https://doi.org/ 10.33472/AFJBS.6.5.2024. 4909-4956

African Journal of Biological Sciences

Harnessing Plant Bioactive Compounds for Anticancer Therapeutics: A Comprehensive Review

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Article History
Volume 6, Issue 5, 2024
Received: 15 Apr 2024
Accepted: 01 May 2024
doi: *10.33472/AFJBS.6.5.2024. 4909-4956*

Abstract:

Plant bioactive compounds, spanning alkaloids, flavonoids, terpenoids, and polyphenols, hold significant promise as potent and safer anticancer agents. This review explores the diverse range of plant-derived compounds, including alkaloids, flavonoids, terpenoids, and polyphenols, investigating their mechanisms of action, preclinical and clinical evidence, and potential integration into cancer treatment regimens. Alkaloids like vincristine and vinblastine disrupt microtubule formation, inducing mitotic arrest and apoptosis. Flavonoids such as quercetin and epigallocatechin gallate exhibit antioxidant properties and modulate crucial signalling pathways in cancer cells. Terpenoids, exemplified by Texans and isoprenoids, target microtubules are signalling proteins for focused anticancer strategies. Polyphenols like resveratrol contribute to cancer prevention via antioxidant and anti-inflammatory mechanisms. Preclinical evidence underscores their efficacy, with more clinical trials completed for resveratrol than quercetin. Understanding their mechanisms, particularly of compounds like resveratrol and quercetin, sheds light on their specific targets within cancer cells. Exploring plant bioactive compounds presents a promising avenue for innovative and less toxic anticancer therapeutics, aligning with the global imperative to enhance cancer care.

Keywords: Plant Bioactive Compounds, Anticancer Agents, Flavonoids, Alkaloids, Polyphenols, Terpenoids, Anti-cancer mechanism.

1. Introduction

Cancer requires a treatment approach that goes beyond the usual methods due to its complex nature and ability to adapt. In this pursuit of innovative therapeutic solutions, the vast repository of plant bioactive compounds emerges as a beacon of promise, offering a wellspring of novel anticancer agents (1). Within the verdant world of flora lies a diverse chemical arsenal that holds the potential to revolutionize the terrain of cancer treatment. This review embarks on a comprehensive exploration of the multifaceted potential inherent in plant-derived compounds, delving into their current status, intricate mechanisms of action, and the promising prospects, they hold as impactful anticancer therapeutics. The sheer breadth of bioactive compounds residing within plants encompasses an array of chemical classes: alkaloids, flavonoids, terpenoids, and polyphenols, each possessing distinctive properties that make them formidable contenders for anticancer applications (2). Alkaloids, such as vincristine and vinblastine derived from the Madagascar periwinkle, exhibit a remarkable ability to disrupt microtubule formation, inducing mitotic arrest and apoptosis in cancer cells(3). These compounds specifically target the highly proliferative nature of cancer cells, underscoring their precision in cancer therapy. Flavonoids, another class of plant bioactive compounds, exhibit diverse mechanisms of action (4). Quercetin, found in apples and onions, demonstrates antioxidant properties and interferes with signalling pathways crucial for cancer cell survival (5). Similarly, epigallocatechin gallate (EGCG) from green tea modulates signalling cascades, inhibiting proteins like Akt and mTOR that are often dysregulated in cancer cells (6). The multifaceted nature of flavonoids allows them to act on various fronts, contributing to their potential as impactful anticancer agents(7). Terpenoids, including taxanes like paclitaxel, represent a vital component of the plant's chemical repertoire. Paclitaxel disrupts microtubule dynamics during cell division, leading to mitotic arrest and subsequent apoptosis in cancer cells (8). The precision with which taxanes target the cell cycle highlights their potential as potent weapons against cancer (9). Isoprenoids, another class of terpenoids, play a role in post-translational modification of proteins like Ras and Rho, offering a targeted approach to inhibit cancer cell growth(10).

Polyphenols, exemplified by resveratrol, contribute to cancer prevention through antioxidant and anti-inflammatory mechanisms(11). These compounds, found in red grapes and certain berries, showcase a potential for disrupting early stages of carcinogenesis(12). The ability of polyphenols to modulate cellular processes and mitigate oxidative stress positions them as valuable players in the anticancer arsenal (13). This study is aimed at identifying natural bioactive compounds which have been reported to be active against

different types of cancer, the clinical trials that were undergone especially that of Resveratrol and Quercetin, challenges and opportunities in plant based anticancer therapies. The objective of this comprehensive exploration is to meticulously unravel the intricate tapestry woven by these compounds and discern their potential as potent weapons against the relentless adversary that is cancer and to compare the clinical trials of Resveratrol and Quercetin. Understanding the diverse mechanisms through which plant-derived compounds act on cancer cells provides a foundation for their integration into novel therapeutic strategies. As researchers continue to unveil the intricacies of these compounds and their interactions with cancer biology, the promise of a more targeted, effective, and less toxic approach to cancer treatment comes into focus. In the verdant world of plant bioactive compounds, a revolution in anticancer therapeutics is poised to unfold, offering new hope in the ongoing battle against this complex and resilient disease. In this review, we summarize novel studies and viewpoints on the efficacy of Plant bioactive compounds on cancer therapy.

The results of the review showed that mainly clinical trials with Resveratrol and Quercetin completed the trials. Number of trials was conducted in Resveratrol than quercetin. But particularly quercetin was effectively showed anticancer activity against prostate cancer patients (Table 1).

Trial Number	**Years**	**Location**	**Condition (Only Significant for Article)**	**Number Recruited**	**Substance**	**Outcome Measure**	**Status**
NCT00098969	12.2004–12.2012	United States, United Kingdom	Unspecified Adult Solid Tumor Protocol Specific	40	Resveratrol	In plasma, urine and feces, there was an accumulation of Concentration of Resveratrol and its Metabolites. Drug safety was evaluated in Participants.	Completed
NCT00256334	06.2005–04.2009	United States	Colon cancer	11	Resveratrol	Wnt Gene expression was determined.	Completed
NCT00433576	02.2007–09.2014	United States	Adenocarcinoma of the Colon Adenocarcinoma of the Rectum Colon Cancer (Stage I–III) Rectal Cancer (Stage I–III	20	Resveratrol	Pharmacodynamics of Resveratrol are assessed Concentrations of Biomarkers considered	Completed
NCT01476592	11.2011–10.2013	United States	Neuroendocrine Tumor	7	Resveratrol	Tumor biopsy specimens show Notch1 Activation	Completed
NCT01912820	01-01-2014—10-06-2021	Unites States	Prostate cancer	32	Quercetin	Green tea polyphenols, quercetin and their metabolite concentration in blood and prostate tissue Protein and gene expression of COMT in prostate tissue	Completed

Table 1. List of different clinical trials conducted trials conducted with bioactive substances on different cancers and their outcome

Plant Bioactive Compounds and Anticancer Potential:

There are different bioactive compounds with anticancer properties. The researches are still continuing in many aspects of this domain (Table. 2).

Compound	**Source**	**Mechanism of Action**	**Anti-Cancer Effects**	**References**
Vinca Alkaloids	Vinca plants (e.g., periwinkle)	Disruption of microtubule and its formation. This results in arrest of cell division.	Since they cause microtubule disruption and cell division arrest, they are used in treating leukemia and lymphomas	(14)
Quercetin	Found in fruits, vegetables, and grains	Causes apoptosis. It is an antioxidant and it has anti-inflammatory effects.	Anticancer activity is by reduction of inflammation, induction of programmed cell death. It results in cell division arrest.	(15)
Paclitaxel	Extracted from the Pacific yew tree	Since it causes microtubule stabilization, it inhibits cell division.	Stabilization of microtubule. It is used in the management of breast, ovarian, and lung cancers	(16)
Resveratrol	Found in red wine, grapes, and some berries	Antioxidant, anti-inflammatory, and anti-proliferative effects	May inhibit the growth of various cancer cells, particularly in breast and colon cancer	(17)

Table 2. List of different bioactive compounds and their anticancer properties

Plant-derived compounds encompass a vast array of phytochemicals, including alkaloids, flavonoids, terpenoids, and polyphenols, known for their diverse biological activities(18). Many of these compounds have exhibited remarkable anticancer potential through various mechanisms, such as apoptosis induction, cell cycle arrest, and angiogenesis inhibition(19). Unlocking the vast potential of plant bioactive compounds in the realm of anticancer therapeutics has become a focal point of research, offering a promising avenue for innovative and less toxic cancer treatments(18). Within the intricate tapestry of flora, a diverse array of bioactive compounds, spanning alkaloids, flavonoids, terpenoids, and polyphenols, have emerged as a potent arsenal against the complex landscape of cancer(20). Alkaloids, such as vinblastine and vincristine derived from the Madagascar periwinkle, disrupt cellular dynamics by targeting microtubules during cell division, inducing mitotic arrest and apoptosis(8). Flavonoids, abundant in fruits and teas, modulate signalling pathways crucial for cancer cell survival and growth. The polyphenol EGCG from green tea exemplifies this, inhibiting proliferation and promoting apoptosis (21). Terpenoids, including paclitaxel from the Pacific yew tree, contribute to anticancer effects by disrupting microtubule dynamics, preventing their disassembly during cell division (22). Polyphenols, like resveratrol from grapes, regulate cellular homeostasis, inhibiting cell cycle progression and inducing apoptosis (23). Collectively, these compounds orchestrate a sophisticated cellular response, offering a multifaceted approach to impede cancer progression(24). Furthermore, the synergistic combination of different classes of plant bioactive compounds enhances their overall anticancer potency, addressing the heterogeneity of cancer and minimizing the likelihood of resistance (25). Challenges in bioavailability and formulation optimization persist, presenting opportunities for innovative solutions, including nanotechnology for improved delivery (26). As we navigate this intricate landscape, the mechanisms through which plant bioactive compounds inhibit cancer cells unveil a precision medicine approach embedded in nature, paving the way for transformative advancements in anticancer therapeutics.

Alkaloids as Anticancer Agents:

Alkaloids, ubiquitous in the plant kingdom, stand as formidable warriors in the crusade against cancer, showcasing significant importance in both inhibition and prevention of this pervasive disease (Table. 3). Vincristine and vinblastine, derived from the Madagascar periwinkle (*Catharanthus roseus*), epitomize the profound impact of alkaloids in cancer therapeutics (27)(14). These compounds, by disrupting microtubule formation, intricately

sabotage the cellular machinery, leading to mitotic arrest and subsequent apoptosis—a meticulously orchestrated dance that specifically targets rapidly dividing cancer cells (8).

Mechanism of Action	Description	References
Binding Site	It binds to the β-tubulin subunit of tubulin dimers.	(28)
Inhibition of Assembly	Polymerization of tubulin dimmers needed for formation of microtubules. Prevents the polymerization prevention occurs with Vinca alkaloids.	(29)
Stabilization of Dimers	Stabilizes tubulin dimers, preventing their incorporation into the microtubule lattice.	(30)
Disruption of Dynamics	Disrupts the normal dynamic assembly and disassembly of microtubules.	(31)
Cell Cycle Arrest	Induces arrest in the metaphase of mitosis by preventing mitotic spindle formation.	(32)
Induction of Apoptosis	The disruption of microtubule dynamics and cell cycle arrest can lead to apoptosis.	(33)

Table 3. Showing the different mechanism of actions of Vinca alkaloids. Note the same action that causes the disruption of microtubules result in apoptosis of cancer cells.

The significance of these alkaloids lies not only in their direct assault on cancerous growth, but also in their selectivity, discriminating against healthy cells with a pace of division distinct from the rampant proliferation seen in malignancies (Table. 4). This precision is a crucial aspect in mitigating side effects commonly associated with traditional cancer treatments. Adding to the arsenal of alkaloid contributions is camptothecin, sourced from the Chinese Happy Tree (*Camptotheca acuminata*) (34). This alkaloid exhibits potent topoisomerase inhibition, a mechanism that impairs the crucial processes of DNA replication

and repair within cancer cells(35). By disrupting these fundamental genetic mechanisms, camptothecin serves as a molecular saboteur, inducing lethal DNA damage selectively in cancerous cells (36). The ability of alkaloids like camptothecin to specifically target the intricate machinery that fuels cancer progression underscores their pivotal role in preventing the relentless spread of malignant cells.

Mechanism of Action	Description	References
Interaction with Topoisomerase I	Forms a complex with topoisomerase I during its normal catalytic cycle.	(37)
Stabilization of DNA-Enzyme Complex	Stabilizes the cleavable complex formed by topoisomerase I and the DNA strand break.	(36)
Formation of Covalent Complex	Promotes the formation of a covalent linkage between topoisomerase I and the DNA.	(38)
Prevention of DNA Re-ligation	Inhibits the enzyme's ability to reseal the broken DNA strand, preventing re-ligation.	(37)
Accumulation of DNA Strand Breaks	Leads to the accumulation of unrepaired DNA strand breaks in the cellular genome.	(36)
Activation of DNA Damage Responses	Triggers cellular responses to DNA damage, including cell cycle arrest and apoptosis.	(39)
Cell Cycle Arrest	Induces cell cycle arrest as a result of the persistent DNA damage.	(40)
Apoptosis (Programmed Cell Death)	Ultimately leads to programmed cell death (apoptosis) due to the unrepaired DNA damage.	(40)

Table 4. Different mechanism of actions of campothecin.

Beyond their direct actions on cancer cells, alkaloids also wield preventive properties, acting as nature's guardians against the initiation and promotion of cancer. The intricate interplay of alkaloids with various cellular pathways involved in carcinogenesis marks them as promising agents in cancer prevention. Through their anti-inflammatory, antioxidant, and immunomodulatory activities, alkaloids create an environment that is inhospitable to the initiation of cancerous transformations(41). This prevents aspect is particularly crucial in the context of cancer, given its multifaceted etiology involving genetic, environmental, and lifestyle factors. The importance of alkaloids in cancer inhibition and prevention extends further into the realm of personalized medicine (42). As our understanding of cancer heterogeneity deepens, the need for targeted therapies becomes increasingly paramount. Alkaloids, with their diverse structures and mechanisms of action, offer a rich repertoire of options that can be tailored to the specific characteristics of individual cancers (43). This versatility is a key asset in the ongoing quest for precision medicine, where treatment strategies are finely tuned to the unique molecular profiles of patients' tumors.

Furthermore, alkaloids serve as pioneers in the development of novel therapeutic modalities (44). As traditional treatment approaches often come with debilitating side effects, the exploration of alkaloids opens avenues for more tolerable and patient-friendly interventions (45). By harnessing the intricate biological warfare that alkaloids wage against cancer cells, researchers are unravelling innovative treatment modalities that aim to minimize collateral damage to healthy tissues, consequently improving the quality of life for cancer patients. The multifaceted nature of alkaloids also positions them as agents that can synergize with existing therapeutic modalities (46). Combining alkaloids with conventional treatments, such as chemotherapy or radiation, holds the potential to enhance efficacy while minimizing the doses of these often-toxic interventions. This not only addresses the issue of drug resistance but also mitigates the adverse effects associated with aggressive cancer therapies (46).

The alkaloids emerge as linchpins in the intricate tapestry of cancer inhibition and prevention. From the disruption of microtubules to topoisomerase inhibition, these compounds enact a precise and selective assault on cancer cells, showcasing their importance in the therapeutic landscape (31). Their preventive roles, manifested through anti-inflammatory and antioxidant activities, underscore their significance in impeding the initiation of carcinogenesis. As personalized medicine and innovative therapeutic modalities take center stage, alkaloids stand as versatile players, offering tailored interventions for diverse cancers. In the ongoing battle against cancer, alkaloids not only represent potent

weapons but also beacons of hope, illuminating a path toward more effective, targeted, and tolerable anticancer strategies.

Flavonoids: Nature's Antioxidant Warriors and Anticancer Allies:

Flavonoids, pervasive in the natural kingdom, emerge as nature's antioxidant warriors and formidable allies in the fight against cancer, showcasing their intricate roles in maintaining cellular health and preventing malignancies (7). These polyphenolic compounds, abundant in fruits, vegetables, and teas, play a pivotal role in safeguarding cells from oxidative stress—a fundamental process implicated in various diseases, including cancer(47). Quercetin, a flavonoid found in apples, onions, and citrus fruits, exemplifies the antioxidant prowess of these compounds(48). By neutralizing reactive oxygen species (ROS) and inhibiting oxidative damage to cellular components such as DNA, proteins, and lipids, quercetin demonstrates a preventive role in the early stages of carcinogenesis(48). The ability of flavonoids to modulate cellular signalling pathways is another facet of their anticancer arsenal. Epigallocatechin gallate (EGCG), a flavonoid abundant in green tea, showcases potent anti-proliferative effects by interfering with signalling cascades involved in cell survival and growth(6). The multifaceted nature of flavonoids extends beyond antioxidant and anti-proliferative activities. They exhibit anti-inflammatory properties by suppressing pro-inflammatory signalling pathways, contributing to an environment unfavourable for cancer initiation and progression (7). Moreover, flavonoids play a role in inducing apoptosis, the programmed cell death crucial for maintaining tissue homeostasis(49). Resveratrol, found in grapes, red wine, and peanuts, is a notable example with its ability to trigger apoptosis in various cancer cell types(23). The dynamic interplay of flavonoids with cellular processes positions them as versatile players in cancer prevention and therapy. Furthermore, the concept of hormesis, where low doses of stressors induce adaptive responses, underscores the paradoxical nature of flavonoids—acting as antioxidants at lower concentrations while exerting pro-oxidant effects at higher doses, selectively targeting cancer cells(50). As we unravel the intricacies of flavonoids, their roles in mitigating oxidative stress, modulating signalling pathways, and orchestrating anti-inflammatory and pro-apoptotic responses underscore their importance as nature's allies in the intricate battle against cancer.

Flavonoids, a diverse group of polyphenolic compounds found in plants, have been recognized for their potential to inhibit Cyclin-Dependent Kinases (CDKs), which play a crucial role in regulating the cell cycle(51). The intricate interplay between flavonoids and CDKs represents a promising avenue for cancer prevention and treatment. Quercetin, a well-studied flavonoid present in various fruits and vegetables, has demonstrated significant CDK-

inhibitory effects. Quercetin inhibits CDK4 and CDK6, key regulators of the G1 phase of the cell cycle, preventing the phosphorylation of the retinoblastoma protein (pRb) and subsequently inducing cell cycle arrest.(52) This property is particularly relevant in cancer therapy, where uncontrolled cell cycle progression is a hallmark of malignancy.

Another notable flavonoid, fisetin, found in strawberries and other fruits, has shown inhibitory effects on CDKs. Fisetin specifically targets CDK1, a critical regulator of the G2/M phase transition.(53) By interfering with the activity of CDK1, fisetin induces G2/M-phase cell cycle arrest, preventing cancer cells from progressing through the cell cycle and promoting their apoptotic elimination.(54) Epigallocatechin gallate (EGCG), a major flavonoid in green tea, has been extensively studied for its CDK-inhibitory properties. EGCG can inhibit multiple CDKs, including CDK1, CDK2, and CDK4, leading to cell cycle arrest at various checkpoints.(55) This broad-spectrum inhibition of CDKs contributes to the anticancer effects of EGCG, making it a promising candidate for cancer prevention and therapy.

Resveratrol, found in grapes and red wine, is another flavonoid known for its ability to inhibit CDKs (Table. 5). Resveratrol has been shown to downregulate the expression and activity of CDK2, preventing the phosphorylation of its downstream targets and inducing G1-phase cell cycle arrest.(56) This effect is particularly relevant in the context of cancer, where dysregulation of the G1 phase is a common feature.(57) The molecular mechanisms underlying flavonoid-mediated CDK inhibition are multifaceted. Flavonoids can directly bind to CDKs, interfering with their catalytic activity. Additionally, flavonoids may influence the expression levels of CDKs and their regulatory partners, including cyclones and cyclin-dependent kinase inhibitors (CKIs), to orchestrate a finely tuned control of the cell cycle.

Flavonoid	**Plant Source**	**Mechanism of Action on CDKs**	**Potential CDK Targets**	**Reference**
Quercetin	Fruits, Vegetables	Inhibition of CDK4 and CDK6 activity; interference with cyclin D binding; upregulation of p21 and p27; induction of apoptosis	CDK4, CDK6	(52)
Kaempferol	Fruits,	Inhibition of CDK1, CDK2,	CDK1, CDK2,	(58)

Flavonoid	Plant Source	Mechanism of Action on CDKs	Potential CDK Targets	Reference
	Vegetables	CDK4, and CDK6; upregulation of p21; cell cycle arrest	CDK4, CDK6	
Apigenin	Vegetables, Herbs	Inhibition of CDK1, CDK2, CDK4, and CDK6; induction of p21; cell cycle arrest	CDK1, CDK2, CDK4, CDK6	(59)
Luteolin	Herbs, Vegetables	Inhibition of CDK1, CDK2, CDK4, and CDK6; upregulation of p21; induction of apoptosis	CDK1, CDK2, CDK4, CDK6	(60)
Genistein	Soybeans, Legumes	Inhibition of CDK1, CDK2, CDK4, and CDK6; upregulation of p21; induction of cell cycle arrest and apoptosis	CDK1, CDK2, CDK4, CDK6	(61)
Naringenin	Citrus Fruits	Inhibition of CDK2; downregulation of cyclin A; induction of cell cycle arrest	CDK2	(62)
Fisetin	Fruits, Vegetables	Inhibition of CDK1, CDK2, CDK4, and CDK6; upregulation of p21 and p27; induction of apoptosis	CDK1, CDK2, CDK4, CDK6	(54)

Table 5. Different flavonoids and their action on CDKs

The significance of flavonoid-mediated CDK inhibition extends beyond cell cycle regulation. CDKs are integral components of various cellular processes, and their dysregulation is a hallmark of cancer.(63) By specifically targeting CDKs, flavonoids hold the potential to disrupt the uncontrolled proliferation of cancer cells and induce their programmed cell death, providing a targeted and less toxic approach to cancer therapy.(64) The flavonoids' ability to inhibit CDKs represents a critical aspect of their multifaceted

anticancer effects.(14) The examples of quercetin, fisetin, EGCG, and resveratrol underscore the diverse ways in which flavonoids can modulate CDK activity, offering a promising avenue for the development of novel therapeutic strategies against cancer.(65) As research in this field progresses, the precise mechanisms and therapeutic potential of flavonoid-mediated CDK inhibition continue to be elucidated, providing valuable insights for future anticancer interventions.

Terpenoids: Aromatic Hydrocarbons with Anticancer Potency:

Terpenoids, a diverse class of aromatic hydrocarbons derived from isoprene units, have emerged as potent players in the realm of cancer research, showcasing remarkable anticancer potency.(66) With their structural diversity and widespread occurrence in plants, fungi, and even some marine organisms, terpenoids present a vast reservoir of bioactive compounds that exhibit multifaceted effects on cancer cells.(67) The intricate molecular mechanisms underlying their anticancer properties are a subject of intense investigation, offering promising avenues for the development of novel therapeutic strategies. One notable group of terpenoids is the taxanes, exemplified by paclitaxel, originally derived from the Pacific yew tree.(22) Paclitaxel has become a cornerstone in cancer chemotherapy, particularly in the treatment of breast, ovarian, and lung cancers.(68) Its mechanism of action revolves around its ability to stabilize microtubules, crucial components of the cell's structural framework involved in cell division. By preventing microtubule disassembly, paclitaxel induces mitotic arrest and subsequent apoptosis, inhibiting the uncontrolled proliferation of cancer cells.(69) The success of paclitaxel underscores the potential of terpenoids as indispensable tools in the fight against cancer.

Isoprenoids, another subgroup of terpenoids, include farnesyl pyrophosphate and geranylgeranyl pyrophosphate, which play crucial roles in post-translational modification of proteins such as Ras and Rho.(70) Dysregulation of Ras proteins is implicated in various cancers, and the inhibition of their activity by isoprenoids presents a promising anticancer strategy.(71) Terpenoids like farnesyltransferase inhibitors (FTIs) have been developed to disrupt Ras signalling, inhibiting cancer cell growth and inducing apoptosis.(72). This targeted approach highlights the versatility of terpenoids in addressing specific molecular aberrations that drive cancer progression. Artemisinin, a sesquiterpene lactone derived from the sweet wormwood plant, has gained attention for its potent antimalarial properties.(73) Interestingly, artemisinin and its derivatives have also demonstrated anticancer activity.(74) These compounds induce cell cycle arrest and apoptosis in cancer cells, with a particular affinity for cells with elevated iron levels.(75) The precise mechanisms of artemisinin's

anticancer effects are still under investigation, but it exemplifies the diverse and unexpected avenues through which terpenoids can combat cancer. Notably, terpenoids derived from essential oils, such as limonene and perillyl alcohol, exhibit promising anticancer activities.(76) Limonene, found in citrus fruits, has shown chemo preventive effects against various cancers.(77) It induces apoptosis, inhibits cancer cell proliferation, and disrupts signalling pathways involved in tumour development.(78) Perillyl alcohol, derived from mint and cherries, has demonstrated efficacy against a range of cancers, including breast, pancreatic, and prostate cancers.(79).(80) Its mechanisms involve the inhibition of post-translational modifications of proteins and interferes with cell cycle progression. (81)

Moreover, the triterpenoid oleanolic acid, found in olive oil, has exhibited anticancer properties through multiple mechanisms. Oleanolic acid induces apoptosis, inhibits angiogenesis, and modulates immune responses against cancer cells.(82) Its multifaceted effects highlight the potential of terpenoids as agents that can address various hallmarks of cancer. The anti-inflammatory and antioxidant properties of certain terpenoids further contribute to their anticancer potential.(83) Terpenoids like boswellic acid, derived from frankincense, exhibit anti-inflammatory effects by inhibiting enzymes involved in inflammation.(84) Chronic inflammation is a key driver of cancer, and the ability of terpenoids to mitigate inflammation positions them as agents that can disrupt the tumor-promoting microenvironment.(85).(86) Additionally, the antioxidant effects of terpenoids protect cells from oxidative stress, a factor implicated in cancer development.(87) The terpenoid lycopene, abundant in tomatoes, demonstrates antioxidant properties and has been associated with a reduced risk of certain cancers, particularly prostate cancer(Table 6).(88)

Terpenoid	**Plant Source**	**Anticancer Mechanism**	**Targets/Pathways**	**References**
Taxol (Paclitaxel)	Pacific Yew Tree (*Taxus brevifolia*)	Stabilizes microtubules, inhibits mitosis, induces apoptosis	Microtubules (tubulin polymerization)	(89)
Artemisinin	Sweet Wormwood (*Artemisia annua*)	Generates reactive oxygen species (ROS), disrupts the cell cycle	Induction of oxidative stress, cell cycle arrest	(90)
Curcumin	Turmeric	Induces apoptosis,	NF-κB, Bcl-2, caspases,	(91)

Terpenoid	Plant Source	Anticancer Mechanism	Targets/Pathways	References
	(*Curcuma longa*)	inhibits proliferation and angiogenesis	MAPK, PI3K/Akt, COX-2, VEGF	
Ginsenosides	Ginseng (*Panax ginseng*)	Inhibits cell proliferation, induces apoptosis	MAPK, PI3K/Akt, NF-κB, Bcl-2, caspases, p53	(92)
Betulinic Acid	Birch Bark (*Betula spp.)*	Induces apoptosis, inhibits angiogenesis	Apoptotic proteins, Bcl-2, caspases, angiogenic factors	(93)
Limonene	Citrus Peel (*Citrus spp*.)	Inhibits tumor growth, induces apoptosis, anti-angiogenic	p38 MAPK, PI3K/Akt, caspases, VEGF, MMPs	(94)

Table 6. List of different terpenoids and their anticancer mechanism, targets and pathways.

The challenges in terpenoid-based anticancer therapies include issues of bioavailability and formulation optimization. Many terpenoids have poor water solubility, limiting their effective delivery to cancer cells.(95) Researchers are exploring innovative approaches, including nanotechnology, to enhance the bioavailability of terpenoids and improve their therapeutic efficacy.(96) The terpenoids, with their aromatic hydrocarbon structures and diverse functional groups, stand out as potent anticancer agents.(97) The taxanes, isoprenoids, sesquiterpene lactones, triterpenoids, and essential oil-derived terpenoids collectively exemplify the rich and varied landscape of anticancer terpenoids.(98) Their ability to target specific molecular pathways, induce apoptosis, disrupt cell cycle progression, and modulate the tumor microenvironment underscores their potential as valuable tools in the fight against cancer.(99) As research continues to unravel the intricacies of terpenoid mechanisms and innovative delivery methods are explored, these aromatic hydrocarbons are poised to play an increasingly pivotal role in shaping the future of anticancer therapeutics.

Polyphenols: Guards of Cellular Health and Suppressors of Tumorigenesis:

Polyphenols, a diverse group of naturally occurring compounds found abundantly in plants, have garnered considerable attention for their potential role as guardians of cellular health and potent suppressors of tumorigenesis.(13) This comprehensive exploration delves into the multifaceted aspects of polyphenols, examining their diverse structures, mechanisms of action, and the accumulating evidence supporting their impact on cellular health and cancer prevention.(100) Polyphenols constitute a vast and structurally diverse group of compounds, encompassing flavonoids, phenolic acids, polyphenolic amides, and other subclasses.(101) Flavonoids, such as quercetin, catechins, and anthocyanins, are ubiquitous in fruits, vegetables, and beverages like tea.(102) Phenolic acids, including ferulic acid and ellagic acid, are found in grains, fruits, and nuts.(103) The intricate structures of these compounds contribute to their antioxidant properties and bioactivity.(47)

One hallmark of polyphenols is their potent antioxidant activity.(104) Acting as scavengers of reactive oxygen species (ROS) and free radicals, polyphenols help maintain cellular redox balance.(105) Oxidative stress, induced by an imbalance between ROS production and the cellular antioxidant defense system, is implicated in various diseases, including cancer.(106) Polyphenols' ability to neutralize ROS underscores their role as cellular guardians, protecting against oxidative damage and preserving overall cellular health.(107) Chronic inflammation is a recognized contributor to cancer development, and polyphenols exhibit anti-inflammatory effects that can mitigate this risk.(108) Quelling inflammatory pathways, such as NF-κB and COX-2, polyphenols interfere with the inflammatory milieu that promotes tumorigenesis.(109) By modulating immune responses and cytokine production, polyphenols contribute to creating an anti-inflammatory microenvironment that hinders cancer initiation and progression.(109)

Polyphenols exert their anticancer effects through the modulation of crucial signaling pathways. Resveratrol, found in red grapes, activates sirtuins and AMP-activated protein kinase (AMPK), influencing cellular processes like apoptosis and autophagy.(110) Epigallocatechin gallate (EGCG) from green tea interferes with the PI3K/Akt pathway, inhibiting cell survival signals.(111)

Understanding the specific pathways targeted by different polyphenols provides insights into their diverse mechanisms of action against tumorigenesis. Maintaining genomic stability is paramount in preventing cancer, and polyphenols contribute to this by various means.(112) They enhance DNA repair mechanisms, protect against DNA damage caused by

oxidative stress, and regulate cell cycle progression.(113) .(114) By safeguarding the integrity of the genetic material, polyphenols play a crucial role in preventing the accumulation of mutations that could lead to cancer.(115) Polyphenols exhibit pro-apoptotic effects, promoting programmed cell death in cancer cells.(116) They activate signaling pathways that induce apoptosis, preventing the survival of aberrant cells.(117) Additionally, polyphenols stimulate autophagy, a cellular process that removes damaged components and inhibits the formation of tumors.(118) This dual action highlights the multifaceted nature of polyphenols in orchestrating cellular responses against cancer. Angiogenesis, the formation of new blood vessels, is a critical process for tumor growth, and polyphenols can inhibit this by targeting vascular endothelial growth factor (VEGF) and other angiogenic factors.(119) Moreover, polyphenols interfere with metastatic processes by inhibiting cell migration and invasion.(120) These anti-angiogenic and anti-metastatic properties underscore the potential of polyphenols in curbing cancer progression.

The journey from preclinical studies to clinical evidence reinforces the anticancer potential of polyphenols.(121) Preclinical studies, often conducted in cell lines and animal models, demonstrate the efficacy of polyphenols in inhibiting tumor growth, inducing apoptosis, and modulating key cellular pathways.(122) Clinical trials, albeit with some complexities due to bioavailability and individual variations, provide encouraging evidence supporting the cancer-preventive effects of polyphenols in human populations.(123) Despite the promising findings, challenges such as bioavailability, metabolism, and the need for standardized clinical trials persist. Overcoming these hurdles requires innovative approaches, including the development of delivery systems that enhance polyphenol bioavailability and rigorous study designs that account for individual variations.(124) Future directions involve exploring synergies between polyphenols and conventional cancer therapies, unraveling the intricacies of their interactions with gut microbiota, and identifying specific polyphenols or combinations with enhanced therapeutic potential.(125). (126)

The, polyphenols emerge as versatile compounds that act as guards of cellular health and suppressors of tumorigenesis.(127) Their antioxidant properties, anti-inflammatory effects, modulation of signaling pathways, preservation of genomic stability, and impact on apoptosis, autophagy, angiogenesis, and metastasis collectively contribute to their anticancer potential.(128) Preclinical and clinical evidence underscores their promise in the prevention and treatment of cancer.(129) As we unravel the complexities of polyphenols and refine their integration into cancer care, these compounds stand as nature's allies in the ongoing battle

against this formidable disease, offering a holistic approach to cellular health and cancer prevention.

Mechanisms of Action: Unravelling the Anticancer Potential

The quest for effective anticancer agents has led researchers to explore the rich reservoir of bioactive compounds derived from plants.(130) These compounds, with their diverse chemical structures and biological activities, have demonstrated significant potential in preventing and treating various types of cancer.(131) Understanding the mechanisms through which plant compounds exert their anticancer effects is crucial for harnessing their full therapeutic potential.(132) In this exploration, we delve into the intricate mechanisms of action that underpin the anticancer properties of these plant-derived compounds.(133) One prominent class of plant compounds with well-documented anticancer potential is flavonoids.(134) These polyphenolic compounds, abundant in fruits, vegetables, and teas, exhibit a range of activities that contribute to their anticancer effects.(135) Flavonoids act as potent antioxidants, neutralizing reactive oxygen species (ROS) that can induce DNA damage and contribute to cancer initiation.(7) Quercetin, a flavonoid found in apples and onions, exemplifies this antioxidant activity.(136) By reducing oxidative stress, quercetin protects cells from genetic mutations and aberrant growth, inhibiting the early stages of carcinogenesis.(137)

Flavonoids also modulate key signalling pathways involved in cancer progression.(138) Epigallocatechin gallate (EGCG), a major flavonoid in green tea, interferes with signalling cascades related to cell survival and growth.(139) EGCG inhibits the activity of proteins like Akt and mTOR, which are often dysregulated in cancer cells.(140) This disruption of signalling pathways induces apoptosis (programmed cell death) and inhibits the uncontrolled proliferation of cancer cells, showcasing the multifaceted nature of flavonoid mechanisms.(116) Terpenoids, another class of plant compounds derived from isoprene units, exhibit diverse mechanisms of action with potent anticancer effects.(67) Taxanes, such as paclitaxel from the Pacific yew tree, disrupt microtubule dynamics during cell division.(141) By stabilizing microtubules, taxanes induce mitotic arrest and subsequent apoptosis in rapidly dividing cancer cells.(31) This interference with the cell cycle is a hallmark mechanism underlying the efficacy of taxanes in various cancer treatments, illustrating the precision with which plant compounds target cancer-specific vulnerabilities.(142)

Isoprenoids, including farnesyl pyrophosphate and geranylgeranyl pyrophosphate, play pivotal roles in post-translational modification of proteins like Ras and Rho.(143)

Dysregulation of Ras proteins is implicated in several cancers, and isoprenoids present a targeted approach to inhibit their activity.(144) Farnesyltransferase inhibitors (FTIs), a class of isoprenoids, disrupt Ras signalling, inhibiting cancer cell growth and inducing apoptosis.(145) The specificity of isoprenoids in targeting key molecular players implicated in cancer progression highlights their potential as precise and tailored anticancer agents.(146) Sesquiterpene lactones, exemplified by artemisinin from the sweet wormwood plant, showcase unique mechanisms of action with promising anticancer effects.(147) Artemisinin and its derivatives have an affinity for cancer cells with elevated iron levels.(75) Through a process called the Fenton reaction, these compounds generate free radicals selectively in cancer cells, leading to oxidative stress and apoptosis.(148) The selective cytotoxicity of sesquiterpene lactones towards cancer cells emphasizes their potential as targeted therapeutics.(149)

Alkaloids, a diverse group of nitrogen-containing compounds found in plants, exhibit varied mechanisms that contribute to their anticancer activities.(43) Vincristine and vinblastine from the Madagascar periwinkle disrupt microtubule formation, inducing mitotic arrest and apoptosis.(14).(8) These alkaloids specifically target the highly proliferative nature of cancer cells, underscoring their precision in cancer therapy.(45) Additionally, alkaloids like camptothecin inhibit topoisomerases, essential enzymes involved in DNA replication and repair.(35) By preventing these enzymes from functioning, camptothecin induces DNA damage and apoptosis, offering a distinctive mechanism of action against cancer. The interactions between plant compounds and the immune system also play a crucial role in their anticancer effects.(150) Immunomodulation is a key mechanism through which some plant compounds enhance the body's ability to recognize and eliminate cancer cells.(151) For instance, polysaccharides found in medicinal mushrooms, such as beta-glucans, activate immune cells like macrophages and natural killer cells.(152) These activated immune cells then target and destroy cancer cells, contributing to the overall antitumor response.(153) Furthermore, the phenomenon of hormesis, where low doses of stressors induce adaptive responses in cells, adds another layer to the mechanisms of plant compounds in cancer prevention.(50).(154) Low concentrations of certain plant compounds, such as resveratrol, can induce stress responses in cancer cells, leading to cell cycle arrest and apoptosis.(155) This hormetic effect allows for a nuanced and selective impact on cancer cells, minimizing damage to normal cells.(156)

Challenges in utilizing plant compounds for anticancer therapy include issues of bioavailability, formulation optimization, and standardization.(157) Many of these

compounds have poor water solubility, affecting their absorption and delivery to target tissues.(158) Researchers are exploring innovative solutions, including nanotechnology and novel delivery systems, to enhance the bioavailability and effectiveness of plant compounds in cancer treatment.(159) The mechanisms of action underlying the anticancer potential of plant compounds are diverse and multifaceted. From antioxidant and immunomodulatory effects to disruption of signalling pathways and interference with crucial cellular processes, plant compounds showcase a sophisticated repertoire of actions against cancer.(41) The precision with which these compounds target cancer-specific vulnerabilities, coupled with their potential for synergistic combinations.(125)

Preclinical and Clinical Evidence: Bridging the Gap from Bench to Bedside:

The journey from discovering the anticancer potential of plant compounds in preclinical studies to translating these findings into effective clinical treatments represents a critical bridge in oncology research.(160) As researchers delve into the wealth of bioactive compounds derived from plants, preclinical evidence provides a foundation for understanding mechanisms and efficacy, paving the way for clinical trials that ultimately determine the safety and effectiveness of these compounds in human cancer patients.(161) Preclinical studies, conducted primarily in laboratory settings and animal models, serve as the initial proving ground for anticancer plant compounds.(162) These investigations aim to unravel the mechanisms underlying the observed anticancer effects and provide crucial insights into the compounds' potential efficacy.(163) Flavonoids, a diverse class of polyphenolic compounds, have garnered significant attention in preclinical studies.(164) Quercetin, for example, exhibits anticancer properties by interfering with signaling pathways and inducing apoptosis in cancer cells.(165) Preclinical investigations have elucidated the intricacies of quercetin's interactions with cellular targets, highlighting its potential as a targeted therapy.(52) Terpenoids, including taxanes like paclitaxel, have shown promising results in preclinical studies.(166) These compounds disrupt microtubule dynamics, leading to mitotic arrest and apoptosis in cancer cells.(29) The effectiveness of taxanes in preclinical models has been instrumental in shaping their subsequent use in clinical settings, particularly in treating breast, ovarian, and lung cancers.(167) Alkaloids, such as vincristine and vinblastine, have demonstrated significant anticancer effects in preclinical studies by disrupting microtubule formation.(168) These findings laid the groundwork for the development of vinca alkaloids as chemotherapy agents in various malignancies.(27)

Sesquiterpene lactones, exemplified by artemisinin, showcase potent anticancer properties in preclinical investigations.(147) Artemisinin's ability to selectively target cancer cells with

elevated iron levels, inducing oxidative stress and apoptosis, has been elucidated in preclinical models, providing a rationale for its exploration in clinical trials.(75) Clinical trials represent the crucial phase where promising preclinical findings are tested in human subjects.(161) These trials follow a rigorous process, typically comprising multiple phases, to evaluate the safety, efficacy, and potential side effects of anticancer plant compounds.

Flavonoids, known for their antioxidant and anti-inflammatory properties, have entered clinical trials to assess their anticancer potential.(169) Clinical studies involving flavonoid-rich diets or flavonoid supplements aim to determine their impact on cancer prevention and treatment.(170) For example, trials investigating the role of epigallocatechin gallate (EGCG) from green tea in preventing cancer recurrence have provided valuable insights into its clinical utility.(171) Terpenoids, particularly taxanes like paclitaxel, have undergone extensive clinical testing.(172) Paclitaxel's efficacy in various cancer types, including breast and ovarian cancers, has been validated in clinical trials.(173) These trials not only establish the compound's effectiveness but also contribute to optimizing dosage regimens and identifying potential side effects. Alkaloids, such as vinca alkaloids derived from the Madagascar periwinkle, have demonstrated efficacy in clinical settings.(14) Vinorelbine and vincristine, derived from vinca alkaloids, have been utilized in clinical trials for different cancers, emphasizing their translation from preclinical promise to established clinical interventions.(174) Clinical trials exploring sesquiterpene lactones like artemisinin derivatives have expanded, particularly in the context of combinatory treatments.(175) Studies investigating artemisinin-based therapies, alone or in combination with conventional treatments, aim to assess their efficacy and safety in human cancer patients.(176) The translation of preclinical evidence to clinical applications is not without challenges.(177) Bioavailability, dosage optimization, and potential side effects are critical considerations.(178) Preclinical studies often use higher concentrations of compounds than feasible in clinical settings, necessitating careful adjustments to achieve therapeutic efficacy without undue toxicity.(179) Moreover, the heterogeneity of cancer, varying patient responses, and the complex interplay of factors in a clinical setting contribute to the intricacies of translating preclinical findings.(180) The design of clinical trials must account for these complexities, emphasizing the importance of well-structured protocols and patient selection criteria.(181) Despite these challenges, the translational journey from preclinical insights to clinical applications offers significant opportunities. Combining plant compounds with conventional treatments, exploring synergies, and identifying patient populations that

may benefit the most represent avenues for enhancing the clinical impact of these compounds.(182)

The journey of anticancer plant compounds from preclinical discovery to clinical validation represents a synergistic interplay between laboratory investigations and real-world applications. Preclinical insights provide the foundational understanding of mechanisms and efficacy, guiding the design of clinical trials.(183) Clinical trials, in turn, offer invaluable data on safety, optimal dosages, and patient responses, shaping the landscape of evidence-based cancer care.(184) As the field advances, continued collaboration between researchers, clinicians, and pharmaceutical developers is essential.(185) This collaborative effort ensures that the promise demonstrated in preclinical studies evolves into tangible clinical benefits for cancer patients. By bridging the gap from bench to bedside, anticancer plant compounds hold the potential to augment the arsenal of therapeutic options, offering new hope in the ongoing battle against cancer.(186)

Challenges and Opportunities in Plant-Based Anticancer Therapeutics:

Plant-based anticancer therapeutics presents a promising frontier in oncology research, offering a rich source of bioactive compounds with potential therapeutic benefits.(160) However, as researchers delve into harnessing the power of plants for cancer treatment, they encounter a spectrum of challenges and opportunities that shape the trajectory of this innovative approach.(187)

Bioavailability: One significant challenge lies in optimizing the bioavailability of plant compounds.(188) Many bioactive molecules from plants have low solubility, affecting their absorption and distribution in the body.(189) Overcoming this hurdle requires innovative formulations, such as nanotechnology, to enhance the delivery of these compounds to target tissues while maintaining their stability.(190)

Standardization: The inherent variability in plant-derived compounds poses a challenge in ensuring consistent quality and efficacy.(191) Standardization of plant extracts is crucial for reproducibility in clinical trials and the development of reliable therapeutic interventions.(192) Establishing standardized protocols for cultivation, harvesting, and extraction is essential to mitigate variability across different batches of plant-based products.(193)

Clinical Translation: Moving from preclinical success to clinical efficacy is a complex process. While preclinical studies provide valuable insights, translating these findings into

effective clinical treatments requires meticulous planning and rigorous evaluation. Patient heterogeneity, diverse cancer types, and variations in treatment responses present challenges in designing clinical trials that capture the broad spectrum of potential applications.(194)

Interaction with Conventional Therapies: Integrating plant-based therapeutics with conventional cancer treatments introduces challenges related to potential interactions.(195) Understanding how these compounds interact with chemotherapy, radiation, or immunotherapy is crucial to avoid adverse effects or unintended consequences. Optimizing combination therapies for enhanced efficacy while minimizing side effects poses a delicate balancing act.(196)

Opportunities:

Synergistic Combinations: One of the key opportunities lies in exploring synergistic combinations of plant-based compounds with existing anticancer therapies.(25) Combining these agents has the potential to enhance treatment efficacy, reduce side effects, and overcome resistance mechanisms.(197) Identifying optimal combinations through preclinical and clinical studies can open new avenues for personalized and effective cancer treatments.

Immunomodulation: Plant compounds often exhibit immunomodulatory effects, influencing the body's immune response against cancer cells.(198) This provides an opportunity to harness the immune system's inherent capabilities to recognize and eliminate cancer.(199) Plant-based immunomodulators can be explored as adjuvants in cancer immunotherapy, potentially improving overall treatment outcomes.(200)

Chemoprevention: Plant compounds with proven safety profiles present opportunities for chemoprevention, particularly in individuals at high risk of developing certain cancers.(201) Integrating plant-based interventions as preventive strategies may help reduce the incidence of cancer and enhance overall public health.(202)

Diverse Molecular Targets: The vast array of bioactive compounds in plants offers a multitude of molecular targets for cancer therapy. From interfering with specific signaling pathways to inducing apoptosis and inhibiting angiogenesis, these compounds act on diverse fronts.(20) Identifying and understanding these targets provides opportunities for designing targeted therapies tailored to the molecular characteristics of individual cancers.

The challenges and opportunities in plant-based anticancer therapeutics reflect the dynamic landscape of this evolving field.(187) Overcoming bioavailability issues, standardizing plant extracts, and navigating the complexities of clinical translation are hurdles that researchers

must address.(189) However, the potential for synergistic combinations, immunomodulation, chemoprevention, and targeting diverse molecular pathways offer exciting prospects for the development of effective and well-tolerated plant-based interventions in the fight against cancer.(25).(198) As the scientific community continues to unravel the complexities of plant compounds and their interactions, the integration of plant-based therapeutics into mainstream cancer care holds promise for a more comprehensive and personalized approach to cancer treatment and prevention.

Future Directions: From Bench to Bedside and Beyond:

The future directions of plant compounds in cancer research hold tremendous promise, with ongoing advancements poised to propel these natural agents from the bench to the bedside and beyond.(186) As our understanding of the intricate interactions between plant compounds and cancer biology deepens, several key directions emerge, shaping the trajectory of this innovative approach to cancer prevention and treatment.

a. Personalized Medicine:

Advancements in molecular profiling and genomics are paving the way for personalized cancer treatment.(203).(204) Plant compounds, with their diverse array of bioactive molecules, offer a rich source for tailoring treatments based on an individual's genetic makeup and the specific molecular characteristics of their cancer.(205) Precision medicine strategies can leverage the unique properties of plant compounds to develop targeted therapies that address the molecular vulnerabilities of each patient's cancer.(206)

b. Synergistic Combinations:

The future holds exciting prospects for the integration of plant-based compounds with conventional cancer therapies. Synergistic combinations can enhance treatment efficacy while potentially reducing side effects.(25) Combinatorial approaches that leverage the strengths of both plant compounds and standard treatments may represent a new frontier in cancer care.(182) Ongoing research seeks to identify optimal combinations, dosage regimens, and treatment sequences for improved outcomes.

c. Immunomodulation and Immunotherapy:

Plant compounds exhibit immunomodulatory effects that can influence the body's immune response against cancer.(198) Future research is likely to explore the potential of these

compounds as adjuvants in cancer immunotherapy.(151) Harnessing the immune system's ability to recognize and eliminate cancer cells, plant-based immunomodulators could play a pivotal role in enhancing the effectiveness of immunotherapeutic interventions.

d. Nanotechnology for Enhanced Delivery:

Addressing the challenge of bioavailability, future research will likely focus on innovative delivery mechanisms, with nanotechnology at the forefront.(190) Nanoparticle-based formulations can improve the solubility and stability of plant compounds, facilitating their efficient delivery to target tissues.(207) This approach not only enhances therapeutic efficacy but also minimizes potential side effects associated with high doses.(208)

e. Biomarker Discovery and Validation:

Identifying reliable biomarkers associated with the response to plant-based therapies is a critical avenue for future research.(209) Biomarkers can aid in patient stratification, allowing for more precise selection of individuals who are likely to benefit from specific plant compounds.(210) Validating these biomarkers will be crucial for advancing plant-based interventions into mainstream clinical practice.

f. Chemoprevention and Integrative Medicine:

The preventive potential of plant compounds offers a unique opportunity to explore their role in chemoprevention. Integrative medicine approaches that incorporate plant-based interventions alongside lifestyle modifications may contribute to reducing cancer risk.(196) Future studies can delve into the long-term impact of such interventions and their integration into comprehensive cancer prevention strategies.

g. Natural Compounds in Targeted Therapies:

Advancements in understanding the molecular mechanisms of cancer allow for the identification of specific targets that drive tumor growth. Plant compounds, with their ability to interact with diverse molecular pathways, can be explored as components of targeted therapies.(211) Future research may focus on elucidating the precise mechanisms of action of plant compounds and their potential to disrupt specific oncogenic signaling pathways.

The future directions of plant compounds in cancer research are characterized by a convergence of precision medicine, innovative delivery strategies, and a deeper understanding of the intricate interplay between plant compounds and cancer biology. From personalized medicine to synergistic combinations and the exploration of

immunomodulation, the trajectory is dynamic and holds the promise of transforming how we prevent and treat cancer.(161) As ongoing research translates these possibilities from the bench to the bedside and beyond, the integration of plant-based interventions into mainstream cancer care is likely to evolve, ushering in a new era of comprehensive and personalized approaches to cancer prevention and treatment.(186).(205)

4. Conclusion:

In conclusion, the exploration of plant bioactive compounds represents a vast and diverse frontier with profound implications for the development of effective anticancer therapeutics. The intricate tapestry woven by alkaloids, flavonoids, terpenoids, and polyphenols presents a myriad of options for researchers and clinicians venturing into the realm of cancer treatment. The rich chemical diversity within these compounds allows for a multifaceted approach, targeting various hallmarks of cancer through distinct mechanisms of action. Alkaloids, exemplified by vincristine and vinblastine, disrupt microtubule formation, inducing mitotic arrest and apoptosis.(45) Flavonoids, such as quercetin and epigallocatechin gallate, showcase antioxidant properties and modulate signaling pathways critical for cancer cell survival.(169) Terpenoids, including taxanes and isoprenoids, exhibit potent effects on microtubules and signaling proteins like Ras, offering targeted strategies against cancer.(66) Polyphenols, encompassing a broad range of compounds like resveratrol, contribute to cancer prevention through antioxidant and anti-inflammatory mechanisms.(135)

As these plant-derived compounds transition from bench to bedside, their integration into clinical practice holds immense promise.(186) Ongoing research seeks to unravel the nuanced interactions between these compounds and cancer biology, paving the way for personalized and targeted therapies.(205) The versatility of plant bioactive compounds allows for tailored interventions, addressing the unique molecular characteristics of individual cancers. The holistic potential of plant-based interventions extends beyond conventional treatments, offering avenues for combination therapies and synergistic approaches.(182).(25) Harnessing the power of nature's pharmacopeia, researchers and clinicians stand at the forefront of a transformative era in cancer care. The continued exploration and understanding of plant-derived compounds, coupled with their integration into clinical protocols, hold the potential to reshape the landscape of cancer treatment, providing patients with novel and effective therapeutic options.

References

1. Naeem A, Hu P, Yang M, Zhang J, Liu Y, Zhu W, et al. Natural Products as Anticancer Agents: Current Status and Future Perspectives. Molecules. 2022 Nov 30;27(23): 8367. Do: 10.3390/molecules27238367.

2. Dehelean CA, Marcovici I, Soica C, Mioc M, Coricovac D, Iurciuc S, et al. Plant-Derived Anticancer Compounds as New Perspectives in Drug Discovery and Alternative Therapy. Molecules. 2021 Feb 19;26(4):1109. DOI 10.3390/molecules26041109

3. Chu Y, Tian Z, Yang M, Li W. Conformation and energy investigation of microtubule longitudinal dynamic instability induced by natural products. Chem Biol Drug Des. 2023 Sep;102(3):444–56. DOI 10.1111/cbdd.14189

4. Wen K, Fang X, Yang J, Yao Y, Nandakumar KS, Salem ML, et al. Recent Research on Flavonoids and their Biomedical Applications. Curr Med Chem. 2021;28(5):1042–66. DOI 10.2174/0929867327666200713184138

5. Xu D, Hu MJ, Wang YQ, Cui YL. Antioxidant Activities of Quercetin and Its Complexes for Medicinal Application. Molecules. 2019 Mar 21;24(6):1123.DOI 10.3390/molecules24061123

6. Kciuk M, Alam M, Ali N, Rashid S, Głowacka P, Sundaraj R, et al. Epigallocatechin-3-Gallate Therapeutic Potential in Cancer: Mechanism of Action and Clinical Implications. Molecules. 2023 Jul 6;28(13):5246.DOI 10.3390/molecules28135246

7. Kopustinskiene DM, Jakstas V, Savickas A, Bernatoniene J. Flavonoids as Anticancer Agents. Nutrients. 2020 Feb 12;12(2):457. DOI: 10.3390/nu12020457

8. van Vuuren RJ, Visagie MH, Theron AE, Joubert AM. Antimitotic drugs in the treatment of cancer. Cancer Chemother Pharmacol. 2015;76:1101–12. DOI: 10.1007/s00280-015-2903-8

9. Prota AE, Lucena-Agell D, Ma Y, Estevez-Gallego J, Li S, Bargsten K, et al. Structural insight into the stabilization of microtubules by taxanes. eLife. 12:e84791. doi.org/10.7554/eLife.84791

10. Haney SL, Holstein SA. Targeting the Isoprenoid Biosynthetic Pathway in Multiple Myeloma. Int J Mol Sci. 2022 Dec 21;24(1):111. DOI: 10.3390/ijms24010111

11. Recalde MD, Miguel CA, Noya-Riobó MV, González SL, Villar MJ, Coronel MF. Resveratrol exerts anti-oxidant and anti-inflammatory actions and prevents oxaliplatin-induced mechanical and thermal allodynia. Brain Res. 2020 Dec 1;1748:147079. DOI: 10.1016/j.brainres.2020.147079

12. Ren B, Kwah MXY, Liu C, Ma Z, Shanmugam MK, Ding L, et al. Resveratrol for cancer therapy: Challenges and future perspectives. Cancer Lett. 2021 Sep 1;515:63–72. DOI: 10.1016/j.canlet.2021.05.001

13. Liu HM, Cheng MY, Xun MH, Zhao ZW, Zhang Y, Tang W, et al. Possible Mechanisms of Oxidative Stress-Induced Skin Cellular Senescence, Inflammation, and Cancer and the Therapeutic Potential of Plant Polyphenols. Int J Mol Sci. 2023 Feb 13;24(4):3755. DOI: 10.3390/ijms24043755

14. Dhyani P, Quispe C, Sharma E, Bahukhandi A, Sati P, Attri DC, et al. Anticancer potential of alkaloids: a key emphasis to colchicine, vinblastine, vincristine, vindesine, vinorelbine and vincamine. Cancer Cell Int. 2022 Jun 2;22:206. doi.org/10.1186/s12935-022-02624-9

15. Quercetin as an innovative therapeutic tool for cancer chemoprevention: Molecular mechanisms and implications in human health - PMC [Internet]. [cited 2024 Jan 23]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7774748/

16. Weaver BA. How Taxol/paclitaxel kills cancer cells. Mol Biol Cell. 2014 Sep 15;25(18):2677–81. doi: 10.1091/mbc.E14-04-0916

17. Mohanraj, K. G., Varshini, V., & Somasundaram, J. (2021). Knowledge and Awareness On The Association Between Higher Body Mass Index and Plantar Fasciitis Among Chennain Population-A Survey. Int J Dentistry Oral Sci, 8(03), 1957-1962.

18. BABU, B. V., & MOHANRAJ, K. G. (2020). Knowledge, frequency and health hazards of overuse of mobile phone among Chennai population-A questionnaire based survey. International Journal of Pharmaceutical Research (09752366), 12(4).

19. Zheng Z, Zhang L, Hou X. Potential roles and molecular mechanisms of phytochemicals against cancer. Food Funct. 2022 Sep 22;13(18):9208–25. **DOI: https://doi.org/10.1039/D2FO01663J**

19. Ranjan A, Ramachandran S, Gupta N, Kaushik I, Wright S, Srivastava S, et al. Role of Phytochemicals in Cancer Prevention. Int J Mol Sci. 2019 Oct 9;20(20):4981. doi: 10.3390/ijms20204981

20. Akshaya, A., & Ganesh, K. (2022). Knowledge, prevalence, and impact on social distancing on coronavirus (COVID-19) infection spread in young, adult, and aged population: a survey. ECS Transactions, 107(1), 14063.

21. Thangapazham RL, Passi N, Maheshwari RK. Green tea polyphenol and epigallocatechin gallate induce apoptosis and inhibit invasion in human breast cancer cells. Cancer Biol Ther. 2007 Dec;6(12):1938–43. DOI: 10.4161/cbt.6.12.4974

22. Sharifi-Rad J, Quispe C, Patra JK, Singh YD, Panda MK, Das G, et al. Paclitaxel: Application in Modern Oncology and Nanomedicine-Based Cancer Therapy. Oxid Med Cell Longev. 2021 Oct 18;2021:3687700. DOI: 10.1155/2021/3687700

23. Jang JY, Im E, Kim ND. Mechanism of Resveratrol-Induced Programmed Cell Death and New Drug Discovery against Cancer: A Review. Int J Mol Sci. 2022 Nov 8;23(22):13689. DOI: 10.3390/ijms232213689

24. USHANTHIKA, T., & MOHANRAJ, K. G. (2020). Knowledge, Awareness and Risk Factors of Smartphone Addiction in Young Adult Population. International Journal of Pharmaceutical Research (09752366), 12(3).

25. Pezzani R, Salehi B, Vitalini S, Iriti M, Zuñiga FA, Sharifi-Rad J, et al. Synergistic Effects of Plant Derivatives and Conventional Chemotherapeutic Agents: An Update on the Cancer Perspective. Medicina (Kaunas). 2019 Apr 17;55(4):110. doi: 10.3390/medicina55040110

26. Pai S, Hebbar A, Selvaraj S. A critical look at challenges and future scopes of bioactive compounds and their incorporations in the food, energy, and pharmaceutical sector. Environ Sci Pollut Res Int. 2022;29(24):35518–41. DOI: 10.1007/s11356-022-19423-4

27. Yuvaraj, A., Sangeetha, S., & Kavitha, S. (2020). Perception of general public regarding pros and cons of technological advancements during lockdown due to covid 19 pandemic-an online survey. International Journal of Current Research and Review, 227-233.

28. Multiple Microtubule Alterations Are Associated with Vinca Alkaloid Resistance in Human Leukemia Cells1 | Cancer Research | American Association for Cancer Research [Internet]. [cited 2024 Jan 23]. Available from: https://aacrjournals.org/cancerres/article/61/15/5803/507607/Multiple-Microtubule-Alterations-Are-Associated

29. Inhibition of tubulin-microtubule polymerization by drugs of the Vinca alkaloid class - PubMed [Internet]. [cited 2024 Jan 23]. Available from: https://pubmed.ncbi.nlm.nih.gov/1260766/

30. Microtubule destabilising agents: far more than just antimitotic anticancer drugs - PMC [Internet]. [cited 2024 Jan 23]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5237681/

31. Mukhtar E, Adhami VM, Mukhtar H. Targeting Microtubules by Natural Agents for Cancer Therapy. Mol Cancer Ther. 2014 Feb;13(2):275–84. DOI: 10.1158/1535-7163.MCT-13-0791

32. González-Cid M, Cuello MT, Larripa I. Mitotic arrest and anaphase aberrations induced by vinorelbine in hamster cells in vitro. Anticancer Drugs. 1997 Jun;8(5):529–32. DOI: 10.1097/00001813-199706000-00017

33. Chiu WH, Luo SJ, Chen CL, Cheng JH, Hsieh CY, Wang CY, et al. Vinca alkaloids cause aberrant ROS-mediated JNK activation, Mcl-1 downregulation, DNA damage, mitochondrial dysfunction, and apoptosis in lung adenocarcinoma cells. Biochemical Pharmacology. 2012 May 1;83(9):1159–71. DOI: 10.1016/j.bcp.2012.01.016

34. Khaiwa N, Maarouf NR, Darwish MH, Alhamad DWM, Sebastian A, Hamad M, et al. Camptothecin's journey from discovery to WHO Essential Medicine: Fifty years of promise. Eur J Med Chem. 2021 Nov 5;223:113639. DOI: 10.1016/j.ejmech.2021.113639

35. Liu LF, Desai SD, Li TK, Mao Y, Sun M, Sim SP. Mechanism of action of camptothecin. Ann N Y Acad Sci. 2000;922:1–10. DOI: 10.1111/j.1749-6632.2000.tb07020.x

36. The role of single strand break repair pathways in cellular responses to camptothecin induced DNA damage - ScienceDirect [Internet]. [cited 2024 Jan 23]. Available from: https://www.sciencedirect.com/science/article/pii/S0753332220300652

37. Pommier Y, Barcelo J, Rao VA, Sordet O, Jobson AG, Thibaut L, et al. Repair of Topoisomerase I-Mediated DNA Damage. Prog Nucleic Acid Res Mol Biol. 2006;81:179–229. DOI: 10.1016/S0079-6603(06)81005-6

38. Hertzberg RP, Busby RW, Caranfa MJ, Holden KG, Johnson RK, Hecht SM, et al. Irreversible trapping of the DNA-topoisomerase I covalent complex. Affinity labeling of the camptothecin binding site. Journal of Biological Chemistry. 1990 Nov;265(31):19287–95. https://doi.org/10.1016/S0021-9258(17)30656-7

39. Ferrara L, Kmiec EB. Camptothecin enhances the frequency of oligonucleotide-directed gene repair in mammalian cells by inducing DNA damage and activating homologous recombination. Nucleic Acids Res. 2004;32(17):5239–48. DOI: 10.1093/nar/gkh822

40. Chiu CF, Lin YQ, Park JM, Chen YC, Hung SW, Chiu CC, et al. The novel camptothecin derivative, CPT211, induces cell cycle arrest and apoptosis in models of human breast cancer. Biomed Pharmacother. 2020 Aug;128:110309. DOI: 10.1016/j.biopha.2020.110309

41. Bafna A, Mishra S. Antioxidant and Immunomodulatory Activity of the Alkaloidal Fraction of Cissampelos pareira Linn. Sci Pharm. 2010;78(1):21–31. doi: 10.3797/scipharm.0904-16

42. Therapeutic value of steroidal alkaloids in cancer: Current trends and future perspectives [Internet]. [cited 2024 Jan 23]. Available from: https://onlinelibrary.wiley.com/doi/epdf/10.1002/ijc.31965

43. Olofinsan K, Abrahamse H, George BP. Therapeutic Role of Alkaloids and Alkaloid Derivatives in Cancer Management. Molecules [Internet]. 2023 Jul [cited 2024 Jan 23];28(14). Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10386240/

44. Aryal B, Raut BK, Bhattarai S, Bhandari S, Tandan P, Gyawali K, et al. Potential Therapeutic Applications of Plant-Derived Alkaloids against Inflammatory and Neurodegenerative Diseases. Evidence-Based Complementary and Alternative Medicine. 2022 Mar 9;2022:e7299778. DOI: 10.1155/2022/7299778

45. Daley S kay, Cordell GA. Alkaloids in Contemporary Drug Discovery to Meet Global Disease Needs. Molecules. 2021 Jun 22;26(13):3800. DOI: 10.3390/molecules26133800

46. Drug Delivery Systems and Combination Therapy by Using Vinca Alkaloids - PMC [Internet]. [cited 2024 Jan 23]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4997956/

47. Padmapriya, A., Preetha, S., Selvaraj, J., & Sridevi, G. (2022). Effect of Carica papaya seed extract on IL-6 and TNF-α in human lung cancer cell lines-an In vitro study. Research Journal of Pharmacy and Technology, 15(12), 5478-5482.

48. Xu D, Hu MJ, Wang YQ, Cui YL. Antioxidant Activities of Quercetin and Its Complexes for Medicinal Application. Molecules. 2019 Mar 21;24(6):1123. doi: 10.3390/molecules24061123

49. Abotaleb M, Samuel SM, Varghese E, Varghese S, Kubatka P, Liskova A, et al. Flavonoids in Cancer and Apoptosis. Cancers (Basel). 2018 Dec 28;11(1):28. doi: 10.3390/cancers11010028

50. Son TG, Camandola S, Mattson MP. Hormetic Dietary Phytochemicals. Neuromolecular Med. 2008;10(4):236–46. DOI: 10.1007/s12017-008-8037-y

51. Zhang J, Zhang L, Xu Y, Jiang S, Shao Y. Deciphering the binding behavior of flavonoids to the cyclin dependent kinase 6/cyclin D complex. PLoS One. 2018 May 1;13(5):e0196651.

52. Yousuf M, Khan P, Shamsi A, Shahbaaz M, Hasan GM, Haque QMR, et al. Inhibiting CDK6 Activity by Quercetin Is an Attractive Strategy for Cancer Therapy. ACS Omega. 2020 Oct 14;5(42):27480–91.

53. Xu X, Ding Y, Jin J, Xu C, Hu W, Wu S, et al. Post-translational modification of CDK1–STAT3 signaling by fisetin suppresses pancreatic cancer stem cell properties. Cell & Bioscience. 2023 Sep 24;13(1):176.

54. Afroze N, Pramodh S, Shafarin J, Bajbouj K, Hamad M, Sundaram MK, et al. Fisetin Deters Cell Proliferation, Induces Apoptosis, Alleviates Oxidative Stress and Inflammation in Human Cancer Cells, HeLa. Int J Mol Sci. 2022 Feb 1;23(3):1707.

55. Negri A, Naponelli V, Rizzi F, Bettuzzi S. Molecular Targets of Epigallocatechin—Gallate (EGCG): A Special Focus on Signal Transduction and Cancer. Nutrients. 2018 Dec;10(12):1936.

56. Athar M, Back JH, Kopelovich L, Bickers DR, Kim AL. Multiple molecular Targets of Resveratrol: Anti-carcinogenic Mechanisms. Arch Biochem Biophys. 2009 Jun 15;486(2):95–102.

57. Foster DA, Yellen P, Xu L, Saqcena M. Regulation of G1 Cell Cycle Progression. Genes Cancer. 2010 Nov;1(11):1124–31.

58. Zhang Q, Chen L, Gao M, Wang S, Meng L, Guo L. Molecular docking and in vitro experiments verified that kaempferol induced apoptosis and inhibited human HepG2 cell proliferation by targeting BAX, CDK1, and JUN. Mol Cell Biochem. 2023 Apr 1;478(4):767–80.

59. Zhu Y, Wu J, Li S, Wang X, Liang Z, Xu X, et al. Apigenin inhibits migration and invasion via modulation of epithelial mesenchymal transition in prostate cancer. Mol Med Rep. 2015 Feb;11(2):1004–8.

60. Lin LF, Chiu SP, Wu MJ, Chen PY, Yen JH. Luteolin Induces microRNA-132 Expression and Modulates Neurite Outgrowth in PC12 Cells. PLoS One. 2012 Aug 16;7(8):e43304.

61. George J, Banik NL, Ray SK. Genistein Induces Receptor and Mitochondrial Pathways and Increases Apoptosis during Bcl-2 Knockdown in Human Malignant Neuroblastoma SK-N-DZ Cells. J Neurosci Res. 2010 Mar;88(4):877–86.

62. Arul D, Subramanian P. Inhibitory effect of naringenin (citrus flavonone) on N-nitrosodiethylamine induced hepatocarcinogenesis in rats. Biochem Biophys Res Commun. 2013 May 3;434(2):203–9.

63. Casimiro MC, Crosariol M, Loro E, Li Z, Pestell RG. Cyclins and Cell Cycle Control in Cancer and Disease. Genes Cancer. 2012 Nov;3(11–12):649–57.

64. Ak S, D C, N M. The natural flavones, acacetin and apigenin, induce Cdk-Cyclin mediated G2/M phase arrest and trigger ROS-mediated apoptosis in glioblastoma cells. Molecular biology reports [Internet]. 2021 Jan [cited 2024 Jan 24];48(1). Available from: https://pubmed.ncbi.nlm.nih.gov/33394232/

65. Kashyap D, Garg VK, Tuli HS, Yerer MB, Sak K, Sharma AK, et al. Fisetin and Quercetin: Promising Flavonoids with Chemopreventive Potential. Biomolecules. 2019 May 6;9(5):174.

66. Thoppil RJ, Bishayee A. Terpenoids as potential chemopreventive and therapeutic agents in liver cancer. World J Hepatol. 2011 Sep 27;3(9):228–49.

67. Advances in Pharmacological Activities of Terpenoids - Wenqiang Yang, Xu Chen, Yanli Li, Shaofen Guo, Zhen Wang, Xiuling Yu, 2020 [Internet]. [cited 2024 Jan 24]. Available from: https://journals.sagepub.com/doi/10.1177/1934578X20903555

68. Lin S, Peng T, Meng Y, Cao C, Gao P, Wu P, et al. Comparison of one-week versus three-week paclitaxel for advanced pan-carcinomas: systematic review and meta-analysis. Aging (Albany NY). 2022 Feb 26;14(4):1959–82.

69. Foland TB, Dentler WL, Suprenant KA, Gupta ML, Himes RH. Paclitaxel-induced microtubule stabilization causes mitotic block and apoptotic-like cell death in a paclitaxel-sensitive strain of Saccharomyces cerevisiae. Yeast. 2005 Sep;22(12):971–8.

70. Holstein SA, Wohlford-Lenane CL, Wiemer DF, Hohl RJ. Isoprenoid pyrophosphate analogues regulate expression of Ras-related proteins. Biochemistry. 2003 Apr 22;42(15):4384–91.

71. Gysin S, Salt M, Young A, McCormick F. Therapeutic Strategies for Targeting Ras Proteins. Genes Cancer. 2011 Mar;2(3):359–72.

72. Dai X, Sun Y, Zhang T, Ming Y, Hongwei G. An overview on natural farnesyltransferase inhibitors for efficient cancer therapy. J Enzyme Inhib Med Chem. 35(1):1027–44.

73. Vydyam P, Dutta D, Sutram N, Bhattacharyya S, Bhattacharyya MK. A small-molecule inhibitor of the DNA recombinase Rad51 from Plasmodium falciparum synergizes with the antimalarial drugs artemisinin and chloroquine. Journal of Biological Chemistry. 2019 May;294(20):8171–83.

74. Crespo-Ortiz MP, Wei MQ. Antitumor Activity of Artemisinin and Its Derivatives: From a Well-Known Antimalarial Agent to a Potential Anticancer Drug. J Biomed Biotechnol. 2012;2012:247597.

75. Chen GQ, Benthani FA, Wu J, Liang D, Bian ZX, Jiang X. Artemisinin compounds sensitize cancer cells to ferroptosis by regulating iron homeostasis. Cell Death Differ. 2020 Jan;27(1):242–54.

76. Ahmed TA, Almehmady AM, Alharbi WS, Alshehri AA, Almughem FA, Altamimi RM, et al. Incorporation of Perillyl Alcohol into Lipid-Based Nanocarriers Enhances the Antiproliferative Activity in Malignant Glioma Cells. Biomedicines. 2023 Oct 12;11(10):2771.

77. Feng T, Zhang Q, Li Q, Zhu T, Lv W, Yu H, et al. LUAD transcriptomic profile analysis of d-limonene and potential lncRNA chemopreventive target. Food Funct. 2020 Aug 1;11(8):7255–65.

78. Ye Z, Liang Z, Mi Q, Guo Y. Limonene terpenoid obstructs human bladder cancer cell (T24 cell line) growth by inducing cellular apoptosis, caspase activation, G2/M phase cell cycle arrest and stops cancer metastasis. J BUON. 2020;25(1):280–5.

79. Chebet JJ, Ehiri JE, McClelland DJ, Taren D, Hakim IA. Effect of d-limonene and its derivatives on breast cancer in human trials: a scoping review and narrative synthesis. BMC Cancer. 2021 Aug 6;21:902.

80. da Silva CEH, Gosmann G, de Andrade SF. Limonene and Perillyl Alcohol Derivatives: Synthesis and Anticancer Activity. Mini Rev Med Chem. 2021;21(14):1813–29.

81. Markouli M, Strepkos D, Papavassiliou AG, Piperi C. Targeting of endoplasmic reticulum (ER) stress in gliomas. Pharmacol Res. 2020 Jul;157:104823.

82. Hu C, Cao Y, Li P, Tang X, Yang M, Gu S, et al. Oleanolic Acid Induces Autophagy and Apoptosis via the AMPK-mTOR Signaling Pathway in Colon Cancer. J Oncol. 2021 Jul 14;2021:8281718.

83. Ge J, Liu Z, Zhong Z, Wang L, Zhuo X, Li J, et al. Natural terpenoids with anti-inflammatory activities: Potential leads for anti-inflammatory drug discovery. Bioorganic Chemistry. 2022 Jul 1;124:105817.

84. Kumar A, Sharma S, Mishra S, Ojha S, Upadhyay P. ADME Prediction, Structure-activity Relationship of Boswellic Acid Scaffold for the Aspect of Anticancer & Anti-inflammatory Potency. Anticancer Agents Med Chem. 2023;23(13):1499–505.

85. Greten FR, Grivennikov SI. Inflammation and Cancer: Triggers, Mechanisms and Consequences. Immunity. 2019 Jul 16;51(1):27–41.

86. Kłos P, Chlubek D. Plant-Derived Terpenoids: A Promising Tool in the Fight against Melanoma. Cancers. 2022 Jan;14(3):502.

87. Gutiérrez-del-Río I, López-Ibáñez S, Magadán-Corpas P, Fernández-Calleja L, Pérez-Valero Á, Tuñón-Granda M, et al. Terpenoids and Polyphenols as Natural Antioxidant Agents in Food Preservation. Antioxidants (Basel). 2021 Aug 8;10(8):1264.

88. Moran NE, Thomas-Ahner JM, Wan L, Zuniga KE, Erdman JW, Clinton SK. Tomatoes, Lycopene, and Prostate Cancer: What Have We Learned from Experimental Models? J Nutr. 2022 Mar 12;152(6):1381–403.

89. Rowinsky EK, Donehower RC, Jones RJ, Tucker RW. Microtubule changes and cytotoxicity in leukemic cell lines treated with taxol. Cancer Res. 1988 Jul 15;48(14):4093–100.

90. Efferth T, Romero MR, Wolf DG, Stamminger T, Marin JJG, Marschall M. The antiviral activities of artemisinin and artesunate. Clin Infect Dis. 2008 Sep 15;47(6):804–11.

91. Aggarwal BB, Kumar A, Bharti AC. Anticancer potential of curcumin: preclinical and clinical studies. Anticancer Res. 2003;23(1A):363–98.

92. Yun TK, Lee YS, Lee YH, Kim SI, Yun HY. Anticarcinogenic effect of Panax ginseng C.A. Meyer and identification of active compounds. J Korean Med Sci. 2001 Dec;16 Suppl(Suppl):S6-18.

93. Fulda S, Scaffidi C, Susin SA, Krammer PH, Kroemer G, Peter ME, et al. Activation of mitochondria and release of mitochondrial apoptogenic factors by betulinic acid. J Biol Chem. 1998 Dec 18;273(51):33942–8.

94. Crowell PL. Prevention and therapy of cancer by dietary monoterpenes. J Nutr. 1999 Mar;129(3):775S-778S.

95. Kaps A, Gwiazdoń P, Chodurek E. Nanoformulations for Delivery of Pentacyclic Triterpenoids in Anticancer Therapies. Molecules. 2021 Mar 21;26(6):1764.

96. Milosheska D, Roškar R. Use of Retinoids in Topical Antiaging Treatments: A Focused Review of Clinical Evidence for Conventional and Nanoformulations. Adv Ther. 2022 Dec;39(12):5351–75.

97. Terpenoid - an overview | ScienceDirect Topics [Internet]. [cited 2024 Jan 26]. Available from: https://www.sciencedirect.com/topics/nursing-and-health-professions/terpenoid

98. Masyita A, Mustika Sari R, Dwi Astuti A, Yasir B, Rahma Rumata N, Emran TB, et al. Terpenes and terpenoids as main bioactive compounds of essential oils, their roles in human health and potential application as natural food preservatives. Food Chem X. 2022 Jan 19;13:100217.

99. Yang H, Dou QP. Targeting Apoptosis Pathway with Natural Terpenoids: Implications for Treatment of Breast and Prostate Cancer. Curr Drug Targets. 2010 Jun;11(6):733–44.

100. Sharma E, Attri DC, Sati P, Dhyani P, Szopa A, Sharifi-Rad J, et al. Recent updates on anticancer mechanisms of polyphenols. Frontiers in Cell and Developmental Biology [Internet]. 2022 [cited 2024 Jan 26];10. Available from: https://www.frontiersin.org/articles/10.3389/fcell.2022.1005910

101. Pandey KB, Rizvi SI. Plant polyphenols as dietary antioxidants in human health and disease. Oxid Med Cell Longev. 2009;2(5):270–8.

102. Panche AN, Diwan AD, Chandra SR. Flavonoids: an overview. J Nutr Sci. 2016 Dec 29;5:e47.

103. Shahidi F, Ambigaipalan P. Phenolics and polyphenolics in foods, beverages and spices: Antioxidant activity and health effects – A review. Journal of Functional Foods. 2015 Oct 1;18:820–97.

104. Shen N, Wang T, Gan Q, Liu S, Wang L, Jin B. Plant flavonoids: Classification, distribution, biosynthesis, and antioxidant activity. Food Chem. 2022 Jul 30;383:132531.

105. Mu K, Kitts DD. Intestinal polyphenol antioxidant activity involves redox signaling mechanisms facilitated by aquaporin activity. Redox Biol. 2023 Oct 28;68:102948.

106. Schieber M, Chandel NS. ROS Function in Redox Signaling and Oxidative Stress. Curr Biol. 2014 May 19;24(10):R453–62.

107. Rudrapal M, Khairnar SJ, Khan J, Dukhyil AB, Ansari MA, Alomary MN, et al. Dietary Polyphenols and Their Role in Oxidative Stress-Induced Human Diseases: Insights Into Protective Effects, Antioxidant Potentials and Mechanism(s) of Action. Front Pharmacol. 2022 Feb 14;13:806470.

108. Chronic Inflammation in Cancer Development - PMC [Internet]. [cited 2024 Jan 27]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3342348/

109. Yahfoufi N, Alsadi N, Jambi M, Matar C. The Immunomodulatory and Anti-Inflammatory Role of Polyphenols. Nutrients. 2018 Nov 2;10(11):1618.

110. Koushki M, Amiri- Dashatan N, Ahmadi N, Abbaszadeh H, Rezaei- Tavirani M. Resveratrol: A miraculous natural compound for diseases treatment. Food Sci Nutr. 2018 Oct 26;6(8):2473–90.

111. Ferrari E, Bettuzzi S, Naponelli V. The Potential of Epigallocatechin Gallate (EGCG) in Targeting Autophagy for Cancer Treatment: A Narrative Review. Int J Mol Sci. 2022 May 28;23(11):6075.

112. Pereira QC, dos Santos TW, Fortunato IM, Ribeiro ML. The Molecular Mechanism of Polyphenols in the Regulation of Ageing Hallmarks. Int J Mol Sci. 2023 Mar 14;24(6):5508.

113. Ahmad S, Tan ML, Hamid S. DNA repair mechanisms: Exploring potentials of nutraceutical. Journal of Functional Foods. 2023 Feb 1;101:105415.

114. Azqueta A, Collins A. Polyphenols and DNA Damage: A Mixed Blessing. Nutrients. 2016 Dec 3;8(12):785.

115. Yan Z, Zhong Y, Duan Y, Chen Q, Li F. Antioxidant mechanism of tea polyphenols and its impact on health benefits. Animal Nutrition. 2020 Jun 1;6(2):115–23.

116. Chimento A, De Luca A, D'Amico M, De Amicis F, Pezzi V. The Involvement of Natural Polyphenols in Molecular Mechanisms Inducing Apoptosis in Tumor Cells: A Promising Adjuvant in Cancer Therapy. Int J Mol Sci. 2023 Jan 14;24(2):1680.

117. Kalimuthu S, Se-Kwon K. Cell Survival and Apoptosis Signaling as Therapeutic Target for Cancer: Marine Bioactive Compounds. Int J Mol Sci. 2013 Jan 24;14(2):2334–54.

118. Kiruthiga C, Devi KP, Nabavi SM, Bishayee A. Autophagy: A Potential Therapeutic Target of Polyphenols in Hepatocellular Carcinoma. Cancers (Basel). 2020 Feb 29;12(3):562.

119. Cerezo AB, Winterbone MS, Moyle CWA, Needs PW, Kroon PA. Molecular structure- function relationship of dietary polyphenols for inhibiting VEGF- induced VEGFR- 2 activity. Mol Nutr Food Res. 2015 Nov;59(11):2119–31.

120. Chen X, Chang L, Qu Y, Liang J, Jin W, Xia X. Tea polyphenols inhibit the proliferation, migration, and invasion of melanoma cells through the down-regulation of TLR4. Int J Immunopathol Pharmacol. 2018 Jan 23;31:0394632017739531.

121. Recent Advances in Research on Polyphenols: Effects on Microbiota, Metabolism, and Health - Rajha - 2022 - Molecular Nutrition & Food Research - Wiley Online Library [Internet]. [cited 2024 Jan 27]. Available from: https://onlinelibrary.wiley.com/doi/10.1002/mnfr.202100670

122. Anticancer Efficacy of Polyphenols and Their Combinations - PMC [Internet]. [cited 2024 Jan 27]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5037537/

123. Del Bo' C, Bernardi S, Marino M, Porrini M, Tucci M, Guglielmetti S, et al. Systematic Review on Polyphenol Intake and Health Outcomes: Is there Sufficient Evidence to Define a Health-Promoting Polyphenol-Rich Dietary Pattern? Nutrients. 2019 Jun 16;11(6):1355.

124. Jia W, Zhou L, Li L, Zhou P, Shen Z. Nano-Based Drug Delivery of Polyphenolic Compounds for Cancer Treatment: Progress, Opportunities, and Challenges. Pharmaceuticals (Basel). 2023 Jan 10;16(1):101.

125. Vladu AF, Ficai D, Ene AG, Ficai A. Combination Therapy Using Polyphenols: An Efficient Way to Improve Antitumoral Activity and Reduce Resistance. Int J Mol Sci. 2022 Sep 6;23(18):10244.

126. Wang X, Qi Y, Zheng H. Dietary Polyphenol, Gut Microbiota, and Health Benefits. Antioxidants (Basel). 2022 Jun 20;11(6):1212.

127. Khan H, Reale M, Ullah H, Sureda A, Tejada S, Wang Y, et al. Anti-cancer effects of polyphenols via targeting p53 signaling pathway: updates and future directions. Biotechnol Adv. 2020;38:107385.

128. Abdal Dayem A, Choi HY, Yang GM, Kim K, Saha SK, Cho SG. The Anti-Cancer Effect of Polyphenols against Breast Cancer and Cancer Stem Cells: Molecular Mechanisms. Nutrients. 2016 Sep 21;8(9):581.

129. Zhou Y, Zheng J, Li Y, Xu DP, Li S, Chen YM, et al. Natural Polyphenols for Prevention and Treatment of Cancer. Nutrients. 2016 Aug 22;8(8):515.

130. Díaz-Torres RDC, Alonso-Castro AJ, Carrillo-Inungaray ML, Carranza-Alvarez C. Chapter 6 - Bioactive compounds obtained from plants, their pharmacological applications and encapsulation. In: Bhat RA, Hakeem KR, Dervash MA, editors. Phytomedicine [Internet]. Academic Press; 2021 [cited 2024 Jan 27]. p. 181–205. Available from: https://www.sciencedirect.com/science/article/pii/B9780128241097000170

131. Subramaniam S, Selvaduray KR, Radhakrishnan AK. Bioactive Compounds: Natural Defense Against Cancer? Biomolecules. 2019 Nov 21;9(12):758.

132. Greenwell M, Rahman PKSM. Medicinal Plants: Their Use in Anticancer Treatment. Int J Pharm Sci Res. 2015 Oct 1;6(10):4103–12.

133. Khan T, Ali M, Khan A, Nisar P, Jan SA, Afridi S, et al. Anticancer Plants: A Review of the Active Phytochemicals, Applications in Animal Models, and Regulatory Aspects. Biomolecules. 2019 Dec 27;10(1):47.

134. Ullah A, Munir S, Badshah SL, Khan N, Ghani L, Poulson BG, et al. Important Flavonoids and Their Role as a Therapeutic Agent. Molecules. 2020 Nov 11;25(22):5243.

135. Briguglio G, Costa C, Pollicino M, Giambò F, Catania S, Fenga C. Polyphenols in cancer prevention: New insights (Review). International Journal of Functional Nutrition. 2020 Nov 1;1(2):1–1.

136. Anand David AV, Arulmoli R, Parasuraman S. Overviews of Biological Importance of Quercetin: A Bioactive Flavonoid. Pharmacogn Rev. 2016;10(20):84–9.

137. Salama YA, El-karef A, El Gayyar AM, Abdel-Rahman N. Beyond its antioxidant properties: Quercetin targets multiple signalling pathways in hepatocellular carcinoma in rats. Life Sciences. 2019 Nov 1;236:116933.

138. Almatroodi SA, Alsahli MA, Almatroudi A, Verma AK, Aloliqi A, Allemailem KS, et al. Potential Therapeutic Targets of Quercetin, a Plant Flavonol, and Its Role in the Therapy of Various Types of Cancer through the Modulation of Various Cell Signaling Pathways. Molecules. 2021 Jan;26(5):1315.

139. Singh BN, Shankar S, Srivastava RK. Green tea catechin, epigallocatechin-3-gallate (EGCG): mechanisms, perspectives and clinical applications. Biochem Pharmacol. 2011 Dec 15;82(12):1807–21.

140. Tauber AL, Schweiker SS, Levonis SM. From tea to treatment; epigallocatechin gallate and its potential involvement in minimizing the metabolic changes in cancer. Nutrition Research. 2020 Feb 1;74:23–36.

141. Swamy MK, Vasamsetti BMK. 2 - Taxol: Occurrence, chemistry, and understanding its molecular mechanisms. In: Swamy MK, Pullaiah T, Chen ZS, editors. Paclitaxel [Internet]. Academic Press; 2022 [cited 2024 Jan 27]. p. 29–45. Available from: https://www.sciencedirect.com/science/article/pii/B9780323909518000096

142. Huang Q, Mei Z, Han X. Efficacy and safety of taxanes combined with chemotherapy drugs in advanced triple negative breast cancer: A meta-analysis of 26 randomized controlled trials. Front Oncol. 2022 Aug 31;12:972767.

143. Jeong A, Suazo KF, Wood WG, Distefano MD, Li L. Isoprenoids and Protein Prenylation: Implications in the Pathogenesis and Therapeutic Intervention of Alzheimer's Disease. Crit Rev Biochem Mol Biol. 2018 Jun;53(3):279–310.

144. Use of Synthetic Isoprenoids to Target Protein Prenylation and Rho GTPases in Breast Cancer Invasion | PLOS ONE [Internet]. [cited 2024 Jan 27]. Available from: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0089892

145. Farnesyltransferase Inhibitor - an overview | ScienceDirect Topics [Internet]. [cited 2024 Jan 27]. Available from: https://www.sciencedirect.com/topics/neuroscience/farnesyltransferase-inhibitor

146. Mo H, Jeter R, Bachmann A, Yount ST, Shen CL, Yeganehjoo H. The Potential of Isoprenoids in Adjuvant Cancer Therapy to Reduce Adverse Effects of Statins. Front Pharmacol. 2019 Jan 4;9:1515.

147. Ivanescu B, Miron A, Corciova A. Sesquiterpene Lactones from Artemisia Genus: Biological Activities and Methods of Analysis. J Anal Methods Chem. 2015;2015:247685.

148. Huang QF, Li YH, Huang ZJ, Jun M, Wang W, Chen XL, et al. Artesunate carriers induced ferroptosis to overcome biological barriers for anti-cancer. Eur J Pharm Biopharm. 2023 Sep;190:284–93.

149. Saavedra E, Estévez-Sarmiento F, Said M, Eiroa JL, Rubio S, Quintana J, et al. Cytotoxicity of the Sesquiterpene Lactone Spiciformin and Its Acetyl Derivative against the Human Leukemia Cell Lines U-937 and HL-60. Int J Mol Sci. 2020 Apr 16;21(8):2782.

150. Li F, Jiang T, Li Q, Ling X. Camptothecin (CPT) and its derivatives are known to target topoisomerase I (Top1) as their mechanism of action: did we miss something in CPT analogue molecular targets for treating human disease such as cancer? Am J Cancer Res. 2017 Dec 1;7(12):2350–94.

151. Pan P, Huang YW, Oshima K, Yearsley M, Zhang J, Arnold M, et al. The immunomodulatory potential of natural compounds in tumor-bearing mice and humans. Crit Rev Food Sci Nutr. 2019;59(6):992–1007.

152. Mirończuk-Chodakowska I, Kujawowicz K, Witkowska AM. Beta-Glucans from Fungi: Biological and Health-Promoting Potential in the COVID-19 Pandemic Era. Nutrients. 2021 Nov 6;13(11):3960.

153. Gun SY, Lee SWL, Sieow JL, Wong SC. Targeting immune cells for cancer therapy. Redox Biol. 2019 Mar 20;25:101174.

154. Calabrese V, Cornelius C, Dinkova-Kostova AT, Calabrese EJ, Mattson MP. Cellular Stress Responses, The Hormesis Paradigm, and Vitagenes: Novel Targets for Therapeutic Intervention in Neurodegenerative Disorders. Antioxid Redox Signal. 2010 Dec 1;13(11):1763–811.

155. Shamim U, Hanif S, Albanyan A, Beck FWJ, Bao B, Wang Z, et al. Resveratrol-induced apoptosis is enhanced in low pH environments associated with cancer. Journal of Cellular Physiology. 2012;227(4):1493–500.

156. Bao J, Huang B, Zou L, Chen S, Zhang C, Zhang Y, et al. Hormetic Effect of Berberine Attenuates the Anticancer Activity of Chemotherapeutic Agents. PLoS One. 2015 Sep 30;10(9):e0139298.

157. Pharmaceuticals | Free Full-Text | Status and Challenges of Plant-Anticancer Compounds in Cancer Treatment [Internet]. [cited 2024 Jan 27]. Available from: https://www.mdpi.com/1424-8247/14/2/157

158. Cao J, Cao J, Wang H, Chen L, Cao F, Su E. Solubility improvement of phytochemicals using (natural) deep eutectic solvents and their bioactivity evaluation. Journal of Molecular Liquids. 2020 Nov 15;318:113997.

159. Li Z, Jiang H, Xu C, Gu L. A review: Using nanoparticles to enhance absorption and bioavailability of phenolic phytochemicals. Food Hydrocolloids. 2015 Jan 1;43:153–64.

160. Asma ST, Acaroz U, Imre K, Morar A, Shah SRA, Hussain SZ, et al. Natural Products/Bioactive Compounds as a Source of Anticancer Drugs. Cancers (Basel). 2022 Dec 15;14(24):6203.

161. Choudhari AS, Mandave PC, Deshpande M, Ranjekar P, Prakash O. Phytochemicals in Cancer Treatment: From Preclinical Studies to Clinical Practice. Front Pharmacol. 2020 Jan 28;10:1614.

162. Steele VE, Lubet RA. The Use of Animal Models for Cancer Chemoprevention Drug Development. Semin Oncol. 2010 Aug;37(4):327–38.

163. Molecules | Free Full-Text | Unravelling the Anticancer Mechanisms of Traditional Herbal Medicines with Metabolomics [Internet]. [cited 2024 Jan 28]. Available from: https://www.mdpi.com/1420-3049/26/21/6541

164. German-Ponciano LJ, Rosas-Sánchez GU, Rivadeneyra-Domínguez E, Rodríguez-Landa JF. Advances in the Preclinical Study of Some Flavonoids as Potential Antidepressant Agents. Scientifica (Cairo). 2018 Feb 1;2018:2963565.

165. Shahbaz M, Naeem H, Momal U, Imran M, Alsagaby SA, Al Abdulmonem W, et al. Anticancer and apoptosis inducing potential of quercetin against a wide range of human malignancies. International Journal of Food Properties. 2023 Sep 22;26(1):2590–626.

166. Mony TJ, Elahi F, Choi JW, Park SJ. Neuropharmacological Effects of Terpenoids on Preclinical Animal Models of Psychiatric Disorders: A Review. Antioxidants. 2022 Sep;11(9):1834.

167. Michaud LB, Valero V, Hortobagyi G. Risks and Benefits of Taxanes in Breast and Ovarian Cancer. Drug-Safety. 2000 Nov 1;23(5):401–28.

168. Mukhtar E, Adhami VM, Mukhtar H. Targeting Microtubules by Natural Agents for Cancer Therapy. Mol Cancer Ther. 2014 Feb;13(2):275–84.

169. Bisol Â, de Campos PS, Lamers ML. Flavonoids as anticancer therapies: A systematic review of clinical trials. Phytotherapy Research. 2020;34(3):568–82.

170. Cheon M, Chung M, Park Y. Association between Dietary Intake of Flavonoids and Cancer Recurrence among Breast Cancer Survivors. Nutrients. 2021 Aug 30;13(9):3049.

171. Mereles D, Hunstein W. Epigallocatechin-3-gallate (EGCG) for clinical trials: more pitfalls than promises? Int J Mol Sci. 2011;12(9):5592–603.

172. Update on the Antitumor Activity of Paclitaxel in Clinical Trials - Eric K. Rowinsky, 1994 [Internet]. [cited 2024 Jan 28]. Available from: https://journals.sagepub.com/doi/abs/10.1177/10600280940280S505?journalCode=aopd

173. Kumar S, Mahdi H, Bryant C, Shah JP, Garg G, Munkarah A. Clinical trials and progress with paclitaxel in ovarian cancer. Int J Womens Health. 2010 Nov 19;2:411–27.

174. Depierre A, Lemarie E, Dabouis G, Garnier G, Jacoulet P, Dalphin JC. A phase II study of Navelbine (vinorelbine) in the treatment of non-small-cell lung cancer. Am J Clin Oncol. 1991 Apr;14(2):115–9.

175. Xu C, Zhang H, Mu L, Yang X. Artemisinins as Anticancer Drugs: Novel Therapeutic Approaches, Molecular Mechanisms, and Clinical Trials. Frontiers in Pharmacology [Internet]. 2020 [cited 2024 Jan 28];11. Available from: https://www.frontiersin.org/articles/10.3389/fphar.2020.529881

176. Li X, Zhou Y, Liu Y, Zhang X, Chen T, Chen K, et al. Preclinical Efficacy and Safety Assessment of Artemisinin-Chemotherapeutic Agent Conjugates for Ovarian Cancer. eBioMedicine. 2016 Dec 1;14:44–54.

177. Sayed N, Khurana A, Godugu C. Pharmaceutical perspective on the translational hurdles of phytoconstituents and strategies to overcome. Journal of Drug Delivery Science and Technology. 2019 Oct 1;53:101201.

178. Aungst BJ. Optimizing Oral Bioavailability in Drug Discovery: An Overview of Design and Testing Strategies and Formulation Options. Journal of Pharmaceutical Sciences. 2017 Apr 1;106(4):921–9.

179. Preclinical Toxicology - an overview | ScienceDirect Topics [Internet]. [cited 2024 Jan 28]. Available from: https://www.sciencedirect.com/topics/pharmacology-toxicology-and-pharmaceutical-science/preclinical-toxicology

180. Sadida HQ, Abdulla A, Marzooqi SA, Hashem S, Macha MA, Akil ASAS, et al. Epigenetic modifications: Key players in cancer heterogeneity and drug resistance. Translational Oncology. 2024 Jan 1;39:101821.

181. Spreafico A, Hansen AR, Abdul Razak AR, Bedard PL, Siu LL. The Future of Clinical Trials Design in Oncology. Cancer Discov. 2021 Apr;11(4):822–37.

182. Ulrich-Merzenich GS. Combination screening of synthetic drugs and plant derived natural products—Potential and challenges for drug development. Synergy. 2014 Sep 1;1(1):59–69.

183. Seca AML, Pinto DCGA. Plant Secondary Metabolites as Anticancer Agents: Successes in Clinical Trials and Therapeutic Application. International Journal of Molecular Sciences. 2018 Jan;19(1):263.

184. Pelusi J. Incorporating Clinical Trial Data Into Daily Cancer Care. J Adv Pract Oncol. 2012;3(6):378–84.

185. Blevins D, Farmer MS, Edlund C, Sullivan G, Kirchner JE. Collaborative research between clinicians and researchers: a multiple case study of implementation. Implementation Science. 2010 Oct 14;5(1):76.

186. Plants as a Source of Anticancer Agents: From Bench to Bedside - PMC [Internet]. [cited 2024 Jan 28]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9369847/

187. Xie X, Zhang Y, Li F, Lv T, Li Z, Chen H, et al. Challenges and Opportunities from Basic Cancer Biology for Nanomedicine for Targeted Drug Delivery. Curr Cancer Drug Targets. 2019;19(4):257–76.

188. Abourashed EA. Bioavailability of Plant-Derived Antioxidants. Antioxidants. 2013 Dec;2(4):309–25.

189. Rein MJ, Renouf M, Cruz- Hernandez C, Actis- Goretta L, Thakkar SK, da Silva Pinto M. Bioavailability of bioactive food compounds: a challenging journey to bioefficacy. Br J Clin Pharmacol. 2013 Mar;75(3):588–602.

190. Chehelgerdi M, Chehelgerdi M, Allela OQB, Pecho RDC, Jayasankar N, Rao DP, et al. Progressing nanotechnology to improve targeted cancer treatment: overcoming hurdles in its clinical implementation. Molecular Cancer. 2023 Oct 9;22(1):169.

191. Calixto JB. Efficacy, safety, quality control, marketing and regulatory guidelines for herbal medicines (phytotherapeutic agents). Braz J Med Biol Res. 2000 Feb;33:179–89.

192. Shan J, Rodgers K, Lai CT, Sutherland S. Challenges in natural health product research: The importance of standardization. Proceedings of the Western Pharmacology Society. 2007 Feb 1;50:24–30.

193. Bitwell C, Indra SS, Luke C, Kakoma MK. A review of modern and conventional extraction techniques and their applications for extracting phytochemicals from plants. Scientific African. 2023 Mar 1;19:e01585.

194. El-Sayes N, Vito A, Mossman K. Tumor Heterogeneity: A Great Barrier in the Age of Cancer Immunotherapy. Cancers (Basel). 2021 Feb 15;13(4):806.

195. Alfonzetti T, Yasmin-Karim S, Ngwa W, Avery S. Phytoradiotherapy: An Integrative Approach to Cancer Treatment by Combining Radiotherapy With Phytomedicines. Frontiers in Oncology [Internet]. 2021 [cited 2024 Jan 28];10. Available from: https://www.frontiersin.org/journals/oncology/articles/10.3389/fonc.2020.624663

196. O'Brien K, Ried K, Binjemain T, Sali A. Integrative Approaches to the Treatment of Cancer. Cancers. 2022 Jan;14(23):5933.

197. Biomedicines | Free Full-Text | Plant-Derived Bioactive Compounds in Colorectal Cancer: Insights from Combined Regimens with Conventional Chemotherapy to

Overcome Drug-Resistance [Internet]. [cited 2024 Jan 28]. Available from: https://www.mdpi.com/2227-9059/10/8/1948

198. The Immunomodulatory Potential of Selected Bioactive Plant-Based ...: Ingenta Connect [Internet]. [cited 2024 Jan 28]. Available from: https://www.ingentaconnect.com/content/ben/acamc/2017/00000017/00000006/art00003

199. A guide to cancer immunotherapy: from T cell basic science to clinical practice | Nature Reviews Immunology [Internet]. [cited 2024 Jan 28]. Available from: https://www.nature.com/articles/s41577-020-0306-5

200. Vaccines | Free Full-Text | Plant-Derived Nutraceuticals and Immune System Modulation: An Evidence-Based Overview [Internet]. [cited 2024 Jan 28]. Available from: https://www.mdpi.com/2076-393X/8/3/468

201. Wang H, Khor TO, Shu L, Su Z, Fuentes F, Lee JH, et al. Plants Against Cancer: A Review on Natural Phytochemicals in Preventing and Treating Cancers and Their Druggability. Anticancer Agents Med Chem. 2012 Dec;12(10):1281–305.

202. Science-Driven Nutritional Interventions for the Prevention and Treatment of Cancer - PMC [Internet]. [cited 2024 Jan 28]. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10749912/

203. Malone ER, Oliva M, Sabatini PJB, Stockley TL, Siu LL. Molecular profiling for precision cancer therapies. Genome Medicine. 2020 Jan 14;12(1):8.

204. Verma M. Personalized Medicine and Cancer. J Pers Med. 2012 Jan 30;2(1):1–14.

205. Efferth T. Personalized Cancer Medicine: From Molecular Diagnostics to Targeted Therapy with Natural Products. Planta Med. 2010 Aug;76(11):1143–54.

206. Plant natural modulators in breast cancer prevention: status quo and future perspectives reinforced by predictive, preventive, and personalized medical approach | EPMA Journal [Internet]. [cited 2024 Jan 28]. Available from: https://link.springer.com/article/10.1007/s13167-018-0154-6

207. Nano based drug delivery systems: recent developments and future prospects | Journal of Nanobiotechnology | Full Text [Internet]. [cited 2024 Jan 28]. Available from: https://jnanobiotechnology.biomedcentral.com/articles/10.1186/s12951-018-0392-8

208. Vinothini K, Rajan M. Chapter 9 - Mechanism for the Nano-Based Drug Delivery System. In: Mohapatra SS, Ranjan S, Dasgupta N, Mishra RK, Thomas S, editors. Characterization and Biology of Nanomaterials for Drug Delivery [Internet]. Elsevier; 2019 [cited 2024 Jan 28]. p. 219–63. (Micro and Nano Technologies). Available from: https://www.sciencedirect.com/science/article/pii/B978012814031400009X

209. Shekar N, Vuong P, Kaur P. Analysing potent biomarkers along phytochemicals for breast cancer therapy: an in silico approach. Breast Cancer Res Treat. 2024 Jan 1;203(1):29–47.

210. Ahmad A, Imran M, Ahsan H. Biomarkers as Biomedical Bioindicators: Approaches and Techniques for the Detection, Analysis, and Validation of Novel Biomarkers of Diseases. Pharmaceutics. 2023 Jun;15(6):1630.

211. Hashem S, Ali TA, Akhtar S, Nisar S, Sageena G, Ali S, et al. Targeting cancer signaling pathways by natural products: Exploring promising anti-cancer agents. Biomedicine & Pharmacotherapy. 2022 Jun 1;150:113054.