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Review Article

Exploring Mechanisms of Tumorigenesis and Plant-Based Therapies: A Comprehensive Review of Cancer Pathogenesis and Treatment Strategies

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ABSTRACT

Plant-based compounds have emerged as promising candidates for cancer prevention and treatment due to their ability to modulate metabolizing enzymes, target protein kinases, Matrix metalloproteinases (MMPs), cell cycle progression, Nuclear factor kappa B (NF-κB) signaling, and Cyclooxygenase-2 (COX-2). This review aim to investigate the mechanisms driving tumorigenesis, cancer formation, and to explore the potential of plant-derived compounds in cancer chemotherapy. The study employed a systematic approach in the review of relevant and current literature using online search engines. Plant-based compounds, including flavonoids, polyphenols, and glucosinolates, possess antioxidant properties that reduce DNA damage, induce Phase II enzyme activity, detoxify carcinogens, and inhibit Phase I enzymes. They also regulate protein kinase pathways, inhibit dysregulated lipid kinase signaling, and suppress tumor growth, invasion, metastasis, and angiogenesis. Plant-based therapies targeting NF-κB and COX-2 demonstrate efficacy in suppressing NF-κB activation, modulating gene expression, inhibiting COX-2, and enhancing cancer cell sensitivity to conventional treatments. Plant-derived compounds effectively scavenge free radicals and modulate oxidative stress and cancer-associated signaling pathways. Preclinical studies validate their efficacy in reducing oxidative stress, inhibiting tumor growth, and suppressing metastasis. Recent advancements highlight the importance of genetic alterations, epigenetic modifications, tumor microenvironment, and cancer metabolism in tumorigenesis. Targeted therapies derived from plants, such as curcumin and Epigallocatechin gallate, show promise in targeting specific pathways. Plant-derived compounds also exhibit anti-angiogenic and immune-modulatory properties and can disrupt cancer metabolism. However, comprehensive clinical trials are necessary to evaluate their safety, efficacy, and integration into standard cancer treatment protocols, offering the potential to revolutionize cancer management.

Keywords: Plant-based compounds, Cancer prevention, Cancer treatment, Antioxidant properties, Tumor growth, Targeted therapies.

Introduction

Cancer, a complex and dynamic disease, poses significant challenges in modern medicine due to its multifaceted mechanisms of tumorigenesis and cancer formation.[1] Extensive research has identified genetic mutations, aberrant signaling pathways, and dysregulated cellular processes as key contributors to cancer development.[2,3] While conventional therapies have made progress, there is a growing need for innovative approaches. Plant-targeted therapies have emerged as promising options, utilizing diverse plant compounds directly and addressing the underlying mechanisms of cancer.[1,4] This review explores the intricate pathways and drivers behind cancer development while highlighting the potential of plant-derived compounds, such as phytochemicals and botanical formulations, in targeting and combating cancer at various stages.

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By integrating current knowledge and clinical trials, this review aims to provide a comprehensive understanding of plant-targeted therapies, their interactions with tumorigenesis mechanisms, and their potential to update cancer treatment.

Another focus of this review is to unravel the molecular landscape of cancer by examining the mechanisms driving tumorigenesis and cancer formation. This review highlights the role of genetic mutations, dysregulated signaling cascades, and altered cellular processes in cancer development. It also explores the therapeutic potential of plant-targeted therapies, specifically the various plant-derived compounds available. The review delves into how these compounds modulate key cellular processes and impact tumor growth and metastasis through their effects on proliferation, apoptosis, angiogenesis, and immune response. By integrating the latest research findings and clinical trials, it aims to provide a comprehensive synthesis of current knowledge on plant-targeted therapies in cancer treatment. Additionally, it discusses the challenges and future directions in the field, emphasizing the potential for personalized and combination therapies that merge plant-based agents with conventional treatments. Ultimately, the review aims to shed light on the intricate relationship between tumorigenesis, cancer formation, and plant-targeted therapies, offering new insights and inspiring further research in pursuit of innovative and effective cancer treatments.

Cancer is a significant global health issue, leading to millions of deaths worldwide annually. The most common types of cancer vary across regions, but lung, breast, colorectal, prostate, and stomach

cancers are prevalent globally. Nigeria, Africa's most populous country, has a rising burden of cancer, particularly breast, cervical, prostate, liver, and colorectal cancers. Modifiable risk factors such as tobacco use, sedentary lifestyle, unhealthy diets, infections, and exposure to environmental carcinogens contribute to the high prevalence of cancer in Nigeria. However, challenges exist in cancer control, including limited awareness and knowledge, inadequate healthcare infrastructure, financial constraints, and cultural beliefs. Efforts are being made in Nigeria to address these challenges through cancer control programs, awareness campaigns, screening initiatives, and collaborations with international partners. Research and collaboration are essential in understanding the prevalence, risk factors, and patterns of cancer in Nigeria, and resource allocation and funding are crucial to effectively combat the rising cancer burden.

Methodology

This research employed a systematic approach to investigate the mechanisms driving tumorigenesis, cancer formation, and the potential of plant-derived targeted therapies. Approximately eighty academic journals were thoroughly reviewed, focusing on relevant articles related to the research topic. In addition, online search engines such as Google were utilized to access the databases of Science Direct and PubMed using specific keywords. Google Scholar was also utilized to gather additional information by formulating probes and questions. The collected data were extracted, analyzed, and synthesized to identify recurring themes and significant findings. Finally, a comprehensive review article was composed, incorporating insights from the literature review and online search engines.

Mechanisms Driving Tumorigenesis and Cancer Formation

Dysregulation of Protein Kinases Signaling Pathways

Protein kinases play a critical role in cell signaling pathways, regulating various cellular processes essential for normal cell function.[5] However, when these kinases become dysregulated or malfunctioning, they can contribute to tumorigenesis and cancer formation.[4,5] Several specific protein kinase pathways have been identified as significant players in cancer development. The Ras protein-Mitogen Activated Protein Kinase (Ras-MAPK) pathway, involving mutations in Ras and downstream kinases, leads to uncontrolled cell growth and survival.[6] Dysregulation of the phosphatidylinositol-3 kinase-Ak Strain Transformin-mammalian Target of Rapamycin (PI3K-Akt-mTOR) pathway through mutations in PI3K or Akt activation promotes uncontrolled cell proliferation and resistance to cell death.[7] Abnormal activation of the Janus kinase/signal transducer and activator of transcription (JAK-STAT) signaling pathway, often caused by genetic alterations or cytokine signaling dysregulation, supports cell survival, proliferation, and immune evasion in cancer cells.[8] Dysregulation of the Cyclin-dependent kinase (CDK) pathway, through overexpression of cyclins or loss of CDK inhibitors, leads to uncontrolled cell cycle progression and genomic instability.[9] The dysregulation of receptor tyrosine kinase (RTK) pathways, such as epidermal growth factor receptor (EGFR), human epidermal growth factor receptor 2 (HER2), and insulin-like growth factor 1 receptor (IGF-1R), is associated with uncontrolled cell growth, survival, and angiogenesis in cancer.[10] Aberrant activation of the Src family kinase pathway promotes tumor progression, metastasis, and angiogenesis in various cancer types.[11] These protein kinase pathways offer potential targets for the development of targeted therapies in cancer treatment.

Plant-Derived Targeted Therapies for Modulating Protein Kinases Signaling Pathways

Plant-derived compounds have shown promise as targeted therapies for modulating protein kinases involved in cancer.[10-12] Examples include resveratrol from grapes and berries, which inhibits the Ras-MAPK pathway; quercetin from fruits and vegetables, which targets the PI3K-Akt-mTOR pathway; curcumin from turmeric, which disrupts the JAK-STAT pathway; flavopiridol from *Dysoxylum binectariferum*, which affects the Cyclin-CDK pathway; green tea extract containing EGCG, which inhibits receptor tyrosine kinases (RTKs) like EGFR and HER2; and genistein from soybeans, which targets the Src family kinase pathway.[11,13] These plant-derived compounds offer advantages such as lower toxicity and greater accessibility.

Dysregulation of Lipid Kinase Signaling Pathways

Lipid kinase signaling pathways, involving enzymes that phosphorylate lipid molecules, play a significant role in tumorigenesis and cancer formation.[14] Dysregulation of these pathways can contribute to cancer development through various mechanisms. The well-studied PI3K-Akt pathway involves the activation of PI3K, leading to the generation of phosphatidylinositol 3,4,5-trisphosphate (PIP3), which recruits Akt and promotes cell survival, growth, and resistance to apoptosis.[15,16] PIP3-mediated signaling also regulates other molecules, such as PDK1 and mTOR, crucial for cell growth and proliferation.[15,17] Sphingolipid signaling, driven by sphingosine kinase (SphK) and sphingosine-1-phosphate (S1P), promotes cell proliferation, migration, and angiogenesis.[14] Dysregulated phospholipase D (PLD) activity, generating phosphatidic acid (PA), is associated with cancer progression and affects cell proliferation, migration, and cytoskeletal remodeling. Lysophosphatidic acid (LPA) signaling, generated by PLD or autotaxin (ATX), stimulates cell proliferation, survival, and angiogenesis.[18-20] Targeting these dysregulated lipid kinase signaling pathways holds promise for developing novel anticancer therapies.

Plant-Derived Targeted Therapies for Modulating Lipid Kinases Signaling Pathways

Several plant-derived compounds have shown potential as targeted therapies against dysregulated lipid kinase signaling pathways implicated in tumorigenesis.[11,12] Natural compounds like curcumin and resveratrol have been studied for their inhibitory effects on the PI3K-Akt pathway, suppressing cell survival and growth in various cancer types.[11,13] Additionally, certain botanical extracts, such as green tea catechins and grape seed proanthocyanidins, have demonstrated inhibitory effects on sphingolipid signaling by targeting SphK and reducing S1P levels, thereby impeding cancer cell proliferation and migration.[21] Moreover, plant-based compounds like quercetin and genistein have shown the potential to inhibit PLD activity and modulate downstream signaling pathways involved in cell proliferation and survival.[20,22,23] These plant-derived compounds offer promising avenues for developing novel targeted therapies against dysregulated lipid kinase signaling pathways in cancer.

Disruption of Hormonal Signaling Pathways

Hormones such as estrogen (E), androgens, growth hormone/IGFs, thyroid hormones (TH), and prolactin (PRL) can contribute to tumorigenesis and cancer formation when their levels or signaling pathways are disrupted. Estrogen, primarily produced by the ovaries, can drive uncontrolled cell proliferation, inhibit apoptosis, promote angiogenesis, induce DNA damage, and modify gene expression patterns, leading to breast and uterine cancer.[24] Androgens, including testosterone (T) and dihydrotestosterone (DHT), can activate androgen receptors in prostate cancer cells, promoting cell proliferation, inhibiting apoptosis, and interacting with growth factor signaling pathways.[25,26] Growth hormones and IGFs can enhance cell proliferation and survival through their effects on cell growth, survival, and angiogenesis. In contrast, dysregulated thyroid hormone signaling can promote cell proliferation, inhibit apoptosis, and enhance angiogenesis, contributing to thyroid cancer.[27,28] Prolactin can stimulate cell proliferation, inhibit apoptosis, promote angiogenesis, and modulate the immune response, potentially promoting breast and prostate cancer development.[29] Targeted therapies, such as Selective estrogen receptor modulators (SERMs), Androgen deprivation therapy (ADT), and inhibitors of hormone signaling pathways, have been developed to prevent or treat hormone-driven cancers.[30,31]

Plant-Derived Targeted Therapies for Modulating Hormonal Signaling Pathways

Targeted therapies derived from plants have shown promise in modulating hormone-driven cancers. Phytoestrogens, in various plants like soybeans and flaxseeds, possess estrogenic or antiestrogenic

properties and can act as natural SERMs, inhibiting estrogen receptor signaling.[32,33] Plant-derived compounds like resveratrol, present in grapes and berries, have been studied for their antiandrogenic effects, potentially inhibiting androgen receptor activation in prostate cancer.[34,35] Some botanical extracts, such as green tea extract, contain polyphenols that can modulate growth hormone/IGF signaling pathways and exhibit anticancer properties.[36] Certain plant compounds, including flavonoids and polyphenols from sources like cruciferous vegetables and berries, have demonstrated the potential to interfere with thyroid hormone signaling and inhibit thyroid cancer growth.[37] While targeted therapies specifically derived from plants against prolactin signaling in cancer are limited, further research to explore natural compounds with potential anti-prolactin effects is greatly needed.

Dysregulation of Remodeling and Degradation of the Extracellular Matrix (ECM) by Matrix Metalloproteinases (MMPs)

Matrix metalloproteinases (MMPs) contribute to cancer formation by dysregulating the remodeling and degradation of the extracellular matrix (ECM). Their upregulation in cancer leads to ECM breakdown, facilitating tumor invasion and metastasis by creating paths for cancer cells to migrate through surrounding tissue and enter the blood or lymphatic vessels. Additionally, MMPs promote tumor angiogenesis by degrading ECM surrounding blood vessels and releasing pro-angiogenic factors stored in the ECM.[38,39] They also play a crucial role in cancer cell migration and metastasis by cleaving cell adhesion molecules, releasing growth factors and cytokines, and stimulating cancer cell proliferation, survival, and motility.[38] MMPs contribute to immune evasion by modifying the ECM composition, hindering immune cell infiltration into tumors, and degrading immune-related molecules. Furthermore, MMPs activate latent growth factors and cytokines within the ECM, promoting cell proliferation, survival, and angiogenesis. They also participate in tissue remodeling associated with tumor growth, altering tissue architecture and promoting interactions between cancer cells and surrounding stromal cells.[38,39] MMPs can activate other pro-MMPs, amplifying ECM degradation and facilitating tumor invasion and metastasis. Targeting MMPs has shown promise as a therapeutic strategy for impeding tumor progression and metastasis, but further research is required to fully comprehend their involvement in cancer and develop effective MMP inhibitors.[38,40]

Plant-Derived Targeted Therapies for Modulating Matrix Metalloproteinases (MMPS)

MMPs play a significant role in tumor invasion, metastasis, and angiogenesis through their involvement in extracellular matrix remodeling. Various plant-derived compounds exhibit MMP-inhibitory properties, such as polyphenols (e.g., EGCG, resveratrol, quercetin), curcumin, and triterpenoids (e.g., ursolic acid, oleanolic acid)[41] These compounds have shown promising preclinical evidence, including suppression of MMP expression and activity, inhibition of tumor invasion and metastasis, and attenuation of angiogenesis.[41]

Dysregulation of Cell Cycle Progression:

Dysregulation of cell cycle progression is a key factor in cancer development. Normal cells undergo a tightly regulated cell cycle, but cancer cells bypass checkpoints and exhibit uncontrolled proliferation. This leads to the rapid division of cancer cells and the accumulation of genetic alterations, driving tumor growth.[42,43] Additionally, dysregulated cell cycle progression can cause genetic instability, resulting in DNA mutations and chromosomal abnormalities. The loss of cell cycle checkpoints and alterations in cyclins and cyclin-dependent kinases (CDKs) further disrupt the regulation of cell cycle progression in cancer cells. These abnormalities allow cancer cells to evade apoptosis and persist with damaged DNA. Furthermore, dysregulated cell cycle progression contributes to tumor heterogeneity and clonal evolution, enabling the emergence of subpopulations with distinct genetic characteristics, and promoting tumor progression, metastasis, and resistance to therapies.[42-44]

Plant-Derived Targeted Therapies for Cell Cycle Progression

Dysregulation of cell cycle progression is a key characteristic of cancer, and targeting this process using plant-based compounds presents a promising strategy for cancer treatment.[45] Flavonoids (such as fisetin, myricetin, quercetin and naringenin), polyphenols (such as Epigallocatechin-3-Gallate, Xanthohumol), and alkaloids (such as berberine) derived from plants have demonstrated the ability to inhibit cell cycle progression through modulation of key regulatory proteins involved in cell cycle control. These compounds induce cell cycle arrest, inhibit cell proliferation, and promote apoptosis in cancer cells.[45-47]

Dysregulation of Phase I and Phase II Metabolizing Enzymes

Phase I and Phase II metabolizing enzymes play critical roles in the metabolism of xenobiotics, and their dysregulation or alteration can contribute to tumorigenesis. Phase I enzymes, such as cytochrome P450 (CYP450), can activate pro-carcinogens, converting them into reactive intermediates that bind to DNA and cause genetic mutations.[48] Certain Phase I enzymes can also generate reactive oxygen species (ROS) during metabolism, leading to oxidative stress and DNA damage. Additionally, Phase I enzymes can inactivate chemotherapeutic agents, reducing their effectiveness and promoting drug resistance.[49-51]

Phase II enzymes, including glutathione-S-transferases (GSTs), UDP-glucuronosyltransferases (UGTs), and sulfotransferases (SULTs), play a role in detoxification by conjugating reactive metabolites with endogenous compounds for elimination. An imbalance between Phase I and Phase II enzymes in cancer cells can result in reduced Phase II enzyme activity, leading to the accumulation of reactive metabolites and increased DNA damage. Epigenetic regulation further influences the expression of these enzymes, with aberrant DNA methylation and histone modifications affecting their metabolic capacity and contributing to cancer development.[48,52,53]

Understanding the impact of dysregulated Phase I and Phase II enzymes on cellular metabolism and detoxification pathways is crucial for developing targeted cancer prevention and treatment strategies. Identifying ways to modulate these enzymes or restore their balance, may enhance the efficacy of chemotherapeutic agents, reduce the activation of procarcinogens, and improve detoxification processes, ultimately offering new avenues for managing and treating cancer.[43,54]

Plant-Derived Targeted Therapies for modulating Phase I and Phase II Metabolizing Enzymes

Plant-derived compounds can modulate Phase I enzymes, such as cytochrome P450 (CYP450), through downregulation or inhibition, reducing the activation of procarcinogens. Additionally, herbal extracts containing active constituents can influence Phase I enzyme activity. Plant-based compounds targeting Phase II enzymes, including glutathione-S-transferases (GSTs) and UDP-glucuronosyltransferases (UGTs), can enhance detoxification processes by stimulating the synthesis and utilization of glutathione or inducing enzyme expression and activity.[55,56] Preclinical studies demonstrate the ability of plant compounds to modulate enzyme expression or activity, inhibit pro-carcinogen activation, and enhance detoxification. However, clinical evidence is limited, and challenges such as bioavailability optimization, combination therapy identification, and safety evaluations remain. Overall, plant-based targeted therapies against Phase I and II metabolizing enzymes hold promise for cancer treatment and warrant further investigation.[55,56]

Dysregulation of Nuclear Transcription Factor kappa B (NF-κB) Signaling

NF-κB, a nuclear transcription factor, plays a critical role in cancer development by regulating various cellular processes. Dysregulation of NF-κB signaling is linked to tumorigenesis through multiple mechanisms. Persistent activation of NF-κB leads to chronic inflammation, fostering a tumor-promoting inflammatory microenvironment. Additionally, NF-κB promotes cell survival by inhibiting apoptosis and controlling the expression of anti-apoptotic genes, enabling the accumulation of genetic alterations.[57-60] It stimulates cell proliferation, enhances the production of growth

factors, and regulates angiogenic factors, promoting tumor cell growth, invasion, and metastasis. NF-κB activation triggers the epithelial-mesenchymal transition, facilitating cancer cell migration and metastasis. It also contributes to immune evasion by regulating immune checkpoint molecules and inhibiting anti-tumor immune responses.[59,60] Moreover, NF-κB interferes with DNA repair mechanisms, leading to genomic instability and increased susceptibility to DNA damage, key drivers of tumorigenesis. Understanding these mechanisms is vital for developing targeted therapies aimed at disrupting NF-κB signaling and suppressing tumor growth and progression.[61]

Plant-Derived Therapies for Modulating NF-κB Signaling

NF-κB is involved in various cellular processes related to cancer development and progression, and dysregulated NF-κB signaling is associated with tumorigenesis. Plant-derived compounds, including polyphenols, alkaloids, and terpenoids, have shown promising effects in inhibiting NF-κB signaling through different mechanisms.[11,13] Preclinical studies have demonstrated their efficacy in suppressing NF-κB activation and sensitizing cancer cells to treatment. However, further clinical research is needed to establish their effectiveness and address challenges such as bioavailability and potential interactions. Overall, plant-based therapies targeting NF-κB present a promising avenue for cancer treatment.[11,13]

Plant-based compounds, including polyphenols (e.g., curcumin, resveratrol, green tea catechins), alkaloids (e.g., berberine), and terpenoids (e.g., celastrol, betulinic acid, ursolic acid), have shown promise in targeting NF-κB signaling in cancer. These compounds inhibit NF-κB activation through various mechanisms, such as blocking upstream signaling pathways, preventing nuclear translocation, and interfering with DNA binding. Preclinical studies demonstrate their ability to suppress NF-κB activation, inhibit NF-κB-regulated gene expression, induce apoptosis, and enhance cancer cell sensitivity to chemotherapy and radiotherapy.[11,13]

Dysregulation of Cyclooxygenase-2 (COX-2) Expression

Cyclooxygenase-2 (COX-2) is an enzyme involved in inflammation and the production of prostaglandins, and its dysregulated expression has been linked to cancer development. COX-2 contributes to tumorigenesis through various mechanisms. It promotes chronic inflammation, which creates a favorable environment for cancer growth, by inducing the synthesis of prostaglandins that enhance tumor cell survival, proliferation, angiogenesis, and metastasis while suppressing immune responses.[62,63] COX-2 also regulates cell proliferation and survival by promoting cell cycle progression and activating growth factor signaling pathways, leading to uncontrolled cell division and reduced apoptosis. Additionally, COX-2 plays a role in angiogenesis by inducing the expression of angiogenic factors that support the formation of new blood vessels crucial for tumor growth. It is involved in cancer cell invasion and metastasis by regulating the expression of matrix metalloproteinases and promoting the epithelial-mesenchymal transition.[62] COX-2 can modulate immune responses by impairing the activity of immune cells and promoting immunosuppressive factors, enabling immune evasion by cancer cells. Furthermore, it contributes to genetic instability by increasing the production of reactive oxygen species, leading to DNA damage and the accumulation of genetic alterations in cancer cells.[62,63]

Plant-Derived Targeted Therapies for Modulating Cyclooxygenase-2 (COX-2) Expression

Plant-derived therapies targeting cyclooxygenase-2 (COX-2) in cancer treatment have gained attention due to the enzyme's involvement in inflammation and cancer development. Polyphenols, terpenoids, and flavonoids derived from plants have shown inhibitory effects on COX-2 expression and activity through various mechanisms, offering potential targeted interventions against COX-2 in cancer. For example, (-)-epigallocatechin-3-gallate, the major polyphenol of green tea have been shown to significantly inhibit constitutive COX-2 mRNA and protein overexpression in human colorectal cancer cell lines (HT-29 and HCA-7).[64] Preclinical studies have demonstrated the efficacy of plant-based therapies such as caffeic and chlorogenic acid in suppressing cancer growth and progression by modulating COX-2, inhibiting prostaglandin production, inducing apoptosis, inhibiting angiogenesis, and enhancing sensitivity to conventional therapies.[65] However, further clinical trials are needed to establish their efficacy and safety. Challenges in developing plant-based COX-2 inhibitors include bioavailability, tissue penetration, and drug interactions, which require addressing through formulation optimization, effective combinations with standard therapies, and targeted delivery systems. Plant-derived therapies targeting COX-2 hold promise for cancer treatment.[64,65]

Excessive Oxidative Stress

Oxidation, characterized by generating reactive oxygen species (ROS), plays a complex role in cancer development. While low levels of ROS are necessary for normal cellular processes, excessive oxidative stress can result in detrimental effects, including DNA damage, genomic instability, and the promotion of cancer formation.[66,67] ROS-induced DNA damage leads to mutations and genomic instability, altering critical genes involved in growth control and DNA repair, thereby facilitating uncontrolled cell proliferation and cancer development. Oxidative stress activates oncogenic pathways, such as PI3K/Akt and MAPK, promoting cell survival, proliferation, and resistance to apoptosis.[66,68] Additionally, oxidative stress triggers chronic inflammation, immune dysregulation, and alterations in cellular signaling, which foster a microenvironment conducive to tumor growth, angiogenesis, tissue remodeling, and immune evasion. Epigenetic modifications induced by oxidative stress can further contribute to tumor initiation and progression by altering gene expression patterns.[40,66,68] Furthermore, oxidative stress disrupts mitochondrial function, leading to increased ROS generation and perpetuating genomic instability, impaired energy metabolism, and compromised apoptotic signaling - all associated with cancer development. Understanding these mechanisms offers potential cancer prevention and treatment strategies by targeting oxidative stress and its associated pathways.[66-68]

Plant-Derived Antioxidants for Curtailing Excessive Oxidative Stress

Oxidative stress, characterized by an imbalance between reactive oxygen species (ROS) production and antioxidant defense mechanisms, plays a crucial role in cancer development. Plant-derived compounds have emerged as potential targeted therapies against oxidative stress in cancer treatment.[11] Plants polyphenols, carotenoids, and flavonoids possess antioxidant and anti-inflammatory properties, effectively scavenging ROS, modulating oxidative stress, and modulating cellular signaling pathways associated with cancer progression. Preclinical studies have shown the efficacy of plant-based therapies in reducing oxidative stress, inhibiting tumor growth, and suppressing metastasis.[11,69]

Recent Advancements in Cancer Research

Recent advancements in cancer research have yielded significant insights into the molecular mechanisms driving tumorigenesis and cancer formation. Genetic alterations, including driver mutations and non-coding RNA dysregulation, have provided valuable knowledge about key signaling pathways and their roles in various cancer types.[70,71] Epigenetic modifications, such as DNA methylation and histone modifications, have become important regulators of gene expression and cancer development.[72-73] The tumor microenvironment, encompassing immune cells, stromal cells, and extracellular matrix components, has been recognized as a critical factor in tumor progression, with factors like chronic inflammation and immune evasion influencing tumorigenesis.[73-75] Metabolic alterations, including the Warburg effect and dysregulated lipid and amino acid metabolism, contribute to the energetic and biosynthetic needs of cancer cells.[76] Furthermore, genetic and phenotypic tumour heterogeneity has been increasingly acknowledged for its impact on therapeutic resistance and relapse, with advanced sequencing technologies enabling the characterization of distinct cancer cell subpopulations.[77] The complex interplay between cancer cells and the immune system, along with the identification of immune checkpoints,

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has paved the way for immunotherapies targeting cancer. Additionally, defects in DNA repair pathways and genomic instability play a role in the accumulation of genetic alterations in cancer cells.[67,78,79]
These recent discoveries have significantly enhanced our understanding of the molecular intricacies underlying cancer development and have implications for targeted therapies, personalized medicine approaches, and the identification of novel biomarkers for cancer diagnosis, prognosis, and treatment selection. Ongoing research continues to expand our knowledge of additional molecular mechanisms and further refine our comprehension of the complex nature of cancer.

Cancer Metabolism
Cancer metabolism is characterized by altered metabolic pathways that support the rapid growth and survival of tumor cells. Key metabolic pathways involved in cancer metabolism include the Warburg effect, where cancer cells preferentially undergo glycolysis even in the presence of oxygen, the Pentose Phosphate Pathway (PPP), the Tricarboxylic Acid (TCA) cycle, fatty acid synthesis, glutaminolysis, and one-carbon metabolism.[79,80] Specific enzymes play crucial roles in these pathways, such as Hexokinase 2 (HK2), Pyruvate kinase M2 (PKM2), Lactate dehydrogenase A (LDHA), Glucose-6-phosphate dehydrogenase (G6PD), Transketolase (TKT), Transaldolase (TALDO), Isocitrate dehydrogenase (IDH), Succinate dehydrogenase (SDH), Acetyl-CoA carboxylase (ACC), Fatty acid synthase (FASN), Glutaminase (GLS), Glutamate dehydrogenase (GLUD), Serine hydroxymethyltransferase (SHMT), and Methylenetetrahydrofolate reductase (MTHFR).[79,80]
These dysregulated metabolic pathways provide cancer cells the necessary energy and building blocks for rapid growth. Consequently, targeting these specific pathways and enzymes has emerged as a promising therapeutic strategy for cancer treatment. Ongoing research focuses on the development of inhibitors and modulators that can effectively disrupt these metabolic pathways, offering potential anticancer agents for future clinical applications.[80]

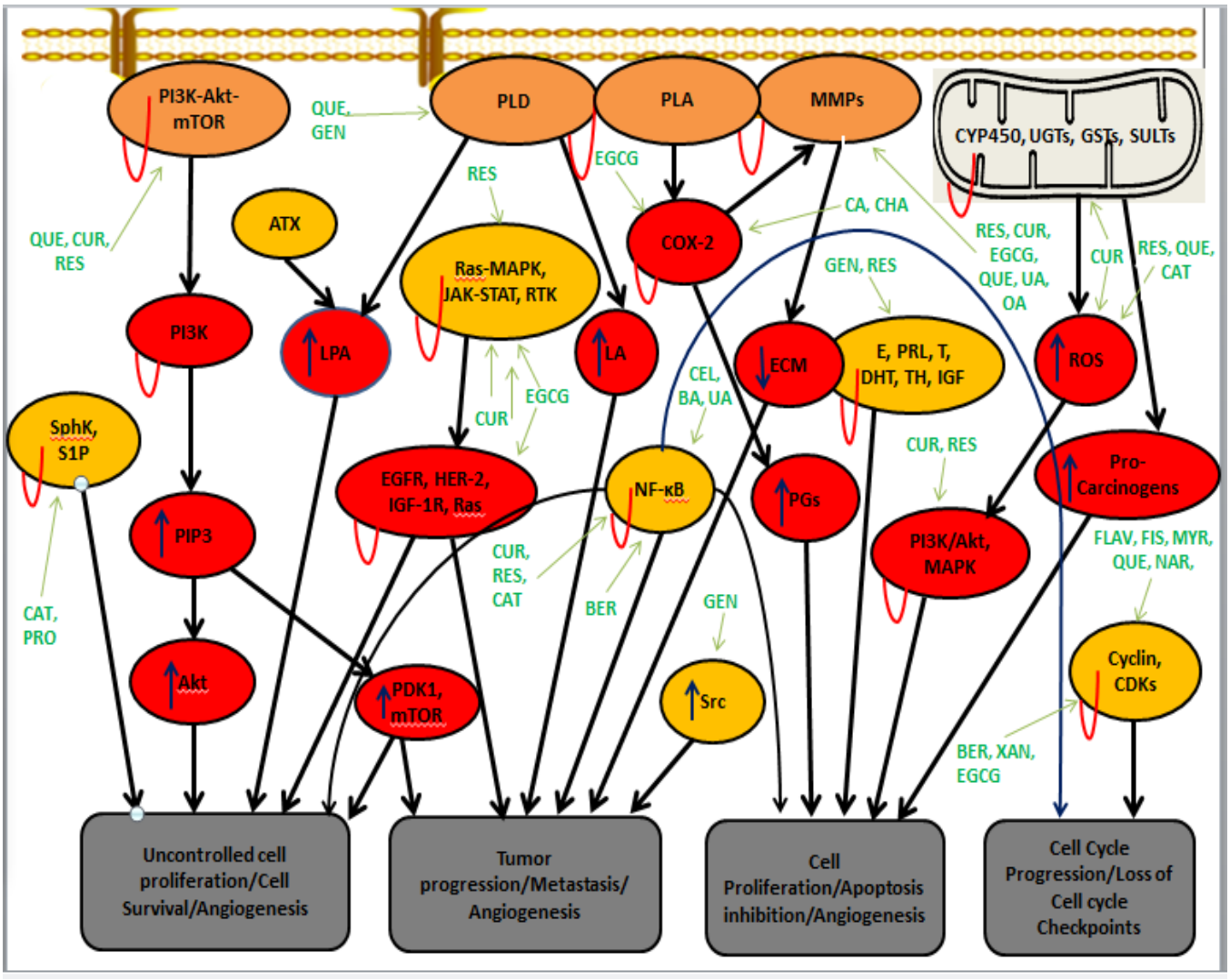

Figure 1: Mechanistic pathways of inhibibition or modulation of carcinogenesis/tumorogenesis by Plant-Derived Therapies.
Key: BA = Betulinic acid, BER = Berberine, CA = Caffeic acid, CAT = Catechins, CEL = Celastrol, CHA = Chlorogenic acid, CUR = Curcumin, EGCG = Epigallocatechin-3-gallate, FIS = Fisetin, FLAV = Flavopiridol, GEN = Genistein, MYR = Myricetin, NAR = Naringenin, OA = Oleanolic acid, QUE = Quercetin, RES = Resveratrol, UA = Ursolic acid, XAN = Xanthohumol.
= Dysregulation, = Activation/Generation, = Inhibition/Breakdown

Recent Advances in Plant-Derived Therapies

Recent advancements in cancer research have paved the way for plant-based targeted therapies. These therapies capitalize on the discoveries related to genetic alterations, epigenetic modifications, the tumor microenvironment, and cancer metabolism. For instance, natural compounds like curcumin and epigallocatechin gallate (EGCG) have shown potential in targeting KRAS and EGFR signaling pathways, respectively. Additionally, plant-derived compounds such as resveratrol and vorinostat exhibit inhibitory effects on DNA methyltransferases and histone deacetylases, offering strategies to counter epigenetic modifications in cancer cells.[11,13]

Plant-based anti-angiogenic agents and immune modulators have emerged as potential therapeutic options in the tumour microenvironment. Compounds found in green tea (e.g. (-)-epigallocatechin-3-gallate), grapes (e.g. resveratrol), and turmeric (e.g. curcumin)[81] have demonstrated anti-angiogenic properties, while polysaccharides from medicinal mushrooms like reishi and turkey tail exhibit immunomodulatory effects. Moreover, targeting cancer metabolism through plant-derived glycolysis and fatty acid synthesis inhibitors has shown promise. Compounds like honokiol and berberine inhibit glycolytic enzymes, disrupting the Warburg effect, while gossypol inhibits key enzymes involved in fatty acid synthesis. Despite these advancements, further research and clinical trials are needed to evaluate the efficacy, safety, and integration of plant-derived targeted therapies into standard cancer treatment protocols.[11-13]

Challenges and Prospects for Cancer Management

Managing cancer with current therapeutic agents such as chemotherapy, radiation therapy, targeted therapies, immunotherapy, and hormonal therapies presents challenges. These include limited efficacy due to resistance development, adverse effects impacting patient quality of life, lack of specificity leading to toxicity in healthy tissues, cost and accessibility barriers for newer therapies, and the emergence of resistance mechanisms. However, hope for improved outcomes exists through ongoing research and developments in cancer treatment.

Promising strategies include precision medicine and personalized approaches that target specific molecular alterations unique to each patient's tumor, combination therapies that enhance efficacy and overcome resistance, advancements in immunotherapy utilizing immune checkpoint inhibitors, CAR-T cell therapies, and cancer vaccines, identification of novel targets and pathways for more effective treatments, advances in drug delivery systems to improve efficacy and reduce toxicity, and integrating supportive care and symptom management to alleviate side effects and enhance patient outcomes.

Conclusion

In conclusion, recent advancements in cancer research have greatly expanded our understanding of the molecular mechanisms driving tumorigenesis and cancer formation. Genetic alterations, epigenetic modifications, the tumor microenvironment, metabolic dysregulation, and tumor heterogeneity have all been identified as crucial factors contributing to cancer development and progression. These discoveries have profound implications for targeted therapies, personalized medicine approaches, and the identification of novel biomarkers for cancer diagnosis, prognosis, and treatment selection.

Furthermore, the emerging field of cancer metabolism has shed light on altered metabolic pathways in cancer cells, providing the necessary energy and building blocks for their rapid growth. Targeting specific enzymes and pathways involved in cancer metabolism has shown promise as a therapeutic strategy. Additionally, recent advancements in plant-derived targeted therapies have capitalized on our growing knowledge of cancer biology. Compounds derived from plants have demonstrated potential in targeting key signaling pathways, modulating the tumor microenvironment, and disrupting cancer metabolism. However, further research and clinical trials are required to evaluate the efficacy, safety, and integration of these therapies into standard cancer treatment protocols. Continued research efforts hold the potential to revolutionize cancer treatment and improve patient outcomes.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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