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Phytochemicals as emerging anticancer agents: A systematic review of mechanisms and therapeutic potential

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Abstract
The restrictions of current radiation therapy, chemotherapy, and surgical methods such as toxicology, drug resistance, and considerable cost have led to a large need for less dangerous and more effective remedies. Malignancy is a major worldwide health epidemic that claims millions of lives each year. Given their varied pharmacological characteristics and low side effects, phytochemicals bioactive substances derived from plants have shown great promise as cancer prevention and treatment agents. The anticancer potential of several important phytochemical classes, such as volatile alkaline substances, terpenoids, polyphenols, and saponins, is examined in this systematic review. By altering important biological processes implicated in dividing cells, dying off, angioplasty metastasis, and oxidative stress, these compounds have been shown in numerous studies to have anticancer effects.
In a variety of *in vitro* and *in vivo* models, compounds like lycopene, curcumin, resveratrol, quercetin, and epigallocatechin gallate (EGCG) have demonstrated strong anticancer activity. Furthermore, the distribution and therapeutic effectiveness of these phytochemicals have been enhanced by developments in drug delivery systems based on nanotechnology. The review also emphasizes how phytochemicals and traditional chemotherapeutic agents can work in concert to improve the results of cancer treatment. To confirm preclinical results and guarantee the compounds' safety, stability, and ideal dosage, more clinical research is necessary. All things considered, phytochemicals are a critical resource for the creation of new, less harmful anticancer drugs that can enhance current treatment modalities and enhance patient care.

Keywords: Phytochemicals, anticancer activity, natural compounds, cancer therapeutics, apoptosis induction

Introduction
With an estimated 9.6 million people worldwide dying of cancer in 2020, cancer is a major global health concern and the cause of significant morbidity and mortality [1]. Without a doubt, another of the biggest healthcare issues of this century is the prevalence of cancer in our day and age. It is a traumatic number to deal with statistically. In 2018, 9.6 million patients died out of the 17 million new cases that were reported, according to Cancer Research UK. By 2040, there will be nearly 27 million new cases of cancer annually if it keeps up this pace. If we consider the global space station, where we undoubtedly fail to notice what colors or the strength of the material we are looking at, we may wonder how far we have come in the fight against cancer. Yet, if we stand back before interfering with our thoughts with thousands of of target genes, substances and potential or likely medications, the basic concept of various cancer types is "uncontrolled cell division" [2]. Since herbal medicine has been shown to be safe and to have few or no negative side effects, particularly when compared to synthetic drugs, there has been a slow resurgence of interest in using medicinal plants in developing nations in recent years. Promoting the beneficial effects of herbal medicine and assessing its suitability as a supplier of new drugs are two of the most significant aspects of traditional medicine worldwide. Studying medicinal plants with a folklore reputation in greater detail is crucial. For centuries, people all over the world, including in nations like Bangladesh, Pakistan, and India on the Indian subcontinent, have utilized plants for medical purposes [3]. To put it briefly, cell division has been a basic

process since the beginning of life on Earth. Proliferation while asymmetric cell division result from symmetric cell division. One instructive step in differentiation is division. Insufficiently symmetric cell division has been identified as the primary cause of cancer [4]. Although plants are clearly an effective source of nourishment and warmth, their potential as an element of medicine is not as well known. Plants have been used for nearly as long as human civilization as a source of sustenance, refuge, and medicinal products [5].

Importance of phytoconstituents

antioxidant flavonoids, terpenoids or and phenolic elements (Fig. 1) are examples of substances that have been extensively researched for their potential to combat cancer because of their low risk of cancer and broad availability [6]. According to recent studies, eating a diet high in fruits and vegetables may lower your risk of developing several types of cancer in people [7]. Numerous bioactive characteristics of phytochemicals make them indispensable in the pursuit of efficient and customized treatments [8].

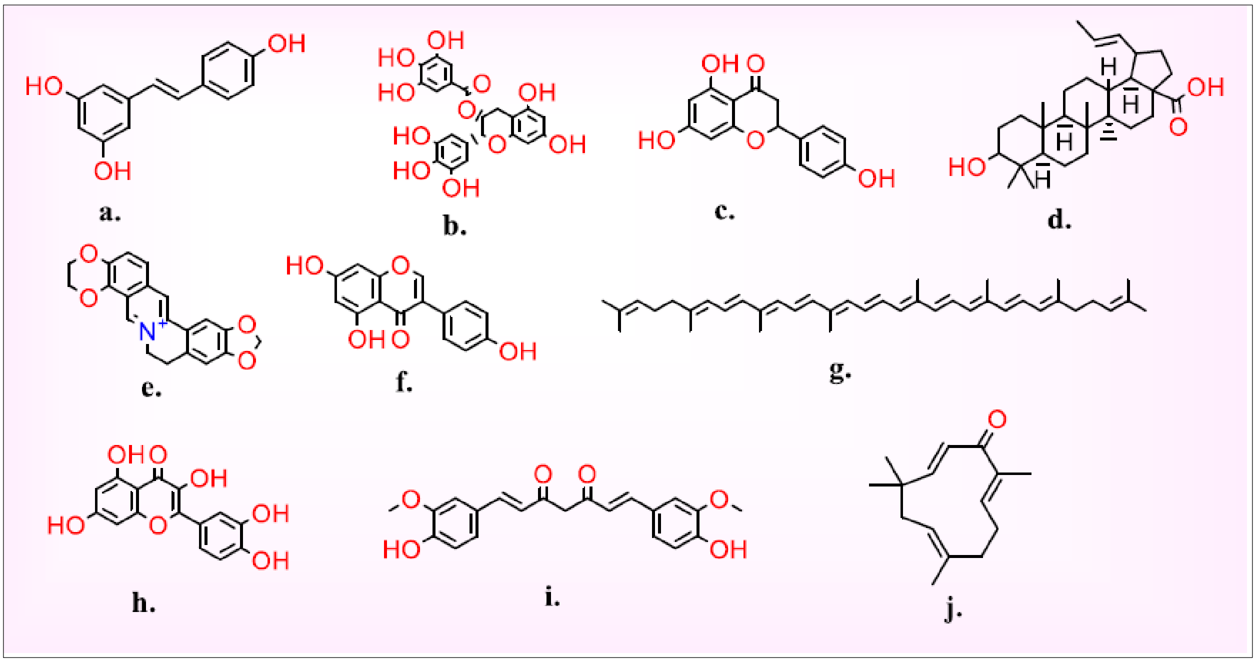

Fig 1: Structure of phytoconstituents - (a) resveratrol, (b) EGCG, (c) naringenin, (d) betulinic acid, (e) berberine, (f) genistein, (g) lycopene, (h) quercetin, (i)curcumin, (j) zerumbone.

Oncogenesis, another name for tumorigenesis, is a process that starts with initiation and continues through encouragement and progression. A series of changes in both epigenetic and genetic elements are involved in this process. By interacting with multiple interrelated signaling pathways, phytochemicals can interfere with any of these stages and have antiangiogenic, antibacterial, anti-inflammatory, and pro-apoptotic effects [9]. Targeting the tumor microenvironment, or TME, and cancer stem cells from breast cancer (CSCs), which are essential for the initiation, spread, and resistance to the treatment of cancer, has proven to be a promising application for phytoconstituents. A tiny, extremely carcinogenic subset of carcinoma of the breast stem cells is immune to standard treatments [10]. Numerous bioactive characteristics of phytochemicals make them indispensable in the pursuit of efficient and customized treatments [11]. Alkaloids, the flavonoids, terpenoids, chlorophyll, and polyphenols are just a few of the many substances that are classified as phytochemicals. The anticancer effects of these naturally occurring compounds have been thoroughly investigated, and both clinical and preclinical tests have demonstrated their notable potency [12]. For instance, curcumin, which is taken from the plant that produces turmeric, Curcuma longa, has been found to be a very strong polyphenol with significant anticancer effects by Health Canada's research [13]. Because of their capacity to obstruct cell division, the alkaloids vinblastine and vincristine, each of which are extracted from Madagascar periwinkle, are used to treat childhood leukemia and Hodgkin's lymphoma [14].

Table1: Known phytochemicals, their source, and therapeutic use

Sr.no	Name	Source	Therapeutic use	Reference
1	Vincristine	Catharanthus roseus	Lymphocytic leukemia	[15].
2	Artemisinin	Artemisia annua	Liver, breast, and pancreatic cance	[16]
3	Vinblastin	Catharanthus roseus	Lymphocytic leukemia	[17].
4	Curcumin	Curcuma longa	Colon adenocarcinoma	[18]
5	Podophyllotoxin	Podophyllum peltatum	Non-small-cell lung carcinoma	[19]

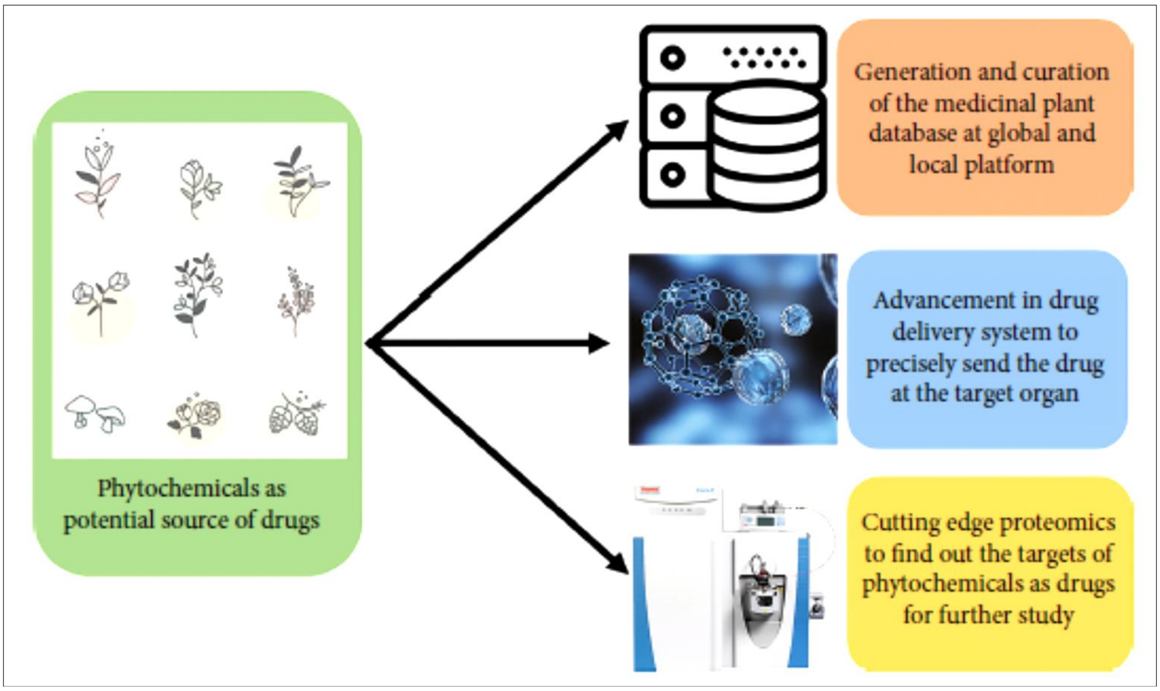

Fig 2: Phytochemicals can be used as drugs based on medicinal plant database, omics study to find the target, and efficient drug delivery system

Anticancer medicinal plants: Plants are the primary source of raw materials used in treatment, and cultures that consume a lot of botanical herbal products tend to have lower cancer rates. For instance, soybeans are a major nutritious source of saponins, which have been proposed as potential anticancer agents. Recently, there has been a lot of interest in examinations for plants. For instance, the main dietary source of saponins which have been proposed as potential anticancer agents is soybeans. Recently, there has been a lot of interest in using plants to prevent and treat cancer [20] ~ 292 ~ journals of Pharmacognosy and Phytochemistry.

Cassia auriculata

Cassia auriculata is a member of the Cesalpinaceae family, which has been shown to have antioxidant and wound-healing properties. Indian traditional medicine has a long history of using plant products to treat cancer. In traditional medicine, fresh Cassia auriculata flowers are frequently used to treat rheumatism. According to reports, the plant has astringent, hepatoprotective, antidiabetic, antiperoxidative, antihyperglycemic, and microcidal properties. The pharmacological activities of the Cassia auriculata plant are caused by alkaloids, phenols, glycosides, flavonoids, tannin, saponins, enzymes, protein, carbohydrates, and derivatives of anthraquinine. All concentrations of the ethanolic extract of Cassia auriculata flowers exhibit anticancer activity, according to the MTT assay [21].

Cucurbita maxima

Pumpkin, or Cucurbita maxima, is a member of the Cucurbitaceae family of plants. Around the world, the family of plants is widely grown for both medicinal and vegetable purposes. Its fruits and aerial parts are both frequently eaten as vegetables. In many nations, including China, India, Yugoslavia, Brazil, and America, the plant has long been used as medicine. Most nations have historically used it as an antibacterial, antitumor, antihypertensive, anti-inflammatory, immune-modulating, and anti-diabetic medication. Flavonoids and other components of medicinal plants and phenols, which have no negative effects, regulate genetic pathways to play a major role in cancer control. All concentrations of the compound extracted from the separated ethyl acetate fraction of Cucurbita maxima flowers exhibit anticancer activity, according to the MTT assay. The CTC50 (212µg/ml) value against the human bladder cancer HePG2 cell line was 72.05µg/ml, 68.94µg/ml, 54.22µg/ml, 43.19µg/ml, and 37.80µg/ml for the sample concentrations of 1000 µg/ml, 500µg/ml, 250µg/ml, 125µg/ml, and 62.5µg/ml, respectively [22].

Cynodon dactylon

As a member of the Poaceae family, Cynodon dactylon is believed to possess numerous medicinal qualities, such as anti-helmintic, anti-diuretic, anti-inflammatory, and hepatoprotective activity. It is also used to treat urinary tract infections, prostatitis, and dysentery. It has historically been used to treat diabetes, jaundice, kidney problems, urinay diseases, gastrointestinal disorders, constipation, and pain in the abdomen. Diuretics, constipation, syphilis, wound infections, and piles are all treated with the entire plant. Cynodon dactylon is used to treat nasal bleeding and dysentery by acting as an antihaemorrhagic. Hot cuts and wounds are treated externally with the astringent plant juice. It is used to treat chronic diarrhea, epilepsy, insanity, and catarrhal ophthalmia hysteria. The plant is used as a traditional treatment for rheumatic affections, snake bites, gout, coughing, calculus, carbuncles, and anasarca. On a normal vero cell line, the nontoxic dose of Cynodon dactylon petroleum ether revealed that cell viability was 97% at a concentration of 0.007 mg/ml, which decreased as concentration increased. The extract demonstrated strong cytotoxic effects on the Hep-2 laryngeal malignancy line. Using cyclophosphamide as a PC-control, 96.2% cancer death was noted. Cynodon dactylon petroleum ether extract at a concentration of 10 mg/ml demonstrated a cytotoxicity inhibition percentage of 93.5%, which was equal to the positive control level [/23]. These particular instances, along with the relevant literature, offer compelling proof of phytochemicals' potential as anticancer agents. But it's crucial to recognize the drawbacks and complexities of its application. These include issues with bioavailability, preparation standardization, and potential drug interactions, all of which need to be thoroughly assessed to guarantee reliable pharmacological action and the best possible therapeutic outcome [24].

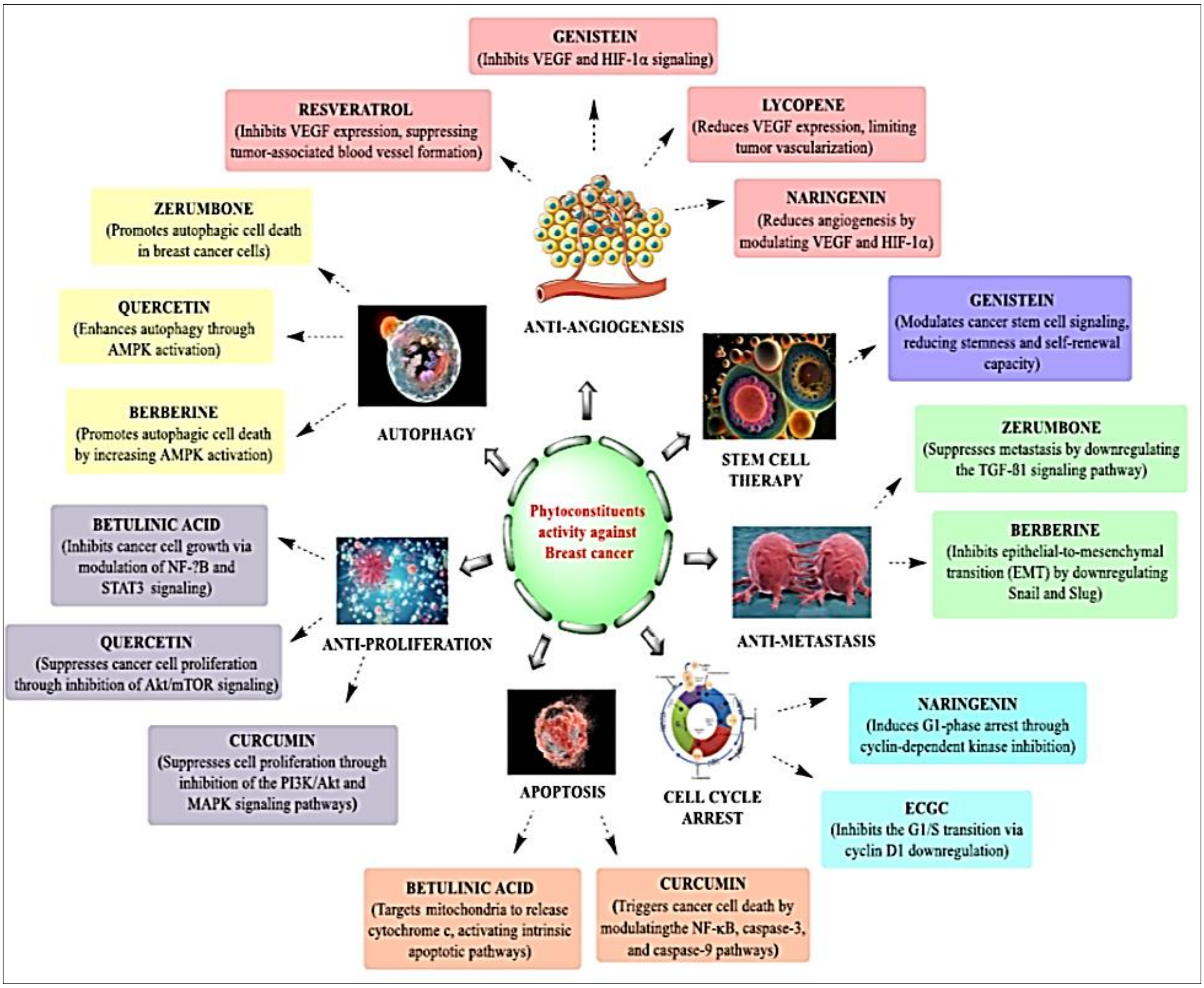

Fig 3: Phytochemicals and their specific pathways of action against breast cancer. This figure illustrates the key phytochemicals (e.g., resveratrol, curcumin, genistein, quercetin, zerumbone, lycopene, naringenin, EGCG, berberine, and betulinic acid) and their associated pathways involved in breast cancer treatment. Each pathway, autophagy, anti-angiogenesis, stem cell therapy, anti-metastasis, anti-proliferation, apoptosis, and cell cycle arrest, is depicted with corresponding mechanisms and examples of effective phytochemicals.

Emerging Trends and Technologies in Phytoconstituent Research: It is anticipated that some fascinating developments in the study of phytoconstituents will lead to innovations in the creation of anticancer drugs. Nanotechnology and machine learning are two new fields of study [25]. Large datasets can be analyzed using machine learning, a branch of artificial intelligence, to find significant trends and connections. Large plant compound databases have been mined for possible anticancer activities using algorithms that apply machine learn in phytoconstituent research, which has experimental design [26].

Anticancer action mechanisms include

1. Induction of apoptosis through death-receptor and mitochondrial pathways [27].
2. Cell-cycle arrest via cyclin-dependent kinase inhibition [28].
3. Inhibition of VEGF/HIF-1α to prevent angiogenesis [29].
4. Reduction of COX-2 and NF-κB for anti-inflammatory effects [30].
5. Epigenetic modification, which includes DNA methyltransferases and histone deacetylase inhibition [31].

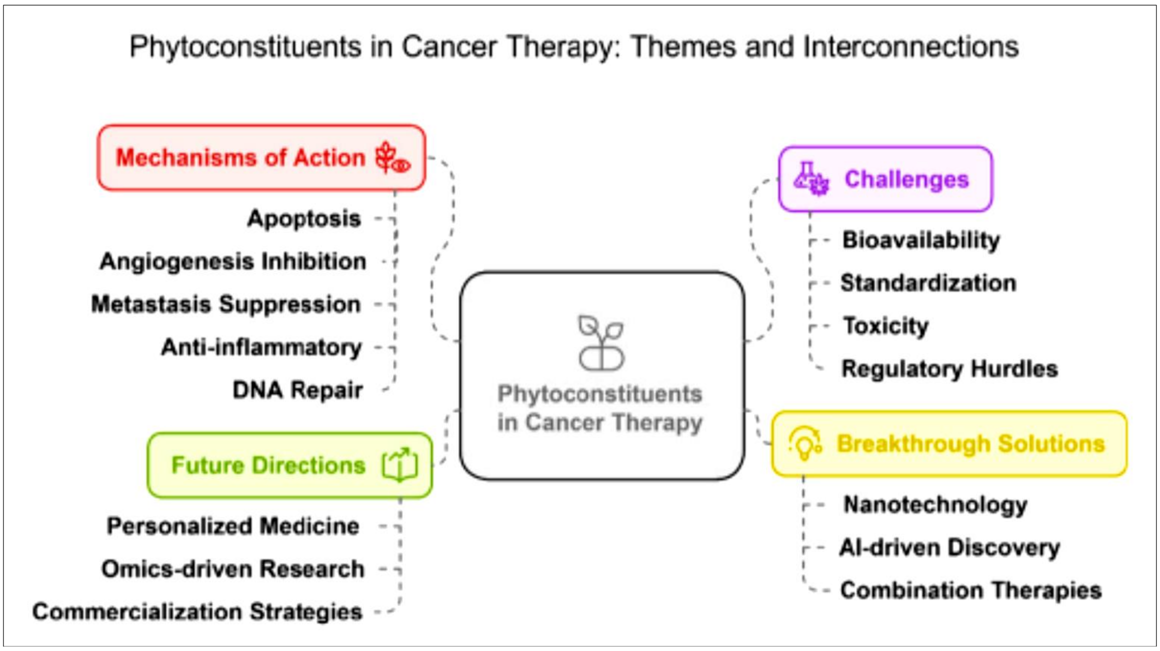

Fig 4: Central themes and associations in phytoconstituent analyses for cancer therapy. The diagram shows the key role of phytochemicals in cancer treatment associated with four prevalent themes: mechanisms of action (e.g., apoptosis, angiogenesis inhibition), challenges (e.g., bioavailability, regulatory barriers), breakthrough solutions (e.g., advances in nanotechnology, AI-assisted discovery), and future directions (e.g., personalized medicine). Dotted lines indicate associations between themes (e.g., nanotechnology tomeet bioavailability challenges).

Challenges and Limitations

1. **Poor pharmacokinetics and bioavailability:** The therapeutic potential of most phytochemicals, including curcumin, resveratrol, and quercetin, is limited by their poor systemic distribution, fast metabolism, and low oral bioavailability. [32].
2. Extracts Are Not Standardized Due to variations in plant origin, conditions of growth, and extraction methods, plant-derived formulations frequently have different chemical compositions, which might lead to inconsistent experimental study results. [33].
3. **Inadequate Clinical Evidence:** Despite the fact that many phytochemicals show promising preclinical efficacy, there aren't enough extensive controlled clinical studies to verify their efficacy and safety in people. [34].
4. **Issues with Toxicity and Dose Optimization:** It can be difficult to determine the ideal therapeutic dosage of phytochemicals because low doses can be ineffective and high doses can be toxic. [35].
5. **Complexity about Mechanisms of Action:** Because phytochemicals frequently target several signaling pathways at once, it can be challenging to identify particular molecular targets or forecast whether they will have antagonistic or synergistic effects. [36]. Experimental Model Variability It is challenging to compare results and reach consistent conclusions because different studies use different cell lines, models of animals and experimental setups. [37].
6. **Experimental Model Variability:** It is challenging to compare results and reach consistent conclusions due to variations in the types of cells, animal models, and conditions of research among studies. [37].
7. Limited Knowledge of Pharmacodynamics Many phytochemicals still have poorly understood detailed pharmacodynamic profiles that limit their application in clinical settings. These profiles include absorption, metabolism and and tissue distribution [38].
8. **Possible Herb-Drug Interactions:** Using phytochemicals and traditional chemotherapeutics at the same time may change how drugs are metabolized, which could result in unfavorable herb-drug interactions [39].
9. **Stability and Storage Restrictions:** When exposed to heat, light, or oxygen, phytochemicals frequently become chemically unstable, which shortens formulations' shelf lives and decreases their potency [40].
10. **Regulatory and Quality Control Challenges:** Phytochemical-based products lack global regulatory harmonization in quality, safety, and efficacy evaluation, leading to inconsistent market standards [41].

Future Perspectives

1. **Clinical applications and random controlled trials:** Although the majority of phytochemicals have demonstrated potent anticancer effects both *in vitro* and *in vivo*, they do not yet have sufficient clinical validation. To verify therapeutic potential in humans, future research must concentrate on extensive, carefully planned randomized controlled trials [42].
2. **Enhancement of bioavailability and pharmacokinetics:** Many powerful phytochemicals, such as resveratrol and curcumin, have low stability and solubility. Their bioavailability and use in medicine can be improved by polymeric nanoparticles, liposomes, and nanoformulations [43].
3. **Innovative drug delivery methods:** To reduce systemic toxicity and improve therapeutic index, solid-lipid nanoparticles, nanocarriers, and micelles should be investigated for specifically targeted plant-based delivery to tumors [44].
4. **Combination therapeutic approaches:** Phytochemicals can be used in conjunction with conventional immunotherapeutic or chemotherapeutic agents to increase efficacy and decrease resistance.

Future studies ought to look into mechanisms of synergy [45].

5. **Harmonization of plant extracts:** Inconsistent outcomes arise from variations in the phytochemical content, extraction techniques, and plant source. Reproducibility requires chemical profiling and standardized procedures [46].
6. **Thorough safety and toxicology assessment:** Before phytochemicals can be used in clinical settings, long-term safety research, organ-specific toxicity, and evaluations of interactions with traditional medications are essential [47].
7. **Research based on omics and systems biology:** To identify molecular targets, signals, and markers of phytochemical response, the use of proteomics, genomics, and metabolomics techniques should be applied [48].
8. **AI and computational methods for discovery:** Virtual screening, molecular docking, and artificial intelligence can speed up the process of finding and refining novel plant chemicals and related compounds [49].
9. **Prodrug design and structural modification:** Phytochemicals' pharmacokinetic characteristics and therapeutic potency can be enhanced by chemically altering natural scaffolds [50].
10. **Tumor-type-specific and personalized healthcare approach:** Future research must examine mechanisms specific to tumor subtypes and tailored treatment approaches, as phytochemicals may not be broadly beneficial [51].

Applications of Phytochemicals with Anticancer Potential

1. Chemoprevention: By preventing the earliest stages, promotion, and progression of carcinogenesis, phytochemicals function as chemopreventive agents. Curcumin, resveratrol (red wine), and epigallocatechin gallate (also called EGCG) are among the compounds that improve purifying enzymes, destroy reactive oxygen molecules (ROS), and inhibit inflammatory mediators like NF-κB and COX-2 [52].
2. Direct Anticancer Action By triggering cell-cycle arrest, autophagy, and apoptosis, phytochemicals specifically target cancer cells. Oncogenic pathways like PI3K/AKT, MAPK, and STAT-3 are inhibited by curcumin, ginseng, and quercetin [53].
3. Adjuvant therapy, or chemosensory stimulation Some phytochemicals make resistant cancer cells more sensitive to chemotherapeutic medications. For instance, by blocking P-glycoprotein and improving intracellular drug retention, quercetin and resveratrol are believed to reverse resistant to multiple drugs (MDR) [54].
4. Delivery Systems Based on Nanocarriers the delivery of nanocarriers (liposomes, micelles, and nanoparticles) enhances the pharmacokinetics and cancer targeting of many phytochemicals, which have low solubility and bioavailability [55].
5. Modulation of the immune system to improve anticancer immunity, phytochemicals can modulate immune responses. Curcumin, resveratrol, and berberine are among the compounds that suppress tumor-associated inflammation, alter cytokines, and boost cytotoxic T-cell activity [56].
6. Getting Past Multidrug Resistance (MDR) Natural substances increase sensitivity to chemotherapy by blocking efflux transporters like P-gp, MRP1, and BCRP. Alkaloids and flavonoids, for example, inhibit mitochondrial survival signaling and drug-resistance pathways [57].
7. Regulation of Epigenetics Oncogene activation is caused by aberrant epigenetic adjustments that can be reversed by phytochemicals. As the histone deacetylase (HDAC) and the enzyme DNA methyl (DNMT), respectively, inhibitors, substances such as genistein, sulfuric acid, and curcumin reactivate tumor suppressor genes [58].
8. Drug Discovery Lead Molecules Strong anticancer medications are synthesized using phytochemicals as structural templates. Clinically approved chemotherapy drugs with natural origins include camptothecin (from campsite acuminata) and taxol (from Taxus brevifolia), among other plants [59].
9. Combination Treatment By lowering toxicity and working in concert to target several signaling pathways, phytochemicals can improve the effectiveness of radiation and chemotherapy. For example, curcumin exhibits enhanced anticancer activity when paired with doxorubicin or cisplatin [60].
10. Dietary and Nutraceutical Uses Frequent ingestion of foods high in phytochemicals, such as cruciferous vegetables, green tea, turmeric, and soy, is associated with a decreased risk of cancer. For at-risk groups, these bioactives serve as nutrients in chemopreventive strategies [61].

Comparison of study types / approaches for Phytochemicals with Anticancer Potential:

1. **Isolation & Lead Discovery for Natural Products: Method:** Using this approach, bioactive compounds are extracted and isolated from plants, then their structures are clarified and their bioactivity is evaluated [62].
2. **In Laboratory Mechanistic Studies Approach:** Examines the molecular mechanisms behind phytochemicals' anticancer effects using cell culture models [63].
3. ***In vivo* Clinical Models Approach:** This method uses animal models to assess phytochemicals' safety and effectiveness in a whole-organism setting [64].
4. **Clinical Trials Approach:** This method uses human research to evaluate the effectiveness, safety, and tolerability of phytochemicals as therapies for cancer [65].
5. **Research on Epidemiology Method:** Observational research that examines the connection between phytochemical intake in the diet and the risk of cancer [66].
6. **Research on Combination Therapy Method:** Examines how combining phytochemicals with traditional chemotherapeutic agents can have a synergistic effect [67].
7. **Advanced Formulation & Delivery Methods Method:** Creates innovative delivery methods to increase phytochemicals' absorption and targeted delivery [68].
8. **Computational & In Laboratory Studies Approach:** Makes use of computational models to forecast how

phytochemicals will interact with targets linked to cancer [69].

9. **Studies on Pharmacokinetics and Formulation Method:** Evaluates phytochemicals' absorption, distribution, metabolism, and excretion (ADME) characteristics in order to maximize their potential for therapeutic use [70].

Conclusion

The current systematic review highlights the significant role of phytochemicals as potential anticancer agents, emphasizing their multifaceted mechanisms of action, including modulation of apoptosis, cell cycle arrest, inhibition of angiogenesis, and suppression of metastasis. A diverse array of bioactive compounds, including flavonoids, alkaloids, terpenoids, phenolics, and organosulfur compounds, demonstrates promising anticancer effects across various cancer models, both *in vitro* and *in vivo*. These phytochemicals not only exhibit cytotoxicity toward malignant cells but also show selective targeting, reducing damage to normal tissues, which underlines their therapeutic advantage over conventional chemotherapy.

Even with the encouraging preclinical data, there are still a number of obstacles to overcome before these discoveries can be used in clinical settings. Low pharmacokinetic data, poor solubility, fast metabolism, and low bioavailability are some of the main drawbacks. Furthermore, direct comparison and reproducibility are challenging due to variations in extraction techniques, concentrations, and experimental models. An important research gap is highlighted by the review, which also notes the dearth of comprehensive clinical trials to confirm the safety and effectiveness of these substances in human populations.

In addition to examining synergistic effects with currently available chemotherapeutic agents, future research should concentrate on increasing the accessibility of phytochemicals using sophisticated delivery systems like nanoparticles, liposomes, and conjugates. To create standardized treatment protocols, thorough molecular and cellular mechanistic research is essential, as is carefully planned clinical testing. Additionally, by taking into consideration each patient's unique genetic and metabolic characteristics, the incorporation of phytochemicals into precision medical strategies presents the possibility of personalized cancer prevention and treatment.

To sum up, phytochemicals are a potentially useful natural resource for the prevention and treatment of cancer. These bioactive substances could enhance traditional treatments, lessen side effects, and make a substantial contribution to the development of anticancer treatments in the future with sustained, thorough research and technical developments in drug distribution and molecular pharmacology.

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