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Review Paper

Phytomedicine in Cancer Therapy: Pharmacokinetic Modulation, Molecular Mechanisms and Translational Challenges

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ABSTRACT

Phytomedicine has emerged as a promising strategy in cancer therapy due to its multi-targeted actions which create lower toxicity while building synergies with traditional chemotherapy drugs. The review demonstrates how plant-based bioactive substances affect drug absorption through their pharmacokinetic properties which enhance drug delivery systems while fighting against drug resistance. Various phytoconstituents such as polyphenols and flavonoids and alkaloids and terpenoids exert anticancer effects through their ability to control vital molecular pathways which include apoptosis and cell cycle arrest and angiogenesis inhibition and immune system regulation. Despite positive results from preclinical studies the clinical development of phytomedicine encounters major obstacles which include difficulties with plant extraction and research variability and the absence of standardized plant-based drugs. The therapeutic capabilities of phytomedicines have grown through advancements in delivery systems which use nanotechnology and new strategies for pharmacokinetic control. The review investigates existing obstacles which hinder research progress and addresses regulatory matters while providing future outlooks to establish phytomedicine as an accepted area of cancer treatment. Phytomedicine serves as a useful complementary treatment method for cancer but requires thorough testing and product development to achieve successful cancer treatment results.

INTRODUCTION

The world faces a significant health problem because cancer cases and deaths continue to rise despite improvements in standard treatment methods which include chemotherapy and radiotherapy [1]. Drug resistance and treatment toxicity and high costs of treatment create a need for research to discover safer and more effective treatment options. Phytomedicine uses plant-based bioactive compounds to develop treatments which demonstrate multiple anticancer effects while maintaining safe toxicity levels. Scientists have found that curcumin and resveratrol and quercetin

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act as phytochemicals which control essential biological functions such as apoptosis and cell proliferation and angiogenesis. The process of clinical translation faces major obstacles because of three factors: poor bioavailability and rapid metabolism and absence of standardized procedures [2]. The field of drug delivery systems has achieved progress through recent developments in nanotechnology which provide effective solutions to existing problems. The review examines how phytomedicine affects cancer treatment through its impact on pharmacokinetics which leads to different molecular mechanisms that create difficulties for research to succeed [3].

2. Overview of Phytomedicine in Cancer Therapy – Phytomedicine functions as an essential component of cancer treatment because it contains multiple bioactive compounds which work against multiple targets while producing less harmful effects than other treatments. Plant-derived compounds such as polyphenols, alkaloids, flavonoids, and terpenoids have demonstrated potential in inhibiting tumor growth, inducing apoptosis, and modulating key signaling pathways. The research on phytomedicines as adjuvants for traditional treatments has increased because they show potential to improve treatment results while decreasing treatment side effects. The treatment approach solves the problem of drug resistance through its ability to target multiple molecular sites which exist in cancer cells. Various plant-derived compounds with anticancer potential are summarized **Table 1**.

Table 1: Major phytochemicals and their plant sources with anticancer activity [4,5,6]

Phytochemical	Plant Source	Class	Anticancer Activity
Curcumin	*Curcuma longa*	Polyphenol	Induces apoptosis, anti-inflammatory
Resveratrol	*Vitis vinifera*	Polyphenol	Anti-proliferative, antioxidant
Quercetin	Fruits & vegetables	Flavonoid	Cell cycle arrest, apoptosis
EGCG	*Camellia sinensis*	Catechin	Anti-angiogenic, anti-metastatic
Vincristine	*Catharanthus roseus*	Alkaloid	Inhibits microtubule formation
Paclitaxel	*Taxus brevifolia*	Terpenoid	Stabilizes microtubules

2.1 Historical Perspective – The practice of using plants to treat cancer originated in ancient medical systems that included Ayurveda and Traditional Chinese Medicine and Egyptian medicine. The first herbal medicines doctors used were designed to relieve symptoms and to prevent tumor growth [7]. The scientific validation of phytomedicine began in the 20th century with the discovery of plant-derived anticancer drugs like paclitaxel (from Taxus brevifolia) and vincristine (from Catharanthus roseus). These discoveries demonstrated that natural products function as essential sources of chemotherapy drugs while they created the basis for contemporary research in phytopharmaceutical development [8].

2.2 Current Trends in Oncology – Recent research in oncology emphasizes the integration of phytomedicine with advanced therapeutic strategies. Researchers are now studying how to combine phytochemicals with conventional chemotherapy and targeted therapy to achieve better treatment results while decreasing harmful effects. Modern approaches use nanotechnology-based delivery systems to develop better pharmacokinetic properties which improve drug bioavailability and enable precise medication distribution [9]. Phytoconstituents are being used in personalized medicine and molecular-targeted therapies to control particular cellular signaling pathways. The growing number of clinical trials together with evidence-based studies establishes phytomedicine as an effective complementary treatment for cancer management [10].

3. Pharmacokinetic Modulation of Phytomedicines – The therapeutic effectiveness of phytomedicines used in cancer treatment depends on their pharmacokinetic behavior which determines their medical effectiveness. The clinical development of plant-derived anticancer compounds faces obstacles because their pharmacokinetic properties do not support medical use. The primary obstacles which need to be solved include five major issues [11]. The first issue affects bioavailability because the body can only absorb a limited amount of the drug while the second issue causes unpredictable treatment results [12]. Phytomedicine researchers have made pharmacokinetic modulation their primary research area because it helps them achieve better treatment results and successful medical use [13]. Key pharmacokinetic challenges and their possible solutions are summarized in **Table 2**. Pharmacokinetic barriers associated with phytochemicals are illustrated in **Figure 1**.

Table 2: Pharmacokinetic limitations of phytomedicines and enhancement strategies

Limitation	Description	Example	Strategy
Poor solubility	Low water solubility	Curcumin	Nanoparticles, liposomes
Low bioavailability	Poor absorption	Resveratrol	Bioenhancers (piperine)
Rapid metabolism	First-pass metabolism	EGCG	Structural modification
Fast elimination	Short half-life	Quercetin	Sustained release systems
Non-specific targeting	Low tumor accumulation	Many phytochemicals	Targeted drug delivery

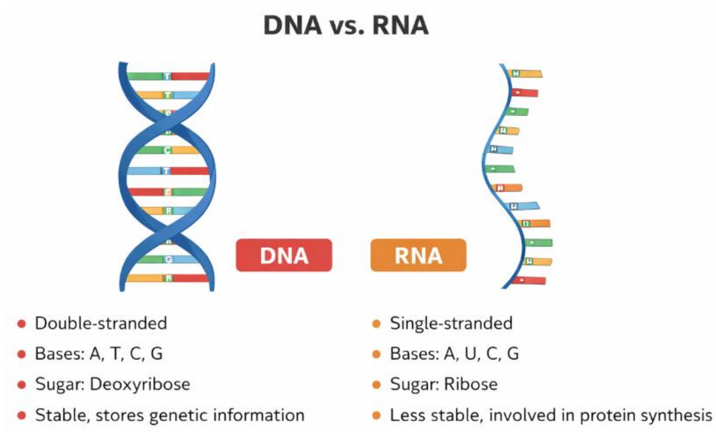

Figure 1. Pharmacokinetic limitations of phytomedicines including poor absorption, rapid metabolism, and fast elimination, along with enhancement strategies such as nanocarriers, bioenhancers, and targeted delivery systems to improve bioavailability.

3.1 Absorption and Bioavailability – The most common method for taking phytomedicines involves oral administration, but their gastrointestinal absorption remains challenging because many phytoconstituents do not absorb well. This situation occurs because of two main factors: The substances have low water solubility (e.g., curcumin and resveratrol). The substances have low ability to pass through biological membranes. The substances lose their effectiveness when they encounter gastric and intestinal conditions. Intestinal enzymes and efflux transporters such as P-glycoprotein (P-gp) work to decrease intracellular drug levels by sending substances back into the intestinal lumen. The levels of systemic availability for most phytochemicals remain extremely low [14]. The therapeutic usefulness of curcumin remains restricted because it has less than 1% oral bioavailability.

3.2 Distribution and Targeting – The body system sends absorbed phytochemicals through its bloodstream to different body parts. The compounds in the body distribute themselves through the body. The compounds in the body distribute themselves through the body, which leads to three specific outcomes: Tumor sites experience only limited compound accumulation. Cancer tissues show decreased levels of therapeutic compounds. There is a risk of unexpected effects occurring outside the intended treatment area [15]. The degree of protein binding in plasma shows a direct relationship to the unbound state of active compounds. The medical field continues to face its biggest obstacle because specialists cannot yet develop specific methods for attacking tumors. Modern treatment methods use active targeting with ligands and receptors together with passive targeting based on the enhanced permeability and retention effect to increase drug delivery to tumors.

3.3 Metabolism and Elimination – The human body metabolizes phytomedicines through multiple pathways which start at the liver and intestinal mucosa and include two types of metabolic reactions. The first type of metabolic reaction which includes oxidation and reduction and hydrolysis through cytochrome P450 enzymes represents Phase I metabolic processes. The second type of metabolic reaction which includes glucuronidation and sulfation and methylation represents Phase II metabolic processes. The metabolic processes transform active substances into metabolites which have decreased or no active potential. The body processes resveratrol quickly by converting it into glucuronide and sulfate conjugates which decrease its biological effects [16]. The body eliminates phytochemicals through renal and biliary systems which leads to shorter half-lives and reduced systemic exposure. The requirement for this treatment demands multiple dosing throughout the day but this approach proves to be neither practical nor successful in actual medical environments.

4. Molecular Mechanisms of Anticancer Activity - Phytomedicines demonstrate strong anticancer activity because they attack various molecular pathways that control tumor development and its onset. Phytochemicals function differently from standard treatments which focus on one specific target because they affect multiple cellular activities including apoptosis and cell growth and blood vessel formation and cancer spread [17]. The multi-targeted approach of these treatments enables better treatment results for complex cancer biology and drug resistance challenges. The major molecular targets of phytochemicals are summarized in **Table 3.** The molecular mechanisms of phytomedicines are summarized in **Figure 2.**

Table 3: Molecular targets and mechanisms of phytochemicals in cancer therapy

Phytochemical	Target Pathway	Mechanism
Curcumin	NF-κB, PI3K/Akt	Induces apoptosis, inhibits proliferation
Resveratrol	p53, MAPK	Cell cycle arrest, apoptosis
Quercetin	CDKs	Cell cycle inhibition
EGCG	VEGF	Anti-angiogenesis
Genistein	Tyrosine kinase	Inhibits tumor growth

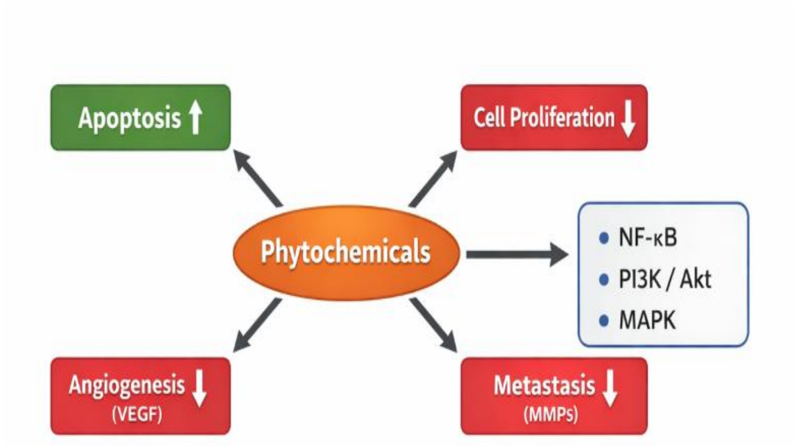

Figure 2. Molecular mechanisms of phytomedicines in cancer therapy showing induction of apoptosis, inhibition of cell proliferation, suppression of angiogenesis, and prevention of metastasis through modulation of key signaling pathways such as NF-κB, PI3K/Akt, and MAPK.

4.2 Cell Cycle Arrest – The uncontrolled growth of cells represents the main characteristic of cancer. Phytochemicals stop cancer cell growth through their ability to induce cell cycle suspension at particular checkpoints. These compounds control essential proteins which include cyclins and cyclin-dependent kinases (CDKs) and the tumor suppressor gene p53. Quercetin stops cells at the G0/G1 phase while curcumin functions to prevent cell cycle progression through the G2/M phase. Phytochemicals stop cancer cell growth by blocking cell cycle development which leads to cancer cell death. This mechanism plays a crucial role in controlling tumor expansion [18].

4.3 Anti-angiogenic Effects – Tumors require angiogenesis to develop and stay alive because this process delivers essential oxygen and nutrients to their fast-growing cancer cells. Phytochemicals disrupt angiogenesis by attacking fundamental control mechanisms which include vascular endothelial growth factor and hypoxia-inducible factor-1α. The researchers show that they can inhibit matrix metalloproteinases which play a role in breaking down extracellular matrix and creating new blood vessels [19]. The compounds epigallocatechin gallate and curcumin show powerful anti-angiogenic effects because they restrict blood vessel development which leads to tumor growth.

4.4 Anti-metastatic Activity – Metastasis involves a complex mechanism that enables cancer cells to move from their main tumor site to different body parts. Phytochemicals prevent cancer cells from spreading by blocking epithelial-mesenchymal transition (EMT), which serves as an essential mechanism for their movement and invasion. They downregulate MMP-2 and MMP-9 enzymes which help with tissue invasion while they also regulate the function of cell adhesion molecules. Phytomedicines block the signaling pathways which control cell movement and invasion patterns thus stopping the spread of cancer [20]. The anti-metastatic effect of this treatment method plays a vital role in decreasing deaths linked to cancer.

4.5 Modulation of Signaling Pathways – Phytochemicals maintain their ability to combat cancer through their ability to control essential signaling pathways which determine whether cells will survive or multiply or experience inflammatory responses. The NF-κB pathway establishes connections between inflammatory processes and the ability of cancer cells to survive. The PI3K/Akt/mTOR pathway controls the process of cellular development through its influence on cellular metabolic activities. The MAPK pathway maintains control over the process of cell division [21]. Phytomedicines block these pathways to achieve two effects: they reduce tumor development while increasing cancer cell death through apoptosis. Phytochemicals offer their most important benefit to cancer treatment through their capacity to control multiple biological pathways.

4.6 Immunomodulatory Effects – Phytochemicals demonstrate two effects against cancer cells because they kill cancer cells through direct cytotoxicity while boosting immune defense mechanisms of the body. The test substances activate T-lymphocytes together with natural killer (NK) cells while they boost cytokine production that controls immune functions. The immunomodulatory effect enables better cancer cell detection and destruction which enhances total anticancer defense mechanisms [22].

5. Synergistic Effects with Conventional Therapies – The practice of combining phytomedicines with standard cancer treatments has become widely studied because this method improves treatment outcomes while decreasing treatment-associated complications. Phytochemicals function as chemosensitizers and radiosensitizers which boost cancer cell treatment response to chemotherapy and radiotherapy. The combined treatment method creates an effective solution which resolves the drawbacks of standard single treatment methods. Phytochemicals significantly enhance the efficacy of chemotherapeutic agents through multiple mechanisms. The compounds curcumin resveratrol and quercetin create changes to essential signaling pathways which control the survival and growth of cancer cells. Curcumin improves doxorubicin and cisplatin drug performance through its NF-κB signaling inhibition which increases drug efficacy. The combination produces a synergistic effect which enables physicians to decrease drug amounts while still achieving required treatment results. Phytomedicine-based combination therapy provides another essential benefit because it minimizes all treatment-associated adverse reactions. Conventional anticancer drugs lead to severe toxic effects which include damage to the liver and kidneys and suppression of bone marrow production. Phytochemicals present protective benefits to normal cells because they contain both antioxidant and anti-inflammatory capabilities. Curcumin and green tea polyphenols work together to lower oxidative stress and inflammation which results in better patient tolerance and enhanced quality of life. Phytochemicals function as radiosensitizers which improve radiotherapy treatment results. The compounds create excessive oxidative stress which leads to DNA destruction in cancer cells and prevents their ability to repair DNA.

Recent clinical studies evaluating phytomedicines in cancer therapy are listed in **Table 4.**

Table 4: Selected clinical studies on phytomedicine in cancer therapy

Phytochemical	Cancer Type	Study Type	Outcome
Curcumin	Breast cancer	Clinical trial	Reduced tumor progression
Resveratrol	Colon cancer	Clinical trial	Anti-proliferative effect
Green tea extract	Prostate cancer	Clinical study	Reduced PSA levels
Genistein	Breast cancer	Clinical trial	Hormonal modulation

6. Nanotechnology-Based Phytomedicine Delivery Systems – Researchers found that nanotechnology developed into a successful method which solved the pharmacokinetic issues that restricted phytomedicine usage in cancer therapy. The clinical use of phytochemicals is severely restricted because they have multiple problems which include poor solubility and low bioavailability and rapid metabolism and non-specific distribution [23] . The nanocarrier-based delivery systems provide new methods to develop plant-derived compounds because they boost stability and enable accurate delivery while raising therapeutic effectiveness. The nanoparticles enhance both solubility and stability of hydrophobic phytochemicals which include curcumin and resveratrol because they wrap these substances in materials that are safe for human use. This process allows the active components to maintain their integrity during physiological conditions, which results in extended time periods of active vessel movement. The target location can sustain elevated levels of medication throughout time. The primary benefit of nanotechnology lies in its capacity to deliver drugs directly to specific treatment sites. The EPR effect enables nanocarriers to passively target tumor tissues because they accumulate in those areas through their enhanced ability to penetrate blood vessel walls[24]. The process of surface modification through ligand attachment which includes antibodies and peptides and folic acid enables active targeting, which delivers drugs directly to cancer cells while protecting healthy tissues from harm. Research has led to the creation of several nanocarrier systems which enable the effective delivery of phytomedicine through these systems: Liposomes: Improve drug solubility and reduce toxicity. Solid lipid nanoparticles (SLNs): Provide controlled drug release and enhanced stability. Polymeric nanoparticles: Offer sustained release and targeted delivery. Nano emulsions and micelles: Enhance absorption and bioavailability. The systems enable higher cellular absorption of phytochemicals which leads to better delivery in the cells. The systems enable higher cellular absorption of phytochemicals which leads to better delivery in the cells. The technology of nanotechnology enables scientists to create drug delivery systems which release medications in a controlled manner and maintain therapeutic drug concentrations throughout a long time period. The system decreases the number of required doses which leads to better patient adherence to treatment. The method reduces the peak toxicity issues which occur with traditional methods of drug delivery. The advantages of the system have been achieved yet three major obstacles continue to exist which include nanotoxicity risks, difficulties in producing products at a large scale, issues with product stability and challenges with meeting regulatory requirements [25]. The process of clinical translation requires both standardization and long-term safety assessment. Advanced nanotechnology approaches for phytomedicine delivery are shown in **Figure 3**.

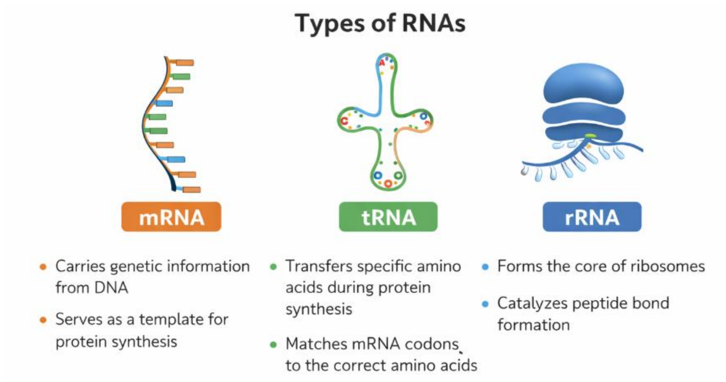

Figure 3. Nanotechnology-based targeted delivery of phytomedicines demonstrating enhanced permeability and retention (EPR) effect, improved tumor targeting, and increased therapeutic efficacy of phytochemicals.

7. Translational Challenges in Phytomedicine – The ongoing research for phytomedicine has made important progress yet its investigators face difficulties when they attempt to transform phytochemical compounds into effective cancer treatment methods. The process of developing these treatments from their research stage to their use in medical practice faces multiple obstacles which include scientific challenges technical difficulties and regulatory requirements [26]. The complete medical benefits of phytomedicines can only be achieved after researchers successfully remove the existing obstacles. Key translational challenges and potential solutions are summarized in **Table 5**.

Table 5: Challenges and possible solutions in phytomedicine translation

Challenge	Description	Solution
Lack of standardization	Variable composition	Quality control protocols
Poor bioavailability	Low systemic exposure	Nano formulations
Regulatory issues	No clear guidelines	Harmonized regulations
Limited clinical trials	Insufficient evidence	Large-scale RCTs
Safety concerns	Herb–drug interactions	Toxicity studies

7.1 Standardization and Quality Control – Phytomedicine faces its most significant obstacle because researchers cannot create standardized procedures. The chemical composition of plant-derived compounds can vary significantly depending on factors such as plant species, geographical location, harvesting time, and extraction methods. The resulting variability causes both efficacy and safety of the product to become inconsistent. The establishment of standardized extraction procedures and quality control measures and reproducible formulations stands as vital requirement for clinical acceptance.

7.2 Clinical Validation – The anticancer properties of phytochemicals have been demonstrated through multiple in vitro studies and multiple in vivo studies. The existing clinical trials of these phytochemicals fail to provide adequate evidence of their safety and effectiveness for human use. The scientific community has not accepted these findings because of three main factors. The research requires the execution of substantial randomized controlled trials to determine their treatment effectiveness. The anticancer properties of phytochemicals have been demonstrated through multiple in vitro studies and multiple in vivo studies. The existing clinical trials of these phytochemicals fail to provide adequate evidence of their safety and effectiveness for human use [27]. The scientific community has not accepted these findings because of three main factors. The research requires the execution of substantial randomized controlled trials to determine their treatment effectiveness.

7.3 Regulatory Barriers – Phytomedicines encounter complicated regulatory problems because different countries classify them as either dietary supplements or drugs. The absence of clear regulatory guidelines for herbal-based anticancer therapies complicates the approval process. The process of bringing products to market faces delays because of problems related to intellectual property rights and standardization.

7.4 Safety and Toxicity Concerns – The safety of phytomedicines is widely accepted, but their usage at high doses or with standard medications can lead to harmful effects. The combination of herbs and medications can create interactions that affect how drugs are processed and their effectiveness. The absence of long-term toxicity studies and safety assessments creates doubts about their clinical application.

7.5 Manufacturing and Scalability Issues – The production of phytomedicine formulations at large scale faces difficulties in achieving consistent results and maintaining product stability and controlling production expenses. The commercial viability of nanoparticles as advanced delivery systems is restricted by their need for complex manufacturing procedures.

7.6 Lack of Pharmacokinetic and Pharmacodynamic Data – Comprehensive data on pharmacokinetics (PK) and pharmacodynamics (PD) of phytochemicals are often insufficient. This limitation results in difficulties for clinicians to achieve accurate dose calculations while monitoring treatment and forecasting patient results. The existing gap requires both advanced analytical methods and organized research investigations for its complete resolution.

8. Future Perspectives and Emerging Trends – The future of phytomedicine in cancer therapy depends on combining cutting-edge technologies with established traditional methods. Scientists use nanotechnology-based delivery systems and AI-driven drug discovery and network pharmacology to improve their ability to identify and optimize and deliver phytochemicals. Personalized medicine now enables the development of customized phytoconstituents which match the unique genetic and molecular characteristics of each individual [28]. The rising interest in combination therapies and multi-targeted approaches and synergistic formulations will lead to better treatment results. Omics technologies including genomics and proteomics and metabolomics research provide scientists with new tools to study how phytomedicines operate at the molecular level. Clinical research needs strengthening while standardization must improve and regulatory frameworks require clear development to enable successful implementation of these technologies in mainstream oncology [29].

CONCLUSION

Phytomedicine serves as an emerging cancer treatment method which uses multiple pathways to fight cancer while causing less harm to patients and producing combined treatment effects with standard medical procedures. The clinical development of preclinical anticancer candidates remains restricted because their active compounds face challenges with bioavailability and standardization and regulatory requirements. Phytochemicals achieve better therapeutic results through new methods that improve their pharmacokinetics and deliver them using nanotechnology delivery systems. The medical community requires both clinical testing and standardized product development and better regulatory frameworks to determine their value in contemporary cancer treatment. Phytomedicine demonstrates potential as a supplementary treatment method for cancer which requires different medical fields to work together for its successful implementation in clinical settings [30].

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