figure 2: Traffic light plot illustrating the risk of bias assessment for in vivo preclinical animal studies using the Robvis tool

Traffic light plot illustrating the risk of bias measurement of the eight in vitro experimental studies were assessed with the Robvis software, as shown in **Figure 3**. Low risk of bias denoted by green circles and some concerns was denoted by yellow circles. The plot indicated a consistent trend of low risk in random sequence generation, incomplete outcome reporting, and selective reporting, whereas the domain of allocation concealment and blinding always had some concerns. The certainty of evidence based on a GRADE framework was low, mainly because of the sheer indirectness of computational predictions based on the clinical outcome, methodological heterogeneity across docking platforms, and the limited number of experimental validations of the included studies.

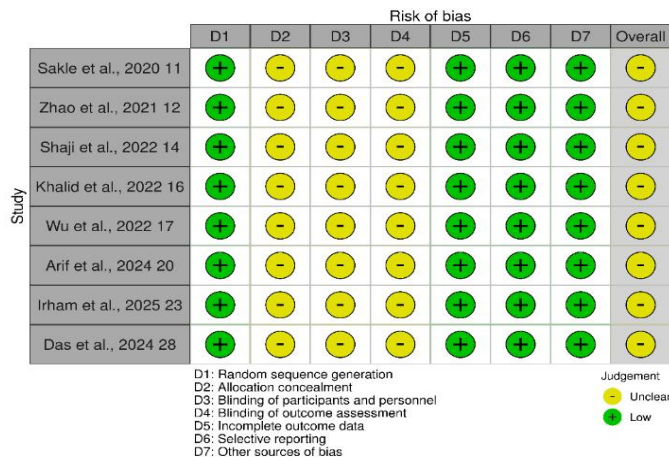


Figure 3: Traffic light plot depicting the risk of bias assessment for in vitro experimental studies using Robvis toll

Overall, the studies demonstrated substantial variation in computational approaches, phytochemical sources, cancer types, molecular targets, and validation methods. The following discussion interprets these findings in the context of current evidence on computational phytochemical discovery and anticancer mechanisms

DISCUSSION

This systematic review summarized 18 original research studies which used artificial intelligence and computational pharmacology models such as network pharmacology, molecular docking, molecular dynamics simulation, QSAR modelling and machine learning to identify and predict the anticancer properties of plant-derived bioactive compounds. This integrative strategy demonstrated a reproducible convergence strategy in phytochemical targets and signaling pathways that would remain invisible in single-compound or single-cancer studies, providing a more general and transferable framework for guiding future in silico phytochemical oncology pipelines. Together, these methods have evolved into the backbone of modern phytochemical drug discovery, allowing large libraries of compounds to be screened simultaneously against a variety of cancer-relevant targets, and accelerating the process of identifying leads for experimental validation.

Among the 18 included studies, the most prevalent method was network pharmacology, followed by molecular docking. The frequent emergence of AKT1, EGFR, TP53, ESR1, and MAPK3 as central targets for phytochemicals derived from a broad range of plants and interrogating multiple cancers was biologically significant ²⁹. The PI3K/Akt/mTOR pathway was one of the most frequently overactive survival pathways in human cancer, and has been widely documented to be regulated by natural products ³⁰.

The most frequently identified bioactive compound, quercetin was identified in studies targeting breast cancer, hepatocellular carcinoma, and lung cancer with inhibition of AKT1 and EGFR, suppression of MAPK, and induction of apoptosis. This multifaceted activity was consistent with its reported modulation of PI3K/Akt, NF-κB and Notch pathways in a variety of tumors ³¹. Resveratrol has displayed anticancer activities, particularly in endometrial cancer and HCC, where it targeted TP53, AKT1, PIK3CA, CASP3, and EGFR via the PI3K/Akt and MAPK pathways ³². Resveratrol has shown cytoprotective effects through scavenging of reactive oxygen species, further justifying its inclusion in the virtual screening cycle for designing anti-cancer drugs³³. The multiple hits on different oncogenic targets by structurally diverse phytochemicals support their polypharmacological activity and multi-target mechanisms, extending beyond conventional single-target approaches ³⁴.

The epidermal growth factor receptor (EGFR) emerged as the most prominent molecular target, Featuring in studies of breast, lung, liver, colorectal and cervical cancers. EGFR, commonly mutated in non-small cell lung cancer (NSCLC), has been extensively targeted by established therapies and continues to be explored through emerging immunotherapeutic strategies ³⁵. Plant-based EGFR inhibitors identified by high-throughput virtual screening and machine learning-driven QSAR studies were an opportune approach to address this clinical challenge.

The use of machine learning in two studies expanded phytochemical discovery beyond traditional network pharmacology approaches, by allowing large-scale activity prediction from molecular fingerprints using Random Forest, Support Vector Machine (SVM), k-Nearest Neighbour (kNN) and XGBoost models. This enabled the discovery of candidate molecules from the hundreds of thousands of natural product scaffolds present in the databases with a computational speed that could not be achieved with experimental screening. The in vivo study that validated the new candidate compounds and the experimental evidence that plant-derived withanolide E from *Physalis peruviana* exhibited anticancer activity in DMBA-induced breast cancer models ^{36, 37}, together strengthen the growing evidence that phytochemicals prioritized by computational approaches can have preclinical activity.

The results from studies related to hepatocellular carcinoma (HCC) focused on phytochemicals for the treatment of HCC, with network pharmacology analyses pinpointing RELA, SQSTM1, AKT1, EGFR, and TNF as potential targets. Natural products have demonstrated significant potential in targeting autophagic signaling pathways in HCC ³⁸, and the active compounds identified in the included studies, such as curcumol, quercetin, and *Solanum surattense* compounds, regulated PI3K/Akt, MAPK and NF-κB pathways that were strongly associated with autophagic and apoptotic processes in liver cancer ³⁹. The in vitro validation studies demonstrated target gene down-regulation in human liver cancer cell lines, thereby validating the computational findings, and highlighting the significance of network pharmacology-predicted targets in HCC.

However, critical translational gaps remain, and the PROBAST-based risk of bias assessment revealed that the majority of included studies were at high risk of bias, due to limitations in the analysis domain, specifically a lack of external validation and reliance solely on computational predictions without experimental confirmation. Only one study had a low overall risk of bias, due to the inclusion of both in vitro and in vivo validation. Pure in silico investigations were consistently evaluated as high-risk, emphasizing the importance of prospective experimental validation. Pharmacokinetic filters used for screening (oral bioavailability $\geq 30\%$, Lipinski's Rule of Five) don't completely predict in vivo properties. Phytochemicals like quercetin, curcumin, and resveratrol were heavily metabolized, have poor systemic bioavailability, and insufficient penetration into the tumor, limiting the amount of active drug that can reach the target site.

Limitations of this review are process-related (e.g., confined to English-language, full-text articles published in 2020–2025 in four databases), which can lead to language and publication bias. Also, there was certain subjectivity inherent in the adapted application of the PROBAST and SYRCLE tools to assess the risk of bias, and the exclusion of non-peer-reviewed literature (e.g., conference abstracts) could have left some developing results out. There was a risk of publication bias towards positive docking results, which increases the apparent consistency in silico agreement. Future research should focus on hybrid validation strategies (integrating in vitro and in vivo assays from the outset), adopt standardized reporting guidelines for computer-aided drug design, and use of nano-formulation strategies to enhance the translational potential of in silico-prioritized phytochemicals.

CONCLUSION

Computational pharmacology techniques (including network pharmacology, molecular docking, molecular dynamics simulation, and machine learning) have become essential to discovering plant-derived leads for cancer treatment. Across 18 original studies, a wide range of phytochemicals were shown to engage high-priority promising targets (AKT1, EGFR, TP53, ESR1) through signaling pathways (PI3K/Akt, MAPK, NF- κ B). Although the overall certainty of evidence was very low because of the indirect nature of the computational models, the plausibility of biological findings was supported by consistent experimental verification in some of the studies. Transparent reporting, prospective in vitro/in vivo validation, and drug delivery approaches (nano-formulations) are critical steps that are needed to translate these computational findings into anticancer leads for future research.

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