CHAPTER 17

# Natural Products in Cancer Prevention and Therapy

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**ABSTRACT:** Cancer continues to be a significant global health concern due to its high mortality rates, resistance to traditional treatments, and unchecked cellular proliferation. Radiation therapy, chemotherapy, and surgery have long been the main procedures to cure cancer. Nevertheless, the drawbacks of these conventional therapies, mostly toxicity, resistance, and tumor heterogeneity, culminate in the pressing need for new, as well as more potent alternatives. Because of their various bioactive chemicals and multi-target mechanisms, natural products, especially those derived from plants, have shown great promise as cancer treatments. Natural phytochemicals regulate oxidative stress, cell cycle, apoptosis, metastasis, angiogenesis, and epigenetic changes and demonstrate strong anticancer effects. Compounds including vincristine, quercetin, and paclitaxel have been verified in clinical studies, demonstrating their promising activities as adjuvants and chemotherapeutics. Even with encouraging outcomes, problems including complicated regulatory pathways, poor bioavailability, and unstable formulations still exist. But developments in pharmacogenomics, AI-driven compound discovery, and nanotechnology are transforming personalized medicine and natural product research. In order to harness nature's pharmacological arsenal for safer and more effective cancer medicines, future strategies should concentrate on integrating omics technologies, improving clinical translation, and building regulatory frameworks.

Cancer is a disease due to genetic mutations primarily in somatic cells which leads to abnormal cell growth, forming a subset of neoplasm and may spread to other body parts. This may lead to tumor formation, a collection of mass or lump which spreads diffusely (Saini et al., 2020). In 2020, approximately 10 million people died due to cancer and nearly 19.3 million new cancer cases were reported (excluding nonmelanoma skin cancers). Female breast cancer was at the top with almost 2.3 million (11.7%) new cases, surpassing lung cancer (11.4%), followed by colorectal, prostate, and stomach cancers with 10, 7.3, and 5.6% new cases, respectively (Sung et al., 2020). In 2022, almost 9.7 million people died due to cancer and approximately 20 million new cases were reported (including NMSC). The estimations propose that, in a lifetime, about 1 in 5 women or men face cancer, while about 1 in 12 women and 1 in 9 men die due to cancer (Bray et al., 2024).

For many decades, only a few treatment options like surgery, chemotherapy, and radiation therapy (solely or in combination) were used to treat cancer (Roy & Li, 2016). However, due to cell's resistance against these therapies, such as chemotherapeutic drugs (paclitaxel and cisplatin), make them less effective. Furthermore, severe side effects of these treatments like neuropathy, myelosuppression, and cardiotoxicity further reduce their efficiency, impacting life of the patient. Moreover, cancer's ability to evade therapy and its heterogeneous nature, such as immune evasion and tumor heterogeneity, further present challenging hindrances. To overcome these limitations of

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conventional therapies, there is growing interest to explore the nature as a potential therapeutic alternative to treat cancer. Natural products consist of vast bioactive compounds having structural diversity and pharmacological properties offering solutions to limitations posed by conventional therapies (Cotino-Nájera et al., 2023).

The history and contextual exploration of plant species to treat cancer can be traced back to the Ebers papyrus in 1500 BC. However, early on 20$^{th}$ century, work began to explore natural plant-derived anti-cancer molecules for modern drug development systematically (Khan et al., 2019). For instance, for the past 4,000 years, marijuana (*Cannabis sativa*) and poppy (*Papaver somnniferum*) have been used as a medicine (Calixto, 2019). The event that opened new doors for exploring herbal medicines was the isolation of alkaloid morphine from poppy in 1806, caffeine from *Coffea arabica* in 1820, codeine from poppy in 1824, atropine from *Atropa belladonna* in 1831, and digoxin from *Digitalis lanata* in 1869. Natural compounds are beneficial as they do not pose adverse effects and can battle carcinogenesis via affecting its various signaling pathways. That's why in the last 40 years, only 29 out of 240 approved antitumor drugs were synthetic drugs. Additionally, synthetic compounds along with pharmacophores from natural sources mimicking natural products have been approved as antitumor drugs for the past 10 years. Phytochemicals such as leucovorin (in 1950), carzinophilin (in 1954) and actinomycin D (in 1964) were among the first antineoplastic drugs discovered in beginnings of cancer research (Newman and Cragg, 2020). The current chapter discusses the role of natural products in cancer treatment and prevention.

## CLASSIFICATION OF ANTICANCER NATURAL COMPOUNDS

Natural products, having anti-cancerous properties, are extracted from diverse sources and are classified into different types on the basis of their structure (Figure 1).

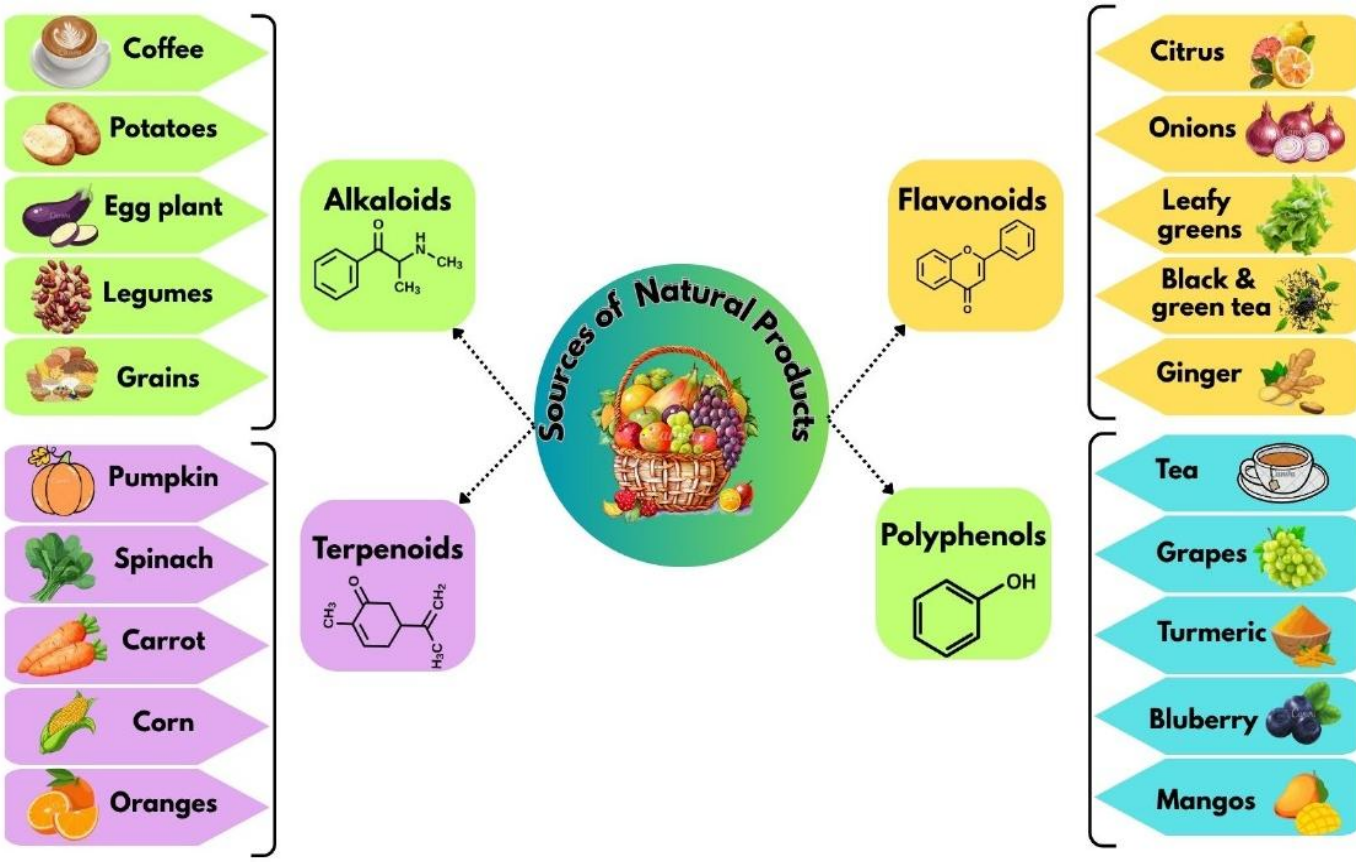


**Fig 1.** Classification and sources of natural products

## Alkaloids

Alkaloids are secondary metabolites that consist of a nitrogen ring, which makes them unique and responsible for their therapeutic and biological activities. In 1950s, Robert Noble and Charles Beer accidentally discovered the first alkaloid from *Catharanthus roseus* that was used in cancer treatment (Banyal et al., 2023). These compounds do not directly kill cancer cells, but their anti-tumor mechanisms involve autophagy, cell apoptosis, necrosis, cell cycle arrest, and also the inhibition of cell growth, cell proliferation, differentiation, migration and invasion. Furthermore, to resist cancer, alkaloids can also modulate immune response and mechanisms. Vinblastine and vincristine are dimeric indole alkaloids that are the most promising compounds of numerous commercially available chemotherapeutic drugs for breast cancer, lymphosarcoma, reticulum, leukemia, lung cancer, sarcoma and Hodgkin's disease (Aslam et al., 2010).

## Flavonoids

Flavonoids are polyphenols having a basic flavan structure of 15-carbon phenylpropanoid chain, forming two aromatic rings and connected via heterocyclic pyran ring (Kopustinskiene et al., 2020). They show anticancer properties such as affecting initiation and elevation stages of cancer, arresting cell cycle, inducing apoptosis via encouraging tumor suppressor genes, discouraging proto-oncogenes and many other cancer-promoting factors (Tiwari et al., 2019). Flavonoids such as hesperidin and genistein are capable of upregulating tumor suppressor genes (e.g., JNK and BAX) and downregulating BCL-2 and other proto-oncogenes, which leads to apoptosis via inhibiting cell proliferation and cell survival (Lee et al., 2019). Quercetin, luteolin, kaempferol, apigenin, genistein, hesperidin, ellagic acid, epicatechin, delphinidin, naringenin, daidzein, and epigallocatechin gallate are some flavonoids belonging to different classes of flavonoids which have been proven to show anticancer properties (Montané et al., 2020).

## Terpenoids

Terpenoids are the largest class of Natural compounds consisting of 5-carbon isoprene units, further classified on the basis of differential structure including monoterpenoids, diterpenoids, triterpenoids, hemiterpenoids, sesquiterpenoids, tetraterpenoids, polyterpenoids classes and sesterterpenoids (Huang et al., 2012). Along with each subclass, having a unique and diverse set of biological properties, terpenoids also possess anticancer activities by targeting various interconnected stages involved in cancer development like cell death, cell proliferation, angiogenesis, and metastasis (Luo et al., 2019). The anticancer mechanisms of terpenoids involved in cell death and epigenetic modifications target NF-κB, JAK-STAT, activator protein-1 (AP-1), metalloproteinases (MMPs), DNA topoisomerase I and II, ER blocking, p53 activation, proteasome inhibition, calcium ATPase pump activity, and promoting modulation in DNA minor grooves (Ghantous et al., 2010).

## Polyphenols

Polyphenols belong to the diverse group of natural compounds characterized by the presence of more than one phenolic ring and can further be categorized into several subgroups like lignans, stilbenes, and phenolic acids, with each subgroup possessing specific biological and therapeutic properties (Durazzo et al., 2019). They are abundantly present in plants, predominantly in fruits like grapes and berries, vegetables, beverages like wine and tea, and also in nuts. Polyphenols possess anticancer activities via modulating various cancer-related mechanisms such as induction of apoptosis via modulating various signaling pathways, antioxidant activity during cancer treatment, and angiogenesis inhibition (Jenca et al., 2024). *In vitro* studies suggest that they demonstrated more anticancer capability than other natural products via modulating NF-kB and Nrf2 activation, and influencing the function of PI3K and MAPK in cancer cells, hence controlling cancer cell progression (Sharma et al., 2022). Resveratrol, for example, a stilbene present in grapes, has been studied and demonstrated as an anticancer agent via inhibiting cell proliferation and apoptosis induction in various cancer cell lines (Jenca et al., 2024). Moreover, the synergistic properties of polyphenols with other conventional cancer therapies propose a promising advantage over individual drug value, opening a gateway for developing more drugs with

greater efficacy to entangle the cancer (Sharma et al., 2022).

## MECHANISTIC INSIGHTS INTO ANTICANCER PROPERTIES

### Cell cycle arrest and apoptosis induction

In normal cells, activities of cyclins are strictly controlled by transcription factors specific to various processes such as several CDK inhibitors, cell cycle, and protein degradation. In tumor cells, however, their uncontrolled regulation leads to abnormal cell division and cell growth. Therefore, targeting cyclins in tumor cells is considered an encouraging anticancer strategy (Suski et al., 2021). There are several plant-derived natural products that are capable of causing eventual cell death by arresting the cell cycle progression in tumor cells. Quercetin can stop the cell cycle in S phase, an ultimatum towards apoptosis induction in cancer cells, particularly in breast cancer (Zhang et al., 2024). In ovarian cancer, treatment with honokiol, another natural product, results in cell cycle arrest at sub-G0/G1 phase. The cell proliferation in canine memory carcinoma cell lines is inhibited by paclitaxel, which also causes cell cycle arrest at G2/M phase. Capsaicin in MDA-MB-231 cell line associated with triple-negative breast cancer, reduces the cancer cell viability via decreasing the CDK8 expression, and also induces the cell cycle arrest at G2/M phase. Moreover, in combination therapy, resveratrol causes cell cycle arrest at the G2/M phase through the upregulation of cell cycle inhibitors like p27 and p21, and tumor suppressor p53. Nobiletin and its metabolites show antitumor activity via modulating several pathways, like overexpression of cyclin D1, CDK1, CDK4, CDK6, p21, caspase, and Bax, in addition to PARP, ultimately results into cell cycle arrest and apoptosis (Sun et al., 2019).

Apoptosis, the controlled cell death, is triggered by the involvement of cell-surface death receptors like Fas by their ligands (the extrinsic pathway) or by the permeabilization of mitochondrial outer membrane by pro-apoptotic proteins of the BCL-2 family (the intrinsic pathway). The final cell death in the so-called execution phase of apoptosis is caused by a family of proteases called caspases, which are activated by both pathways (Lossi, 2022). Cancer results from apoptosis being deregulated. Therefore, looking for a method to cause this activity in cancer cells may help prevent the growth and development of cancer. Natural compounds generated from plants and plant extracts are very promising options for anticancer treatments. For instance, the most potent anticancer impact on colorectal cancer cells has been demonstrated by the hot water extract of *Melissa officinalis*. This natural compound hinders the ability of cells to migrate, reduces cell proliferation, and is responsible to initiate caspase-dependent apoptotic cell death. In human bladder cancer cell lines, another triterpene compound xanthoceraside causes cell death by inhibiting the PI3K/Akt/Bcl-2/Bax signaling pathway (Chai et al., 2021). By altering the expression of Bcl-2 family proteins, triggering caspases, and focusing on different signaling pathways like NF-κB, PI3K/Akt, and MAPK, curcumin has validated anticancer benefits across a variety of cancer types. In cancer cells, this natural compound triggers the initiation of both extrinsic and intrinsic apoptotic pathways (Jenca et al., 2024). β-Peltatin, another natural compound which is persuasively cytotoxic in nature with respect to its role in cancer suppression. Pancreatic cancer cells are first arrested at the G2/M phase by β-Peltatin, which then induces apoptosis. β-Peltatin dramatically inhibits the development of BxPC-3 cell xenografts that are subcutaneously implanted. Cell cycle arrest and cellular death are regularly caused by β-Peltatin through the up-regulation of cyclin B1 and p-Histone H3 (Ser10) and the downregulation of proteins that are associated in G2/M phase control and apoptosis suppression (Wu et al., 2023).

### Antioxidant and anti-inflammatory effects

In the microenvironment of chronic inflammation, the macrophages prevailed mostly. To battle infection, those macrophages along with other leukocytes produce bulky amounts of NOS and ROS. Nonetheless, the persistence of these infection-combating chemicals is harmful in an environment of ongoing tissue damage and cellular proliferation. Mutagenic substances, such as peroxynitrites, which react with DNA and induce mutations in proliferating stromal and epithelial cells, may be produced by them. To worsen DNA

damage, macrophages along with the T-lymphocytes, may release macrophage migration inhibitory factors and tumour necrosis factor-alpha (TNF-α). The impairment of p53-dependent protective responses is caused by the migration inhibitory factor; therefore, this leads to the buildup of oncogenic mutations. Additionally, migration inhibitory factor interferes with the Rb-E2F pathway, which leads to carcinogenesis (Singh et al., 2019). There are several polyphenolic compounds like curcumin, quercetin and resveratrol that possess anti-inflammatory and antioxidant properties, thus helping to overcome the side effects of the conventional cancer therapies. They can scavenge free radicals directly by giving them a hydrogen atom through the presence of OH groups, or indirectly by inhibiting the production of ROS or inducing the Nrf2 pathway (Stepanic et al., 2015).

Natural compounds such as berberine are well known for their antioxidant and anti-inflammatory actions. According to research, Berberine can stop breast cancer cell lines from migrating when they sustain scratches, as well as inhibit TNF-α and IL-6 expressions. The progression of breast cancer is hampered by increased expression of these cytokines (Zhao & Zhang, 2020). Another anti-inflammatory substance that prevents T cells from releasing pro-inflammatory cytokines is resveratrol (Malaguarnera, 2019). Resveratrol targets a major component of T cells called Th17. Resveratrol inhibits the activation of the NF-kB pathway by reducing the acetylation of p65/RelA through the activation of sirtuin-1. Moreover, STAT3 deacetylation instigated by active sirtuin-1 might avert the activation of retinoid orphan receptor gamma t (RORγt) and IL-17 synthesis (Delmas et al., 2020). Due to RORγt inhibition of Th1 differentiation, the Th1/Th2 balance is shifted in indulgence of anti-inflammatory (Th2) and immunoregulatory (Treg) responses. Additionally, resveratrol treatment also results in amplified M2 macrophage levels, which are anti-inflammatory. By blocking NF-kB and COX-2 signaling and inflammasome activation as well, LPS-tempted macrophage activation and resveratrol averts (Malaguarnera, 2019). The antioxidant activities of Epigallocatechin gallate (EGCG) make it an auspicious anti-inflammatory and anticancer agent. It alters the expression of NF-κB, ERK, and MAPK, signaling proteins, ROS, and triggers apoptosis and Nrf2/Keap1 signaling. Similar to other flavonoids, EGCG disturbs Nrf2, which inhibits inflammation and oxidative damage (Neganova et al., 2021).

## Inhibition of Angiogenesis and Metastasis

Because angiogenesis and metastasis are closely related, inhibiting angiogenesis may also have an impact on metastasis. Thus, focusing on vital proteins inhibiting both metastasis and angiogenesis might be a unique way to treat cancer cells and increase their effectiveness (Prome et al., 2024). To delay the spread of cancer, various researchers propose that natural compounds can precisely target pathways concerning metastasis and angiogenesis, and bind firmly with a variety of proteins. The four most important proteins which are highly significant in angiogenesis and metastasis, are matrix metalloproteinase-2 (MMP-2), metalloproteinase-9 (MMP-9), basic fibroblast growth factor (bFGF) and vascular endothelial growth factor D (VEGF-D). VEGFD is a strong angiogenesis factor that encourages malignancy, whereas bFGF expression is linked to the growth and further prognosis of cancerous tumors. The cancer cells' growth, their invasion and ultimate metastasis are affected by both proteins MMP-2 and MMP-9. Despite having structural similarities, MMP-2 and MMP-9 together contribute significantly to carcinogenesis. Every one of these proteins is essential for the angiogenesis and metastatic pathways of cancer (Song et al., 2021). Among the most promising natural substances that bind with these target proteins to inhibit angiogenesis and carcinogenesis are quercetin, homoharringtonine, viniferin, and protopine (Prome et al., 2024). *Azadirachta indica* produces terpenoids (primarily lupeol) which dock to the AKT binding pocket and suppress the production of pro-angiogenic mRNAs, MMP2, HIF-1, and VEGFR (Akinloye et al., 2021). Polyphenol Curcumin inhibits the p38 MAPK pathway as well as HIF-1α, which in turns down-regulates VEGF (Lv et al., 2020). Apigenin was also demonstrated to reduce TGF-β-induced VEGF expression by downregulating the FAK/Src/Akt pathway and preventing the nuclear translocation as well as phosphorylation of Smad2 and Smad3 (Mirzoeva et al., 2014).

## Epigenetic Modulation and Gene Regulation

DNA methylation on CpG islands, acetylation and deacetylation of the histone protein and remodeling of chromatin materials are examples of epigenetic alterations that regulate transcription through the spatiotemporal regulation of transcription factors (Mancarella & Plass, 2021). Disturbances in these epigenetic modifiers (responsible for loss or gain of function) frequently result in significant phenotypes that may be predisposed to cellular memory loss and, in turn, to the mechanism of carcinogenesis. Recently, compounds (epidrugs) that work specifically for one or more epigenetic modifiers have been used in the treatment techniques that target the epigenome. In fact, some specific epidrugs have already received approval and are being used in clinical settings to treat cancer with chemotherapy (Khan et al., 2021). Curcumin inhibits the particular DNMTs in cancer cells that are in charge of DNA methylation along with hypomethylation-mediated oncogene activation. Additionally, it suppresses the expression of tumor-suppressive (miR-29a, miR-181b, miR-16, miR-34a, and miR-15a) and oncogenic (miR-19a and miR-19b) miRNAs, as well as histone acetyltransferases (HATs) and histone deacetylases (HDACs), which are in charge of histone modifications (Fabianowska-Majewska et al., 2021). By preventing lactylation of a histone linked to metabolic stress, the triterpene anti-tumor drug demethylzeylasteral (DML) inhibited the growth of liver cancer stem cells (LCSCs). Mechanistically, the rise in H3 histone lactylation effectively aided the development of hepatocellular carcinoma (HCC), whereas DML resisted. DML blocked two histone modification sites that were reported to promote tumorigenesis: H3K9la and H3K56la (Pan et al., 2022). Natural compounds such as ginkgetin, shikonin, icaritin, triptolide, resveratrol, hypericin, ginsenosides, baicalin, berberine, artemisinin, and apigenin block the MYC oncogene, a key pathway to carcinogenesis that causes a number of malignancies (Chan et al., 2024). Different natural products exhibit distinct anti-cancer mechanisms (Table 1). Figure 2 presents the impacts of natural products on tumor cells.

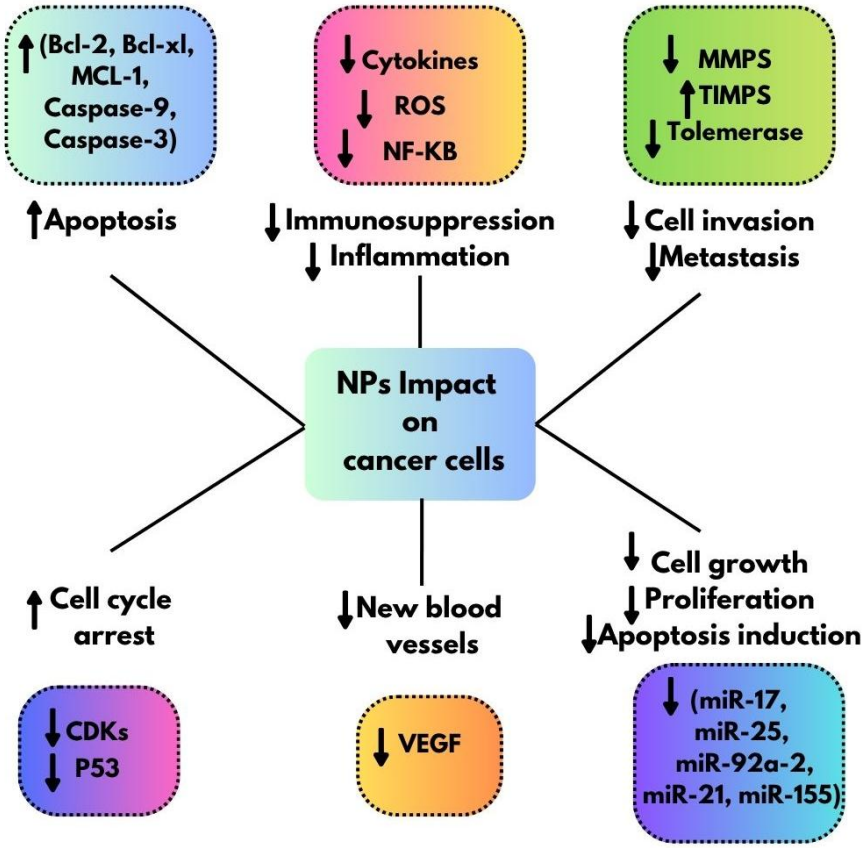


**Fig 2.** Impacts of natural products (NP) on cancer cells

**Table 1.** Natural products and their anti-tumor mechanisms

| Anticancer Compound | Cancer type | Mechanism | Reference |
|---|---|---|---|
| **Curcumin** | Breast cancer | Inhibiting new blood vessel development, reducing tumor progression via downregulating VEGF, inhibiting endothelial cell migration and tube formation | (Ferhi et al., 2019) |
| **Resveratrol** | Liver Cancer | Hinders the development and maturation of new blood vessels, reducing tumor growth and subsequent metastasis via downregulating (VEGF) and inhibiting endothelial cell migration as well as tube formation | (Chanvorachote et al., 2016) |
| **Quercetin** | Breast Cancer | Ominously reduces the Bax expression in MCD-7 cell lines associated with human breast cancer and reduces the apoptosis catalog | (Khorsandi et al., 2017) |
| **Oxymatrine** | Ovarian Cancer | Its expression cleaves Bax and asparaginase 3, mitigates the expression of Bcl-2, instigates further apoptosis, and increases the vulvar scale | (Shanmugam et al., 2017) |
| **Ginsenoside** | Liver Cancer | Cell prolifireation inhibition, apoptosis-induction in HUVECs cells, MMP-2, Wnt/β-catenin/glypican-3 signaling pathway, and VEGF downregulation | (Xu et al., 2024) |
| **Betulinic acid** | Ovarian Cancer | Increases the nuclear condensation, apoptosis in ovarian cancer cell line A2780, and also upsurges the expressions of caspase-3, -8, -9, and Bax, and vice versa for Bcl-2, also induces apoptosis via the mitochondrial pathways | (Lee et al., 2019) |
| **Plumbagin and dihydrotanshinone I** | Liver cancer and prostate cancer | ICD inducers of cancer hepatocytes, ICD induction in prostate cancer, and CRT, ATP release, and encourage pro-inflammatory genes leading to a delay in tumor growth and persistent survival | (Han et al., 2022) |
| **Hinesol** | Pulmonary Cancer | Proliferation induction, apoptosis progression in non-small cell lung cancer cell lines, does so via increasing Bax expression, and constraining the Bcl-2 expression | (Guo et al., 2019) |
| **Atractylenolide** | Gastric Cancer | Provoke apoptosis of human colon cancer HCT-116 cells by endorsing apoptosis-associated genes, amending the Bcl-2 and Bax-associated apoptosis signaling pathway, and also regulating the expression of p-53 and caspase-3 | (Wu et al., 2020) |

## CLINICAL TRIALS AND TRANSLATIONAL RESEARCH

### Plant-Derived Anticancer Agents in Clinical Trials

The supplementation of natural compounds in all phases of clinical trials has been observed, and thus so far, some investigations have given us some clues about the ongoing trends related to these queries. For example, from clinical trial phases I-III, it was seen that there was a consistent rise in natural products and natural product-derived substances (from around 35% in phase I to 45% in phase III), while synthetics showed an inverse trend (from roughly 65% in phase I to 55% in phase III). Moreover, toxicity tests conducted *in vitro* and *in silico* showed that those nanoparticles and their derivatives were less harmful than their synthetic counterparts. These findings emphasize the potential advantages of giving natural products and their derivatives priority as starting points and provide insightful information for effective natural products-based medication development (Ahmed, et al., 2025; Ahmed et al., 2025). Studies on quercetin's pharmacokinetics in humans have revealed that it lowers the incidence of prostate cancer by 27%, according to a clinical case-control study. Moreover, the chemoprevention of prostate cancer can be elucidated by quercetin. A diet high in quercetin is associated with a decreased risk of prostate cancer, according to epidemiologic research, and some *in vivo* animal studies have confirmed quercetin's chemopreventive effect on prostate cancer (Yang et al., 2015). Potential anti-cancer medications called camptothecins have been

authorized for clinical usage and are used to treat breast, liver, small- and non-small-cell lung cancer, and metastatic colorectal cancer (Guo et al., 2022). When used in conjunction with other chemotherapy regimens, paclitaxel enhances response rates, lowers the risk of local tumour recurrence, and raises the possibility of breast-conserving surgery, according to clinical trials on neoadjuvant therapy. According to the KEYNOTE-522 trial, the pathological complete response (pCR) rate increased to 64.8% when pembrolizumab was added to a PTX-based regimen, as opposed to 51.2% when chemotherapy was used alone (Marra & Curigliano, 2021).

The clinical effectiveness of natural compounds, like paclitaxel, demonstrates their potential to enhance or even replace conventional medical treatments. However, their incorporation into traditional treatment regimens requires rigorous clinical testing to determine their safety and effectiveness when used in addition to or instead of synthetic drugs. It is crucial to conduct comprehensive scientific research to determine the safety and efficacy of natural compounds in treating a variety of medical conditions, even if they often have low toxicity and tolerance. To determine the potential benefits and drawbacks of using these natural chemicals as medical treatments, clinical trials are essential. An increasing recognition and acceptance of the advantages provided by natural chemicals in modern medicine is indicated by the ongoing process of integrating and carrying out thorough evaluations (Chunarkar-Patil et al., 2024).

### Challenges in Drug Development and Formulation

Even though laboratories are finding more and more new natural chemicals each year, only a small number of them have been shown likely to have pharmacological potential for clinical trials. Due to their low bioavailability and diminished bioactivity, the majority of bioactive natural products have restricted druggability after extraction (Tang et al., 2023). Additionally, they have a number of disadvantages, such as an unpleasant taste and a pervasive odor, that lower patient compliance. In reality, their weak solubility, slow rate of dissolution and instability at high pH levels further restrict their usage in therapy, resulting in little to no therapeutic impact and requiring huge doses to produce one. Especially, oxidation and degradation process takes place quickly during storage, lessening the active ingredient and consequently, the nutritional worth of plant derivatives (Puglia et al., 2017).

Furthermore, combining chemotherapeutic treatments with less deleterious natural substances, which help tumor management, is consistently becoming a novel approach for tumor treatment (Wu et al., 2023). Combining chemotherapy medications with phytochemicals has been shown in various studies to produce synergistic sensitization, reverse drug resistance, lessen the toxicity burden and adverse effects of chemotherapeutic medications (Xu et al., 2022). Even while combination therapy has advantages over monotherapy, clinical results are still not ideal because two medications used together may have antagonistic effects. As a result, exact control over the mode of administration is necessary to regulate the dosage and timing of each medicine combination (Gao et al., 2022). Combining nanomedicines and natural products can additionally augment therapeutic efficiency, combat drug resistance, and also lessen side effects, resulting in the optimal drug combination. The primary goal of nanomedicine, a primarily new drug delivery method with a size range of 1–1000 nm, is to better balance the toxicity and effectiveness of combination or embedded chemotherapeutic medications. Dendrimers, liposomes, micelles, host-guest supramolecules, inorganic systems, and supramolecules are examples of nanoscale drug delivery systems that have been created for dual or multi-drug co-delivery (Hu et al., 2021).

## FUTURE PROSPECTS AND EMERGING TRENDS

Another leading edge in the manufacturing of medicines derived from plants is synthetic biology. This multi-disciplinary field projects and constructs new biological components, tools, and systems by fusing biology and engineering concepts. Advancement in intricate plant biosynthesis processes in microbial hosts like yeast (*S. cerevisiae*) or bacteria (*E. coli*) is termed as synthetic biology in the perspective of medication manufacturing. Researchers can use these fast-growing microbes' tranquil cultivation and hasty

growth rates to construct useful compounds on an industrial scale via the introduction of the genes needed for the production of plant-derived secondary metabolites into them. For example, scientists have engineered *S. cerevisiae* and *E. coli* strains to produce taxadiene, which serves as a precursor for paclitaxel (Qin et al., 2025). The rapid advancement of sequencing technology has resulted in the public availability of numerous protein and RNA sequences and entire genome sequences through databases such as NCBI and UniProt. The sequences reveal vital information about protein engineering, bioinformatics, genetic engineering and synthetic biology. Scientists use advanced genetic modification techniques to enhance metabolic systems and biosynthetic pathways which results in optimized conditions for producing specific natural products (Wang et al., 2022).

The identification of new phytochemicals is another critical factor to take into account. The modern research process requires both intricate metrics and AI-based data processing systems because these tools enable scientists to find potential bioactive molecules and create detailed models of target component groupings. Scientists have adopted AI methods to study natural products which marks a fundamental shift in their research methods because AI enables them to perform precise compound extraction and to arrange natural products into chemical and medical classifications and discover new compounds. Natural microtubule inhibitors, for instance, ixabepilone and paclitaxel have been important examples of natural product success in drug discovery in the anticancer therapy arena. Other β-microtubule inhibitors, containing bruceine D, V, and eleutherobin, have recently been discovered using DL models, emphasizing the prominence of DL in the discovery of powerful natural product-based medications. Nonetheless, there is impendence for advancement via successive initiatives. Enhancing hit recognition and reducing cold start problems may be achieved by pre-training DL models on larger chemical spaces and enlarging training data sets to contain more varied compounds. Moreover, generative models offer an innovative alternative to directed message passing neural networks (DMPNN), allowing for the creation of new molecular structures outside of known chemical space (Jia et al., 2022). Pharmacogenomics and personalized medicine developments present substantial opportunities for phytochemical safety evaluation and dosage optimization. Genetic variations may alter these substances' therapeutic effects and possible toxicity by affecting their absorption, distribution within organs, metabolism within the body, and excretion. Finding genetic markers that are responsible for predisposing people to particular reactions to phytochemicals is made easier by the combination of pharmacogenomic profiling and genomic data. This method not only improves dosage accuracy but also lowers the possibility of toxicities and adverse reactions, increasing therapeutic efficacy on a patient-by-patient basis (Hussain et al., 2022). Additionally, the combination of transcriptomics, proteomics, and metabolomics has transformed the research on natural products by revealing systems-level insights into the intricate interactions between cellular processes and phytochemicals (Liang et al., 2024).

In order to recruit the safety of anticancer medicines concentrated on natural compounds, regulatory concerns have become decisive. Regulatory bodies should verbalize explicit guidelines for their development, clinical testing, and registration procedures while taking into account the specific traits and means of action involved. Systems for pharmacovigilance and post-marketing surveillance should also be put in place to keep an eye on the long-term efficacy and safety of treatments based on phytoconstituents. Regulations and guidelines for the registration and post-marketing monitoring of plant-based medications and products based on phytoconstituents have been established by regulatory bodies such as the FDA and EMA (Romes et al., 2021).

Research into phytoconstituents as an anticancer agent has a bright future. To promote more advancement in this field, researchers must combine modern science and traditional medicine, investigate emerging trends and technologies, deal with issues of intellectual property, market access and commercialization, and take standardization and regulatory considerations into account. With more innocuous, more operative, and customized therapeutic alternatives derived from nature's pharmacopoeia, such discoveries might enable a revolutionary shift in the treatment of cancer.

## CONCLUSION

A model change in oncology is embodied by the integration of natural compounds into cancer treatments. Plant-derived constituents, including alkaloids, flavonoids, terpenoids, and polyphenols, provide multi-embattled approaches to address the complexity of cancer, portraying centuries of traditional therapy and supported by modern scientific evidence. These natural products prevent tumor growth by mechanisms such as cell cycle arrest, angiogenesis inhibition, apoptosis induction, and epigenetic modulation, and also have a lesser safety profile than many synthetic medications. Growing data from preclinical research and clinical trials support their preeminence as adjuvants to conventional treatments as well as individual medicines. But there are still a number of issues, like lower bioavailability, unhinged formulation, and regulatory barriers.

Advances in pharmacogenomics, nanotechnology, and AI-abetted drug discovery provide new opportunities for maximizing the dosage, improving medication transport, and customizing treatment for each patient in order to resolve these problems. Furthermore, turning these chemicals into efficient, standardized, and widely available cancer treatments will require interdisciplinary cooperation that combines traditional knowledge with state-of-the-art research. Natural products are potentially extremely important compounds in the prevention and treatment of cancer in the future, provided that they are continuously innovated and thoroughly evaluated.

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