

APPLICATIONS OF PHYTOCHEMICALS IN CANCER THERAPY

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ABSTRACT

Since cancer is still one of the main causes of illness and death worldwide, new, safer, and more effective treatment approaches are needed. Targeting several oncogenic pathways, including as apoptosis induction, angiogenesis inhibition, metastasis suppression, and immunological modulation, phytochemicals—bioactive substances derived from medicinal plants—have shown encouraging anticancer activities. Alkaloids (vincristine, camptothecin), flavonoids (quercetin, genistein), terpenoids (paclitaxel, artemisinin), and polyphenols (curcumin, resveratrol) are among the most researched phytochemicals. They have strong anticancer effects by inducing DNA damage, inhibiting survival signaling pathways (NF-κB, MAPK, PI3K/Akt), and modifying oxidative stress. Despite these encouraging therapeutic qualities, drug resistance, fast metabolism, and low bioavailability limit the clinical application of phytochemicals. The review suggests novel treatment approaches that combine the best features of conventional medical systems.

KEYWORDS: Apoptosis, Chemoprevention, Drug Resistance, Targeted Therapy, Natural Products, Phytochemicals, and Cancer Therapy.

INTRODUCTION

The World Health Organization (WHO) estimates that cancer accounts for almost one in six deaths globally. Cancer is a broad category of illnesses marked by the unchecked growth of so-called cancer stem cells, which can produce a population of malignant cells that can spread to an entire organ or, in the worst situations, to other tissues, creating metastases.^[1,2] The WHO has determined that random somatic mutations, reactive oxygen species (ROS), ionizing radiation, and chemical and biological agents are the most frequent causes of malignant transformation of cells among the many potential explanations underlying this abnormal cell activity.^[3]

Surgery, immunotherapy, radiation, chemotherapy, photodynamic treatment, or a combination of these are some of the therapeutic options that suffer from poor bioavailability, rapid clearance, rapid evolution of drug resistance, and adverse effects due to lack of specificity. Several approaches, such as the creation of inactive prodrugs or the integration of the active ingredients into delivery systems, have been studied to boost the effectiveness of traditional anticancer medications and reduce their toxicity to healthy cells, opening the door to actively targeted therapies.^[4]

After cardiovascular illnesses, cancer is the most common disease and has become a significant health

concern. Approximately 18 million new cases of cancer were reported worldwide in 2018; by 2030, this figure is predicted to rise to over 23 million new cases per year.^[5] Chemotherapy is successful, but it has significant drawbacks, including cancer cells chemoresistance, recurrence, and damage to healthy cells, all of which lower quality of life. As a result, a lot of people use complementary and alternative medicine (CAM).^[6]



Globally, there were about 10 million cancer-related deaths and 19.3 million new instances of cancer in 2020. Breast cancer accounted for the majority of new instances, with lung, colon, prostate, skin, and stomach cancers following.^[7]

Several approaches, such as the creation of inactive prodrugs or the integration of the active ingredients into delivery systems, have been studied to boost the effectiveness of traditional anticancer medications and reduce their toxicity to healthy cells, thereby paving the way for actively targeted therapies. However, research into alternate sources, particularly plants, has been prompted by the urgent need for new and more potent chemicals for cancer treatment.^[8,9]

PHYTOCHEMICALS

Plants naturally contain bioactive substances called phytochemicals. Polyphenols, alkaloids, flavonoids, and terpenoids are only a few of the many adaptable substances that make up phytochemicals. As seen in Figure 1, these bioactive compounds can be used in anticancer therapy because they can specifically control cellular processes.^[10,11]

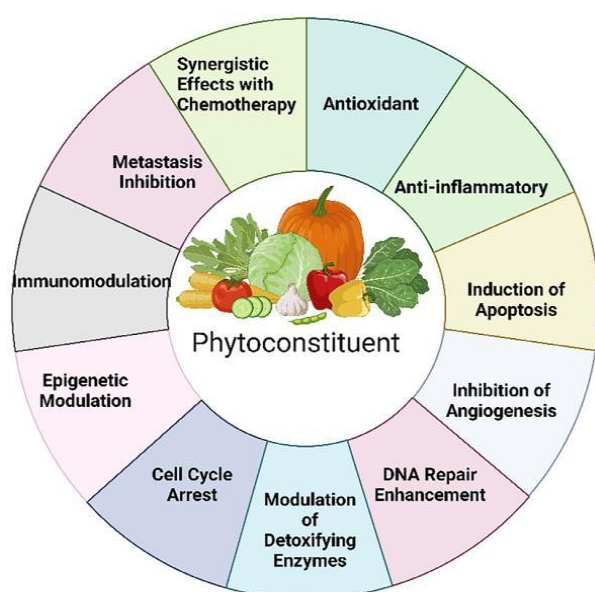


Figure 1: Phytochemicals have a variety of biological effects, such as direct effects on antioxidant activity, anti-inflammatory processes, apoptosis induction, angiogenesis inhibition, DNA repair enhancement, detoxifying enzyme modulation, cell cycle arrest, immunomodulation, epigenetic modulation, and metastasis inhibition. They also help create synergistic effects when combined with chemotherapy.

The development of phytochemical based anti-cancer agents involves the extraction, separation, and purification of different compounds. The separated compounds are further tested on various cell lines in vitro and in vivo. The traditional knowledge that involved the selection of plants, collection methods, preparation of drugs, and their use was passed on from generation to generation. The drugs were used in various forms, such as teas, powders, formulations, decoctions, etc.^[12,13]

The phytochemicals efficiently target a variety of malignancies and reduce their intensity by minimizing their hallmarks. The phytochemicals' chemoprotective effects are achieved by altering the cancer-related nutrient signaling pathways. Because they target several pathways and show synergistic efficacy when paired with current medications, phytochemicals hold promise in oncology.^[14] However, more investigation and clinical validation are required to determine the effectiveness of reaching full potential and deeper integration in creating all-encompassing cancer care methods. Stronger cross-disciplinary and cross-sectoral collaborations are necessary to achieve this goal.^[15,16]

The development of phytochemicals as anticancer medicines is still difficult, despite their potential. These naturally occurring bioactive substances have favorable safety profiles, multimodal activities, and the potential to be useful in the treatment of cancer.^[17] Innovative strategies must be continuously developed to address the rising incidence of cancer. When combined with traditional treatments, bioactive phytochemicals can open up new avenues in oncology. Accelerating progress toward lessening the impact of cancer on people and society requires effective collaboration between researchers and health professionals at all levels, legislators, and patient organizations.^[18] As a result, phytochemicals play an important part in cancer treatment. Because they are naturally occurring substances, they present a potentially safer and less hazardous substitute for traditional therapeutic practices, which could improve patient quality of life and treatment efficacy. In order to achieve complete clinical validation, future research should concentrate on resolving current issues and improving treatment regimens. Utilizing phytochemicals to their fullest capacity could greatly aid in the battle against cancer, offering people all across the world new treatment options and hope.^[14]

vital resource for the creation and identification of novel, powerful medications is phytochemicals.^[19] DNA damage, cell cycle obstruction, apoptosis, and changes in signaling pathways are some of the consequences.^[20] Many plant-based anti-cancer drugs, including vincristine, taxol, paclitaxel, derivatives of camptothecin, chinconine, etc., have been approved for usage.^[21] Curcumin, which comes from the roots of *Curcuma longa* L., has been proven in numerous studies to have anticancer properties by causing apoptosis, which stops cancer cells from proliferating and causes cell cycle arrest in a variety of cancer cell lines.^[22] In a number of in vivo studies, several organosulfur components derived from the *Allium sativum* L. plant, such as S-allylcysteine, exhibit tumor growth retardation.^[23] Green tea's epigallocatechin-3-gallate (EGCG), a crucial phytochemical, has antimicrobial and anti-cancer properties. Alkaloids like vinblastine and vincristine, which are utilized in the present treatment of several cancer types, including breast cancer (BC), lung cancer,

lymphomas, and leukemia, are abundant in the *Catharanthus roseus* (L.) plant.^[24] *Gymnema sylvestre* is the source of gymnemagenol, which exhibits encouraging anti-cancer potential against hepatic cancer cell lines. Gymnemagenol demonstrated an IC₅₀ value of 37 g/m in the MTT assay, which was used to assess the phytochemical's anti-proliferative action against HeLa cell lines.^[25] In a different investigation, baicalein, which was extracted from *Oroxylum indicum*, demonstrated an anticancer effect on human cancer cell

lines by preventing the growth of the HL-60 cell line.^[26]

CLASSIFICATION

Lignans, alkaloids, terpenes, phytoalexins, triterpenes, steroids, stilbenoids, bibenzyls, phenols, flavonoids, and other compounds make up the majority of secondary metabolites. It is well known that the most common and structurally varied phytochemicals are phenols. The phytochemical classification is shown in Figure 2.

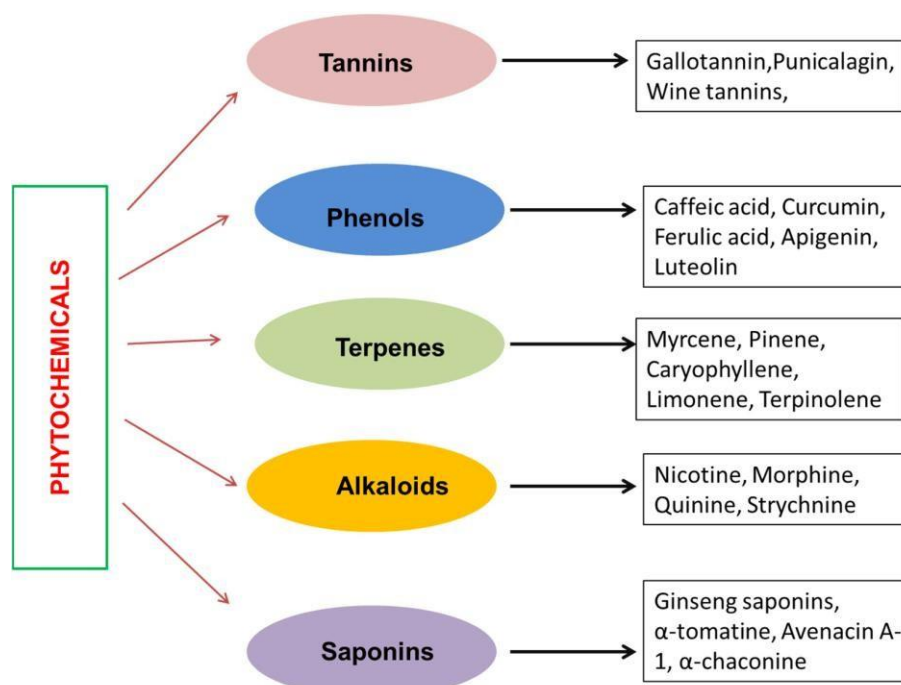


Figure 2: The diverse phytochemicals originating from plant sources are distinguished into five major classes based on their chemical structure and properties. The figure illustrates the different classes and gives examples of each type.

1. Phenolic Compounds and Their Role in Cancer Management

The main constituents of phytochemicals that are extensively dispersed across the kingdom of plants are phenolic compounds. As secondary metabolites, they support defensive mechanisms. Phenolic compounds also have several positive effects on people; their antioxidant qualities are often seen as a major advantage for people in this age of illness. The three main categories of dietary phenolics are flavonoids, phenolic acids, and polyphenols. Aglycones, glycosides, and methylated derivatives are common forms of flavonoids, a broad class of phenols.^[27]

FLAVONOIDS

It has been established that hundreds of flavonoids, including those in fruits, vegetables, tea, and coffee, are widely present in our diet. Since ancient times, flavonoids have been effectively employed to cure a variety of illnesses, and their use continue today. Flavonoids are further categorized as mono-, di-, and oligo-glycosides and typically occur in conjugation with

sugars. Flavonoids are becoming more well-known because of their impact on a range of pharmacological and biological processes. Some effects exerted on biological functions include cytotoxic effects against cancer cell lines, anti-tumor effects, anti-inflammatory effects, and anti-microbial effects. In addition to its medicinal benefits, the class of phytochemicals is well-known for having strong antioxidant properties, which are essential for defending against the damaging effects of reactive oxygen species (ROS) and free radicals.

PHENOLIC ACIDS

The phenolic acids, which include hydroxylbenzoic acid (HBA) and hydroxycinnamic acid (HCA), are widely dispersed and form a variety of groups. They also have a single carboxylic acid functional group. Simple esters with a glucose or hydroxycarboxylic acid group attached are known as HCAs. The presence of hydroxylated aromatic rings distinguishes the distinct molecular structure of the phenolic chemicals that plants make.^[33] The substances are well-known for their antioxidant qualities, which guard against oxidative damage from

ROS and are therefore essential in the development of cancer, cardiovascular diseases (CVDs), neurodegeneration, and many other conditions. These substances target cancer cells because they produce more ROS than healthy cells do.^[34]

Additionally, their capacity to suppress cell proliferation

(extracellular signal-regulated kinase (Erk)1/2, D-type cyclins, and cyclin-dependent kinases (CDKs)), angiogenesis (vascular endothelial growth factor (VEGF) and MIC-1), oncogenic signaling cascades (phosphoinositide 3-kinase (PI3K) and protein kinase B (Akt)), induce apoptosis, and stop cellular migration and metastasis are linked to their anticarcinogenic effects.

PHENOLS	SOURCE	ANTICANCER ACTIVITY	CANCER TYPE
Quercetin	Onions, Apples, Tea	causes apoptosis, inhibits PI3K/Akt/mTOR signaling, and increases Chemosensitivity. ^[28]	Prostate, breast, lung, colon, liver, ovarian, and blood cancers.
Genistein	Soybeans, Legumes	decreases hormone-driven malignancies by blocking tyrosine kinases and estrogen receptors. ^[29]	Breast, prostate, colorectal, and ovarian cancers.
Apigenin	Parsley, Celery, Chamomile	Suppresses angiogenesis and metastasis by downregulating VEGF and MMPs. ^[30]	Liver, lung, cervical, breast, colorectal and pancreatic cancers.
Epigallocatechin Gallate (EGCG)	Green Tea	inhibits angiogenesis and metastasis by inhibiting VEGF, COX-2, and MMPs. ^[31]	Ovarian, liver, lung, breast, and cervical cancer.
Luteolin	Green Pepper, Broccoli, Thyme	inhibits the JAK/STAT3 and MAPK pathways and causes ROS-mediated apoptosis. ^[32]	Breast, lung, colon and prostate cancers.
Curcumin	Turmeric	Inhibits DNMTs and HDACs, modulates immune response by affecting cytokines. ^[35]	Breast, lung, colorectal, head and neck and hematological cancers.
Resveratrol	Grapes, Berries	Modulates sirtuin activity, influences histone acetylation and gene expression. ^[36]	Ovarian, skin, lung cancers.
Fisetin	Strawberries, Apples	Induces apoptosis, inhibits NF-κB signaling, reduces cancer cell proliferation. ^[37]	Melanoma and skin cancer.
Gingerol	Ginger	Inhibits caspase-3 Expression. ^[38]	Gastrointestinal cancer.
Thymoquinone (TQ)	Black cumin seed oil	causing gastric cancer cells to undergo apoptosis and inhibiting STAT3 phosphorylation; decreased STAT3 shown decreased JAK2 and c-Src activity. ^[39]	Kidney, cervix, lung, blood and skin cancers.

2. Alkaloids and their role in cancer treatment

Alkaloids are nitrogen-containing heterocyclic chemicals that interact with DNA and cellular microtubules to cause apoptosis, cell cycle arrest, and metastasis suppression. Typically colorless and non-volatile, the chemicals in this group have a minimally harmful impact

on human cells. Alkaloids suppress cancer cells by preventing the topoisomerase enzyme from doing its job, which further halts DNA replication and encourages cell death.^[40] These factors have led to the adoption of alkaloids as a parent molecule in the creation of substances with positive effects on human health.

ALKALOIDS	SOURCE	ANTICANCER ACTIVITY	CANCER TYPE
Vincristine	Madagascar periwinkle plant (<i>Catharanthus roseus</i>)	Tubulin dimer is bound. - Avoids the production of microtubular structures ^[41]	Acute myeloid leukemia (AML, ANLL) Acute lymphoblastic leukemia (ALL) Hodgkin's lymphoma Non-Hodgkin's lymphoma
Vinblastine	Madagascar periwinkle plant (<i>Catharanthus roseus</i>)	stops microtubules from binding via attaching to tubulin. - Induce mitotic death and apoptosis. ^[42]	Cervical cancer Breast cancer Lung cancer Head and neck cancer Hodgkin's lymphoma Testicular cancer
Vindesine	Madagascar periwinkle plant (<i>Catharanthus roseus</i>)	Possess anti-mitotic activity. ^[43]	Melanoma Lung cancers Uterine malignancies
Colchicine	Seeds of autumn crocus (<i>colchicum autumnale</i>)	Microtubule destabilizers alter the way microtubules assemble. ^[44]	Gastric cancer
Colcemid	Meadow saffron (<i>colchicum autumnale</i>)	Mitotic arrest Kinase inhibition. ^[45]	Lung Cancer
Vinflunine	Madagascar periwinkle plant (<i>Catharanthus roseus</i>)	inhibits the transition from metaphase to anaphase and stops cancer cells from going through mitosis. causes apoptosis to increase. ^[46]	Metastatic Urothelial carcinoma Transitional cell carcinoma Breast cancer
Camptothecin	<i>Camptotheca acuminata</i>	causes apoptosis and DNA breaks by inhibiting topoisomerase I. ^[47]	Solid tumors and leukemias.
Irinotecan	Camptothecin derivative	FDA-approved; inhibits topoisomerase for colorectal cancer I. ^[48]	Colorectal cancer
Topotecan	Camptothecin derivative	S-phase arrest is induced; used for cervical, small-cell lung, and ovarian malignancies. ^[49]	Lung, recurrent ovarian and cervix cancer.
Berberine	<i>Berberis</i> species	increases chemosensitivity, inhibits metastasis, and downregulates NF- κ B. ^[50]	Endometrial, esophageal, pancreatic bladder, gastric, ovarian, lung, breast, prostate cancers.

3. Terpenes and their role in cancer treatment

Terpenes are several different types of phytochemicals. Terpenes come from a variety of sources, including flowers, plants, and insects. The chemicals are what give the plants their flavor and aroma. The quantity and arrangement of isoprene units allow us to categorize terpenes. The most prevalent terpenes are the monoterpene myrcene and the sesquiterpenes α -caryophyllene and α -humulene. In cancer cell lines like

breast and colon cancer, myrcene extracts have demonstrated cytotoxic effects. By causing cell cycle arrest and apoptosis, the terpene cp demonstrates cytotoxic potential against ovarian and lung cancer cell lines.^[167,168] The compound shows anti-proliferative effects in a glioblastoma model. -cp at 20 m inhibits the JAK/STAT pathway in osteosarcoma cells, causing proapoptotic and antiproliferative effects.^[51]

TERPENES	SOURCE	ANTICANCER ACTIVITY	CANCER TYPE
Myrcene	<i>Cannabis sativa</i> , mangoes	Effects of cytotoxicity on cancer cell lines Decreased damage to DNA. ^[52]	Oral, breast and colon cancers.
Limonene	Orange, lemon, grapefruits	shown harmful effects causes cell cycle arrest	Breast, liver, lung, stomach, pancreatic, colon and prostate cancers.
		Reduced cancer cell invasion and migration Induction of autophagy and apoptosis suppressing the PI3K/Akt pathway. ^[53]	
Pinene	Essential oils of	decreased vitality of cells.	T-cells tumors, gastric

	conifers, particularly pine trees.	triggered cell cycle arrest, ROS generation, and apoptosis. ^[54]	cancer, melanoma, prostate and ovarian cancers
Elemene	Curcuma wenyujin (rhizome curcumae)	induced apoptosis and cell cycle arrest MAPK pathway inhibition Decreased invasion and migration of tumors Reduced angiogenesis. ^[55]	Non-small-cell lung cancer, glioma and brain cancer
Valencene	Valencia oranges, citrus fruits.	decreased cell division and worked effectively in concert with doxorubicin. ^[56]	Lung and breast cancers.
Nerolidol	Ginger, lavender, tea tree, lemon grass.	Exhibited cytotoxic effects and induced apoptosis and cell cycle arrest. worked in concert with doxorubicin. ^[57]	Bladder, breast, laryngeal, osteosarcoma and colorectal cancers.
Paclitaxel	Taxus brevifolia (Pacific yew tree)	causes apoptosis, mitotic arrest, and microtubule polymerization. ^[58]	Breast, ovarian, AIDS-related Kaposi sarcoma.

4. Tannins and their role in cancer treatment

Tannins are water-soluble, heterogeneous, high molecular weight (500–3000 Dalton) substances that are prevalent in food and drink and found in large quantities in plants.^[91] Because of their high reactivity, they create intramolecular and intermolecular hydrogen bonds with other macromolecules, including proteins.^[59] Condensed tannins and hydrolyzable tannins are the two groups of tannins. Two groups are used to further categorize hydrolyzable tannins. First are the gallotannins, which hydrolyze to produce a sugar and gallic acid (GA); second are the ellagitannins, which

hydrolyze to produce an extra ellagic acid. Condensed tannins, or proanthocyanidins, make up the second class of tannins. Proanthocyanidins are extremely prevalent polyphenols generated from plants.^[60]

These substances do not hydrolyze in the presence of mild acid, in contrast to the hydrolyzable tannins. Nevertheless, they break down and release red pigments known as phlobaphenes in acidic and alcoholic environments. Less focus is placed on the tannins because of their high structural complexity and polymeric nature.^[61]

TANNINS	SOURCE	ANTICANCER ACTIVITY	CANCER TYPE
Tannic acid (TA)	The Sicilian sumac, tara pods (Caesalpinia spinosa), and nutgalls of Rhus semialata or Quercus infectoria	ERK, AKT, and PKB kinases were phosphorylated, causing both intrinsic and extrinsic cell death, and apoptosis induction with a rise in cell population in the sub-G1 phase ^[62-64]	Prostate, breast, head and neck cancers.
Ellagic acid (EA)	berries, nuts, and fruits, notably in raw walnuts, pomegranates, blackberries, yellow raspberries, strawberries, and chestnuts	EA has anti-tumor efficacy against human bladder cancer both in vitro and in vivo. inhibits the invasion, migration, and proliferation of malignant cells. PD-L1 down-regulation and angiogenesis decrease. inhibition of pathways linked to kinases, including PDK3, SPHK, and PI3K/AKT. ^[65-67]	Lung cancer and bladder cancer.
Procyanidins	Apples, berries (blueberries, cranberries, and aronia), nuts, cocoa or chocolate, grapes (and red wine or grape seed extract), cinnamon, and nuts.	time-dependent and concentration-dependent way. caused apoptosis and cell cycle arrest. Cell cycle arrest and apoptosis were induced, and NSCLC cell growth was inhibited. ^[68]	Breast and non-small cell lung cancer.
Green tea catechins	green tea leaves, particularly the tender buds, and several kinds of green tea goods	EGC (epigallocatechin)~EC (epicatechin) > ECG (epicatechin gallate) Growth inhibition of DU145 prostate cancer cells. ^[69]	Lung and prostate cancers.
Epicatechin (Flavon-3-ol monomer units)	Apples (particularly the peel), tea (green and black), cacao beans (dark chocolate, cocoa powder), and other	20% growth inhibition was noted at 20 g/mL of EC. ^[70]	Human bladder cancer.

	berries		
CONCLUSION Cancer is a disease with many problems that is difficult to treat. Chemoresistance, side effects, and cancer reversal are just a few of the many problems with traditional cancer treatments. The creation of more effective medicinal substances with the least amount of toxicity is desperately needed. Phytochemicals can help lessen the effects of cancer when used in conjunction with existing cancer treatment techniques. By altering the cell signaling pathway and triggering apoptosis in the cancer cells, the phytochemicals affect cancer cells. Furthermore, phytochemical research is being revolutionized by AI-driven drug discovery and precision oncology techniques, which make it possible to identify new bioactive chemicals with improved therapeutic efficacy. The potential for incorporating phytochemicals into customized cancer treatments is enormous, notwithstanding regulatory and translational obstacles. The main goals of future studies should be to standardize regulatory frameworks, carry out extensive clinical trials, and improve their formulation. With further development, phytochemicals may be used as safer, more efficient, and targeted substitutes or supplements to current cancer treatments, assisting in the creation of more inventive and long-lasting oncological medicines.		2017; 16: 96–103. [CrossRef] 7. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. <i>CA Cancer J. Clin.</i> 2021; 71: 209–249. [CrossRef] 8. Ioele, G.; Chieffallo, M.; Occhiuzzi, M.A.; De Luca, M.; Garofalo, A.; Ragno, G.; Grande, F. Anticancer Drugs: Recent Strategies to Improve Stability Profile, Pharmacokinetic and Pharmacodynamic Properties. <i>Molecules</i> , 2022; 27: 5436. [CrossRef] 9. Lichota, A.; Gwozdinski, K. Anticancer Activity of Natural Compounds from Plant and Marine Environment. <i>Int. J. Mol. Sci.</i> , 2018; 19: 3533. [CrossRef] [PubMed] 10. A. Kumar, P. N. Kumar, M. Jose, et al., “Major Phytochemicals: Recent Advances in Health Benefits and Extraction Method,” <i>Molecules</i> , 2023; 28: 887, https://doi.org/10.3390/molecules28020887 . 11. P. A. Pawase, C. Goswami, R. Shams, et al., “A Conceptual Review on Classification, Extraction, Bioactive Potential and Role of Phytochemicals in Human Health,” <i>Future Foods</i> , 2024; 9: 100313, https://doi.org/10.1016/j.fufo.2024.100313 . 12. Ogbonna, J.; Kenekchukwu, F.; Attama, A.; Chime, S. Different approaches to formulation of herbal extracts/phytopharmaceuticals/bioactive phytochemicals—a review. <i>Int. J. Pharm. Sci. Rev. Res.</i> , 2012; 16 : 1–8. 13. Fridlender, M.; Kapulnik, Y.; Koltai, H. Plant derived substances with anti-cancer activity: From folklore to practice. <i>Front. Plant Sci.</i> , 2015; 6: 799. [CrossRef] 14. B. P. George, R. Chandran, and H. Abrahamse, “Role of Phytochemicals in Cancer Chemoprevention: Insights,” <i>Antioxidants</i> , 2021; 10: 1455, https://doi.org/10.3390/antiox10091455 . 15. R. D. Riley, L. Archer, K. I. E. Snell, et al., “Evaluation of Clinical Prediction Models (part 2): How to Undertake an External Validation Study,” <i>BMJ</i> , 2024; 384: e074820. 16. K. Goorts, J. Dizon, and S. Milanese, “The Effectiveness of Implementation Strategies for Promoting Evidence Informed Interventions in Allied Healthcare: A Systematic Review,” <i>BMC Health Services Research</i> , 2021; 21: 241, https://doi.org/10.1186/s12913-021-06190-0 . 17. A. Rudzinska, P. Juchaniuk, J. Oberda, et al., “Phytochemicals in Cancer Treatment and Cancer Prevention—Review on Epidemiological Data and Clinical Trials,” <i>Nutrients</i> , 2023; 15: 1896, https://doi.org/10.3390/nu15081896 . 18. M. Sharma, A. K. Bakshi, N. Mittapelly, et al., “Recent Updates on Innovative Approaches to Overcome Drug Resistance for Better Outcomes in Cancer,” <i>Journal of Controlled Release</i> , 2022; 346: 43–70, https://doi.org/10.1016/j.jconrel.2022.04.007 . 19. Akhtar, M.F.; Saleem, A.; Rasul, A.; Baig,	
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