
**INTERNATIONAL JOURNAL OF CURRENT RESEARCH IN
CHEMISTRY AND PHARMACEUTICAL SCIENCES**

(p-ISSN: 2348-5213; e-ISSN: 2348-5221)

www.ijcrcps.com

(A Peer Reviewed, Referred, Indexed and Open Access Journal)

DOI: 10.22192/ijcrcps

Coden: IJCROO(USA)

Volume 12, Issue 8- 2025

Research Article



DOI: <http://dx.doi.org/10.22192/ijcrcps.2025.12.08.001>

Phytochemicals in Cancer Therapy: Exploring Plant-Derived Alternatives to Conventional Drugs

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Abstract

Cancer remains one of the most difficult health issues globally in the 21st century, accounting for millions of deaths annually across all population demographics. In the medical community, the primary reason for chemotherapy treatment failure is not necessarily a lack of progression as a result of technical advancements or novel treatment protocols, as has been a trend in advances in diagnostics and therapies, but rather because chemotherapeutic agents typically used (e.g., doxorubicin, methotrexate, and cisplatin) have a longstanding history of clinical use. Thus, the conventional chemotherapeutic agents currently used as cancer therapies come up against a unique set of limitations, including, but not limited to; substantial systemic toxicity, the emergence of multidrug resistance (MDR), a lack of specificity, and poor patient tolerance.

In recent decades, the use of plant-derived phytochemicals, are a source of hope in the future of cancer therapies. A metabolite produced from plants for the defense from environmental threat, phytochemicals are organic molecules that occur naturally and have been noted to exhibit many desirable bioactive properties; multi-targeting therapy; safety for use; low toxicity compared with synthetic chemotherapeutic agents. Over the past two decades, there has been sufficient work undertaken in this area to suggest that phytochemicals can provide anticancer activity and that they can act as an adjunctive agent to improve the efficacy of conventional chemotherapy drugs. Accordingly, as a cancer therapy, phytochemicals might offer application as a stand-alone cancer therapy or as a complementary treatment, and they might help treat cancer by improving therapeutic results and patient quality of life.

This review explores the chemotherapeutic characteristics of plant-based phytochemicals on cancer therapy, particularly as adjunctive or alternative therapies in place of traditional chemotherapies. A thorough study of the mechanisms of action of phytochemicals indicates that they exert anticancer effects using many different means

including apoptosis induction, inhibition of angiogenesis, regulation of cell cycle progression, metastasis inhibition, and perturbs signaling through significant pathways such as NF- κ B, PI3K/Akt, MAPK, and STAT3.

Many well-studied phytochemicals, including curcumin, resveratrol, epigallocatechin gallate (EGCG, in green tea), quercetin (in onions), and genistein (in soy) have demonstrated exceptional anticancer activities, showing effective anticancer characteristics in inherently metastatic cancer cell lines and in animal models of metastatic cancers. These phytochemicals not only have cytotoxic capabilities to cancer cells, but also retain protective effects for normal cells, hence limiting collateral damage that would be expected during traditional chemotherapy.

The usefulness of phytochemicals as adjuncts is established by pre-clinical studies and clinical studies. In vitro and in vivo studies have shown that phytochemicals can act synergistically with conventional drugs even at doses that minimize unwanted toxicity. The combined use of phytochemicals and conventional drugs can augment apoptosis in cancer cells, reduce overall tumor volume, and also reduce the required dose of chemotherapeutic agents. For example, the combination of curcumin with either cisplatin or paclitaxel enhances cytotoxicity in both ovarian and breast cancer models, by both enhancing the properties of conventional drugs and by enhancing apoptosis in drug-resistant cells. Furthermore, EGCG was shown to enhance the anticancer effects of doxorubicin and tamoxifen in breast and prostate cancer cells, respectively. These synergistic interactions are of significant clinical relevance, as they may allow oncologists to prescribe lower doses of toxic chemotherapeutic agents without impacting the anticancer effects of delayed toxicity.

Despite having great potential, phytochemicals face several obstacles that must be resolved prior to widespread use in clinical oncology. One of the main concerns is their poor bioavailability, which can be attributed to limited solubility, rapid metabolism and low systemic absorption. Pharmacokinetic barriers can be mitigated through multiple investigational strategies, including: reconnaissance of nanoformulations, such as liposomes, micelles and nanoparticles, conjugation with polymers and/or structural modifications to increase stability and absorption. For instance, nano-curcumin formulations have demonstrated dramatically improved bioavailability and therapeutic efficacy in preclinical cancer models.

Keywords: Phytochemicals, anticancer plants, chemotherapy, doxorubicin, methotrexate, cisplatin, natural products, drug resistance, combination therapy, medicinal plants

Introduction

Cancer continues to be one of the top 10 leading causes of death worldwide contributing to the continual quest for new and effective therapeutic options. Traditional chemotherapeutic agents such as methotrexate, cisplatin, and doxorubicin have been used largely due to their cytotoxic effects towards rapidly growing neoplastic cells however, they are limited by significant side effects, drug resistance, and toxicity compared to normal tissue. These limitations have led to continued interest in phytochemicals as an alternative and sometimes a complementary approach for the management of cancer to gain greater efficacy and reduced adverse effects.

Hippocrates proclaimed, "Let food be thy medicine; let medicine be thy food," approximately 2400 years ago. Plants have been used for thousands of years as traditional

medicine, and modern researchers are identifying many naturally occurring bioactive compounds in plants with promising anti-cancer activity. For example, *Podophyllum hexandrum* (also known as Himalayan mayapple) has podophyllotoxin, which is a bioactive compound and the precursor to the chemotherapeutic drug etoposide which inhibits topoisomerase II. Rhubarb (*Rheum* spp.) has a variety of flavonoids and bioactive chemicals, anthraquinones, and emodin which have shown antiproliferative and pro-apoptotic activity. Fava beans (*Vicia faba*) contain L-DOPA and are bioactive compounds which may decrease oxidative stress properties in cancer cells. Ginkgo biloba is considered an antioxidant and anti-metastasis bioactive compound due to its flavonoid and terpenoid constituents. Camellia sinensis (aka, green tea) contains epigallocatechin gallate (EGCG), which is a phenolic polyphenol with chemopreventive actions.

Furthermore, *Vitis vinifera* (grape) has resveratrol, a stilbenoid that modulates various cancer pathways, including apoptosis and angiogenesis.

This manuscript discusses plant-based phytochemicals as alternatives or adjuncts to traditional chemotherapy detailing their mechanisms of action, efficacy, and the ability of phytochemicals to potentially avoid some of the drawbacks of conventional anti-cancer drugs, such as methotrexate, cisplatin, and doxorubicin. This paper also considered traditional practices and juxtaposed knowledge with research in pharmacology to demonstrate that phytochemicals are a positive avenue to promote cancer treatment.

Research Objectives

1. Assess the Pitfalls of Traditional Chemotherapy

Assess the modes of action, adverse events, and drug resistance associated with common chemotherapeutic drugs (e.g., doxorubicin, methotrexate, cisplatin) to further substantiate the demand for alternatives from plant sources.

2. Investigate the mechanisms of phytochemicals with anticancer properties

Investigate how bioactive products from plants (e.g., curcumin, resveratrol, vinca alkaloids) that affect key pathways of cancer proliferation (apoptosis, cell cycle arrest, angiogenesis, and metastasis).

3. Compare efficacies and adverse event profiles

Compare the efficacy and toxicity potential of these phytochemicals compared to standard drugs, looking at their potential combination therapies as either a synergistic or adjunct.

4. Address drug resistance as well as synergistic strategies

Evaluate how the mechanisms of phytochemicals may overcome mechanisms of resistance (i.e. P-glycoprotein efflux, escape from DNA repair mechanisms) as seen with conventional chemotherapeutics

5. Review tentative clinical and preclinical evidence

Compile the current clinical trial evidence and corresponding preclinical in-vivo (Animal) and in-vitro (cell line) evidence of potential anticancer phytochemicals, while identifying gaps and future directions.

6. Discuss converging challenges and future perspectives

Evaluate obstacles to translation to clinical settings (bioavailability, standardization) and examine potential advancements in nanoformulations or synthetic analogues related to delivery issues.

Literature Review

Source	Focus Area	Finding/Insights	Impact
Amit S Choudhari, Pallavi C Mandave, Manasi Deshpande, Prabhakar Ranjekar, Om Prakash (28 Feb 2020)	Exploring plant-derived phytochemicals as potential anticancer agents through their molecular mechanisms and therapeutic applications.	This review describes a promising role for phytochemicals of plant origin in cancer therapy. They also highlight the need for further investigations of phytochemicals that are in preclinical and clinical studies, as these are the most relevant investigations to harness the anticancer mechanism of action attributed to phytochemicals to develop a novel therapeutic agent or natural product with anticancer properties.	The significance of this study is that it has the potential to inform future cancer treatments derived from phytochemicals of plant origin. Unlike conventional pharmaceutical drugs, these compounds would be considered safe by the regulatory agencies and potentially offer better options for treatment, lower doses, fewer side effects.
Arpita Roy, Shreeja Datta, Karanpreet Singh, Bhatia, Bhumika, Priyanka Jha, Ram Prasad (September 2022)	Exploring multi-targeted cancer treatment approaches using combinatorial therapies, including plant-based secondary metabolites, to overcome the limitations of traditional mono-target chemotherapy.	In this review, we have identified the failure of mono-target chemotherapy as the result of the complex genetic origins of cancer and variability in patient responses. We acknowledge the need for multi-targeted therapies and suggest that combining synthetic drugs with secondary plant metabolites is a pathway to that goal. The combination of therapies can target multiple pathways in cancer formation which can offer a personalized, successful approach to therapy.	The significance of this research is in moving toward multi-targeted combination therapies that use synthetic drugs and plant-derived medicines instead of single-target chemotherapy. With a multi-targeted approach, we can better address the genetic complexity of cancer, improve treatment responses across broader patient populations, limit drug resistance, and lead to personalized, effective, and holistic cancer therapies.

<p>Cristina Adriana Dehelean, Iasmina Marcovici, Codruta Soica, Marius Mioc, Dorina Coricovac, Stela Iurciuc, Octavian Marius Cretu and Iulia Pinzaru (19 February 2021)</p>	<p>Plant-based anticancer agents, their mechanisms, and targeted delivery strategies.</p>	<p>This review emphasizes the significance of naturally-derived compounds in the treatment of cancer, including the well-known examples of taxol and vincristine. Again, it is important to remember that these naturally derived agents must be implemented using formulations with advanced delivery systems to improve efficacy, decrease toxicity, and overcome agent resistance mechanisms related to cont</p>	<p>The study supports the use of natural compounds as a part modern cancer treatment, specifically in developing new methods of overcoming some limitations. Through the use of new delivery systems, these agents can hopefully become better targeted agents with reduced side effects, as well as provide a more sustainable way to treat cancer in the future.</p>
<p>Nikita Sharma, R. Mankamna Kumari, Nidhi Gupta and Surendra Nimesh</p>	<p>Exploring plant extracts and bioactive compounds as effective, natural alternatives for cancer treatment.</p>	<p>This review demonstrates that plant extracts and their bioactive agents have several advantages over conventional cancer treatments. This is due to their chemical diversity, multi-target action, being more cost-effective, and limiting side effects. These natural compounds can also interact with several cellular pathways during the progression of cancer. The review also highlights the potential of these compounds in treating other diseases, showcasing the potential of medicinal plants in current day therapy.</p>	<p>The study highlights the rising significance of medicinal plants as cancer treatment options that are cheaper and safer than conventional treatments. Utilizing a combination of active compounds targeting multiple cancer pathways instead of single targets results in more effectiveness and access with decreased toxicity. The use of medicinal plants has applications in other diseases and proves their value in more holistic and sustainable healthcare.</p>

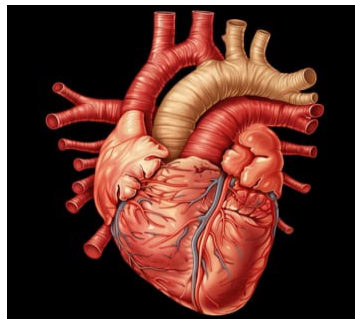
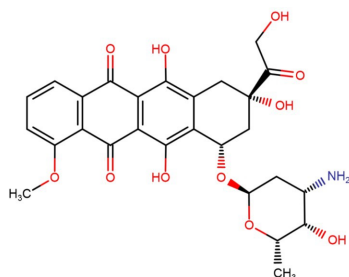
Biswas J, Roy M and Mukherjee A (29 July 2015)	Plant-derived phytochemicals as safe, effective agents for cancer treatment and drug discovery.	This review shows that fruits, vegetables, and spices contain phytochemicals that have anticancer properties. The anticancer compounds target the cancer cells and do not have adverse effects on regular processed cells, thus are safer than chemotherapy. With the increasing drug resistance and consequent toxicity of current cancer therapies, natural products can be templates for developing new therapies which are non-toxic, and many of the compounds described in the review are already in clinical or preclinical trials.	This research emphasizes the important therapeutic impact of plant-derived phytochemicals, which offer safer-targeted cancer therapies. There is great potential in the development of new and effective anticancer drugs that reduce the negative side effects and combat drug resistance encountered in contemporary therapies. This represents an important advancement in the future development of cancer treatment.
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Methodology

This study was accomplished through the use of a structured and systematic literature review. As a starting point, we considered cancer as a disease. It was important for us to understand the biological mechanisms of cancer, the various types of cancer and its development and spread at the cellular level. We also considered the most widely used cancers drugs, i.e., doxorubicin, cisplatin, methotrexate and paclitaxel. In particular, we considered each drug - its chemical structure, the therapeutic role, and focused on the side effects associated with each drug, including their ID form. In reviewing the distribution of cancers in published medical articles and clinical observations, we evaluated components such as, but not reliant on, alkylating agents, anthracyclines, and heavy metals - these components seem to cause toxic effects in humans and in some cases warning signs which leads to dying. The side effects include levels of organ

toxicity, immune suppression, nausea, hair loss etc. We then shifted our focus to studying phytochemicals, the presence of plant-based, naturally produced substances found to have anticancer properties. Our analytical review focused on compounds, such as but also not limited to curcumin, resveratrol, genistein and EGCG, that act on cancer pathways such as, but not limited to, cell apoptosis and angiogenesis with little or no impact on healthy cells. We pulled detail information from peer-reviewed journals, scientific reports, & studies focusing on pharmacology from the past five years. We utilized a form of comparative analysis to ascertain the potential value of phytochemicals, both in terms of effectiveness and safety compared to gloomy chemotherapies. Using this methodology provided us the ability to assess current treatment therapies for cancer, and propose phytochemicals as a viable option for reduced toxicity in future therapy.

DOXORUBICIN



Derivatives :-



RHUBARB



Figure 1

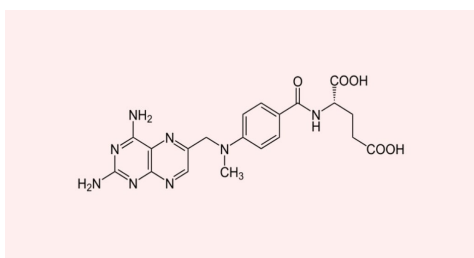
PODOPHYLLUM HEXANDRUM

Radioprotection & Chemoprotection:

Antioxidant Properties: Neutralizes doxorubicin-induced ROS (reactive oxygen species).

Cardioprotection: it may stabilize mitochondrial function in cardiomyocytes.

METHOTEXERATE



Derivatives :-



FAVA BEANS



GINGKO BILOBA

Anti-inflammatory & Immunomodulatory Effects:

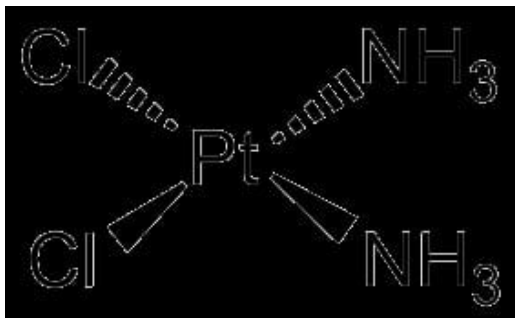
Antioxidant & Joint Protection:

Reduces oxidative stress in synovial fluid, protecting cartilage.

Neuroprotection (for RA-related neuropathy):

Improves microcirculation, which may help with RA-associated nerve pain.

CISPLASTIN



Derivatives :-



CAMILLA SINESIS

Prevention of Kidney Damage (Nephroprotection)
Protect renal tubules from apoptosis (green tea) and fibrosis (grape seed), maintaining kidney function

Urothelial & Bladder Support

Green tea strengthens mucosal lining, while grape seed prevents fibrotic strictures in the urethra.

Conclusions

1. Natural & Sustainable: Phytochemicals offer an ecologically friendly plant-based method of cancer treatment that lessens dependence on synthetic drugs and their associated side effects.



VITIS VINISFERA

2. Cost-Effective: Plant-derived compounds are treatment options that cost less to production than older chemotherapies, thus making them affordable to lower-income populations.

3. Environment-Friendly: In contrast to synthetic drug creation, which is sometimes carried out with hazardous chemicals, the extraction of phytochemicals is less intrusive to the environment and supports sustainable health care.

4. Transportable & Simple To Use: More often than not, most phytochemicals lend themselves to being formulated into orally ingested

supplements, topical ointments, or teas that patients can take with ease as compared to operative procedures.

5. Multitargeted Therapy: While synthetic drugs are designed to tackle single targets, phytochemicals usually set sights on multiple cancer processes, providing a stronger front against the disease and minimizing instances of drug resistance.

6. Decreased Side Effects: Plant-derived substances tend to exhibit lesser toxicity than conventional chemotherapy, thus improving the quality of life of the patients treated.

7. Future Potential: Additional research and clinical trials must be conducted to normalize dosages, maximize bioavailability, and include phytochemicals in standard oncology.

By taking advantage of these strengths, phytochemicals can be a significant complementary or alternative method for treating cancer. They can improve effectiveness while being sustainable and affordable.

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	Website: www.ijcrops.com
	Subject: Phytochemicals
Quick Response Code	
DOI: 10.22192/ijcrops.2025.12.08.001	

How to cite this article:

Tania Ghosh, Khushi Rabari, Khanak Patel. (2025). Phytochemicals in Cancer Therapy: Exploring Plant-Derived Alternatives to Conventional Drugs. Int. J. Curr. Res. Chem. Pharm. Sci. 12(8): 1-9.
 DOI: <https://dx.doi.org/10.22192/ijcrops.2025.12.08.001>