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CLINICAL ROLE OF PHYTOCONSTITUENTS IN CANCER THERAPY: A REVIEW OF THEIR THERAPEUTIC POTENTIAL AND MECHANISMS

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ABSTRACT

Cancer remains one of the leading causes of death worldwide, despite advancements in conventional therapies such as chemotherapy, radiation, and immunotherapy. These therapies frequently have serious adverse effects and limited effectiveness. Bioactive substances originating from plants, known as phytoconstituents, have attracted interest recently as possible cancer treatment agents. The function of several phytoconstituents, such as lignans, phenolic acids, terpenoids, alkaloids, and flavonoids, in modifying cancer-related pathways is examined in this review. These substances have shown a variety of anticancer actions, such as antioxidant qualities, tumour growth inhibition, apoptosis induction, and regulation of important signalling pathways such as the PI3K/Akt, MAPK, and NF-κB pathways. Additionally covered are the ways in which phytoconstituents produce their anticancer effects, including cell cycle arrest, increased chemotherapeutic effectiveness, and tumour microenvironment modification. Additionally, the limitations and possible difficulties in converting these molecules into clinical treatments are discussed. In order to improve patient outcomes and reduce side effects, this review emphasizes the potential of phytoconstituents as supplemental medicines in the treatment of cancer.

1. INTRODUCTION

With an anticipated 19.3 million new cases and about 10 million deaths in 2020, cancer is one of the main causes of death globally.[1] Certain tumours have been successfully treated with

conventional medicines such immunotherapy, radiation, and chemotherapy. However, these modalities frequently result in high relapse rates, resistance development, and severe side effects, making the quest for other therapeutic approaches necessary. The bioactive substances obtained from plants, known as phytoconstituents, have shown promise in the fight against cancer. These organic substances, which include polyphenols, terpenoids, alkaloids, and flavonoids, have a variety of biological properties, including anti-nflammatory, anti-cancer, and antioxidant properties. Phytochemicals are considered promising agents in the fight against cancer because of their capacity to influence a variety of signalling pathways, including those involved in angiogenesis, apoptosis, and immunological modulation. Furthermore, their potential for treatment and efficacy are highlighted by their usage in traditional medicine throughout cultures.[2]

A major cause of death globally, cancer is becoming more common as a result of aging populations, shifting lifestyles, and environmental causes. The World Health Organisation (WHO) estimates that 10 million deaths worldwide in 2020—roughly one in six fatalities—were attributable to cancer. This emphasizes how urgently better cancer treatments are needed. Conventional treatments like radiation, chemotherapy, and surgery have made great progress, but they frequently have drawbacks like toxicity, side effects, and the emergence of resistance. Natural substances, especially phytochemicals, are being investigated as possible cancer treatments as a result of the demand for more specialized, alternative therapeutic approaches.[3] Plants contain bioactive substances called phytochemicals, or phytoconstituents, which have long been known to have therapeutic benefits. Alkaloids, flavonoids, terpenoids, polyphenols, and glycosides are only a few of the kinds of secondary metabolites that plants create. Numerous of these substances have shown anticancer qualities in both clinical and laboratory experiments, making them viable options for cancer treatment and prevention. Phytochemicals are especially appealing for long-term use because they are typically linked to less negative effects than traditional chemotherapeutic drugs.[4]

Numerous phytochemicals have the capacity to interact with important molecular targets implicated in the development of cancer, including oncogenes, tumour suppressor genes, and cell signalling pathways, according to recent study. These pathways allow phytoconstituents to influence processes that are essential for tumour initiation, growth, and spread, including as angiogenesis, cell cycle regulation, apoptosis (Programmed cell death), and metastasis.[5]

With an emphasis on their methods of action, synergistic effects with traditional medicines, and potential for the future in overcoming the obstacles of present cancer treatments, this review attempts to thoroughly examine the function of phytoconstituents in cancer therapy.

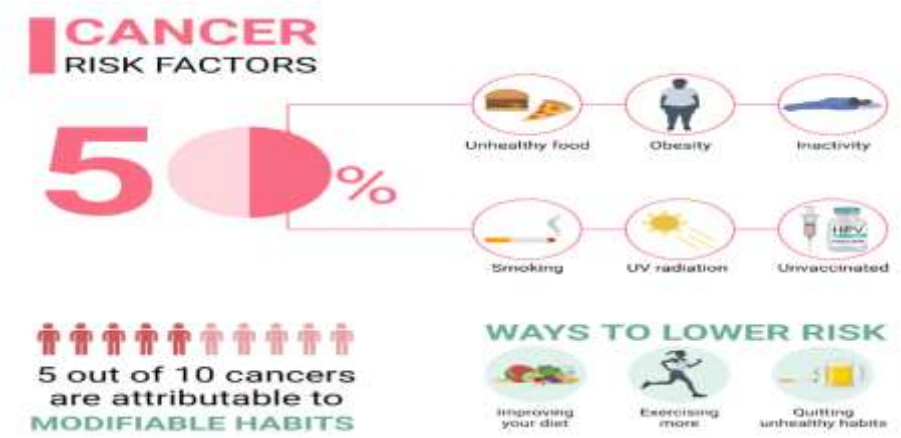

Fig. 1: Cancer risk factors.

2. Phytoconstituents: A natural reservoir of anticancer agents

Definition and Classification

Secondary metabolites, or phytoconstituents, are naturally occurring chemical substances found in plants that are essential to their survival even though they do not directly contribute to growth and reproduction. The plant uses these substances as a defence mechanism against environmental stressors, diseases, and herbivores. Phytochemicals have a wide range of applications in cancer treatment, influencing several processes that control the development, survival, and metastasis of cancer cells. Flavonoids, terpenoids, alkaloids, and polyphenolic chemicals are among the most extensively researched phytoconstituents; each has shown distinct anti-cancer therapeutic properties.[5,6]

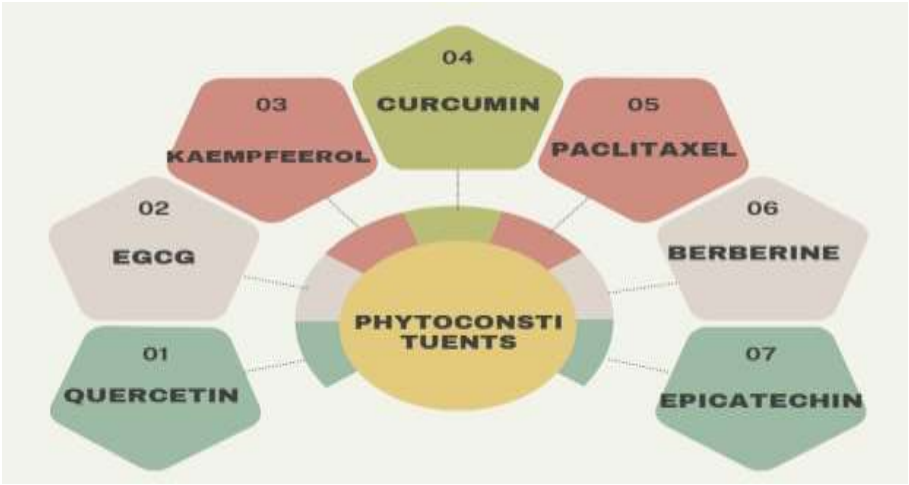

Fig. 2: Phytoconstituents in cancer.

Flavonoids and Their role in cancer therapy

A type of polyphenolic chemicals called flavonoids is widely distributed in fruits, vegetables, and plants. Their methods of action, which include metastasis inhibition, cell cycle modulation, and apoptosis induction, have been thoroughly studied in relation to their anticancer effects. Quercetin, kaempferol, apigenin, and epigallocatechin gallate (EGCG) are a few prominent subtypes of flavonoids that exhibit distinct anticancer characteristics.[8]

Quercetin

Apples, onions, and citrus fruits contain quercetin, which has been demonstrated to have anticancer effects on a number of malignancies, including breast, colorectal, and lung cancer. According to research, quercetin affects the p53 and Bax/Bcl-2 protein families to cause apoptosis. Furthermore, quercetin suppresses the NF-κB signalling pathway, which is frequently hyperactive in cancer cells and promotes tumour survival and treatment resistance.

Epigallocatechin Gallate (EGCG)

One of the main polyphenols in green tea, EGCG, has drawn notice for its potential to slow the spread of cancer. MMPs, which are implicated in tumour cell invasion and metastasis, are known to be suppressed by EGCG. Furthermore, it triggers apoptosis by upregulating the expression of p53 and p21 and activating caspase-3 and caspase-9. Research on the anticancer potential of EGCG has shown that it is effective against lung, prostate, and breast malignancies.[7]

Additionally, it has been demonstrated that EGCG works in concert with chemotherapeutic drugs such as tamoxifen and docetaxel to increase their cytotoxicity while lowering the possibility of chemotherapy adverse effects.[4]

Kaempferol

Kaempferol, found in cruciferous vegetables and fruits like grapes and apples, exhibits anticancer effects by inhibiting cell proliferation and promoting apoptosis. Studies have shown that kaempferol upregulates the **p53** protein and induces cell cycle arrest at the **G1 phase** by downregulating **cyclin D1** and **CDK4**. Additionally, kaempferol has been reported to suppress angiogenesis by inhibiting **VEGF** expression.[5]

Terpenoids and Their role in cancer therapy

Terpenoids are a diverse group of naturally occurring compounds that exhibit various pharmacological activities, including anticancer properties. Terpenoids such as **curcumin**, **boswellic acids**, **ginsenosides**, and **ar-turmerone** have been studied for their ability to modulate cancer-related pathways.

Curcumin

Curcumin, a major bioactive compound in turmeric, has demonstrated potent anticancer effects in preclinical and clinical studies. Curcumin induces apoptosis by activating **caspases** and **p53**, while also inhibiting cell proliferation by blocking the **NF-κB** and **MAPK** pathways. Moreover, curcumin has shown promise in preventing metastasis by suppressing the activity of **MMPs** and inhibiting the formation of new blood vessels through **angiogenesis inhibition**.[8]

Boswellic acids

Boswellic acids, derived from **Boswellia serrata** (frankincense), have been studied for their potential in treating various cancers, including **colon**, **lung**, and **breast cancer**. Boswellic acids exert anticancer effects by inhibiting **5-lipoxygenase** (5-LOX), an enzyme involved in inflammation and cancer progression. This inhibition reduces the proliferation of cancer cells, induces apoptosis, and prevents metastasis.[9,10]

Alkaloids and Their role in cancer therapy

Alkaloids are a diverse group of nitrogen-containing compounds found in plants, many of which have demonstrated anticancer properties. Notable alkaloids used in cancer therapy include **paclitaxel**, **berberine**, **vincristine**, and **camptothecin**.

Paclitaxel

Paclitaxel, a widely used chemotherapeutic agent derived from the **Taxus** species, acts by stabilizing microtubules, preventing their depolymerization, and thereby blocking cell division. It is effective in treating cancers such as **ovarian**, **breast**, **lung**, and **endometrial cancers**. Paclitaxel's mechanism involves **apoptosis induction** through **activation of the intrinsic pathway** via mitochondrial disruption and caspase activation.[12]

Berberine

Berberine, a plant alkaloid found in **Berberis** species, has shown anticancer potential in a variety of cancers, including **lung**, **colorectal**, and **liver cancers**. Berberine acts by inhibiting cancer cell proliferation and inducing apoptosis via the **p53**, **AMPK**, and **Akt/mTOR** pathways. It has also been shown to modulate **autophagy**, a process that regulates cancer cell survival and resistance to chemotherapy.[18]

Polyphenolic Compounds and Their role in cancer therapy

Polyphenolic compounds, including **resveratrol**, **ellagic acid**, and **epicatechins**, have been extensively studied for their anticancer properties.

Resveratrol, a polyphenolic compound found in grapes, red wine, and berries, exhibits anticancer activity by inducing apoptosis, cell cycle arrest, and inhibiting angiogenesis. Resveratrol has been shown to activate the **SIRT1** gene, which regulates cellular stress responses, and inhibit **NF-κB**, a transcription factor involved in cancer progression.[13]

Resveratrol's synergistic effects with chemotherapy agents have been demonstrated, particularly in enhancing the anticancer effects of **doxorubicin** and **paclitaxel**, while reducing their toxic side effects.[4]

Epicatechins

Epicatechins, primarily found in green tea, have demonstrated anticancer properties by inhibiting **MMPs**, **COX-2**, and **VEGF**. These compounds reduce tumour growth and metastasis by affecting angiogenesis and suppressing inflammation in the tumour microenvironment.[10]

3. Mechanisms of action of phytoconstituents in cancer therapy

Phytochemicals from natural sources play a pivotal role in cancer therapy through several mechanisms, including the induction of apoptosis, inhibition of cell proliferation, anti-angiogenesis, immune modulation, and epigenetic modulation. The therapeutic effects of these compounds rely on their ability to target multiple signalling pathways involved in cancer progression, offering a multi-pronged approach to cancer treatment.

Induction of apoptosis

Apoptosis, or programmed cell death, is an essential process for eliminating cancerous cells. Phytochemicals often restore apoptotic pathways in cancer cells by activating key regulatory

proteins such as caspases, p53, and Bcl-2 family members, which are involved in the intrinsic and extrinsic apoptotic pathways.

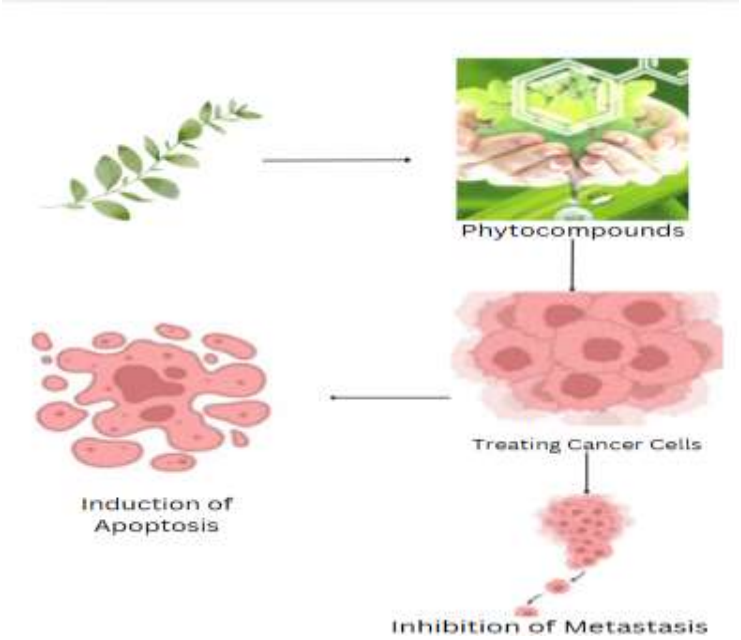

Fig. 3: Mechanism of action.

Curcumin: Curcumin, a polyphenol derived from *Curcuma longa*, has been shown to induce apoptosis by activating caspases and modulating the Bcl-2/Bax ratio. Additionally, curcumin suppresses the **NF-κB** signaling pathway, which plays a crucial role in inhibiting apoptosis and promoting tumor survival. Studies have shown that curcumin activates caspase-3 and caspase-9, leading to mitochondrial disruption and apoptosis in various cancer cell lines, including colon, breast, and prostate cancer.[16]

Resveratrol: Resveratrol, a natural polyphenolic compound found in grapes, has been widely studied for its anticancer properties. It activates the **p53** tumor suppressor gene, which leads to cell cycle arrest and apoptosis. Resveratrol's apoptotic effects are mediated through various mechanisms, including the activation of the intrinsic mitochondrial pathway, as well as the inhibition of **NF-κB** and **Akt** signaling. Additionally, resveratrol has shown synergy with chemotherapeutic agents, improving therapeutic efficacy.[16]

Inhibition of cell proliferation

Uncontrolled cell proliferation is a hallmark of cancer. Phytochemicals inhibit cell cycle progression at various checkpoints, preventing uncontrolled division and tumor growth.

Epigallocatechin Gallate (EGCG): EGCG, a polyphenolic compound from green tea, inhibits cell proliferation by arresting the cell cycle in the **G1 phase**. It does so by downregulating **cyclin D1** and **CDK4**, key regulators of the G1/S checkpoint. This results in the suppression of cancer cell growth, particularly in cancers such as breast, prostate, and colon cancer.[17]

Studies suggest that EGCG may also act synergistically with other chemotherapeutic agents like **5-fluorouracil (5-FU)**, enhancing their anti-cancer effects while reducing toxicity.[7]

Anti-Angiogenic effects

Angiogenesis, the formation of new blood vessels, is essential for tumor growth and metastasis. Phytochemicals exert anti-angiogenic effects by modulating key pro-angiogenic factors, such as **VEGF** (vascular endothelial growth factor) and **HIF-1α** (hypoxia-inducible factor 1 alpha).

Resveratrol: Resveratrol has been shown to suppress the expression of **VEGF**, a critical regulator of angiogenesis, and inhibit the activity of **HIF-1α**, a key transcription factor in the angiogenic process. This leads to reduced tumor blood supply and limits tumor growth. Resveratrol's anti-angiogenic effects are also associated with the inhibition of **Akt** signaling, which regulates endothelial cell proliferation and migration.[18]

Resveratrol also prevents **MMPs** (Matrix metalloproteinases) from facilitating tumor cell invasion and metastasis, further hindering angiogenesis and tumour spread.[19]

Immune modulation

The immune system plays a crucial role in recognizing and eliminating cancer cells. Phytochemicals can enhance immune surveillance by stimulating immune cells such as dendritic cells, natural killer (NK) cells, and T lymphocytes.

Berberine: Berberine, a bioactive alkaloid found in *Berberis* species, has been shown to stimulate immune responses. It enhances dendritic cell maturation and promotes NK cell activity, which increases the ability of the immune system to recognize and kill cancer cells. Berberine also reduces the expression of immune suppressive factors like **TGF-β** and **IL-10**, which often hinder immune responses in the tumour microenvironment.[19]

Additionally, berberine has shown promise in combination with other immunomodulatory therapies, improving immune checkpoint blockade treatments.[20]

Epigenetic modulation

Epigenetic alterations, such as changes in DNA methylation and histone modification, play a pivotal role in cancer progression. Many phytochemicals can reverse these changes and restore normal gene expression.

Curcumin: Curcumin has been shown to inhibit **DNA methyltransferases (DNMTs)** and **histone deacetylases (HDACs)**, enzymes involved in epigenetic regulation. By inhibiting these enzymes, curcumin restores the expression of tumor suppressor genes and enhances the activity of pro-apoptotic genes. These epigenetic effects contribute to curcumin's anticancer properties and its potential as a chemopreventive agent.[21]

Moreover, curcumin's ability to modulate histone acetylation and methylation patterns has been demonstrated to inhibit cancer cell migration and invasion, providing an additional therapeutic mechanism.[16]

4. Key phytoconstituents with anticancer potential

Several phytoconstituents have been identified for their potent anticancer activities. These compounds affect various aspects of cancer cell biology, including apoptosis, cell cycle regulation, metastasis, and angiogenesis.

Alkaloids

Vincristine and Vinblastine: These alkaloids, derived from the *Catharanthus roseus* plant, are widely used in the treatment of leukemias and lymphomas. They work by binding to tubulin and preventing microtubule polymerization, thus arresting mitosis. This leads to cell cycle arrest and apoptosis. Clinical studies have shown that vincristine and vinblastine are effective against various hematological malignancies and solid tumours.[2]

Berberine: Berberine has been reported to induce apoptosis in cancer cells by increasing the levels of **reactive oxygen species (ROS)**, disrupting mitochondrial membrane potential, and activating caspases. Studies have demonstrated that berberine is effective in treating **lung**, **colorectal**, and **liver cancers** by altering key signaling pathways, including **PI3K/Akt** and **AMPK**.[20]

Flavonoids

Quercetin: Quercetin, a flavonoid found in various fruits and vegetables, inhibits cancer cell proliferation by modulating key signalling pathways, including **NF-κB** and **PI3K/Akt**. It also suppresses angiogenesis by downregulating **VEGF** and prevents metastasis by inhibiting **MMPs**. Quercetin has shown efficacy against **breast**, **prostate**, and **colorectal cancers.**[20]

Kaempferol: Kaempferol, another flavonoid, induces apoptosis in cancer cells by activating the **PI3K/Akt** pathway. It also suppresses tumour growth by inhibiting **COX-2** and modulating **NF-κB**. Kaempferol has demonstrated significant anticancer effects in **lung** and **breast cancers**.[21]

Polyphenols

Curcumin: Curcumin, known for its ability to modulate multiple signalling pathways such as **NF-κB**, **Wnt/β-catenin**, and **MAPK**, has been shown to reduce tumour growth, inhibit metastasis, and enhance the effects of chemotherapy. It is particularly effective in treating **colon**, **liver**, and **breast cancers**.[23]

Resveratrol: Resveratrol targets multiple cancer-related pathways, including **STAT3** and **JAK** signalling, to inhibit metastasis and angiogenesis. It also enhances the effects of radiation therapy, reducing radiation-induced toxicity while sensitizing tumour cells.[24]

5. Advances in drug delivery systems

Advances in the role of phytoconstituents in cancer therapy

Recent advancements in cancer therapy emphasize the therapeutic potential of phytochemicals, which can modulate molecular pathways involved in cancer initiation, progression, and metastasis. With growing concerns about chemoresistance and side effects of conventional treatments, phytoconstituents are being explored as adjuncts to enhance chemotherapy, radiotherapy, and immunotherapy. This section focuses on their mechanisms of action, synergistic effects with traditional therapies, and innovations in drug delivery systems.

1. Advancements in mechanisms of action of phytoconstituents

The molecular mechanisms by which phytoconstituents exert anticancer effects have become more defined with recent research. Below are some key areas where advances have been made:

1.1. Modulation of cancer cell signaling pathways

Phytochemicals are increasingly recognized for their ability to modulate key signaling pathways involved in cancer cell proliferation, survival, and metastasis.

NF-κB Pathway: The NF-κB pathway is a central player in cancer progression, regulating inflammation, cell survival, and metastasis. Phytochemicals such as curcumin and epigallocatechin gallate (EGCG) have been shown to inhibit NF-κB activation, reducing tumor growth and enhancing the sensitivity of cancer cells to chemotherapy. Curcumin, for example, directly suppresses NF-κB by inhibiting IκB kinase, thereby preventing the degradation of IκB and blocking the subsequent activation of NF-κB.[31]

PI3K/Akt/mTOR Pathway: The PI3K/Akt/mTOR signaling pathway is often hyperactivated in cancers, leading to uncontrolled cell proliferation. Compounds like quercetin and resveratrol have been shown to suppress this pathway, reducing the survival and proliferation of cancer cells. Quercetin, for instance, inhibits the phosphorylation of Akt and mTOR, which are crucial for cancer cell survival.[32]

1.2. Epigenetic modulation

Phytoconstituents also have the ability to modify epigenetic mechanisms, such as DNA methylation, histone acetylation, and microRNA expression. These epigenetic changes can reverse aberrant gene expression associated with cancer progression.

Curcumin: Curcumin has shown strong epigenetic modulation by inhibiting DNA methyltransferases (DNMTs) and histone deacetylases (HDACs), thereby restoring normal gene expression patterns. Curcumin's ability to reverse epigenetic changes has potential in the treatment of various cancers, including colon and breast cancer.[21]

Resveratrol: Resveratrol also modulates histone deacetylases (HDACs) and enhances acetylation, which plays a role in turning on tumour suppressor genes. Resveratrol has demonstrated promise in reversing DNA methylation and reactivating silenced tumour suppressor genes, further supporting its role as an adjunct to chemotherapy.[33]

2. Advances in synergistic effects of phytoconstituents with conventional cancer therapies

The combination of phytochemicals with conventional cancer therapies has garnered attention due to its ability to enhance the therapeutic efficacy of existing treatments while minimizing their side effects.

2.1. Chemotherapy sensitization

Phytoconstituents such as curcumin, EGCG, and resveratrol have shown promise in sensitizing cancer cells to chemotherapy by modulating drug resistance mechanisms and improving drug efficacy.

Curcumin: Studies have demonstrated that curcumin sensitizes cisplatin and 5-FU treatments in multiple cancers, including ovarian, colorectal, and breast cancer. Curcumin enhances the activity of these drugs by downregulating anti-apoptotic proteins, promoting cell cycle arrest, and inhibiting multidrug resistance proteins. For instance, curcumin has been shown to inhibit NF-κB signaling, which is often involved in chemoresistance.[31]

EGCG: EGCG, a major polyphenol in green tea, enhances the effectiveness of paclitaxel and cisplatin in ovarian and lung cancers. It sensitizes cancer cells to these chemotherapeutic agents by promoting apoptosis and inhibiting anti-apoptotic proteins such as Bcl-2 and surviving.[7]

2.2. Radiosensitization

In addition to chemotherapy, phytochemicals have shown potential in improving the efficacy of radiotherapy by enhancing tumor radiosensitivity and minimizing damage to normal tissues.

Curcumin: Curcumin has been found to sensitize radiotherapy in multiple cancer types. By downregulating NF-κB and modulating cell cycle checkpoints, curcumin enhances radiation-induced apoptosis and reduces radiation-induced DNA damage in normal tissues. Studies show curcumin increases the therapeutic index of radiotherapy by sensitizing tumors while protecting normal cells from radiation-induced injury.[30]

Resveratrol: Resveratrol enhances the effect of radiotherapy by regulating redox homeostasis and enhancing apoptosis. By modulating various signalling pathways, including

JAK/STAT3 and PI3K/Akt, resveratrol synergizes with radiation therapy in breast and lung cancers, reducing resistance and increasing cell death.[18]

3. Advances in drug delivery systems for phytoconstituents

Despite the therapeutic potential of phytoconstituents, their clinical application has been hampered by issues such as poor bioavailability, rapid metabolism, and limited solubility. Recent advances in drug delivery systems have addressed these challenges, enabling the effective use of phytochemicals in cancer therapy.[34]

3.1. Nanotechnology-Based delivery systems

The incorporation of phytochemicals into nanoparticles and nanocarriers has enhanced their bioavailability and targeted delivery to cancer cells. Nanoparticles can improve the solubility of phytoconstituents, protect them from degradation, and enable sustained release.

Curcumin-loaded nanoparticles: Researchers have developed various curcumin-loaded nanoparticles, such as liposomes and polymeric nanoparticles, to overcome curcumin's poor bioavailability. These formulations enhance curcumin's anticancer activity by ensuring higher accumulation in tumors, thus improving therapeutic outcomes.[35]

EGCG-loaded Nanocarriers: EGCG, when encapsulated in liposomes or other nanocarriers, has shown enhanced stability and bioavailability, leading to increased anticancer activity. EGCG-loaded nanoparticles have demonstrated potent inhibitory effects on tumor growth in animal models of breast cancer.[36]

3.2. Targeted drug delivery

In addition to nanotechnology, targeted drug delivery strategies are being developed to enhance the specificity of phytochemicals toward tumor cells, thereby reducing toxicity to normal tissues.

Curcumin-targeted delivery: Curcumin-targeted delivery systems, such as conjugates with antibodies or small molecules, have been developed to target specific tumor markers. These targeted approaches increase curcumin's accumulation at the tumor site and reduce its systemic side effects.[37]

6. Future Directions and Emerging trends

1. Personalized cancer therapy using phytoconstituents

Phytochemicals offer the potential to be integrated into **personalized cancer therapy**, wherein cancer treatments are tailored according to the individual patient's genetic makeup, tumor molecular profile, and environmental factors. As more research is being conducted, phytochemicals have shown promise in becoming key players in this customized approach to cancer treatment.

1.1. Phytochemicals as precision therapeutics

The concept of precision medicine is particularly relevant in cancer therapy, as genetic and epigenetic alterations often determine how a tumor responds to treatments. Phytochemicals, due to their ability to modulate multiple pathways involved in cancer progression, have the potential to be integrated into precision medicine. Phytochemicals such as **curcumin**, **EGCG**, **resveratrol**, and **quercetin** can target specific mutations, deregulated genes, or pathways that are unique to an individual's cancer, thereby improving treatment outcomes and minimizing side effects.

The growing interest in **liquid biopsy** technology and **multi-omics** approaches (genomics, proteomics, and metabolomics) will be instrumental in identifying the best phytochemicals suited for individual patients based on their molecular profiles. For example, integrating **tumor mutational burden (TMB)** and **immune checkpoint receptor profiles** with phytochemical treatment can lead to personalized regimens for enhanced therapeutic response.[19]

1.2. Advanced delivery systems for targeted phytochemical delivery

One of the primary challenges in the clinical application of phytochemicals has been their **bioavailability**, stability, and selective accumulation at the tumor site. To overcome these limitations, novel **drug delivery systems** are being developed that enhance the pharmacokinetics and targeting efficiency of phytochemicals. Nanotechnology, including the use of **liposomes**, **micelles**, and **nanoparticles**, has emerged as a promising solution.

Nanoparticle-based curcumin delivery systems have demonstrated significant improvements in solubility, bioavailability, and anticancer activity, particularly in colon, breast, and pancreatic cancers.[19]

EGCG encapsulated in nanoparticles has been shown to effectively reach the tumor site, increasing its concentration in cancer cells while minimizing off-target effects.[10]

2. Phytochemicals in combination with immunotherapy

The integration of phytochemicals with **immunotherapy** is an emerging and highly promising approach. Immunotherapy, particularly **immune checkpoint inhibitors**, has revolutionized cancer treatment; however, many patients either do not respond or develop resistance. Phytochemicals can potentially enhance the immune response and improve the clinical efficacy of immunotherapies.

2.1. Immunomodulatory effects of phytochemicals

Phytochemicals can modulate the immune system by promoting the activation of immune cells like **T cells**, **NK cells**, and **dendritic cells**. This immune enhancement may sensitize tumors to immune checkpoint inhibitors, improving their response.

EGCG, derived from green tea, has been shown to stimulate **dendritic cells**, enhancing the ability of the immune system to recognize and target tumor cells.[39]

Curcumin has been demonstrated to enhance the presentation of tumor antigens by **macrophages** and **dendritic cells**, improving the activation of **T cells** against cancer cells.[31]

These phytochemicals may also help overcome immune suppression in the tumor microenvironment by modulating inflammatory mediators and cytokine profiles. For example, **resveratrol** has been reported to inhibit the expression of immune checkpoint molecules such as **PD-L1** and **CTLA-4**, overcoming the tumor's immune evasion mechanisms.[39]

2.2. Overcoming immune resistance with phytochemicals

Phytochemicals can act synergistically with immunotherapies by addressing mechanisms of **immune resistance**. Tumor cells often evade immune detection by upregulating immune checkpoint molecules, downregulating **MHC class I molecules**, or secreting immunosuppressive cytokines.

Resveratrol and **quercetin** have been shown to inhibit the **PD-1/PD-L1** axis, a key pathway through which tumors evade immune surveillance.[40]

Berberine has been shown to inhibit the **PD-1/PD-L1** pathway and promote the cytotoxic effects of **T cells** against cancer cells.[39]

3. Epigenetic Reprogramming and Phytochemicals

Epigenetic modifications, such as DNA methylation, histone modification, and non-coding RNA regulation, are critical in cancer progression. As these changes are reversible, they offer a significant opportunity for **epigenetic therapies**.

3.1. Phytochemicals as epigenetic modulators

Phytochemicals can modify epigenetic mechanisms, including DNA methylation and histone modifications, to restore normal gene expression patterns. This can be particularly useful in cancers where epigenetic silencing of tumor suppressor genes plays a key role in progression.

Curcumin has been shown to inhibit **DNA methyltransferases (DNMTs)** and **histone deacetylases (HDACs)**, resulting in the reactivation of tumor suppressor genes and the downregulation of oncogenes. These effects have been demonstrated in **lung**, **colon**, and **breast cancers**.[29]

Resveratrol also modulates epigenetic marks such as **histone acetylation** and **DNA methylation**, contributing to the regulation of genes involved in cancer progression.[28]

3.2. Synergistic epigenetic therapy with phytochemicals

Phytochemicals could be combined with other **epigenetic drugs** (such as **HDAC inhibitors** or **DNMT inhibitors**) to achieve enhanced anticancer effects. For instance, the combination of **curcumin** with **5-aza-2'-deoxycytidine**, a DNA methylation inhibitor, has been shown to restore the expression of silenced tumor suppressor genes and improve the therapeutic outcome in **lung cancer** models.[31]

The combination of phytochemicals with conventional epigenetic therapies could offer a highly effective approach to reversing tumorigenic epigenetic changes and improving cancer treatment.

4. Phytoconstituents in targeted nanomedicine

The advancement of **nanomedicine** has enabled the design of more efficient drug delivery systems, overcoming the limitations of traditional drug administration. Phytochemicals

incorporated into **nanoparticles**, **liposomes**, and **micelles** can be selectively delivered to the tumor site, improving their therapeutic efficacy while minimizing systemic toxicity.

4.1. Nanoparticle-Based phytochemical delivery

Phytochemicals encapsulated in **nanoparticles** have shown increased stability, bioavailability, and selective accumulation in cancer tissues. Advances in nanoparticle design, such as the incorporation of **polymers**, **lipids**, and **biodegradable materials**, have enhanced the delivery of phytochemicals.

Curcumin-loaded nanoparticles have shown improved therapeutic efficacy in various cancers by enhancing solubility and bioavailability. These nanoparticles facilitate the sustained release of curcumin, ensuring prolonged therapeutic effects.[41]

4.2. Ligand-Targeted nanomedicines

To further enhance the specificity of phytochemical delivery, **ligands** (such as **folate**, **EGFR antibodies**, or **RGD peptides**) can be conjugated to nanoparticles, enabling targeted delivery to cancer cells. These targeted systems ensure that phytochemicals accumulate primarily in the tumor, reducing off-target effects.

Folate-targeted curcumin nanoparticles have been shown to improve the selectivity of curcumin delivery to **ovarian cancer cells**, reducing systemic toxicity and enhancing anticancer efficacy.

The future of phytoconstituent-based cancer therapy is marked by exciting advancements in personalized medicine, nanotechnology, immunotherapy, and epigenetic reprogramming. As phytochemicals are integrated into combination therapies with conventional treatments, the therapeutic potential of these compounds will continue to grow. With more research focused on improving the bioavailability, targeting precision, and synergistic effects of phytochemicals, phytoconstituents are poised to play a pivotal role in the next generation of cancer therapies.

CONCLUSION

Phytoconstituents represent a promising class of natural compounds with significant potential in cancer therapy. Their multifaceted mechanisms of action, including antioxidative, anti-inflammatory, and pro-apoptotic effects, provide a strong rationale for their inclusion in cancer treatment regimens. While many phytochemicals have shown potent anticancer

properties in preclinical studies, further clinical trials are needed to confirm their safety, efficacy, and optimal use in combination with conventional therapies. The challenges of bioavailability, dosage optimization, and regulatory approval must also be addressed. Nevertheless, the growing body of evidence suggests that phytoconstituents could play a crucial role in the development of novel, targeted, and less toxic cancer therapies, offering hope for improved clinical outcomes and better quality of life for cancer patients.

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