The American Journal of Applied Sciences
ISSN 2689-0992 Volume 08 - 2026

**Proceedings of Women in Academia, Research and Management for Work-life Initiatives for Sustainable Health & Empowering Safety (WARM-WISHES 2026)**

# Targeting Cancer Hallmarks Through Phytochemicals: An in-Silico Docking Study of Natural Compounds as Inhibitors of Key Oncoproteins

**Nishant Kumar Singh**
Amity Institute of Biotechnology, Amity University Uttar Pradesh, Lucknow 226028, India.

**Tushar Nayyar**
Amity Institute of Biotechnology, Amity University Uttar Pradesh, Lucknow 226028, India.

**Agrimaa Roy**
Amity Institute of Biotechnology, Amity University Uttar Pradesh, Lucknow 226028, India.

**Looba Hasan**
Amity Institute of Biotechnology, Amity University Uttar Pradesh, Lucknow 226028, India.

**Agrika Gupta**
Amity Institute of Biotechnology, Amity University Uttar Pradesh, Lucknow 226028, India.

**Prankur Awasthi**
Amity Institute of Biotechnology, Amity University Uttar Pradesh, Lucknow 226028, India.

**Saba Hasan**
Amity Institute of Biotechnology, Amity University Uttar Pradesh, Lucknow 226028, India.

**Corresponding author:** Dr. Saba Hasan
Assistant Professor
Amity Institute of Biotechnology,
Amity University Uttar Pradesh, Lucknow 226028, India

Received: 17 Apr 2026 | Received Revised Version: 21 Apr 2026 | Accepted: 16 May 2026 | Published: 21 May 2026

DOI: 10.37547/tajas/warm-15

## Abstract

*Cancer is a primary cause of morbidity and mortality worldwide and represents a substantial burden on health care systems. In 2020, there were more than 19.3 million new cases and over 10 million deaths from cancer annually. Despite the progress in traditional therapy, problems like as drug resistance, toxicity and recurrence are still present. Medicinal plant phytochemicals have attracted a lot of interest in the recent years as potential anticancer medications because of their structural diversity, biological activity and relatively low toxicity. The study was conducted to evaluate the anticancer efficacy of some phytochemicals extracted from five traditionally used medicinal plants i.e. Curcuma longa (turmeric), Azadirachta indica (neem), Allium sativum (garlic), Solanum lycopersicum (tomato) and Withania somnifera (ashwagandha) against important oncogenic protein targets by using a structure based molecular docking methodology. A preliminary screening of more than 60 phytochemicals was identified by a detailed literature study and validated by the IMPPAT 2.0 database. The proteins KRAS, EGFR, HER2, HRAS and CTNNB1 crystal structures were retrieved from the RCSB Protein Data Bank. The three-dimensional ligand structures were retrieved from the PubChem database. Molecular docking simulation was performed using CB-Dock2 platform. CB-Dock2 predicts the ligand-protein binding affinity by*

*integrating cavity detection and scoring mechanism of AutoDock Vina. The maximum binding affinity was observed with azadiradione from Azadirachta indica with KRAS (Vina score = –15.3 kcal/mol) showing a somewhat persistent association in the active region of the protein. Other important chemicals included bisdemethoxycurcumin binding to HRAS (–9.4 kcal/mol), sitoindosidelx interacting with EGFR (–10.7 kcal/mol) and nicotiflorin targeting KRAS (–10.9 kcal/mol). Beta-carotene, isotretinoin, and zeaxanthin, carotenoid chemicals from Solanum lycopersicum, showed strong interactions with HER2. The results suggest that phytochemicals from medicinal plants like turmeric, ashwagandha and neem have great anticancer potential and might be lead molecules for developing novel medications.*

Keywords: Phytochemicals, Molecular Docking, Anticancer Activity, Oncogenic Proteins.



**Cite This Article:** Singh, N. K., Nayyar, T., Roy, A., Hasan, L., Gupta, A., Awasthi, P., & Hasan, S. (2026). Targeting Cancer Hallmarks Through Phytochemicals: An in-Silico Docking Study of Natural Compounds as Inhibitors of Key Oncoproteins. The American Journal of Applied Sciences, 154–167. https://doi.org/10.37547/tajas/warm-15

## 1. Introduction

One of the most significant public health issues is the prevalence of cancer globally. In 2020, there were about 10 million cancer-related fatalities and 19.3 million new cases per year (Park et al., 2024). It is a leading cause of death worldwide and has a significant negative impact on economies and healthcare systems everywhere. By 2040, it is predicted that low- and middle-income countries (LMICs) would bear more than 75% of the world's cancer burden (Sivaram et al., 2021). The need for accessible, efficient, and innovative treatment methods is shown by the variations in cancer incidence and mortality among nations as well as the growing costs of healthcare (Guerra-Londono et al., 2025). Due to certain inherent limitations, conventional cancer therapies including radiation, chemotherapy, and surgery have become less successful. Medication resistance, incomplete tumour excision, serious side effects, and the potential for cancer recurrence are among of them (Bandara & Raveendran, 2025; Chaudhari et al., 2024; Burris, 2009). However, most patients develop resistance to non-specific chemotherapeutic therapies, such as those used to treat non-small-cell lung cancer (NSCLC), which provide only modest survival improvements and are linked to high toxicity (Burris, 2009). Furthermore, considering that many patients need long-term, intensive care, the financial expense of these medications is a significant worry (Park et al., 2024). These restrictions highlight the urgent need for more advanced and effective cancer treatments. Immunotherapy and microneedle-based drug delivery systems are examples of innovations that are expanding possibilities, although worries about resistance and response variability still exist (Bandara & Raveendran, 2025; Ganeson et al., 2023). Because of their broad spectrum of bioactivity and chemical variation, phytochemicals—bioactive compounds derived from plants—are becoming a promising class of candidates for the creation of anticancer drugs.

It has been discovered that phytochemicals influence important biological processes associated with cancer, including angiogenesis, metastasis, and apoptosis. Their diversity and structural complexity provide a wealth of distinctive chemical scaffolds that are often difficult to replicate artificially. These substances are thus helpful in the hunt for novel drugs (Permaul Flores et al., 2023). Additionally, their long history of usage in conventional medicine points to a generally favourable safety profile, reducing concerns about undesirable side effects. The importance of phytochemicals is further shown by the practical applications of plant-based anticancer compounds. For example, Paclitaxel (Taxol), produced from the Pacific Yew tree, is often used to treat ovarian, breast, and lung cancers. Similarly, vincristine, which is made from the Madagascar periwinkle plant, has revolutionised the treatment of lymphoma, leukaemia, and a number of childhood cancers (Murayama et al., 2023).

Traditional medical systems across the world have long employed plant-based remedies to treat a variety of illnesses, including cancer. Ethnopharmacology has a role in identifying potential drug candidates from traditional medicinal practices and serves as a crucial

link between traditional knowledge and contemporary scientific research (Su et al., 2021). Since many modern drugs, including certain anticancer therapies, have their roots in traditional medicine, it is crucial to validate and expand this body of knowledge using rigorous scientific methods. There are still significant gaps in our understanding of the precise mechanism of action of phytochemicals, such as flavonoids, polyphenols, terpenoids, and alkaloids, despite the growing evidence of their anticancer potential. These substances have been shown to alter pathways implicated in the development of cancer, such as nuclear factor kappa B (NF-κB) activation, apoptosis, cellular migration, and reactive oxygen species (ROS) signalling (Zheng et al., 2022). To further understand these pathways and use these findings in therapeutic applications, more research is required. By focusing on many molecular sites, curcumin is one of the substances that, when combined with resveratrol and quercetin, has shown superior anticancer benefits. However, challenges including poor absorption restrict these combinations' clinical efficacy. Therefore, co-delivery techniques and formulations based on nanoparticles need further research (Ghobadi & Asoodeh, 2023). Additionally, new research indicates that phytochemicals have a role in immune checkpoint suppression and immunological modulation. Certain phytochemicals may enhance treatment response and reduce immunogenic side effects when used with immune checkpoint inhibitors (Lee et al., 2021; Paudel et al., 2023). Nevertheless, little research has been done on the specific molecular pathways of the immune system components and phytochemicals.

Furthermore, a wide range of bioactivities against cancer cell lines are shown by less well-known compounds, particularly those obtained from plants like Catharanthus roseus. Even while alkaloids like vincristine and vinblastine are used therapeutically, certain newly discovered alkaloids need further research (Pham et al., 2020). The potential of phytochemicals to lower cancer risk has been shown by epidemiological studies; nevertheless, these results usually do not transfer into clinical trials, underscoring the necessity for further well planned human research to determine efficacy and safety (Rudzińska et al., 2023). Examining phytochemicals for less studied cancers is another area of current research that is understudied. Malignancies including bladder and prostate cancer have attracted a lot of attention, but there are opportunities to study these compounds in other cancer types and signalling pathways (Xia et al., 2021).

A computer-based technique called "molecular docking" determines which molecule (ligand) will suit a target (such a protein or nucleic acid) the best. Because it simulates interactions between tiny drugs and target macromolecules, it is essential to structure-based drug development (Dnyandev et al., 2021). Preparing ligands and receptors, performing simulations, and evaluating predicted binding positions and affinities are the typical steps in docking (Schäfer et al., 2024). Without the need for wet-lab research, molecular docking is a quick and affordable method of digitally screening large chemical libraries to identify the most promising drug candidates (Muhammed & Aki-Yalcin, 2024). This expedites the first phases of drug development and improves the effectiveness of subsequent experimental validation (Sahoo et al., 2022). Among the available tools, CB-Dock2 is now a reliable docking platform thanks to the addition of cavity identification, blind docking, and homologous template fitting. With a success rate of over 85% for binding posture prediction, CB-Dock2 is very accurate and user-friendly, making it perfect for cheminformatics and bioinformatics applications (Liu et al., 2022).

Based on their documented phytochemical richness and historic use, five plants were selected for the study. Curcuma longa (turmeric), Azadirachta indica (neem), Allium sativum (garlic), Solanum lycopersicum (tomato), and Withania somnifera (ashwagandha) were the plants chosen. These plants are known to have compounds with pro-apoptotic, anti-inflammatory, and antioxidant properties that are crucial for cancer treatment. For instance, via many cell signalling pathways, curcumin from turmeric inhibits the development of cancer cells and encourages their death (Ahmad et al., 2020). Garlic's anticancer potential is attributed to its organosulfur compounds, which aid in DNA repair and modify immune responses (Bouyahya et al., 2022). These specific phytochemicals have been selected because of their ability to decrease chemoresistance and boost the chemosensitivity of existing cancer treatments (Bouyahya et al., 2022). Additionally, they may be helpful adjuvants in the prevention and treatment of cancer due to their immunomodulatory and anti-inflammatory properties (G Ravelo et al., 2004).

KRAS, EGFR, HRAS, HER2, and CTNNB1 were identified as important oncogenic targets for this study. Members of the RAS family of oncogenes, KRAS and HRAS, are often mutated in several malignancies,

leading to the unchecked activation of cell growth pathways (Aunoble et al., 2000). Members of the epidermal growth factor receptor family, EGFR and HER2, are often overexpressed or mutated and play crucial roles in cell survival and proliferation. β-catenin, a crucial component of the Wnt signalling pathway that has been linked to cancer via its control of gene transcription and cell adhesion, is encoded by the CTNNB1 gene (Sahu & Pattanayak, 2020).

In order to bridge traditional medicine and contemporary drug discovery, the study intends to assess the anticancer potential of phytochemicals from five medicinal plants using molecular docking to ascertain their binding affinities to important cancer protein targets like KRAS, EGFR, HER2, HRAS, and CTNNB1 using the CB-Dock2 platform. Their docking performance will be contrasted with that of well-known synthetic anticancer medications, and in-depth atomic-level molecular interaction studies will be carried out to elucidate the binding mechanisms. Additionally, the study's goal is to identify interesting and understudied phytochemicals from a structural standpoint for upcoming in-vitro and in-vivo validation. By combining pharmacological data with computer predictions, the work also advances the scientific validation of ethnomedical knowledge. All things considered, our approach finds natural compounds that may be low-toxicity, multi-target anticancer prospects and offers a foundation for the creation of safer and more efficient treatment plans.

## 2. Methodology

### *2.1 Phytochemicals Selection/ Selection of Phytochemicals*

Molecular docking investigation was examined for phytochemicals with antioxidant benefits and probable anticancer impact. The present study was conducted on five well known Indian medicinal plants namely Withania somnifera (Ashwagandha), Azadirachta indica (Neem), Curcuma longa (Turmeric), Allium sativum (Garlic) and Solanum lycopersicum (Tomato), that has been extensively used in traditional medicine for its therapeutic properties including anticancer potential. Through extensive literature surveys, including databases such as PubMed Central (https://pmc.ncbi.nlm.nih.gov/), Google Scholar (https://scholar.google.com/), Scopus, ScienceDirect, and SpringerLink, an initial pool of more than 60 phytochemicals was shortlisted based on key terms such as “phytochemicals,” “anti-cancer activity,” and specific plant names.

### *2.2 Phytochemical Validation*

To ensure accuracy and biological relevance, the selected phytochemicals were validated using the IMPPAT 2.0 database (Indian Medicinal Plants, Phytochemistry, and Therapeutics) (https://cb.imsc.res.in/imppat/). This ensured that only well-characterized and experimentally supported phytochemicals from Indian medicinal plants were used. Additional details such as their phytochemical class, therapeutic activity, and plant part were verified and cross-referenced.

### *2.3 Ligand Structure Retrieval, Preparation, and Optimization*

The three-dimensional structures of the validated phytochemicals were retrieved from the PubChem (https://pubchem.ncbi.nlm.nih.gov/) database in .sdf format. The downloaded structures were directly used for docking without additional optimization, as CB-Dock 2 directly supports the, sdf format.

### *2.4 Selection and Preparation of Target Proteins (Protein preparation)*

The protein EGFR (PDB ID: 1M17), HER2 (PDB ID: 3PPO), KRAS (PDB ID: 4JV8), HRAS (PDB ID: 7OGC), and CTNNB1 (PDB ID: 8Y0G) were prepared by retrieved the three- dimensional crystal structures of each from the RCSB Protein Data Bank (https://www.rcsb.org/). Only Homo sapiens-derived, high-resolution X-ray diffraction structures (≤ 2.0 Å) without mutations were selected to ensure data fidelity.

Energy minimization and geometry optimization of all structures were performed using PyMOL v2.5, a built-in tool for preparing structures before docking in UCSF Chimera to add hydrogen atoms and charges to the receptors; then, the proteins were later saved in PDBQT format. This ensured a precise and isolated binding pocket for receptor-ligand interaction analysis.

### *2.5 Structure-Based Molecular Docking simulation via CB-Dock2*

CB-Dock2, a cavity-detection guided molecular docking tool (http://cadd.labshare.cn/cb-dock2/), was employed to predict the binding interactions between selected phytochemicals and protein targets. The program uses AutoDock Vina as docking engine, and provides auto cavity identification, receptor-ligand preparation and

docking simulation. For each run, the protein structures (.pdb format) and ligands (.sdf format) were submitted to the server. The docking was performed against the top five anticipated binding cavities. Binding affinity scores (kcal/mol), cavity coordinates and docking postures were obtained. The best scoring ligand-protein complexes according to the binding affinity were chosen for visualisation and additional interaction analysis.

## 3. Results

### *3.1 Docking Success rate*

All the selected phytochemicals effectively docked with the target proteins and were compatible with the binding pockets identified.

### *3.2 Phytochemical Selection and Validation*

Compounds were chosen based on their reported anticancer efficacy, structural diversity and recognised biological routes. These covered a wide array of chemical classes such flavonoids, terpenoids, carotenoids, withanolides and organosulfur compounds.

The chosen compounds were evaluated using IMPPAT 2.0 database which gave thorough information on plant source, medicinal significance and traditional use of each phytochemical. This resulted in a refined list of representative phytochemicals. Key examples are azadiradione, nicotiflorin, and rutin from neem; withaferin A and sitoindosidelx from ashwagandha; curcumin and bisdemethoxycurcumin from turmeric; lycopene and beta-carotene from tomato; and allixin from garlic. The choice of these phytochemicals is consistent with the research emphasising their function in cancer-related processes including activation of apoptosis, angiogenesis inhibition, regulation of oxidative stress and interference with oncogenic signalling.

### *3.3 Target Proteins*

Five human cancer-associated proteins were selected as molecular targets based on their relevance to key oncogenic pathways and their association with specific phytochemicals as suggested by literature. High-resolution crystal structures corresponding to EGFR, HER2, KRAS, HRAS, and CTNNB1 were successfully obtained. Each structure displayed a well-defined binding domain and was free from major structural irregularities upon inspection. Post-refinement, all protein models were confirmed to be structurally intact, with active sites preserved and cavity regions accessible. The cleaned and validated protein files (*Table 1)* were confirmed to be suitable for molecular docking, ensuring reliable ligand–target interaction analysis in subsequent simulations. The following PDB IDs were selected for each plant were shown and describe in table 1.

**Table 1:** Selected plants with their PDBIDs

| SL/NO | Plant | PDB IDs |
|---|---|---|
| **1.** | *Solanum lycopersicum* | 3PPO |
| **2.** | *Curcuma longa* | 7OGC |
| **3.** | *Allium sativum* | 8Y0G |
| **4.** | *Azadirachta indica* | 4JV8 |
| **5.** | *Withania somnifera* | 1M17 |

### *3.4 Molecular Docking*

Molecular docking of all validated phytochemicals with their respective cancer-associated protein targets was successfully completed using the CB-Dock2 platform. Vina scores, which represent binding energy in kcal/mol, were used to evaluate the interaction strength: the lower (more negative) the score, the stronger the binding potential of the phytochemical to the target protein.

Of all the combinations, the phytochemicals from Neem, Ashwagandha, Turmeric and Tomato showed especially robust binding characteristics. Azadiradione from Azadirachta indica had the greatest binding affinity for KRAS with a Vina score of -15.3 kcal/mol suggesting a

very favourable and stable interaction. Next up, Nicotiflorin, once again from neem, binds to KRAS with –10.9 kcal/mol. Sitoindosidelx, a molecule from Withania somnifera, showed significant binding with EGFR with a docking score of –10.7 kcal/mol. The synthetic reference molecule, Topotecan, which was utilised for comparison with the turmeric compounds, scored –10.6 kcal/mol against HRAS.

Other substances such as Rutin (Neem), Beta-carotene, Isotretinoin and Zeaxanthin (Tomato) and Bisdemethoxycurcumin (Turmeric), Withaferin A (Ashwagandha) also showed significant binding affinity with docking scores in the range of –9.8 to –9.3 kcal/mol. Table 2. Ranked list of the top ten ligand–protein interactions based on their Vina binding scores

**Table 2: Top 10 docking results of selected phytochemicals against cancer-associated target proteins**

| Rank | Plant Source | Phytochemical | Target Protein (PDB ID) | Vina Score (kcal/mol) |
|---|---|---|---|---|
| 1 | Neem | Azadiradione | KRAS (4JV8) | **–15.3** |
| 2 | Neem | Nicotiflorin | KRAS (4JV8) | **–10.9** |
| 3 | Ashwagandha | Sitoindosidelx | EGFR (1M17) | **–10.7** |
| 4 | Turmeric | Topotecan | HRAS (7OGC) | **–10.6** |
| 5 | Neem | Rutin | KRAS (4JV8) | **–9.8** |
| 6 | Tomato | Beta-Carotene | HER2 (3PPO) | **–9.8** |
| 7 | Tomato | Isotretinoin | HER2 (3PPO) | **–9.7** |
| 8 | Tomato | Zeaxanthin | HER2 (3PPO) | **–9.6** |
| 9 | Turmeric | Bisdemethoxycurcumin | HRAS (7OGC) | **–9.4** |
| 10 | Ashwagandha | Withaferin A | EGFR (1M17) | **–9.3** |

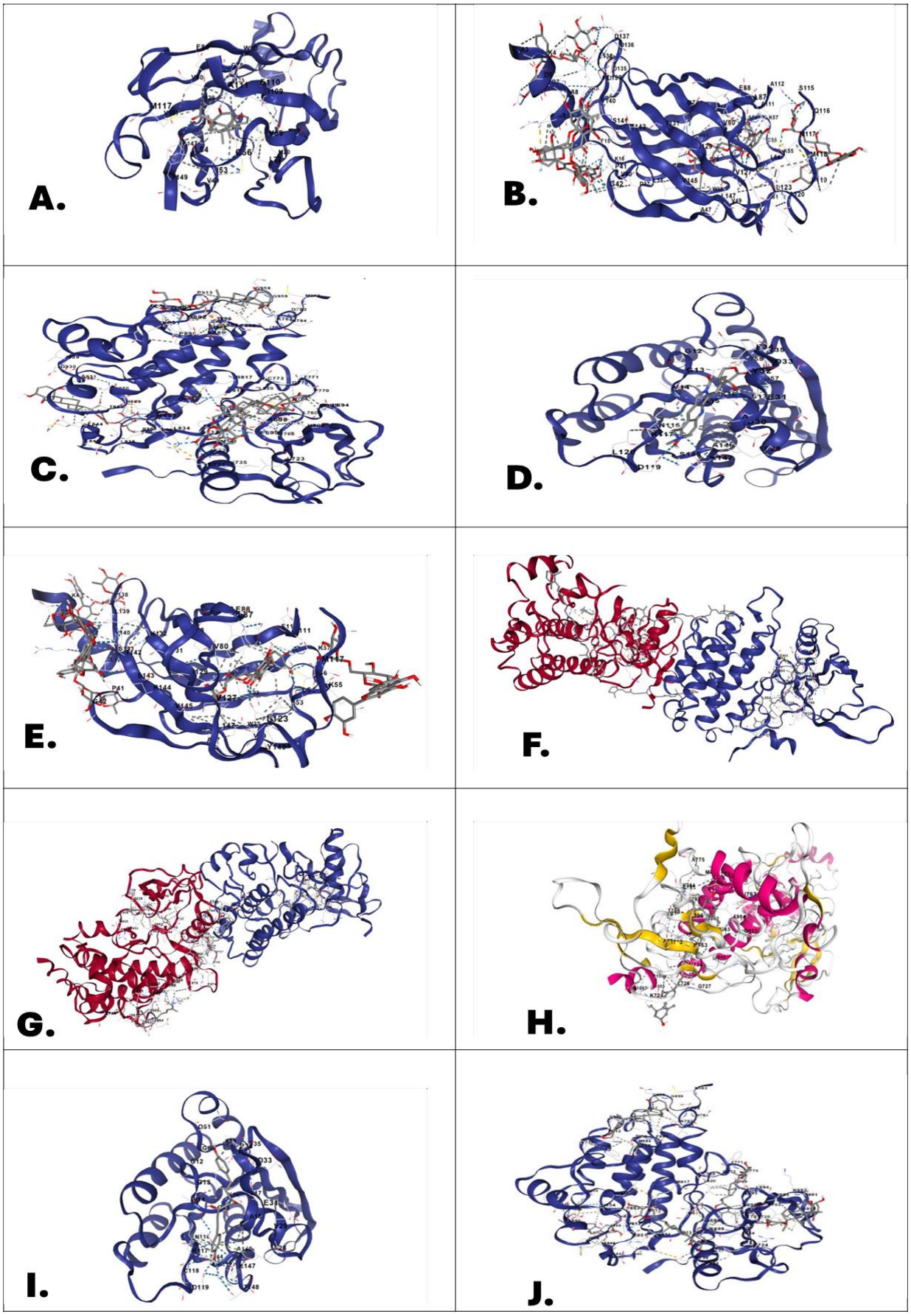
A.
B.
C.
D.
E.
F.
G.
H.
I.
J.

**Figure 1:** Docking results of top 10 phytochemicals against cancer-associated target proteins, showing binding interactions and docking scores. Each panel A. Azadiradione (Neem, Target: KRAS, Vina: –15.3), B. Nicotiflorin (Neem, Target: KRAS, Vina: –10.9), C. Sitoindosidelx (Ashwagandha, Target: EGFR, Vina: –10.7), D. Topotecan (Turmeric, Target: HRAS, Vina: –10.6), E. Rutin (Neem, Target: KRAS, Vina: –9.8), F. Beta-Carotene (Tomato, Target: HER2, Vina: –9.8), G. Isotretinoin (Tomato, Target: HER2, Vina: –9.7), H. Zeaxanthin (Tomato, Target: HER2, Vina: –9.6), I. Bisdemethoxycurcumin (Turmeric, Target: HRAS, Vina: –9.4), J. Withaferin A (Ashwagandha, Target: EGFR, Vina: –9.3) corresponds to one phytochemical.

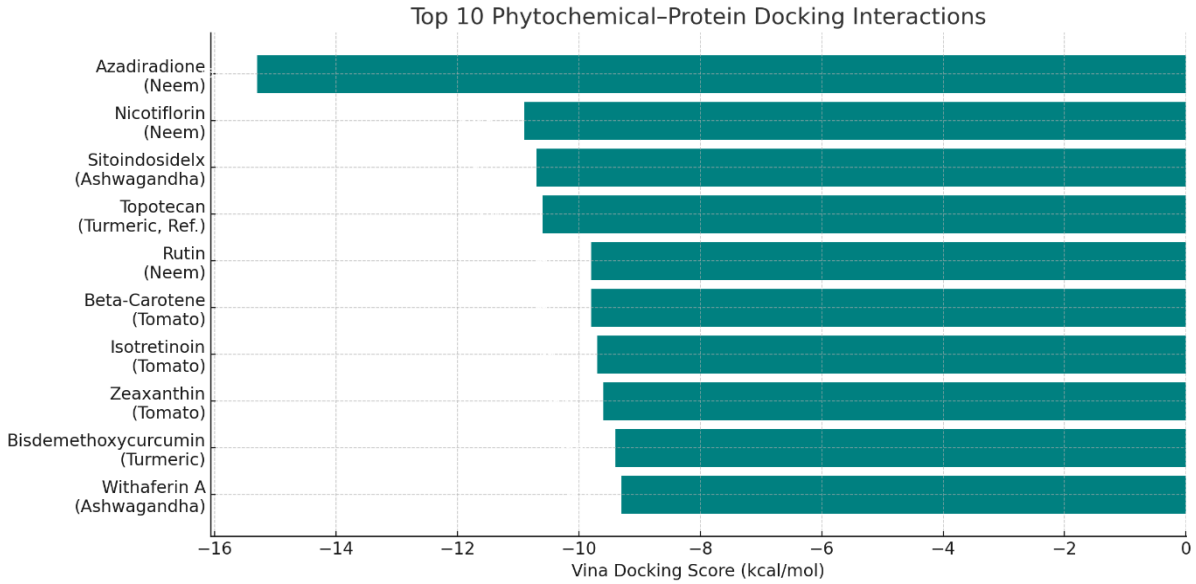


**Figure 2:** Bar graph showing the top 10 ligand–protein interactions based on their Vina docking scores (kcal/mol).

## 4. Discussion

Cancer is one of the most difficult and complicated diseases to cure. Cancer is marked by uncontrolled cell proliferation, evasion of programmed cell death (apoptosis), persistent angiogenesis, and the ability to invade distant organs and metastasise. The tumourigenic behaviours are generally ascribed to genetic aberrations that disrupt important regulatory signalling pathways such as MAPK/ERK, PI3K/AKT, Wnt/β-catenin, and EGFR, culminating in tumour development and progression (Ademosun OT et al., 2024).

Cancer burden globally is increasing at an alarming rate. For example, in 2018, over 18 million new cases were reported, and the number is predicted to exceed 23 million year by 2030 (Majrashi TA et al., 2023). Lung and breast cancers were the most frequent, with over 2.09 million cases each, followed by prostate (1.28 million). With the exception of thyroid cancer where the incidence is disproportionately higher in women (ratio 0.30), cancer incidence is often higher in males than in women, excluding sex-specific malignancies. Cancer is one of the top causes of mortality globally with over 20 million new cases and over 10 million deaths in 2022 . In the US alone, the number of deaths is expected to treble (Fakhri KU et al, 2025), with 6.9 million people aged 80 years or older expected to be diagnosed with cancer (20.5% of all cases) by 2050.

Lung cancer is one of the deadliest cancers, with more than two million new cases diagnosed each year. Preventative approaches should be stressed, since they are the most effective strategy to reduce incidence and death. Plant-based diets have been found to have promise as agents, especially in the prevention of lung cancer and in targeting lung cancer stem cells (Heng WS et al., 2021). Breast cancer is the largest cause of cancer mortality in women, representing 11.6% of all cancer diagnoses, one in four cancers, and one in six cancer-related deaths worldwide (Kodali N et al., 2025). Pancreatic cancer is also a severe concern since it is aggressive and has a dismal prognosis. According to the American Cancer Society Cancer Statistics Center, pancreatic cancer is predicted to be the 10th most

diagnosed cancer and the third most deadly disease in 2023 (Casarcia N et al., 2025).

Chemotherapy and radiation are classic medicines that have been proved to be useful in retarding cancer progression, but their usage is limited by adverse effects. This has heightened the attention on the phytochemicals, the natural compounds contained in spices, fruits, vegetables, grains and legumes as possible promising adjuncts to increase the therapeutic efficacy and reduce the toxicity (Jain A et al., 2021). The notion of cancer prevention is phytochemicals, bioactive and non-nutritive substances that are naturally present in plants . They are usually grouped into five major families: phenolics, carotenoids, organosulfur compounds, nitrogen containing compounds and alkaloids. They are responsible for the colour, smell and flavour of plant foods. They have a wide range of biological activities and have been shown to have a high potential to decrease the risk of cancer and regulate pathways implicated in carcinogenesis (Rudzińska A et al., 2023). Over the years several natural compounds have been extensively investigated for their cancer preventative potential. The growing evidence of chemopreventive and therapeutic effects of plant-derived compounds in vitro and in vivo investigations has prompted researchers to launch clinical trials to investigate their pharmacokinetics, efficacy, and safety (George BP et al., 2021).

The structure based molecular docking was performed to evaluate the anticancer potential of phytochemicals from five traditionally used medicinal plants, namely Azadirachta indica, Withania somnifera, Curcuma longa, Solanum lycopersicum, and Allium sativum against five major oncogenic targets, KRAS, EGFR, HRAS, HER2, and CTNNB1. Molecular docking is an in-silico approach to predict the binding mode and binding affinity of small molecules to the macromolecular target [3]. It predicts binding poses by sampling and scoring and estimates the binding strength. It is industry standard in drug design to screen candidates, propose binding modalities, and enhance leads (Le Menestrel T, & Rivas MA, 2024). The docking of these target proteins was done with each phytochemical individually to check the binding affinity and inhibitory effects. This assisted in recognising the powerful ligand-protein interaction, ranking the compounds based on the docking scores, visualising the key binding sites and it underscores molecular docking as a viable method for early stage anticancer drug discovery (Priyadharshini G et al., 2024).

Azadirachta indica has been used in traditional Indian medicine for long time because of its wide spectrum of therapeutic properties. It contains many phytochemicals such as limonoids, flavonoids, phenols, catechins, gallic acid and nimbins which possess high anti-feedant, antiviral, antimalarial, antibacterial and anticancer effects (Sandhir R et al., 2021). Neem showed the most inhibitory potential. Among phytochemicals, azadiradione exhibited the strongest interaction with KRAS with a Vina score of − 15.3 kcal/mol, which was the best among the tested compounds. It established stabilising H-bonds with residues like Gly60 and Lys117 in the GTP-binding pocket, often regarded as “undruggable” owing to its high affinity for GTP/GDP. The two compounds, Nicotiflorin (–10.9 kcal/mol) and Rutin (–9.8 kcal/mol) demonstrated substantial interactions which indicates the potential of synergy in multi-target engagement. Interestingly, another neem chemical, Nimbolide, has been reported to inhibit breast cancer development by disrupting RNF114-mediated ubiquitination and stabilising tumour suppressors such as p21 (Batra N et al, 2022). Withania somnifera (ashwagandha) has anti-cancer, anti-inflammatory and protective properties. It possesses active compounds like Withaferin A and Withanone in its root which induces apoptosis in the breast cancer cells by activation of caspase-3 and downregulation of Bcl-2 and also increases the effectiveness of chemotherapy and radiation (Jawarneh S et al., 2022). Ashwagandha showed potential anti-oncogenic activity particularly against EGFR. Withaferin A specifically inhibited activity of EGFR. The selective interaction was highlighted in the study of Kori et al. (2022). Molecular docking studies indicated the remarkable potential of Withaferin A to act as an EGFR inhibitor in non-small lung cell cancer. Sitoindoside showed highest binding affinity of (-10.7 kcal/mol) followed by Withaferin A (-9.3 kcal/mol) and Withanolide D. Withanone also demonstrated significant binding (-8.3 kcal/mol). These phytochemicals have the pro-apoptotic effects via modifying mitochondrial and endoplasmic reticulum functioning and by affecting pathways such STAT3, Notch and Akt (Atteeq M et al., 2022; Dutta R et al., 2019). Thus, withania phytochemicals emulate ATP-competitive inhibitors and bind to the kinase domain of EGFR and interfere with signal transduction in tumours over expressing EGFR. Curcuma longa is widely known for its chemopreventive potential where Curcumin has been proven to have powerful effects via ROS scavenging, regulation of signalling pathways, induction

of apoptosis and control of cancer microenvironment (George BP et al., 2021). Curcumin is low-cost, has little adverse effects on normal cells and is frequently used in Asian countries. Compounds had strong binding affinities notably towards HRAS. Bisdemethoxy curcumin (-9.4 kcal/mol) and Curcumin (-9.3 kcal/mol) interacted with key residues like Tyr32 and Ser17, in line with their known capabilities to suppress MAPK signalling and trigger apoptosis (Cui J et al., 2025). Solanum lycopersicum contains large amount of carotenoids such Beta-Carotene, which exhibited strong binding to HER2 (−9.8 kcal/mol), Isotretinoin (−9.7 kcal/mol) and Zeaxanthin (−9.6 kcal/mol) respectively. Tomato lycopene is a red pigment and its significant anti-oxidant property has been demonstrated to have chemopreventive benefits in various types of malignancies such as prostate, liver, breast and colon (Perveen R et al., 2015). It has dual behaviour, functioning as an antioxidant at low concentration and pro-oxidant at high dose to induce apoptosis (Lekhak N et al., 2024; Kapała A et al., 2024). Besides, S. lycopersicum offers a wide range of medicinal benefits such as anti-inflammatory, anticancer and cardioprotective activities (Abdel-Razek MA et al., 2025). Allium sativum compounds revealed poor docking scores but strong contact with CTNNB1 (β-catenin), a major effector in Wnt signalling. Allixin (–5.5 kcal/mol) and S-Allylmercapto-L-Cysteine (–4.4 kcal/mol) were shown to bind to transcriptionally active regions of β-catenin, potentially limiting the production of genes that are crucial for the proliferation of the cancer cells.

Comparative docking studies demonstrated that Azadiradione was the most potent phytochemical with substantial affinity towards KRAS. Similarly, good binding affinities of Sitoindosidelx and Curcumin analogues for EGFR and HRAS respectively were also reported which correspond well with their conventional medicinal use in anti-cancer treatment. These compounds can interact with a broad range of targets, reinforcing the concept of polypharmacology, which is mostly considered a required approach to combat tumour heterogeneity and treatment resistance. The highest rated compounds, Azadiradione, Nicotiflorin, Sitoindosidelx, Topotecan, Rutin and Beta-Carotene, showed combined docking scores with high likelihood of interaction with their respective targets. These connections suggest numerous modes of anticancer activity include suppression of receptor tyrosine kinases (EGFR, HER2), interference with GTPase mediated signalling (KRAS, HRAS) and control of transcriptional co-activators (β-catenin). The docking data suggests that these phytochemicals might be used as lead molecules for further in vitro, in vivo and structure based drug development studies.

Molecular docking is an important first step in the search for potential anticancer drugs but it is a predictive technology and must be handled with caution. High Docking scores imply strong binding affinities; however, this doesn't necessarily mean biological activity. Therefore, compounds such as azadiradione and sitoindosidelx, which showed extremely high binding affinities, should be studied further in vitro for their cytotoxicity, pharmacokinetic profile and mode of action to prove therapeutic potential. This investigation underlines the role of phytochemicals in influencing the key oncogenic proteins. Interestingly, the most potent interaction was found with Azadirachta indica where Azadiradione demonstrated binding affinity to KRAS (-15.3 kcal/mol) showing its prospective relevance in inhibiting a prominent cancer-driver gene. Also Sitoindosidelx and Withaferin A from Withania somnifera showed potential interactions targeting EGFR. Likewise, Curcuma longa compounds like Curcumin and Bisdemethoxycurcumin exhibited strong affinities to HRAS, indicating their ability to control the MAPK pathway. Meanwhile compounds of Solanum lycopersicum and Allium sativum revealed weak but significant interaction with HER2 and β-catenin respectively. The data show that Neem, Ashwagandha and Turmeric are extremely promising sources of anticancer phytochemicals. Computational techniques coupled with ethnomedicinal knowledge provide a solid basis for the discovery of novel plant-derived anti-cancer medicines and the most promising results need experimental validation.

## 5. Conclusion

This research brings to light phytochemicals from medicinal plants as promising possibilities in the development of anticancer medicines. Their high binding affinities and positive interactions with the key oncogenic protein targets, including KRAS, EGFR, HER2, HRAS, and CTNNB1, have been pointed out by the study using molecular docking with the CB-Dock2 platform. The comparative comparison with synthetic anti-cancer medicines further supports the therapeutic significance of the compounds. The discovery of structurally intriguing and underexplored compounds provides a basis for future experimental validation. This

integration is very important because it links the ancient ethnomedicinal knowledge with modern computational pharmacology, which may help to design low-toxicity, multi-target anticancer drugs. Finally, the findings provide a good basis for the advancement of phytochemicals from in silico predictions to in vitro and in vivo investigations, aiming at the improvement of the effectiveness and safety of cancer treatments.

**Declarations**

**Acknowledgement:** Not Applicable

**Funding:** This work did not receive any funding.

**Ethical Approval:** Not required. This work is completely In silico.

**Clinical trial number:** Not applicable

**Consent to Participate:** Not applicable

**Conflicts of interest/Competing interests:** Authors declare that there is no conflict of interest.

**Availability of data and materials:** The datasets used and/or analysed during this study are available from the corresponding author on reasonable request.

**Consent to Participate: NA**

**Consent to Publish: NA**

**Authors Contributions:**

**NKS:** Conceptualization of manuscript and preparation

**TN:** Manuscript preparation

**AR:** Manuscript preparation

**LH:** Manuscript preparation

**AG:** Data analysis

**PA:** Manuscript preparation and analysis

**SH:** Study conception and design

**6. References**

1. Ahmad, R., et al. "Anticancer Potential of Dietary Natural Products: A Comprehensive Review." *Anti-Cancer Agents in Medicinal Chemistry*, vol. 20, no. 2, 2020, pp. 122–236. https://doi.org/10.2174/1871520619666191015103712.

2. Aunoble, B., et al. "Major Oncogenes and Tumor Suppressor Genes Involved in Epithelial Ovarian Cancer (Review)." *International Journal of Oncology*, vol. 16, no. 3, 2000, pp. 567–582. https://doi.org/10.3892/ijo.16.3.567.

3. Bandara, Shehani, and Sreejith Raveendran. "Current Landscape and Future Directions in Cancer Immunotherapy: Therapies, Trials, and Challenges." *Cancers*, vol. 17, no. 5, 2025, p. 821. https://doi.org/10.3390/cancers17050821.

4. Bouyahya, A., et al. "Advances in Dietary Phenolic Compounds to Improve Chemosensitivity of Anticancer Drugs." *Cancers*, vol. 14, no. 19, 2022, p. 4573. https://doi.org/10.3390/cancers14194573.

5. Burris, H. A. "Shortcomings of Current Therapies for Non-Small-Cell Lung Cancer: Unmet Medical Needs." *Oncogene*, vol. 28, no. S1, 2009, pp. S4–13. https://doi.org/10.1038/onc.2009.196.

6. Chaudhary, M., and K. Tyagi. "A Review on Molecular Docking and Its Application." *International Journal of Advanced Research*, vol. 12, no. 3, 2024, pp. 1141–53. https://doi.org/10.21474/ijar01/18505.

7. Chaudhari, et al. 2024. [Full reference not provided in original file—please ensure proper citation.]

8. Dnyandev, Khemnar Manisha, et al. "A Review on Molecular Docking." *International Research Journal of Pure and Applied Chemistry*, May 2021, pp. 60–68. https://doi.org/10.9734/irjpac/2021/v22i330396.

9. Ganeson, Keisheni, et al. "Microneedles for Efficient and Precise Drug Delivery in Cancer Therapy." *Pharmaceutics*, vol. 15, no. 3, 2023, p. 744. https://doi.org/10.3390/pharmaceutics15030744.

10. Ghobadi, Niloofar, and Ahmad Asoodeh. "Co-Administration of Curcumin with Other Phytochemicals Improves Anticancer Activity by Regulating Multiple Molecular Targets." *Phytotherapy Research*, vol. 37, no. 4, 2023, pp. 1688–1702. https://doi.org/10.1002/ptr.7794.

11. Guerra-Londono, Carlos E., et al. "The Increasing Global Burden of Cancer: Implications for Anaesthesia and Peri-Operative Medicine."

*Anaesthesia*, vol. Suppl 80, no. 2, 2025. https://doi.org/10.1111/anae.16514.

**12.** G Ravelo, A., et al. "Recent Studies on Natural Products as Anticancer Agents." *Current Topics in Medicinal Chemistry*, vol. 4, no. 2, 2004, pp. 241–65. https://doi.org/10.2174/1568026043451500.

**13.** Karla A. Lee, Wenjie Ma, Daniel R. Sikavi, David A. Drew, Long H. Nguyen, Ruth C. E. Bowyer, M. Jorge Cardoso, Tove Fall, Maxim B. Freidin, Maria Gomez, Mark Graham, Chuan-Guo Guo, Amit D. Joshi, Sohee Kwon, Chun-Han Lo, Mary Ni Lochlainn, Cristina Menni, Benjamin Murray, Raaj Mehta, Mingyang Song, Carole H. Sudre, Veronique Bataille, Thomas Varsavsky, Alessia Visconti, Paul W. Franks, Jonathan Wolf, Claire J. Steves, Sebastien Ourselin, Tim D. Spector, Andrew T. Chan, on behalf of the COPE consortium, Cancer and Risk of COVID-19 Through a General Community Survey, *The Oncologist*, Volume 26, Issue 1, January 2021, Pages e182–e185, https://doi.org/10.1634/theoncologist.2020-0572

**14.** Liu, Yang, et al. "CB-Dock2: Improved Protein-Ligand Blind Docking by Integrating Cavity Detection, Docking and Homologous Template Fitting." *Nucleic Acids Research*, vol. 50, no. W1, 2022, pp. W159–64. https://doi.org/10.1093/nar/gkac394.

**15.** Murayama, Anju, et al. "Characteristics and Distribution of Scholarship Donations from Pharmaceutical Companies to Japanese Healthcare Institutions in 2017: A Cross-Sectional Analysis." *International Journal of Health Policy and Management*, vol. 12, 2023, p. 7621. https://doi.org/10.34172/ijhpm.2023.7621.

**16.** Muhammed, Muhammed Tilahun, and Esin Aki-Yalcin. "Molecular Docking: Principles, Advances, and Its Applications in Drug Discovery." *Letters in Drug Design & Discovery*, vol. 21, no. 3, 2024, pp. 480–95. https://doi.org/10.2174/1570180819666220922103109.

**17.** Paudel, Sandeep, et al. "Phytochemicals as Immunomodulatory Molecules in Cancer Therapeutics." *Pharmaceuticals*, vol. 16, no. 12, 2023, p. 1652. https://doi.org/10.3390/ph16121652.

**18.** Park, Heesook, et al. "Efficacy and Safety of Natural Killer Cell Therapy in Patients with Solid Tumors: A Systematic Review and Meta-Analysis." *Frontiers in Immunology*, vol. 15, 2024. https://doi.org/10.3389/fimmu.2024.1454427.

**19.** Permaul Flores, Hannah, et al. "Medicine Donations: A Review of Policies and Practices." *Globalization and Health*, vol. 19, no. 1, 2023. https://doi.org/10.1186/s12992-023-00964-3.

**20.** Pham, Hong Ngoc Thuy, et al. "Phytochemicals Derived from Catharanthus Roseus and Their Health Benefits." *Technologies*, vol. 8, no. 4, 2020, p. 80. https://doi.org/10.3390/technologies8040080.

**21.** Rudzińska, Anna, et al. "Phytochemicals in Cancer Treatment and Cancer Prevention—Review on Epidemiological Data and Clinical Trials." *Nutrients*, vol. 15, no. 8, 2023, p. 1896. https://doi.org/10.3390/nu15081896.

**22.** Sahu, R., and S. P. Pattanayak. "Strategic Developments & Future Perspective on Gene Therapy for Breast Cancer: Role of mTOR and Brk/PTK6 as Molecular Targets." *Current Gene Therapy*, vol. 20, no. 4, 2020, pp. 237–258. https://doi.org/10.2174/1566523220999200731002408.

**23.** Sahoo, R. N., et al. "Review on the Use of Molecular Docking as the First Line Tool in Drug Discovery and Development." *Indian Journal of Pharmaceutical Sciences*, vol. 84, no. 5, 2022. https://doi.org/10.36468/pharmaceutical-sciences.1031.

**24.** Schäfer, Marco, et al. "InVADo: Interactive Visual Analysis of Molecular Docking Data." *IEEE Transactions on Visualization and Computer Graphics*, vol. 30, no. 4, 2024, pp. 1984–97. https://doi.org/10.1109/tvcg.2023.3337642.

**25.** Sivaram, Sudha, et al. "Building Capacity for Global Cancer Research: Existing Opportunities and Future Directions." *Journal of Cancer Education*, vol. 36, no. Suppl 1, 2021, pp. 5–24. https://doi.org/10.1007/s13187-021-02043-w.

**26.** Su, Zhaohui, et al. "COVID-19 Vaccine Donations—Vaccine Empathy or Vaccine Diplomacy? A Narrative Literature Review." *Vaccines*, vol. 9, no. 9, 2021, p. 1024. https://doi.org/10.3390/vaccines9091024.

**27.** Xia, Yong, et al. "Natural Phytochemicals in Bladder Cancer Prevention and Therapy." *Frontiers in Oncology*, vol. 11, 2021. https://doi.org/10.3389/fonc.2021.652033.

**28.** Zheng, Zhaodi, et al. "Potential Roles and Molecular Mechanisms of Phytochemicals Against Cancer." *Food & Function*, vol. 13, no. 18, 2022, pp. 9208–25. https://doi.org/10.1039/d2fo01663j.

**29.** Reddy, B. S., & Rao, C. V. (2004). Chemoprevention of cancer by curcumin. In *Cancer Chemoprevention: Promising Cancer Chemopreventive Agents* (pp. 169–175). Humana Press.

**30.** Perveen, R., Suleria, H. A. R., Anjum, F. M., Butt, M. S., Pasha, I., & Ahmad, S. (2015). Tomato (*Solanum lycopersicum*) carotenoids and lycopenes chemistry; metabolism, absorption, nutrition, and allied health claims – A comprehensive review. *Critical Reviews in Food Science and Nutrition, 55*(7), 919–929.

**31.** Lee, I. C., & Choi, B. Y. (2016). Withaferin-A—a natural anticancer agent with pleiotropic mechanisms of action. *International Journal of Molecular Sciences, 17*(3), 290. https://doi.org/10.3390/ijms17030290

**32.** Mattiuzzi, C., & Lippi, G. (2019). Current cancer epidemiology. *Journal of Epidemiology and Global Health, 9*(4), 217–222.

**33.** Dutta, R., Khalil, R., Green, R., Mohapatra, S. S., & Mohapatra, S. (2019). *Withania somnifera* (Ashwagandha) and withaferin A: Potential in integrative oncology. *International Journal of Molecular Sciences, 20*(21), 5310.

**34.** Cosme, P., Rodríguez, A. B., Espino, J., & Garrido, M. (2020). Plant phenolics: Bioavailability as a key determinant of their potential health-promoting applications. *Antioxidants, 9*(12), 1263.

**35.** Liu, Y., Grimm, M., Dai, W., Hou, M., Xiao, Z., Cao, Y., & Yang, L. (2020). CB-Dock: A web server for cavity detection-guided protein–ligand blind docking. *Acta Pharmacologica Sinica, 41*, 138–144. https://doi.org/10.1038/s41401-019-0228-6

**36.** Jain, A., Madu, C. O., & Lu, Y. (2021). Phytochemicals in chemoprevention: A cost-effective complementary approach. *Journal of Cancer, 12*(12), 3686–3694.

**37.** George, B. P., Chandran, R., & Abrahamse, H. (2021a). Role of phytochemicals in cancer chemoprevention: Insights. *Antioxidants, 10*(9), 1455.

**38.** Sandhir, R., Khurana, M., & Singhal, N. K. (2021). Potential benefits of phytochemicals from *Azadirachta indica* against neurological disorders. *Neurochemistry International, 146*, 105023.

**39.** Heng, W. S., Kruyt, F. A., & Cheah, S. C. (2021). Understanding lung carcinogenesis from a morphostatic perspective: Prevention and therapeutic potential of phytochemicals for targeting cancer stem cells. *International Journal of Molecular Sciences, 22*(11), 5697.

**40.** Jawarneh, S., & Talib, W. H. (2022). Combination of Ashwagandha water extract and intermittent fasting as a therapy to overcome cisplatin resistance in breast cancer: An in vitro and in vivo study. *Frontiers in Nutrition, 9*, 863619.

**41.** Kori, M. A., Panera, B. H., & Buwa, V. A. (2022). Molecular docking of phytochemicals as inhibitors of EGFR in non-small cell lung cancer. *Innovare Journal of Medical Sciences, 10*(4), 28–30.

**42.** Atteeq, M., Kumar, V. E., Nambiar, R., De Souza, C., Yuen, A., Le, U., Verma, R., Ghosh, P. M., & Vinall, R. L. (2022). Exploring the therapeutic potential of Neem (*Azadirachta indica*) for the treatment of prostate cancer: A literature review. *Annals of Translational Medicine, 10*(13), 754.

**43.** Majrashi, T. A., Alshehri, S. A., Alsayari, A., Muhsinah, A. B., Alrouji, M., Alshahrani, A. M., Shamsi, A., & Atiya, A. (2023). Insight into the biological roles and mechanisms of phytochemicals in different types of cancer: Targeting cancer therapeutics. *Nutrients, 15*(7), 1704.

**44.** Rudzińska, A., Juchaniuk, P., Oberda, J., Wiśniewska, J., Wojdan, W., Szklener, K., & Mańdziuk, S. (2023). Phytochemicals in cancer treatment and cancer prevention—Review on epidemiological data and clinical trials. *Nutrients, 15*(8), 1896.

**45.** Priyadharshini, G., Sukumaran, G., Dilipan, E., & Ramani, P. (2024). Targeting oral cancer: In silico

docking studies of phytochemicals on oncogenic molecular markers. *Asian Pacific Journal of Cancer Prevention, 25*(6), 2069–2076.

**46.** Le Menestrel, T., & Rivas, M. A. (2024). Smiles2Dock: An open large-scale multi-task dataset for ML-based molecular docking. *arXiv preprint*. https://arxiv.org/abs/2403.00637

**47.** Lekhak, N., & Bhattarai, H. K. (2024). Phytochemicals in cancer chemoprevention: Preclinical and clinical studies. *Cancer Control, 31*, 10732748241302902.

**48.** Ademosun, O. T., Agwamba, E. C., Ahmad, I., Patel, H., Louis, H., Adebayo, A. H., & Ajanaku, K. O. (2024). Cytotoxic and phytochemical screening of *Solanum lycopersicum–Daucus carota* hydro-ethanolic extract and in silico evaluation of its lycopene content as anticancer agent. *Open Chemistry, 22*(1), 20230164.

**49.** Cui, J., Li, H., Zhang, T., Lin, F., Chen, M., Zhang, G., & Feng, Z. (2025). Research progress on the mechanism of curcumin anti-oxidative stress based on signaling pathway. *Frontiers in Pharmacology, 16*, 1548073.

**50.** Kodali, N., Madu, C. O., & Lu, Y. (2025). Phytochemicals in breast cancer prevention and therapy: Mechanisms, efficacy, and future prospects. *Current Issues in Molecular Biology*.

**51.** Casarcia, N., Rogers, P., Guld, E., Iyer, S., Li, Y., Burcher, J. T., Deliberto, L. K., Banerjee, S., & Bishayee, A. (2025). Phytochemicals for the prevention and treatment of pancreatic cancer: Current progress and future prospects. *British Journal of Pharmacology, 182*(10), 2181–2234.

**52.** Abdel-Razek, M. A., Abdelwahab, M. F., Mohamad, S. A., Abou-Zied, H. A., Abdelmohsen, U. R., & Hamed, A. N. (2025). Cytotoxic potential and metabolomic profiling of *Solanum lycopersicum* roots extract and their nanocrystals: An in silico approach. *Integrative Cancer Therapies, 24*, 15347354251335599.

**53.** Kapała, A., Szlendak, M., & Motacka, E. (2025). The anti-cancer activity of lycopene: A systematic review of human and animal studies. *Nutrients, 14*(23), 5152.

**54.** Fakhri, K. U., Sharma, D., Fatma, H., Yasin, D., Alam, M., Sami, N., Ahmad, F. J., Shamsi, A., & Rizvi, M. A. (2025). The dual role of dietary phytochemicals in oxidative stress: Implications for oncogenesis, cancer chemoprevention, and ncRNA regulation. *Antioxidants, 14*(6), 620.