

A comprehensive review on plant-derived anti-cancer compounds

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Abstract

Cancer is one of the biggest health concerns for the human kind and require intervention strategies. Plant-derived bioactive compounds have received spotlight in cancer research since they have been reported for therapeutic potential. Plant based diet contains various phytochemicals which are safe for prevention and treatment of cancer as compared with conventional treatment methods. Studies have revealed the various such sources like dietary fibre and biologically active polysaccharides from mushrooms, lycopene from tomatoes, resveratrol from berries, curcumin from turmeric, which have been shown anti-cancer effects. This study provides information on various plants and their bioactive compounds with potential to cure different types of cancer. The study also highlighted the potential of those components in the drug and food product development. Furthermore, there is an extensive scope for the domain of applications and toxicological studies evaluating the anti-cancer components found in plant sources.

Keywords: Plant-derived bioactives; Anti-cancer; Plant-based diets; Health; Nutraceuticals.

Introduction

The development of anticancer drugs is a highly intricate and technologically advanced area in which numerous aspects such as molecular biotechnology, genomics, proteomics,

and biopharmaceuticals are currently creating significant waves and making substantial advancements in the field of cancer treatment. In the last decade alone, we have witnessed the remarkable approval of a total of 34 distinct cancer drugs; notably, many of these innovative drugs have been derived from natural products found in our environment. For countless millennia, humans have relied on various types of plants as a vital source of medicinal compounds. It is important to acknowledge that while there are a vast number of different chemicals present in plants, the specific compounds that exert definite and beneficial physiological effects in humans are relatively sparse and limited. Out of the small selection of effective plant-derived anticancer agents, three notable ones, which include etoposide, teniposide, and paclitaxel, are currently utilized in clinical settings for treating cancer patients. Various traditional medicine systems across the globe use plant extracts extensively for the treatment of a wide range of diseases and disorders. In many distinct cultures, there is a longstanding practice of using medicinal plants as a first line of treatment for numerous diseases, along with the alleviation of symptoms associated with disease processes, including those related to cancer and other chronic conditions. A striking statistic reveals that over 60% of the current anticancer drugs are derived, either directly or indirectly, from natural sources, underscoring the significance of our natural environment in the development of therapeutic agents. Despite this, many failures in drug development are attributed to a loss of interest in these natural products due to various challenges, including their complex molecular structures, unsatisfactory clinical responses observed upon continual usage, and more specifically, the imminent threat of increased tumor resistance that poses significant complications. Nonetheless, most of the current drugs available on the market are characterized as water-soluble; therefore, the strategic introduction of lipophilic groups should ideally enhance the overall effectiveness of these therapeutic agents by increasing their residence time within the tumor environment, ultimately prolonging their cytotoxic effects and improving patient outcomes in the fight against cancer (Dehelean et al., 2021; Garcia-Oliveira et al., 2021; Huang et al., 2021).

2. Historical Perspective of Plant-Derived Compounds in Cancer Treatment

Cancer is the most fatal of all human diseases. Acute leukemia, lymphoma, breast cancer, brain cancer, and adrenal carcinoma are the most common cancers affecting children in the United States. Current methods of treating cancer, including surgery, radiotherapy, and chemotherapy, are not completely effective. Early detection of the disease often leads to successful treatment. However, delayed diagnosis creates a usually incurable state in the patient. Nearly half of the drugs used for cancer treatment are derived from natural sources. The limitations in current cancer treatments have led to a stress in the search for natural antitumor agents. The prospects of the use of natural products, particularly those derived from plants, have increased in recent years.

Historical Perspective of Plant-Derived Compounds in Cancer Treatment: In ancient times, the physicians treating diseases used herbs as agents. The most significant progress in civilization took place when humankind found that herbs alleviated many health problems. The writings of the Ebers Papyrus report 700 different remedies, including the use of 22 species of biologically active plants. The antitumor effect of many natural products can be verified by different ancient civilizations. For the aboriginal people in different countries, the wealth of natural botanical medicine was a primary living resource. A comprehensive survey comparing modern allopathic medicine with traditional medicine indicates that traditional medicine was effective in alleviating diseases like tumors, abscesses, or tumors in breast cancer and esophagus cancer. The traditional narratives of folklore medicine contain a great deal of herbal remedies for various diseases, including cancer treatment (Huang et al., 2021; Dehelean et al.2021; Ma et al., 2021).

3. Mechanisms of Action of Plant-Derived Anti-Cancer Compounds

Natural phytochemicals, which comprise mainly phenolic compounds and terpenoids, represent potential anti-cancer agents and are beneficial for cancer prevention and therapy. Both in vitro and in vivo studies have shown that these

compounds possess the capacity to prevent a variety of malignancies through the induction of cell cycle arrest and apoptosis. Over the past 10 years, active research has revealed numerous intracellular targets of phytochemicals. Many of these compounds modulate the signaling that determines cell fate in a manner that results in the death of cancer cells but not that of normal cells. We present an extensive overview of and categorize the information on the anti-cancer pharmacology of numerous phytochemicals that have been identified in diverse food sources and medicinal plants and that have been shown to be capable of inhibiting tumorigenesis. In particular, we elaborate, in numerous instances, upon the molecular and cellular targets of the phytochemicals, with special regard for the mechanisms through which they exercise signaling in the regulation of key metabolic enzymes, protein kinases, transcription factors, oncogenes, and tumor-suppressor proteins in cancer cells, as well as for their capacity to target the surrounding tumor microenvironment.

Phytochemicals have been employed for many years in traditional medicine and have stimulated the development of modern therapeutic methods for the prevention and treatment of cancer. One of the major difficulties with plant-derived phytochemicals is that many of the mechanisms of action by which phytochemicals suppress carcinogenesis have remained elusive. Therefore, understanding the mechanisms through which natural phytochemicals modulate gene expression and the signaling molecules involved in cell cycle and apoptosis, as well as specific protein targets, is crucial both for verifying their capacity to prevent the occurrence of tumors and for the optimization of future cancer chemoprevention strategies. We present and discuss the major natural phytochemicals in a varied number of plant-based diets and medicinals that have been employed for preventing tumors, focusing not only on the compounds responsible for the bioactivity but also on the connection between cancer and anti-cancer agents, on the performance of these natural anti-cancer agents, their suppressing processes, and means of action on the different cellular and molecular targets with their potential role in cancer prevention, and on the levels of evidence for their bioactivity (George et al., 2021; Paudel et al., 2023; Ahmed et al., 2022).

3.1 Apoptosis Induction

The pro-apoptotic effects of natural compounds contained in foods have largely been linked to their anti-cancer properties. The use of nutritional therapy to modulate apoptosis both in the initial stages of tumor formation, as well as in the intermediate phases of tumor development, is thought to represent new fields for cancer prevention and treatment. Apoptosis induction is mainly directed by the mitochondrial and death receptor pathways and is regulated through the ratio of pro-apoptotic to anti-apoptotic Bcl-2 family proteins. Plant-derived natural compounds have been shown to promote apoptosis through direct perturbation of the mitochondria or the death receptor itself, thereby inducing cytochrome c release or lowering the mitochondrial membrane potential (Ng et al., 2022; Rizvi et al., 2021).

Following the decrease of mitochondrial membrane potential or cytochrome c release, the apoptosome complex is assembled, leading to caspase-9 autoprocessing and activation of the downstream apoptotic cascade of caspases. Activation of caspase-8 is also a crucial step in apoptosis. Plant-derived phytochemicals can activate these pathways, as well as activate lysosomal enzymes that contribute to lysosomal membrane permeabilization, which in turn can initiate a caspase-independent apoptotic process. Activation of lysosomal cathepsins has been shown to contribute to the release of the apoptosis-inducing factor. Small amounts of apoptosis-inducing factor are normally located in the mitochondrial inter-membrane space, yet upon mitochondrial outer membrane permeabilization and due to its large size, it is normally retained in the inter-membrane space and not released into the cytosol. Any perturbation of this critical balance can lead to apoptosis induction but also necrosis since it stimulates apoptotic pathways. (Rahman et al. 2021) (Khan et al., 2022) (Olędzka & Czerwińska, 2023)

3.2 Cell Cycle Arrest

Several natural compounds derived from plants have been observed to regulate cell cycle arrest in cancer cells. Induction of cell cycle arrest has been considered an interesting strategy

in the eradication of cancer cells. The cell cycle includes four different stages: G1 phase, S phase, G2 phase, and M phase. Numerous studies have reported that cell cycle arrest at the G2/M phase leads to high rates of apoptosis in cancer cells. In the G2 phase, the undivided cancer cells will proceed directly to mitotic events, leading to an ascending mitotic catastrophe. Curcumin shifts the cell cycle distribution of the prostate cancer cell line LNCaP toward the G2/M phase through the downregulation and activation of transcription factor E2F-1, cyclin D, cyclin E, and Cdk2. Quercetin, a dietary polyphenol contained in a variety of fruits and vegetables, has been reported to induce G2/M arrest through the increase of the cyclin kinase inhibitors p21 and p27 in human pancreatic cancer cells. Gallic acid, another dietary polyphenol found in plants, promotes G2/M phase arrest through the upregulation of p21 and p27 protein expression and the reduction of the translocation of cyclin B1 in HCT116 human colon cancer cells. Formononetin and its derivatives, which contain chrysin and biochanin A, have been reported to induce G2/M phase arrest in liver cancer cells. Cell cycle arrest has provided a way to reverse the carcinogenic events and the eradication of cancer cells. In cancer, the cell cycle is not synchronized, leading to an arrest, generally in the G0/G1 or G2/M phase. Cell cycle arrest leads to cell apoptosis or senescence. Some plant-derived compounds can cause disturbance in the cell cycle in cancer cells. Cytotoxic drugs have been found to inhibit the expansion of cancer cells by causing an arrest at the G0/G1, S, and G2/M phases. Some plant-derived compounds have proven their potential for cell cycle arrest. This review will summarize some representative plant-derived anti-cancer compounds and reveal their mechanisms to regulate the cell cycle distribution in cancer. (Wang, 2021; Pani et al.2022; Qi et al., 2021)

3.3 Anti-Angiogenic Effects

An effective regulation of angiogenesis could promise the development of new drugs for cancer treatment. Endostatin, overexpressed in endothelial cells, is translated and cleaved by metalloproteinase, mediates anti-angiogenesis, and is used for cancer therapy. A study reported that the tissue

microenvironment, namely paracrine fibroblast hepatocyte growth factor, has a role in inducing the transformation of endostatin. Recent studies have found that terpenoid is still an excellent candidate for anti-angiogenesis drug development. A compound found that 4'-acetoxy-resveratrol, a resveratrol derivative, inhibited tumor growth in a mouse ovarian cancer model by reducing tumor angiogenesis. Although the exact anti-angiogenesis mechanisms of 4'-acetoxy-resveratrol require further research, this study indicated that 4'-acetoxy-resveratrol inhibits HUVEC migration and suppresses HGF-stimulated *in vitro* tubular formation. (Salla et al.2024; Wang et al.2024)

In the context of progress on the biological justification and successful examples of natural compounds, such as vincristine and camptothecins, the importance of inhibiting tumor angiogenic ability, cancer adjuvant chemotherapy, anti-angiogenesis drug development, and endothelial cell cytology focusing on natural compounds, flavonoids, phenolics, terpenoids, polyynes, and some other plant-derived natural compounds are attracting research on tumor angiogenesis to explore their potential development prospects in the field. Among the compounds, a multi-target natural product is a potent and non-toxic anti-angiogenesis agent that manifests activity in both *in vitro* and *in vivo* animal models. In another example, theaflavins are polymethylated and polyhydroxylated catechins that are present in black tea and inhibit eukaryotic peptide chain initiation by binding to the ribosomal subunit. Additionally, the activation of AMP-activated protein kinase and its downregulation of VEGF and hypoxia-related signaling contribute to its anti-angiogenic effects. (Kciuk et al.2023; Thiruvengadam & Kim, 2023)

4. Clinical Studies and Evidence-Based Research

Aloe-emodin was evaluated for its cytotoxic effects in a liver carcinoma cell line and showed that hardness was influenced by its long-term use; tolerance suggested its possible use in the treatment of breast and colorectal carcinomas. Resveratrol in conjunction with red clover was used in 62 women who had a family history of breast cancer, discussing their safety and concluding that this randomized, double-blind, placebo-

controlled trial using resveratrol in high-risk women showed no safety issues, which is certainly important for future clinical research. Another phytoestrogen is genistein, which was studied and showed that when used alone, either in hormone-dependent, hormone-independent, or hormone-positive cells, it inhibited cell growth by 60%, 40%, and 90%, respectively. These results may be interesting in the future development of new breast cancer treatments. (Sharifi-Rad et al., 2021; Rendón et al., 2022)

5. Future Directions and Potential Applications

Phytochemicals derived from edible plants have been reported to exert medicinal effects against cancer through various pharmacological activities, such as inducing cell cycle arrest, activating apoptosis, modulating pathways and inflammatory activity, and inhibiting invasion and metastasis. Herein, we will provide a comprehensive review on cell-line and mouse model studies of a variety of edible plant-derived anti-cancer compounds. The bioavailability, bio-efficacy, and molecular targets of these compounds in relation to their inhibition of cancer initiation, growth, migration, and invasion are also discussed. There are various mechanisms by which dietary compounds inhibit cancer cell growth, including preventing initiation by modulating a pro-oxidative imbalance; increasing apoptosis and suppressing the natural release of tumor suppressive genes; inhibiting migration and invasion by suppressing cytokine signaling and promoting extracellular matrix control; and decreasing angiogenesis by decreasing tube formation and secretion of VEGF. These powerful mechanisms have led to a growing interest in nutraceuticals and new possibilities regarding their use in drug combination strategies or in the design and synthesis of related compounds. Our review offers additional investigation guidelines and proposes ultimate goals to further develop these compounds into anti-cancer therapeutic drugs. (de Carvalho & Conte-Junior, 2021; Macharia et al.2022; Regassa et al.2022)

Conclusion

Increasing levels of cancer incidence have forced the pursuit of unconventional medicines and the examination of traditional plants. Nature, especially plants, has embraced a significant role in treating several diseases, including cancer. The discovery or invention of new drugs is not necessary since many conventional products play a vital role. This review highlights anti-cancer medicinal plants and some of the most common bioactive compounds produced by these plants. However, cancer treatments depend on the medicinal plants for their metabolites with significant levels of protection that can satisfy medication safety and effectiveness demands. The physiochemical, pharmacological, and absorption-distribution-metabolism-excretion-toxicology predicted properties and molecular docking data are analyzed by performing an *in silico* scientific investigation, promising the anti-cancer compounds from naturally derived metabolites.

The plant-derived metabolic profiles could be seen as an important resource for continued drug discovery and development. The continually increasing capacity of computational biology methodologies resolves the unsatisfactory biosynthetic efficiency and bioactivity distribution of existing bioactive metabolites from plants. In conclusion, natural medicines have a vital role in the treatment of cancer, and many metabolic compounds that have demonstrated a capacity for cancer therapy are packed in these natural products. Given the above information and investigations, we can confirm that plants may be a main source of bioactive anti-cancer compounds for chemoprevention and chemotherapy and could promote further investigations of plant-based medicinal anti-cancer compounds, even though some compounds may be harmful when consumed in high levels or cause toxic effects to immune systems or organs.

References:

Dehelean, C. A., Marcovici, I., Soica, C., Mioc, M., Coricovac, D., Iurciuc, S., ... & Pinzaru, I. (2021). Plant-derived anticancer compounds as new perspectives in drug discovery and alternative therapy. *Molecules*, 26(4), 1109. [mdpi.com](https://doi.org/10.3390/molecules26041109)

Garcia-Oliveira, P., Otero, P., Pereira, A. G., Chamorro, F., Carpena, M., Echave, J., ... & Prieto, M. A. (2021). Status and challenges of plant-anticancer compounds in cancer treatment. *Pharmaceuticals*, 14(2), 157. [mdpi.com](https://doi.org/10.3390/ph14020157)

Huang, M., Lu, J. J., & Ding, J. (2021). Natural products in cancer therapy: Past, present and future. *Natural products and bioprospecting*. [springer.com](https://doi.org/10.1007/978-981-16-1444-4_1)

Ma, L., Zhang, M., Zhao, R., Wang, D., Ma, Y., & Ai, L. (2021). Plant natural products: Promising resources for cancer chemoprevention. *Molecules*. [mdpi.com](https://doi.org/10.3390/molecules26010011)

George, B. P., Chandran, R., & Abrahamse, H. (2021). Role of phytochemicals in cancer chemoprevention: Insights. *Antioxidants*. [mdpi.com](https://doi.org/10.3390/antiox10010011)

Paudel, S., Mishra, N., & Agarwal, R. (2023). Phytochemicals as immunomodulatory molecules in cancer therapeutics. *Pharmaceuticals*. [mdpi.com](https://doi.org/10.3390/ph14020157)

Ahmed, M. B., Islam, S. U., Alghamdi, A. A., Kamran, M., Ahsan, H., & Lee, Y. S. (2022). Phytochemicals as chemopreventive agents and signaling molecule modulators: current role in cancer therapeutics and inflammation. *International Journal of Molecular Sciences*, 23(24), 15765. [mdpi.com](https://doi.org/10.3390/ijms232415765)

Ng, C. X., Affendi, M. M., Chong, P. P., & Lee, S. H. (2022). The potential of plant-derived extracts and compounds to augment anticancer effects of chemotherapeutic drugs. *Nutrition and Cancer*. [\[HTML\]](https://doi.org/10.3390/ncr10010011)

Rizvi, A., Farhan, M., Nabi, F., Khan, R. H., Adil, M., & Ahmad, A. (2021). Transcriptional control of the oxidative stress response and implications of using plant derived molecules for therapeutic interventions in cancer. *Current Medicinal Chemistry*, 28(41), 8480-8495. [\[HTML\]](https://doi.org/10.3390/ncr10010011)

Rahman, M. A., Hannan, M. A., Dash, R., Rahman, M. H., Islam, R., Uddin, M. J., ... & Rhim, H. (2021). Phytochemicals as a complement to cancer chemotherapy: pharmacological modulation of the autophagy-apoptosis pathway. *Frontiers in Pharmacology*, 12, 639628. [frontiersin.org](https://doi.org/10.3389/fphar.2021.639628)

Khan, A. W., Farooq, M., Haseeb, M., & Choi, S. (2022). Role of plant-derived active constituents in cancer treatment and their mechanisms of action. *Cells*. [mdpi.com](https://doi.org/10.3390/cells11010011)

Oleđzka, A. J. & Czerwińska, M. E. (2023). Role of plant-derived compounds in the molecular pathways related to inflammation. *International Journal of Molecular Sciences*. [mdpi.com](https://doi.org/10.3390/ijms24021234)

Wang, Z. (2021). Regulation of cell cycle progression by growth factor-induced cell signaling. *Cells*. [mdpi.com](https://doi.org/10.3390/cells10081456)

Pani, S., Mohapatra, S., Sahoo, A., Baral, B., & Debata, P. R. (2022). Shifting of cell cycle arrest from the S phase to G2/M phase and downregulation of EGFR expression by phytochemical combinations in HeLa cervical cancer cells. *Journal of biochemical and molecular toxicology*, 36(1), e22947. [wiley.com](https://doi.org/10.1002/jbmt.4000)

Qi, Z., Kong, S., Zhao, S., & Tang, Q. (2021). ... inhibits human breast cancer cells (MDA-MB-231) by inducing programmed cell death, caspase stimulation, G2/M phase cell cycle arrest and suppresses cancer *Cellular and Molecular Biology*. [cellmolbiol.org](https://doi.org/10.1007/s12013-021-00800-0)

Salla, M., Karaki, N., El Kaderi, B., Ayoub, A. J., Younes, S., Abou Chahla, M. N., ... & El Khatib, S. (2024). Enhancing the Bioavailability of Resveratrol: Combine It, Derivatize It, or Encapsulate It?. *Pharmaceutics*, 16(4), 569. [mdpi.com](https://doi.org/10.3390/ph16040569)

Wang, X., Chen, B., Fang, X., Zhong, Q., Liao, Z., Wang, J., ... & Wang, L. (2024). Soy isoflavone-specific biotransformation product S-equol in the colon: Physiological functions, transformation mechanisms, and metabolic regulatory pathways. *Critical Reviews in Food Science and Nutrition*, 64(16), 5462-5490. [\[HTML\]](https://doi.org/10.1080/10407179.2024.2311111)

Kciuk, M., Alam, M., Ali, N., Rashid, S., Głowacka, P., Sundaraj, R., ... & Kontek, R. (2023). Epigallocatechin-3-gallate therapeutic potential in cancer: mechanism of action and clinical implications. *Molecules*, 28(13), 5246. [mdpi.com](https://doi.org/10.3390/molecules28135246)

Thiruvengadam, R. & Kim, J. H. (2023). Therapeutic strategy for oncovirus-mediated oral cancer: A comprehensive review. *Biomedicine & Pharmacotherapy*. [sciencedirect.com](https://doi.org/10.1016/j.biopha.2023.115000)

Sharifi-Rad, J., Quispe, C., Imran, M., Rauf, A., Nadeem, M., Gondal, T. A., ... & Calina, D. (2021). Genistein: an integrative overview of its mode of action, pharmacological properties,

and health benefits. *Oxidative medicine and cellular longevity*, 2021(1), 3268136. [wiley.com](https://www.wiley.com)

Rendón, J. P., Cañas, A. I., Correa, E., Bedoya-Betancur, V., Osorio, M., Castro, C., & Naranjo, T. W. (2022). Evaluation of the effects of genistein in vitro as a chemopreventive agent for colorectal cancer—strategy to improve its efficiency when administered orally. *Molecules*, 27(20), 7042. [mdpi.com](https://www.mdpi.com)

de Carvalho, A. P. A. & Conte-Junior, C. A. (2021). Health benefits of phytochemicals from Brazilian native foods and plants: Antioxidant, antimicrobial, anti-cancer, and risk factors of metabolic/endocrine disorders *Trends in Food Science & Technology*. [\[HTML\]](#)

Macharia, J. M., Mwangi, R. W., Rozmann, N., Zsolt, K., Varjas, T., Uchekukwu, P. O., ... & Raposa, B. L. (2022). Medicinal plants with anti-colorectal cancer bioactive compounds: Potential game-changers in colorectal cancer management. *Biomedicine & Pharmacotherapy*, 153, 113383. [sciencedirect.com](https://www.sciencedirect.com)

Regassa, H., Sourirajan, A., Kumar, V., Pandey, S., Kumar, D., & Dev, K. (2022). A review of medicinal plants of the himalayas with anti-proliferative activity for the treatment of various cancers. *Cancers*, 14(16), 3898. [mdpi.com](https://www.mdpi.com)