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Therapeutic Potentials of Plant-Based Compounds for Cancer Therapy

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ABSTRACT

Cancer remains a leading cause of mortality globally due to factors such as aging populations, lifestyle habits, and chemical exposures. While conventional treatments like chemotherapy and radiotherapy are widely used, they are often associated with significant side effects, prompting interest in natural compounds as alternative or complementary therapies. This review explores the anticancer potential of phytochemicals derived from medicinal plants, which have long been utilized in traditional medicine systems. Vital classes of these bioactive compounds which include alkaloids, terpenoids, flavonoids, and polyphenols exhibit diverse anticancer mechanisms including apoptosis induction, inhibition of cell proliferation, modulation of oncogenic signaling pathways, and suppression of metastasis. Notable examples include cepharanthine, paclitaxel, betulinic acid, nobiletin, and curcumin, which target pathways such as PI3K/Akt/mTOR, NF-κB, and Wnt/β-catenin. These phytochemicals not only demonstrate efficacy in preclinical cancer models but also show promise for integration into combinatorial therapeutic regimens. The growing body of evidence supports the continued investigation of plant-based compounds as cost-effective, low-toxicity options in cancer management. By advancing our understanding of their molecular targets and synergistic effects, phytochemicals may significantly contribute to the development of safer, more accessible cancer therapies.

1. Introduction

Cancer currently accounts for approximately one in six deaths worldwide (World Health Organization, 2018). A range of modifiable behavioral and dietary risk factors contribute to this burden, including physical inactivity, tobacco use, excessive alcohol consumption, and insufficient intake of fruits and vegetables. Other contributing factors include an aging global population and exposure to carcinogenic substances such as specific chemicals, metals, and infectious agents (Jemal et al., 2011; Iqbal et al., 2017). These trends highlight the urgent need for effective cancer prevention and treatment strategies. Similarly epidemiological data indicate that approximately 5% of human cancers are attributable to viral infections, another 5% to radiation, and the remaining 90% to chemical exposures. Among chemical causes, tobacco use alone is responsible for about 30% of cases, while the remainder are linked to diet, lifestyle, and environmental factors (Roy et al., 2017). An estimated six million chemical substances have been documented in chemical abstracts, with several identified as potential carcinogens. These carcinogens are broadly classified into genotoxic and non-genotoxic types. Genotoxic carcinogens, particularly the non-alkylating variety, directly interact with the exocyclic amino groups of nucleosides, often through oxidative reactions or direct electrophilic attacks. These interactions can induce molecular alterations such as deamination or tautomeric shifts, ultimately disrupting normal base pairing. Notable examples include nitric oxide, which facilitates oxidative deamination, and formaldehyde, known for forming DNA cross-links (Roy et al., 2018).

Alkylating genotoxic agents can be categorized further into direct-acting and indirect-acting carcinogens. Direct-acting agents, such as ethylnitrosourea, ethyl sulfonate, and methylnitrosourea, interact directly with genomic material. In contrast, indirect-acting carcinogens such as diethylnitrosamine, nitrofurans, ethylene dibromide, N-acetyl-2-aminofluorene, and dimethylhydrazine require metabolic activation by the host organism to form reactive intermediates (Roy et al., 2018). The carcinogenic process involves a series of complex molecular and cellular events, typically progressing through three major stages: initiation, promotion, and progression. These stages collectively transform normal cells into malignant ones (Adewale et al 2024).

Cancer treatment strategies vary based on multiple factors, including cancer type, stage, and extent of metastasis within the body. Although specific treatment modalities may be effective individually, a combinatorial approach is often favored to enhance therapeutic outcomes and ensure comprehensive recovery. Conventional treatments such as chemotherapy, surgical intervention, and radiotherapy remain the cornerstone of cancer therapy; however, these methods are frequently associated with significant adverse effects, necessitating the exploration of alternative or complementary options (Adewale et al 2024a; Adewale et al 2024b).

One promising area of research involves the use of natural compounds, particularly those derived from plants, as potential anticancer agents. Medicinal plants have historically played a significant role in the treatment of various diseases, including cancer. It is estimated that approximately 70,000 plant species from lichens to large trees have been utilized for medicinal purposes across cultures and time periods. The importance of plants in early medicine is evidenced by archaeological findings such as the discovery of a 60,000-year-old burial site in Iraq, which contained remnants of eight medicinal plants,

suggesting both spiritual and therapeutic significance (Pan et al., 2013). Similarly, excavations in Sri Lanka have revealed that the Balangoda people employed plant-based remedies as far back as 30,000 years ago (Perera, 2004). Such findings indicate that the use of plant-derived extracts and isolated compounds represents one of the oldest forms of medical treatment known to humankind.

Plant-derived compounds have historically played a crucial role in cancer therapy. In early comprehensive studies, it was documented that more than 3,000 plant species exhibiting potential anticancer properties (Graham et al., 2000). The systematic exploration of plant sources for anticancer agents began in the 1950s and has since served as a foundation for the development of novel compounds with diverse structural features through synthetic, combinatorial, and biotechnological approaches. Notably, over 60% of the anticancer drugs currently in clinical use have origins in natural products, particularly from plant sources (Cragg & Newman, 2005; Khan, 2014; Adewale et al., 2024).

The therapeutic potential of these plants is attributed to a variety of bioactive secondary metabolites (Oladele et al., 2020; Oladele et al., 2021; Oladele et al., 2024, low-molecular-weight compounds that are not directly involved in primary metabolic processes but serve defensive roles against pathogens and herbivores (Dixon, 2001; Prajapati et al., 2007). These secondary metabolites include flavonoids, phenolic compounds, terpenoids, alkaloids, and sulfur-containing substances (Oladele et al., 2020). Interestingly, taxonomically related plant species often produce structurally and functionally related compounds. Many of these phytochemicals exhibit anti-mutagenic and anticancer activities, acting through mechanisms such as modulation of signal transduction pathways in cells (Verpoorte, 1998).

The objective of this article is to provide a comprehensive review of the anticancer potential of plant-derived phytochemicals. This review aims to categorize key classes of phytochemicals namely alkaloids, terpenoids, flavonoids, and polyphenols and elucidate their molecular mechanisms of action; and assess the therapeutic relevance of these compounds through evidence from preclinical and clinical studies. By analyzing current knowledge, the article seeks to elucidate the value of phytochemicals as promising, low-toxicity alternatives or adjuncts to conventional cancer therapies and to identify potential avenues for future research and clinical application in the field of oncology.

2. Phytochemicals with anticancer properties

2.1 Alkaloids

Alkaloids are a diverse class of naturally occurring compounds that have shown significant potential in drug development, particularly due to their broad pharmacological activities. Several alkaloids derived from medicinal plants have demonstrated anti-proliferative and anti-metastatic effects in both *in vitro* and *in vivo* models of various cancers, including breast cancer. Cepharanthine (CEP) is a biscoclaurine alkaloid extracted from *Stephania cepharantha*. It has exhibited anti-tumor activity across multiple cancer types. In breast cancer cell lines MCF-7 and MDA-MB-231, CEP was shown to suppress cell proliferation and motility. It induced autophagic cell death by interfering with the AKT/mTOR signaling pathway, suggesting its potential as a targeted therapeutic agent (Gao et al., 2017).

Colchicine, an alkaloid derived from *Colchicum autumnale*, functions as a natural tubulin-binding agent with known anti-tumor properties. In cancer cells, colchicine was observed to induce cell cycle arrest at the G2/M phase, leading to apoptosis. This effect is attributed to its disruption of mitotic spindle formation, thereby inhibiting cell division and promoting cell death (Sun et al., 2016). Dehydrocorydaline (DHC), an isoquinoline alkaloid isolated from *Corydalis yanhusuo*, has demonstrated anti-cancer efficacy through the suppression of multiple tumor-promoting proteins. DHC downregulated anti-apoptotic and cell proliferation markers such as BCL-2, CCND1, BCL-3, and CDK1, as well as matrix metalloproteinases MMP2 and MMP9, which are involved in tumor metastasis. Concurrently, it increased the expression of pro-apoptotic proteins, including caspase-3, -8, and -9, indicating its dual role in inhibiting tumor growth and metastatic potential (Huang et al., 2020).

Harmine, a β-carboline alkaloid originally identified in *Peganum harmala*, has also shown promising anti-tumor properties. *In vitro* studies revealed that harmine suppressed breast cancer cell proliferation and migration while inducing apoptosis. *In vivo*, it was effective in reducing tumor growth. Mechanistically, harmine inhibited the expression of several oncogenic proteins, including phosphorylated ERK (pERK), Bcl-2, phosphorylated AKT (pAKT), and the transcriptional co-activator with PDZ-binding motif (TAZ), further supporting its potential use in cancer therapy (Ding et al., 2019). Paclitaxel, commonly known as Taxol (PTX), is a naturally derived isoprenoid metabolite with well-documented antitumor properties. Its primary mechanism of action involves the stabilization of microtubules by binding to β-tubulin, thereby inhibiting microtubule disassembly. This interference disrupts normal mitotic spindle formation, leading to cell cycle arrest at the G2/M phase and promoting apoptotic cell death (Barbuti & Chen, 2015; Gornstein & Schwartz, 2014). In addition to its cytoskeletal effects, paclitaxel has been shown to modulate apoptotic signaling pathways. For instance, a study on canine mammary gland tumor cells demonstrated that PTX treatment resulted in the downregulation of the anti-apoptotic protein Bcl-2 and the upregulation of the pro-apoptotic protein BAX, thereby promoting apoptosis in cancerous cells (Ren et al., 2018).

Irinotecan is a well-established chemotherapeutic agent and one of the most effective inhibitors of topoisomerase I. Its mechanism of action involves pH-dependent structural modifications that enhance its interaction with cellular components. Irinotecan forms a ternary complex with topoisomerase I and DNA, which impedes the re-ligation of the DNA strand and prevents the release of topoisomerase I. When replication forks encounter this stabilized complex, they result in the formation of lethal DNA double-strand breaks (Stenvang et al., 2013). This damage triggers DNA damage checkpoint signaling, replication fork arrest, and ultimately, apoptosis (Xu et al., 2002). Notably, the expression of topoisomerase I is significantly upregulated, reported to be approximately 14 to 16 times higher in cancer cells compared to adjacent normal tissues, which enhances the therapeutic selectivity of irinotecan (Kciuk et al., 2020). Clinically, irinotecan is frequently employed in combination therapies, particularly for the treatment of metastatic colorectal cancer. Common combination regimens include XELIRI, which pairs irinotecan with capecitabine (Hoff et al., 2001); IROX, a combination

of irinotecan and oxaliplatin (Bajetta et al., 2004); and FOLFIRI, which includes leucovorin (LV), 5-fluorouracil (5-FU), and irinotecan (Tournigand et al., 2004). These combination therapies have been shown to improve treatment efficacy and patient outcomes in advanced-stage disease.

Berberine is a naturally occurring isoquinoline alkaloid primarily found in the rhizomes of *Hydrastis canadensis* and *Coptis chinensis*. It has been reported to exhibit a range of pharmacological activities, including anti-tumor, hypolipidemic, and hypoglycemic effects, as well as the ability to induce autophagy through the inhibition of mTOR and Akt signaling pathways (Wang et al., 2020). In lung cancer cells, berberine has been shown to downregulate cyclin D1 and E1 proteins, leading to cell cycle arrest at the G1 phase (Xiao et al., 2018). In colorectal cancer models, the combination of berberine with a heat shock protein 90 (Hsp90) inhibitor significantly reduced the expression of CDK4 and cyclin D1, enhancing the anticancer response (Su et al., 2015). Additionally, in chondrosarcoma cells, berberine promotes the upregulation of p53 and p21 by modulating the Akt and p38 signaling pathways (Eo et al., 2014). Berberine has also been associated with the stabilization of the retinoblastoma (Rb) protein, inhibition of its phosphorylation, and suppression of Rb mRNA degradation, further contributing to its anti-proliferative properties (Chai et al., 2014; Wu et al., 2015).

2.2 Terpenoids

Terpenoid-based nutraceuticals represent a vast and chemically diverse group of natural compounds, comprising approximately 40,000 distinct molecules. This extensive chemical variety makes terpenoids a valuable resource for the development of novel chemotherapeutic agents that are both effective and potentially less toxic (Ateba et al., 2018). Several terpenoid compounds have demonstrated promising anti-cancer properties, particularly in the context of breast cancer. One such compound is α-santalol, a sesquiterpene derived from *Santalum album*. Its therapeutic potential lies in its ability to modulate signal transduction pathways associated with cancer progression. α-Santalol has exhibited anti-tumor activity across various cancer types through the induction of apoptosis and cell cycle arrest. In breast cancer, it inhibits cell migration primarily by suppressing the Wnt/β-catenin signaling pathway (Bommareddy et al., 2018).

Another notable terpenoid is astragaloside IV, a bioactive saponin extracted from the traditional Chinese medicinal plant *Astragalus membranaceus*. Astragaloside IV exhibits a wide range of pharmacological activities, including anticancer, antioxidant, cardioprotective, neuroprotective, and immunomodulatory effects. Recent studies have shown that it activates the expression of *TRHDE-antisense RNA 1* (TRHDE-AS1), a regulatory RNA involved in cancer progression. Both *in vitro* and *in vivo* experiments confirmed that astragaloside IV suppresses cancer cell proliferation and metastasis through upregulation of TRHDE-AS1 (Hu et al., 2021).

Betulinic acid, a pentacyclic triterpenoid found in wild jujube seeds, *Shorea acuminatissima* leaves, and white birch bark, is another compound with demonstrated anti-cancer potential. It exerts its effects by inhibiting topoisomerase activity and cyclin expression, leading to cell cycle arrest. Betulinic acid also interferes with vascular endothelial growth factor (VEGF) signaling and transcription factors such as specificity proteins and NF-κB, ultimately promoting apoptosis via mitochondrial pathways. Additionally, its downregulation of matrix metalloproteinases contributes to its anti-metastatic and anti-angiogenic properties (Luo et al., 2016). Ursolic acid, another pentacyclic triterpenoid, is commonly found in fruits and vegetables and is notably extracted from *Ocimum tenuiflorum*. It has been shown to inhibit cancer cell proliferation by modulating key oncogenic signaling pathways, including epidermal growth factor receptor (EGFR), PI3K/Akt/mTOR, and ERK pathways (Yin et al., 2018).

Lastly, β-caryophyllene oxide, a sesquiterpene obtained from the essential oil of *Myrica rubra*, exhibits anti-cancer activity by inducing apoptosis through caspase-3 activation and downregulating GSK signaling. These effects are mediated through the PI3K/Akt and NF-κB pathways, highlighting its therapeutic relevance in cancer (Hanušová et al., 2017).

2.3 Flavonoids

Flavonoids are naturally occurring polyphenolic compounds recognized for their nutritional value and therapeutic potential in the management of various diseases, including cancer. As the most abundant polyphenols in the human diet, flavonoids are widely present in fruits, vegetables, and plant-based beverages, and they form essential components of numerous herbal formulations. These compounds have been shown to exert anticancer effects by upregulating tumor suppressor genes, thereby inhibiting cancer progression and metastasis across several cancer types (Selvakumar et al., 2020).

One notable flavonoid is nobiletin, a polymethoxylated flavone derived from *Citrus depressa* Hayata. Nobiletin has demonstrated a broad range of pharmacological activities, including cardiovascular protection, anti-tumor effects, immune modulation, and the mitigation of chronic inflammation, oxidative stress, insulin resistance, osteoclastogenesis, and neurodegenerative conditions (Li et al., 2018). In breast cancer models, particularly MDA-MB-468 cells, nobiletin was found to inhibit ERK1/2 signaling, arrest the cell cycle in the G0/G1 phase, suppress cyclin D1 expression, and promote p21 overexpression. Additionally, it reduced the activity of mTOR and AKT pathways and induced apoptosis by downregulating Bcl-xL expression, without altering Bax levels (Noguchi et al., 2016).

Baicalin, another flavonoid isolated from the dried root of *Scutellaria baicalensis* Georgi, has traditionally been used to treat central nervous system disorders, liver diseases, and inflammatory conditions. Similarly, kaempferol, a flavonol derived from *Moringa oleifera* (Ajisebiola et al., 2023, Ajisebiola et al., 2024, Ajisebiola et al., 2024a), is a common dietary flavonoid with anticancer activity. In MDA-MB-453 human breast cancer cells, kaempferol induced G2/M phase cell cycle arrest by inhibiting cyclin-dependent kinase 1 (CDK1) (Akram et al., 2017). Moreover, kaempferol functions as a potent inducer of nuclear factor erythroid 2–related factor 2 (Nrf2), enhancing the expression of antioxidant enzymes such as NAD(P)H:quinone oxidoreductase 1 (NQO1) in MCF-7 cells, thereby contributing to the inhibition of oncogenic transformation (Wang, Yang, et al., 2019).

Icariin, a prenylated flavonol glycoside obtained from *Epimedium sagittatum*, is known for its diverse pharmacological properties, including aphrodisiac effects, bone formation stimulation, central nervous system activity, cardioprotection, and immune regulation. In the context of breast cancer, icariin inhibited the NF-κB/epithelial-mesenchymal transition (EMT) pathway through the upregulation of SIRT6, thereby suppressing the migration and invasion of cancer cells (Song et al., 2020).

2.4 Polyphenols

Polyphenols are naturally occurring compounds characterized by the presence of multiple phenolic groups in their molecular structures. They are widely distributed in the plant kingdom and constitute an essential part of the human diet (Oladele et al., 2025). For centuries, polyphenols have been employed in traditional medicinal systems across diverse cultures. These compounds exhibit a broad spectrum of biological activities, with notable anti-cancer properties. Their mechanisms of action include modulation of cellular transformation, promotion of differentiation, inhibition of proliferation and invasion, suppression of angiogenesis, and induction of apoptosis in cancer cells (Putra et al., 2020; Raman et al., 2018).

Among polyphenol-based nutraceuticals, curcumin, a polyphenolic compound derived from the rhizome of *Curcuma longa*, is particularly well-studied for its therapeutic potential in cancer. The rhizome of *Curcuma longa* (family Zingiberaceae), commonly known as turmeric, is widely used in traditional polyherbal formulations for the treatment of various types of cancer. In addition to its medicinal applications, turmeric is extensively employed as a spice and flavoring agent in Sri Lankan cuisine, where it is referred to as *kaha* in Sinhalese and *manchal* in Tamil (Williamson, 2002; Resorts, 2017). Its therapeutic relevance is largely attributed to curcumin, a bioactive polyphenolic compound with well-documented anti-inflammatory, antioxidant, and anticancer properties (Oladiji and Oladele, 2023). Traditionally valued in Ayurvedic medicine, curcumin has demonstrated pro-apoptotic effects and inhibited epidermal growth factor receptor (EGFR) signaling in MDA-MB-231 cancer cells (Sun et al., 2012). It also suppresses TPA-induced matrix metallopeptidase 9 (MMP-9) expression and cancer cell invasion by downregulating the activation of NF-κB and AP-1. Furthermore, curcumin has been shown to inhibit the translocation of protein kinase C alpha (PKCα) to the cell membrane and reduce the activation of p38 and c-Jun N-terminal kinases (JNKs), key mediators in cancer progression (Kim et al., 2012). It also regulates proteins associated with epithelial-mesenchymal transition (EMT), such as β-catenin, Fibronectin, Slug, N-cadherin, E-cadherin, Vimentin, AXL, and Twist1.

Another polyphenol of interest is protocatechualdehyde, found in the roots of *Salvia miltiorrhiza* and leaves of barley tea. This compound has demonstrated both pro-apoptotic and anti-proliferative effects in human colorectal cancer cells. Its anti-cancer mechanism involves the downregulation of β-catenin expression via NF-κB and GSK-3β-mediated proteasomal degradation, as well as the suppression of cyclin D1 independent of β-catenin (Choi et al., 2014). Pterostilbene, a naturally occurring polyphenol found in *Cyanococcus* species, shares structural similarities with resveratrol but offers improved pharmacokinetics, including enhanced oral bioavailability and a longer half-life, making it a promising candidate for therapeutic use (McCormack & McFadden, 2013).

3. Conclusion

The primary aim of this review was to explore and consolidate existing scientific evidence on the anticancer properties of plant-derived phytochemicals, with a particular emphasis on their efficacy against cancer. Given the rising global cancer burden and the limitations of conventional treatment strategies such as chemotherapy, radiotherapy, and surgery, this article sought to highlight the therapeutic potential of naturally occurring bioactive compounds as complementary or alternative approaches for cancer management. Major findings from the review reveal that a wide array of phytochemicals, including alkaloids (e.g., cepharanthine, colchicine, berberine), terpenoids (e.g., α-santalol, astragaloside IV, betulinic acid), flavonoids (e.g., nobiletin, kaempferol, icariin), and polyphenols (e.g., curcumin, protocatechualdehyde, pterostilbene), possess significant anticancer activities. These compounds exert their effects through diverse mechanisms, including the induction of apoptosis, inhibition of cell proliferation, disruption of angiogenesis and metastasis, and modulation of critical oncogenic signaling pathways such as PI3K/Akt/mTOR, NF-κB, Wnt/β-catenin, and EGFR. This review underscores that many of these natural agents not only show efficacy *in vitro* and *in vivo* but also have lower toxicity profiles compared to conventional chemotherapeutics. Taken together, further research is necessary to bridge the gap between preclinical studies and clinical application. Future investigations should focus on elucidating the precise molecular targets of these phytochemicals, optimizing their pharmacokinetics and bioavailability, and evaluating their efficacy in well-designed clinical trials. Additionally, research into synergistic combinations of plant-derived compounds with standard chemotherapy could yield more effective and less toxic treatment regimens. Advances in biotechnology and drug delivery systems such as nanocarriers and phytochemical-loaded nanoparticles also offer promising avenues for enhancing therapeutic precision and minimizing side effects. Ultimately, integrating phytochemicals into mainstream oncology could significantly contribute to more sustainable, accessible, and patient-friendly cancer care.

References

1. World Health Organization. (2018). Cancer. https://www.who.int/news-room/fact-sheets/detail/cancer
2. Jemal, A., Bray, F., Center, M. M., Ferlay, J., Ward, E., & Forman, D. (2011). Global cancer statistics. CA: A Cancer Journal for Clinicians, 61(2), 69–90. https://doi.org/10.3322/caac.20107
3. Ajisebiola, B.S., Toromade, A.A., Oladele, J.O. et al. Echis ocellatus venom-induced sperm functional deficits, pro-apoptotic and inflammatory activities in male reproductive organs in rats: antagonistic role of kaempferol. BMC Pharmacol Toxicol 25, 46 (2024). https://doi.org/10.1186/s40360-024-00776-0

4. Ajisebiola, B.S., Durodola, B.P., Mustapha, AR.K. et al. Cardio-nephrotoxicity mediated by Echis ocellatus venom and its amelioration through kaempferol's suppressive effect on oxidative stress, inflammation, and apoptosis expression. Clin Phytosci 10, 7 (2024). https://doi.org/10.1186/s40816-024-00370-1

5. Ajisebiola, B. S., Oladele, J. O., & Adeyi, A. O. (2023). Kaempferol from Moringa oleifera demonstrated potent antivenom activities via inhibition of metalloproteinase and attenuation of Bitis arietans venom–induced toxicities. Toxicon, 233, 107242. https://doi.org/10.1016/j.toxicon.2023.107242Iqbal, J., Abbasi, B. A., Mahmood, T., Kanwal, S., Ali, B., Shah, S. A., & Khalil, A. T. (2017). Plant-derived anticancer agents: A green anticancer approach. Asian Pacific Journal of Tropical Biomedicine, 7(12), 1129–1150. https://doi.org/10.1016/j.apjtb.2017.10.016

6. Roy, A. (2017). A review on anti-cancerous activity of a bioactive compound Plumbagin. SF Journal of Plant Physiology, 1(1), 78–79.

7. Roy, A., Jauhari, N., & Bharadvaja, N. (2018). Medicinal plants as a potential source of chemopreventive agents. In Anticancer plants: Natural products and biotechnological implements (pp. 109–139). Springer. https://doi.org/10.1007/978-981-10-8548-7_5

8. Pan, S.-Y., Litscher, G., Gao, S.-H., Zhou, S.-F., Yu, Z.-L., Chen, H.-Q., Zhang, S.-F., Tang, M.-K., Sun, J.-N., & Ko, K.-M. (2014). Historical perspective of traditional indigenous medical practices: The current renaissance and conservation of herbal resources. Evidence-Based Complementary and Alternative Medicine, 2014, Article 525340. https://doi.org/10.1155/2014/525340

9. Perera, D. L. (2004). Truth and myth of green piracy.

10. Graham, J. G., Quinn, M. L., Fabricant, D. S., & Farnsworth, N. R. (2000). Plants used against cancer – An extension of the work of Jonathan Hartwell. Journal of Ethnopharmacology, 73(3), 347–377. https://doi.org/10.1016/S0378-8741(00)00341-X

11. Khan, H. (2014). Medicinal plants in light of history: Recognized therapeutic modality. Evidence-Based Complementary and Alternative Medicine, 2014, 216–219. https://doi.org/10.1155/2014/495370

12. Cragg, G. M., & Newman, D. J. (2005). Plants as a source of anti-cancer agents. Journal of Ethnopharmacology, 100(1–2), 72–79. https://doi.org/10.1016/j.jep.2005.05.011

13. Dixon, R. A. (2001). Natural products and plant disease resistance. Nature, 411(6839), 843–847. https://doi.org/10.1038/35081178

14. Prajapati, N. D., Sharma, S. S. P., Sharma, A. K., & Kumar, T. (2007). A handbook of medicinal plants: A complete source book.

15. Verpoorte, R. (1998). Exploration of nature's chemodiversity: The role of secondary metabolites as leads in drug development. Drug Discovery Today, 3(5), 232–238. https://doi.org/10.1016/S1359-6446(98)01238-2

16. Putra, A., Riwanto, I., Putra, S. T., & Wijaya, I. (2020). Typhonium flagelliforme extract induces apoptosis in breast cancer stem cells by suppressing survivin. Journal of Cancer Research and Therapeutics, 16(6), 1302–1308. https://doi.org/10.4103/jcrt.JCRT_757_19

17. Raman, V., Aryal, U. K., Hedrick, V., Ferreira, R. M., Fuentes Lorenzo, J. L., Stashenko, E. E., Levy, M., Levy, M. M., & Camarillo, I. G. (2018). Proteomic analysis reveals that an extract of the plant Lippia origanoides suppresses mitochondrial metabolism in triple-negative breast cancer cells. Journal of Proteome Research, 17(10), 3370–3383. https://doi.org/10.1021/acs.jproteome.8b00273

18. Sun, X. D., Liu, X. E., & Huang, D. S. (2012). Curcumin induces apoptosis of triple-negative breast cancer cells by inhibition of EGFR expression. Molecular Medicine Reports, 6(6), 1267–1270. https://doi.org/10.3892/mmr.2012.1069

19. Kim, J. M., Noh, E. M., Kwon, K. B., Kim, J. S., You, Y. O., Hwang, J. K., Hwang, B. M., Kim, B. S., Lee, S. H., Lee, S. J., & Jung, S. H. (2012). Curcumin suppresses the TPA-induced invasion through inhibition of PKCα-dependent MMP-expression in MCF-7 human breast cancer cells. Phytomedicine, 19(12), 1085–1092. https://doi.org/10.1016/j.phymed.2012.06.005

20. Choi, J., Jiang, X., Jeong, J. B., & Lee, S. H. (2014). Anti-cancer activity of protocatechualdehyde in human breast cancer cells. Journal of Medicinal Food, 17(8), 842–848. https://doi.org/10.1089/jmf.2013.2992

21. McCormack, D., & McFadden, D. (2013). A review of pterostilbene antioxidant activity and disease modification. Oxidative Medicine and Cellular Longevity, 2013, Article 575482. https://doi.org/10.1155/2013/575482

22. Selvakumar, P., Badgeley, A., Murphy, P., Anwar, H., Sharma, U., Lawrence, K., & Lakshmikuttyamma, A. (2020). Flavonoids and other polyphenols act as epigenetic modifiers in breast cancer. Nutrients, 12(3), 761. https://doi.org/10.3390/nu12030761

23. Li, W., Zhao, R., Wang, X., Liu, F., Zhao, J., Yao, Q., Zhi, W., He, Z., & Niu, X. (2018). Nobiletin-ameliorated lipopolysaccharide-induced inflammation in acute lung injury by suppression of NF-κB pathway in vivo and in vitro. Inflammation, 41(3), 996–1007. https://doi.org/10.1007/s10753-018-0756-3

24. Oladele, J. O., Oyeleke, O. M., Olowookere, B. D., & Babatope, O. D. (2021). Bitter leaf (*Vernonia amygdalina*) modulates nitrobenzene-induced renal damage in rats via suppression of oxido-inflammatory activities. *Scientific Journal of Experimental and Clinical Research, 22*(4), 317–324. https://doi.org/10.2478/sjecr-2020-0040

25. Oladele, J. O., Ajayi, E. I. O., Oyeleke, O. M., Oladele, O. T., Olowookere, B. D., Adeniyi, B. M., Oyewole, O. I., & Oladiji, A. T. (2020). A systematic review on COVID-19 pandemic with special emphasis on curative potentials of Nigeria-based medicinal plants. *Heliyon, 6*(9), e04897. https://doi.org/10.1016/j.heliyon.2020.e04897

26. Noguchi, S., Atsumi, H., Iwao, Y., Kan, T., & Itai, S. (2016). Nobiletin: A citrus flavonoid displaying potent physiological activity. Acta Crystallographica Section C: Structural Chemistry, 72(2), 124–127. https://doi.org/10.1107/S2053229616000451

27. Akram, M., Iqbal, M., Daniyal, M., & Khan, A. U. (2017). Awareness and current knowledge of breast cancer. Biological Research, 50(1), 33. https://doi.org/10.1186/s40659-017-0140-9

28. Wang, X., Yang, Y., An, Y., & Fang, G. (2019). The mechanism of anti-cancer action and potential clinical use of kaempferol in the treatment of breast cancer. Biomedicine & Pharmacotherapy, 117, 109086. https://doi.org/10.1016/j.biopha.2019.109086

29. Song, L., Chen, X., Mi, L., Liu, C., Zhu, S., Yang, T., Luo, X., Zhang, Q., Lu, H., & Liang, X. (2020). Icariin-induced inhibition of SIRT6/NF-κB triggers redox mediated apoptosis and enhances anti-tumor immunity in triple-negative breast cancer. Cancer Science, 111(11), 4242–4256. https://doi.org/10.1111/cas.14589

30. Oladele, J. O., Babatunde, I. O., & Oladele, O. T. (2025). Molecular mechanisms underpinning neuroprotection of nutritional polyphenols. In R. Malviya, K. Pathak, & S. Verma (Eds.), Nanomedicine for neurodegenerative disorders: Selective treatment strategies (1st ed., p. 331). CRC Press.

31. Oladiji, A. T., & Oladele, J. O. (2023). Spices as potential human disease panacea. In L. Kambizi & C. Bvenura (Eds.), Sustainable uses and prospects of medicinal plants (pp. 287–307). CRC Press. https://doi.org/10.1201/9781003206620-16

32. Ateba, S. B., Mvondo, M. A., Ngeu, S. T., Tchoumtchoua, J., Awounfack, C. F., Njamen, D., & Krenn, L. (2018). Natural terpenoids against female breast cancer: A 5-year recent research. Current Medicinal Chemistry, 25(27), 3162–3213. https://doi.org/10.2174/0929867324666170529121244

33. Bommareddy, A., Knapp, K., Nemeth, A., Steigerwalt, J., Landis, T., Vanwert, A. L., Gorijavolu, H. P., & Dwivedi, C. (2018). Alpha-santalol, a component of sandalwood oil, inhibits migration of breast cancer cells by targeting the β-catenin pathway. Anticancer Research, 38(8), 4475–4480. https://doi.org/10.21873/anticanres.12772

34. Hu, S., Zheng, W., & Jin, L. (2021). Astragaloside IV inhibits cell proliferation and metastasis of breast cancer via promoting the long noncoding RNA TRHDE-AS1. Journal of Natural Medicines, 75(1), 156–166. https://doi.org/10.1007/s11418-020-01459-7

35. Luo, R., Fang, D., Chu, P., Wu, H., Zhang, Z., & Tang, Z. (2016). Multiple molecular targets in breast cancer therapy by betulinic acid. Biomedicine & Pharmacotherapy, 84, 1321–1330. https://doi.org/10.1016/j.biopha.2016.10.002

36. Yin, R., Li, T., Tian, J. X., Xi, P., & Liu, R. H. (2018). Ursolic acid, a potential anti-cancer compound for breast cancer therapy. Critical Reviews in Food Science and Nutrition, 58(4), 568–574. https://doi.org/10.1080/10408398.2016.1203284

37. Hanušová, V., Caltová, K., Svobodová, H., Ambrož, M., Skarka, A., Murínová, N., Králová, V., Tomšík, P., & Skálová, L. (2017). The effects of β-caryophyllene oxide and trans-nerolidol on the efficacy of doxorubicin in breast cancer cells and breast tumor-bearing mice. Biomedicine & Pharmacotherapy, 95, 828–836. https://doi.org/10.1016/j.biopha.2017.08.098

38. Gao, S., Li, X., Ding, X., Qi, W., & Yang, Q. (2017). Cepharanthine induces autophagy, apoptosis and cell cycle arrest in breast cancer cells. Cellular Physiology and Biochemistry, 41(4), 1633–1648. https://doi.org/10.1159/000464292

39. Sun, Y., Lin, X., & Chang, H. (2016). Proliferation inhibition and apoptosis of breast cancer MCF-7 cells under the influence of colchicine. Journal of BUON, 21(3), 570–575.

40. Huang, Y., Huang, H., Wang, S., Chen, F., & Zheng, G. (2020). Dehydrocorydaline inhibits the tumorigenesis of breast cancer MDA-MB-231 cells. Molecular Medicine Reports, 22(1), 43–50. https://doi.org/10.3892/mmr.2020.11121

41. Ding, Y., He, J., Huang, J., Yu, T., Shi, X., Zhang, T., Yan, G., Chen, S., & Peng, C. (2019). Harmine induces anti-cancer activity in breast cancer cells via targeting TAZ. International Journal of Oncology, 54(6), 1995–2004. https://doi.org/10.3892/ijo.2019.4751

42. Williamson, E. M. (2002). Major herbs of Ayurveda. Elsevier Science.

43. Resorts. (2017). Ayurvedic medicinal plants of Sri Lanka. http://www.instituteofayurveda.org/plants/

44. Barbuti, A. M., & Chen, Z. S. (2015). Paclitaxel through the ages of anticancer therapy: Exploring its role in chemoresistance and radiation therapy. Cancers, 7(4), 2360–2371. https://doi.org/10.3390/cancers7040889

45. Gornstein, E., & Schwarz, T. L. (2014). The paradox of paclitaxel neurotoxicity: Mechanisms and unanswered questions. Neuropharmacology, 76, 175–183. https://doi.org/10.1016/j.neuropharm.2013.08.016

46. Ren, X., Zhao, B., Chang, H., Xiao, M., Wu, Y., & Liu, Y. (2018). Paclitaxel suppresses proliferation and induces apoptosis through regulation of ROS and the AKT/MAPK signaling pathway in canine mammary gland tumor cells. Molecular Medicine Reports, 17(6), 8289–8299. https://doi.org/10.3892/mmr.2018.8867

47. Stenvang, J., Kümler, I., Nygård, S. B., Smith, D. H., Nielsen, D., Brünner, N., & Moreira, J. M. A. (2013). Biomarker-guided repurposing of chemotherapeutic drugs for cancer therapy: A novel strategy in drug development. Frontiers in Oncology, 3, 313. https://doi.org/10.3389/fonc.2013.00313

48. Xu, Y., & Villalona-Calero, M. A. (2002). Irinotecan: Mechanisms of tumor resistance and novel strategies for modulating its activity. Annals of Oncology, 13(12), 1841–1851. https://doi.org/10.1093/annonc/mdf319

49. Kciuk, M., Marciniak, B., & Kontek, R. (2020). Irinotecan—Still an important player in cancer chemotherapy: A comprehensive overview. International Journal of Molecular Sciences, 21(12), 4919. https://doi.org/10.3390/ijms21134919

50. Adewale, O. O., Ajayi, E. I. O., Oladele, J. O., & Oladiji, A. T. (2024). Nutrition and cancer. In A. T. Oladiji, J. O. Oladele, & E. I. O. Ajayi (Eds.), *Nutrition and diet in health: Principles and applications* (pp. 181–194). CRC Press/Taylor & Francis.

51. Oladele, J. O., Ojuederie, O. B., Oladele, O. T., Ajayi, E. I. O., Olaniyan, M. D., Atolagbe, O. S., … Oyeleke, O. M. (2024). Gastroprotective mechanism of *Talinum triangulare* on ethanol-induced gastric ulcer in Wistar rats *via* inflammatory, antioxidant, and H^+/K^+-ATPase inhibition-mediated pathways. *Drug and Chemical Toxicology*, *48*(2), 281–293. https://doi.org/10.1080/01480545.2024.2365435

52. Hoff, P. M., Ansari, R., Batist, G., Cox, J., Kocha, W., Kuperminc, M., Maroun, J., Walde, D., Weaver, C., Harrison, E., Burger, H. U., Osterwalder, B., Wong, A. O., & Wong, R. (2001). Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: Results of a randomized phase III study. Journal of Clinical Oncology, 19(8), 2282–2292. https://doi.org/10.1200/JCO.2001.19.8.2282

53. Bajeeta, E., Beretta, E., Di Bartolomeo, M., Cortinovis, D., Ferrario, E., Dognini, G., Toffolatti, L., & Buzzoni, R. (2004). Efficacy of treatment with irinotecan and oxaliplatin combination in FU-resistant metastatic colorectal cancer patients. Oncology, 66(1), 31–37. https://doi.org/10.1159/000076289

54. Tournigand, C., André, T., Achille, E., Lledo, G., Flesh, M., Mery-Mignard, D., Quinaux, E., Couteau, C., Buyse, M., Ganem, G., Landi, B., Colin, P., Louvet, C., & de Gramont, A. (2004). FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomized GERCOR study. Journal of Clinical Oncology, 22(2), 229–237. https://doi.org/10.1200/JCO.2004.05.113

55. Wang, Y., Liu, Y., Du, X., Ma, H., & Yao, J. (2020). The anti-cancer mechanisms of berberine: A review. Cancer Management and Research, 12, 695–702. https://doi.org/10.2147/CMAR.S246361

56. Xiao, Y., Tian, C., Huang, T., Han, B., Wang, M., Ma, H., Li, Z., Ye, X., & Li, X. (2018). 8-Cetylberberine inhibits growth of lung cancer in vitro and in vivo. Life Sciences, 192, 259–269. https://doi.org/10.1016/j.lfs.2017.11.033

57. Su, Y. H., Tang, W. C., Cheng, Y. W., Sia, P., Huang, C. C., Lee, Y. C., Jiang, H. Y., Wu, M. H., Lai, I. L., Lee, J. W., & Lee, K. H. (2015). Targeting of multiple oncogenic signaling pathways by Hsp90 inhibitor alone or in combination with berberine for treatment of colorectal cancer. Biochimica et Biophysica Acta (BBA) - Molecular Basis of Disease, 1853(10 Pt A), 2261–2272. https://doi.org/10.1016/j.bbadis.2015.07.003

58. Eo, S. H., Kim, J. H., & Kim, S. J. (2014). Induction of G2/M arrest by berberine via activation of PI3K/Akt and p38 in human chondrosarcoma cell line. Oncology Research, 22(3), 147–157. https://doi.org/10.3727/096504014X13984268343816

59. Chai, Y. S., Yuan, Z. Y., Lei, F., Wang, Y. G., Hu, J., Du, F., Lu, X., Jiang, J. F., Xing, D. M., & Du, L. J. (2014). Inhibition of retinoblastoma mRNA degradation through Poly(A) involved in the neuroprotective effect of berberine against cerebral ischemia. PLOS ONE, 9(6), e90850. https://doi.org/10.1371/journal.pone.0090850

60. Wu, H. L., Chuang, T. Y., Al-Hendy, A., Diamond, M. P., Azziz, R., & Chen, Y. H. (2015). Berberine inhibits the proliferation of human uterine leiomyoma cells. Fertility and Sterility, 103(4), 1098–1106. https://doi.org/10.1016/j.fertnstert.2015.01.011

61. Adewale, O. O., Oyelola, R. F., Adetuyi, O. A., Adebisi, O. A., Adekomi, D. A., & Oladele, J. O. (2024)a. Water-soluble phenolics from *Phoenix dactylifera* fruits as potential reno-protective agent against cisplatin-induced toxicity: Pre- and post-treatment strategies. *Drug and Chemical Toxicology*, *47*(6), 1058–1071. https://doi.org/10.1080/01480545.2024.2329762

62. Adewale, O. O., Oyelola, R. F., Oladele, J. O., & Agbaje, W. B. (2024)b. Assessing the ability of polysaccharides extracted from date palm fruit to salvage Wistar rats from cisplatin-linked hepatic damage. *Pharmacological Research - Modern Chinese Medicine*, *11*, 100400. https://doi.org/10.1016/j.prmcm.2024.100400