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Role of Anti-Inflammatory Natural Products against Colon Cancer

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Abstract

It is predicted that colorectal cancer (CRC) will be a major global health concern in 2040, with an estimated 3.2 million new cases. The illness is the result of complex interactions between genetic and epigenetic alterations, such as chromosomal instability and mutations. Colorectal cancer is developed in several stages, with adenomatous precursors taking decades to progress to aggressive stages. Risk factors include eating habits, family history, genetic predisposition, and an inactive lifestyle. Epigenetic modifications have a major impact on immune regulation, chemo resistance, and tumor genesis and progression. Treatment options include targeted medications, chemotherapy, and nutraceuticals and phytochemicals from medicinal plants. Other treatment options such as chemotherapy and targeted therapies are also available. Recent research on the molecular mechanisms linking inflammatory responses to carcinogenesis is summarized in this article.

Keywords: Colorectal Cancer, Metastasis, Nutraceuticals, Phytochemicals.

Introduction

Colorectal cancer, a common malignancy, is experienced by both men and women. The bloodstream is where water, electrolytes, and certain nutrients are received from the colon, also known as the large intestine. Stool, the waste material, is stored in the rectum, the final section of the colon, before it is eliminated during bowel movements. Colorectal cancer is caused by chronic inflammation of the colon, bowel, or abdomen. During the development and progression of CRC, epigenetic changes and chronic inflammation with genetic changes are commonly seen. Inflammatory cells such as IL-1Beta and TNF alpha, which line the gut, are the types of cells that can become malignant CRC. Colorectal cancer, also known as CRC, is a significant global health issue, accounting for 10% of all cancer cases worldwide. It is the third most common type of cancer globally. In 2020, approximately 1.9 million individuals were affected by colorectal cancer, making it a major public health concern. Furthermore, according to WHO estimates, colorectal cancer has been diagnosed in 5.25 million people globally in the last five years, emphasizing the importance of early identification and screening programs in lowering disease incidence and mortality rates (1).

Background Information

According to previous research, a dramatic rise in the number of colorectal cancer cases in China is projected for 2040, increasing from 0.56 million in 2020 to 0.91 million. Similarly, in the United States, an estimated 0.21 million new cases are expected in 2040. The most new colorectal cancer cases over the next 20 years are also anticipated in these two countries. Due to its high fatality rate, colorectal cancer ranks as the second most common cause of cancer-related fatalities worldwide (2). Increased incidence and mortality rates from colorectal cancer are led by factors such as a sedentary lifestyle, obesity, an aging population, and irregular screening. The need for increased awareness, screening, and prevention efforts is emphasized as a result. Addressing these risk factors through lifestyle modifications and healthcare actions is necessary to reduce the

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burden of CRC (3). Dietary choices, physical inactivity, and hereditary predisposition influence this disease. Colon cancer has traditionally been treated with 5-fluorouracil (5-FU). Colorectal cancer is commonly treated with pharmaceutical medications such as 5-FU, oxaliplatin, irinotecan, or capecitabine (4). DNA synthesis inhibition is achieved by these medications through an enzyme known as thymidylate synthase to reduce tumor growth. Unexpected side effects often accompany its usage, prompting the search for alternative treatments. Phytochemicals and nutraceuticals have been proposed as potential therapies for colon cancer, with examples including limonids, carotenoids, polyphenols, flavonoids, isoflavonoids, anthocyanidins, phytosterols, terpenoids, and phytoestrogens being some examples of phytochemicals (5). These compounds have been found to possess anti-inflammatory, antioxidant, and anti-proliferative properties; oxidative stress reduction and critical molecular pathways focus by them may help in the prevention or slowing down of colon cancer progression. A more secure and efficient way to combat this royal disease may be offered by the cutting-edge techniques. Colorectal cancer (CRC) invasive stages are initiated by adenomatous precursors and can take decades to complete. Development and maintenance of healthy intestines require the adenomatous polyposis coli (APC) tumor suppressor gene; however, it is frequently mutated or deleted in colorectal malignancies and polyps. When APC is deleted or changed, gene regulation is changed, leading to an increased risk of cancer because the expression of other genes is influenced, notably the oncogene c-Myc. Mutations in c-Myc-controlled genes, such as ornithine decarboxylase (ODC), have been identified as the primary cause of colorectal cancer (6). Furthermore, the relationship between disease progression, CRC incidence, and genetic markers has been determined by the field of molecular epidemiology, which integrates genetic, environmental, and epidemiological approaches (7). Microsatellite instability-high (MSI-H) is typically associated with a better prognosis for colorectal cancer because immune checkpoint therapies are more effective on this type of cancer. However, it has been determined that the prognosis is worsened when MSI-H is combined with KRAS mutations. This combination has been associated with increased tumor heterogeneity, immune evasion, and resistance to treatment. The benefits of MSI-H can be nullified by a KRAS mutation, which diminishes immune-related genes and activates pathways that promote tumor growth. Patients with both KRAS-mutated tumors and MSI-H may experience a lower overall survival rate compared to those with only MSI-H (8). Genetic and epigenetic alterations commonly detected in colorectal cancer (CRC) are thought to be critical for the disease's genesis and development. Several genetic and epigenetic processes interact during the intricate process of colorectal cancer development. The three molecular features mentioned - DNA microsatellite instability (MSI), CpG island methylator phenotype (CIMP), and chromosomal instability (CIN) - are important in this process. CIN in genes like APC is caused by mutations that activate the Wnt pathway, resulting in unregulated cell proliferation. Mismatch repair syndrome, or MSI, is caused by gene alterations resulting in DNA replication mistakes. CIMP is distinguished by global genomic hypermethylation, which silences tumor suppressor genes. A study has been reported that these distinct molecular profiles can be used to guide therapeutic and diagnostic approaches to colorectal cancer (9). The CIMP is a widely detected epigenetic marker that is linked to colon and brain cancer. It is characterized by widespread hypermethylation of tumor suppressor gene promoter regions, which results in transcriptional silence and loss of function (10). After years of cancer being believed to be only a hereditary disease, epigenetic changes are now acknowledged to induce tumors, modulate immunity, and confer chemoresistance. The intriguing aspect of epigenetic dysregulation is that recent research has shown it can silence tumor suppressor genes, activate oncogenes, and disrupt signaling networks. According to one study, a high potential for treatment development and a better understanding of cancer mechanisms is seen in epigenetic dysregulation since it can interfere with tumor stop signaling pathways (11). Histone phosphorylation, SUMOylation, and ubiquitination were examined during post-translational modifications, as well as histone acetylation, histone methylation, and DNA methylation in this study. Their impact on cancer

progression was not considered in this study. According to another research, patients with colorectal cancer (CRC) receiving anti-EGFR therapy have a lower response to treatment (12). The findings indicated the presence of CRC cases with 35 BRAC mutations and 39-40% KRAS mutations, and it was revealed in their study that mutations may have a role in the development of colorectal cancer. Further studies should be considered to include cases from the early stages of colorectal cancer in order to highlight the importance of mutation in the prognosis. A worse overall survival rate and resistance to EGFR-targeted treatment can be predicted by BRAF mutations. Enzymes from the large protein kinase family are essential for many biological activities, but their deregulation has been linked to the onset and progression of several cancers. Protein kinase inhibitors have been developed to reduce their activity and prevent uncontrolled cell growth, making them the most commonly targeted proteins in cancer therapy. Protein kinases, which are typically overexpressed or altered in cancer cells, are responsible for constitutive activation and abnormal signaling that promote carcinogenesis. Cancer therapies have the potential to effectively limit tumor growth and proliferation by targeting these kinases (13). Throughout time, a series of genetic and epigenetic changes are undergone by a cell, contributing to the complex and multistep process of cancer development. These modifications, which can include chromosomal instability, mutations, and epigenetic changes, provide cells with a selective advantage, allowing for extremely rapid cell division and proliferation (14). Hereditary colon cancer has been linked to POLD1 and POLE gene mutations (15). New therapeutic options in hypermutated colorectal cancer are revealed by critical investigations of polymerase proofreading domain mutations that overcome MMR deficiency (16). Metastatic illness is the leading cause of colon cancer death. The gene "Metastasis-associated in colon cancer 1" (MACC1) is one that regulates hepatocyte growth factor expression, promoting the development, invasion, and dissemination of colon cancer cells, potentially increasing the risk of metastatic illness. More clinical trials are needed to demonstrate that MACC1 is seen as a promising target for cancer treatments (17). Inflammation, which has both pro- and anti-tumor actions, can impact cancer formation and treatment outcome. In terms of tumor growth and therapeutic resistance, the consequences of acute inflammation can be increased by persistent inflammation, whereas anti-tumor immune responses can be boosted by dendritic cell maturation and antigen presentation. These processes are modulated by several signaling pathways, including cGAS/STING, JAK-STAT, NF-kB, TLR, and MAPK, as well as inflammatory agents, interferons, interleukins, chemokines (CCLs), and growth factors (VEGF and TGF-β) (18). According to one study, obesity could be the major cause of colorectal cancer (CRC) in the non-microsatellite instability-high (MSI-high) subtype. An increased risk of colorectal cancer (CRC) has been linked to smoking, regardless of molecular subtype; this association is highest in cases of BRAF-mut, MSI-H, or CIMP CRC (19). According to another study, CRC subtypes with CIMP and MSI-H status are more closely associated with smoking, indicating a mechanism by which the development of these specific subtypes is influenced by smoking (20). A higher dietary calcium intake has been revealed in a previous study to be associated with a lower risk of colorectal cancer (CRC). According to another study, the incidence of CRC is reduced by 6% for every 300 mg of calcium consumed daily (21). Metabolites produced by ethanol metabolism may assist colon tumorigenesis. Some of the cascades that may be engaged, raising cancer risk, include oxidative stress, lipid peroxidation, DNA adduct formation, epigenetic alterations, epithelial barrier dysfunction, and immunological modulatory effects. Metabolites like acetaldehyde can begin these cascades. Poor eating habits, a lack of fiber and folate, and irregular sleep patterns caused by alcohol use can all contribute to colon cancer (22). The dietary calcium intake total odds ratio (OR) is 0.94 (95% confidence interval [CI] 0.92-0.97) was found. A definite link between moderate to severe alcohol use and an increased risk of CRC is observed; however, some studies suggest that low to moderate alcohol consumption may also pose a modest risk. Acetaldehyde, an alcohol byproduct, is believed to injure the cells lining the colon and rectum, leading to mutations and cancer development. The specific mechanism underlying this

relationship is not fully understood. The gut microbiota can be affected by alcohol, which may result in an increased risk. A protein generated by one subtype of *Fusobacterium nucleatum* (Fna) can stimulate cancer cell proliferation and invasion, ultimately leading to the progression or genesis of colorectal cancer. These findings illuminate the role of the Fna C2 lineage in the development of colorectal cancer (CRC). It is suggested by the finding of the Fna clade bifurcation in another study that Fna C2 is a key part of the Fna enrichment seen in human CRC. Colorectal cancer cell migration and invasion can be prevented by aspirin targeting the Wnt signaling pathway and the epithelial-mesenchymal transition (EMT) (23). In vitro, E-cadherin production was boosted by aspirin in epithelial cells. However, β-catenin, a transcription factor in Wnt signaling, and its downstream targets, c-myc and Lgr5, were found to be less expressed. It was shown that aspirin could be an effective therapeutic treatment for the control and prevention of colorectal cancer (24). Chemotherapy treatments for colorectal cancer often involve the use of chemotherapeutic medications. Tumor cells are directly destroyed by chemotherapy through interference with their ability to divide, such as chromosomal segregation and DNA replication. However, this non-specific strategy targets all quickly reproducing cells in the body, including healthy tissue, which may lead to harm and raise concerns about regeneration in highly replenishing tissues, such as the immune system (25).

Phytochemicals

The development of new therapeutic medicines holds enormous promise through the study of phytochemicals and nutraceuticals from medicinal plants. In addition to being potentially less harmful to healthy cells than synthetic drugs, a wide range of potential anti-cancer agents is offered by phytochemicals and other naturally occurring molecules found in the plant kingdom (26). The pharmacological applications of phytochemicals include antifungal, antibacterial, anti-inflammatory, immunomodulatory, anticancer, anticonvulsant, antipyretic, and analgesic effects. A lower risk of CRC incidence has been demonstrated by individuals who consume a daily diet rich in fibers, fruits, and vegetables due to the presence of polyphenols, flavonoids, and alkaloids in these foods. Phytochemicals found in plants have anti-carcinogenic properties by inducing apoptosis, decreasing angiogenesis and inflammation, inhibiting cancer cell development. Many metabolic pathways involved in the survival of cancer cells are modified by the intensive and extensive applications of phytochemicals, which are still unexplored due to the lack of clinical applications.

Nutraceuticals

This suggests that the use of compounds produced from medicinal plants could be considered as a feasible alternative to existing colon cancer medicines, providing a more secure and organic manner of both prevention and treatment of the disease (27). Phenolic compounds are recognized as some of the most important active molecules with anti-CRC properties. Furthermore, because of their synergistic effects, which can enhance therapeutic efficacy and reduce side effects, the combination of herbal extracts could be seen as a viable strategy for CRC treatment (28). Nutraceuticals are biologically active chemicals found in food that can assist in the prevention, treatment, or improvement of health due to their medical and nutritional properties. Numerous diseases, such as diabetes, atherosclerosis, cancer, and neurological disorders, have been shown to have positive responses to these bioactive compounds, which consist of minerals, lipids, proteins, vitamins, and carbohydrates (29). High-fiber fruits and vegetables may be found to be very beneficial in the prevention of colon cancer cells, and specific supplements may be utilized as chemopreventive medications in the treatment of the disease. Furthermore, it has been demonstrated that polysaccharides derived from plants are capable of inhibiting the development of colon lesions, contributing to the evidence that supports the potential preventive effect of potentials (30). Over 70% of studies have indicated that the therapeutic efficacy of chemotherapy is improved by antioxidants (31). The therapeutic outcomes of treatment can be enhanced by antioxidants, which can also help in reducing side effects by scavenging free radicals that may otherwise harm healthy cells and diminish the therapeutic potential of chemotherapy. Protection from the oxidative

stress caused by chemotherapy is provided by antioxidants for healthy organs, enabling the treatment to more effectively target cancer cells (32). The overexpression of disease-related proteins in cancer cells can be inhibited by antioxidants by focusing on post-transcriptional control. Furthermore, colon cancer can be prevented and overall health maintained through the use of nutraceuticals. Superfoods, such as vegetables, microalgae, and plant derivatives high in vitamins, minerals, and amino acids, can also have a significant impact on health and disease prevention (33). Promising results have been seen in cancer treatment with nutraceuticals, particularly nanoparticles. Anticancer drugs such as methotrexate and cisplatin can be encapsulated in platinum nanoparticles to develop a completely new class of biocompatible and potent chemotherapy treatments. Metallic and metal oxide nanoparticles (NPs) can be linked to biological molecules like peptides, nucleic acids, and antibodies by functionalizing them with various chemical groups. Suitable procedures allow therapeutic agents, such as anticancer medications, to be delivered to specific cells, organs, or biological processes (34).

Carotenoids

Carotenoids, a type of pigment found in fruits and vegetables, have various biological benefits, such as anti-aging, antioxidant, and anti-inflammatory qualities, as well as therapeutic properties for cancer prevention and treatment. The improvement of membrane integrity and cell protection from free radicals, preventing mutagenesis and gastrointestinal cancer, is attributed to carotenoids. According to epidemiological studies, cancer incidence and spread may be prevented by carotenoids; however, a recent expert evaluation by the American Institute for Cancer Research and the World Cancer Research Fund shows that there is insufficient data to support this claim (35). Lipid-soluble, brightly colored carotenoid pigment is believed to be present in algae, bacteria, fungi, and plants, and is referred to as an anticancerous pigment. The upregulation of target genes, viz., Bax and p53, is triggered by Bid through caspase 2, suggesting the apoptotic mechanism of carotenoid. When paired with the carotenoid holocyanixanthin contained in food, the protein tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) drives cancer cells to die and greatly inhibits the proliferation of DLD-1 colon cancer cells. The induction of caspase inhibitor, cleavage of poly (ADP-ribose) polymerase, and nuclear condensation are some of the key anticancer actions of this combination, suggesting that colon cancer cell apoptosis may be regulated (36). Luteolin, a flavonoid, has been shown great promise in cancer treatment, including prostate, colorectal, pancreatic, liver, breast, and ovarian malignancies. The anti-cancer capabilities of this material have been established by its ability to disrupt procarcinogenic regulatory pathways, cause cellular cytotoxicity, induce cell apoptosis, influence the cell cycle, and protect tissue against carcinogenic stimuli (37). It was concluded in this study that the activation of the caspase 13 and caspase 3 cytotoxicity mechanisms is promoted by luteolin, implying the induction of apoptosis. Although it was suggested in this review that luteolin had toxicity and bioactive qualities, very few clinical data were included. Flavonoids included in food have been shown to play a vital role in maintaining homeostasis due to their ability to change critical enzymes and receptors involved in a range of physiological processes. Compounds derived from plants and spices have been used by the traditional medical community for centuries to treat various ailments. Anticancer characteristics have been demonstrated in flavonols through the modulation of signaling pathways involved in angiogenesis, inflammation, apoptosis, metastasis, multidrug resistance, differentiation, and proliferation, thereby reducing cancer start, dissemination, and progression (38). It has been shown that the flavonoid fisetin, abundant in many fruits and vegetables, can accelerate the demise of cancer cells when present in minute amounts. Furthermore, cleaved ADP-ribose, a hallmark of apoptosis, as well as activated caspase-3, have been observed in fisetin-treated colon cancer cells. Additionally, Bcl-2 metabolite production is regulated and Bak protein expression is stimulated by fisetin (39).

Polyphenols

Research on these natural chemicals for CRC therapeutic uses is intriguing since they may provide more targeted and less toxic alternatives to standard chemotherapy. Polyphenols, especially those found in green tea, have been

extensively studied for their biological effects, and in animal experiments, they have been shown to offer protection against various chemically induced cancers. Studies show that phenolic compounds make up about 30% of green tea's dry weight, with 15% flavonols and 0.4% catechins. Flavonols and flavones such as kaempferol, myricetin, quercetin, and apigenin are found in green tea. The quantity and composition of these chemicals vary between different varieties of green tea. Even without glycosylated branches, the flavonol-rich fractions FLA and FLG were found to have a stronger anti-inflammatory effect compared to the catechin-rich green tea extract. Flavonols may have stronger anti-inflammatory activities than catechins, although the concentration of flavonoids in FLG and FLA is lower than in green tea extract (40). A greater impact on inflammation reduction may be seen with flavonols than catechins. The presence of a flavonol molecule in green tea that possesses anti-inflammatory and anti-cancer capabilities was discovered in this study; however, it was also revealed that more in vivo studies are needed to establish their effectiveness.

Curcumin

Curcumin, a secondary metabolite with strong anticarcinogenic properties, is currently being studied in clinical trials for its potential to treat colon issues. COX-2 is targeted by curcumin, and malignant cells are prevented from generating TNF-α and NF-κB proteins. Additionally, IL-6, IL-1, IGF, VEGF, chemokines, and various other factors are affected by curcumin. Curcumin has been identified as a potential chemopreventive medication for digestive tract cancers (41). A study revealed that when curcumin was applied to colorectal cancer cells (HCT 116), neurotensin function was altered, leading to an increase in IL-8 synthesis, a cytokine causing inflammation. Clinical trials are currently being conducted to assess the potential of curcumin, a secondary metabolite with high anticarcinogenic properties, to treat colon disorders. TNF-α and NF-κB protein production in malignant cells are inhibited by curcumin targeting COX-2 at the molecular level. It also affects IL-6, IL-1, IGF, VEGF, and chemokines. Curcumin has been identified as a prospective chemopreventive drug for digestive tract cancers (42). The neurotensin activity of colorectal cancer cells (HCT 116) was altered by curcumin treatment, leading to an increase in the production of the pro-inflammatory cytokine in a time- and dose-dependent manner (43).

Cinnamic Acid

Cinnamic acid, a phenylalanine-derived compound, has shown promise as a therapy for colorectal cancer because it targets cancer stem cells (44). P-methoxycinnamic acid is reported to be contained in brown rice, turmeric, and rice bran. The compound Cinnamic acid was found to have apoptotic activity through the triggering of the ROS mechanism.

Flavonoids

Flavonoids, a plant-based chemical family, have been demonstrated to have anti-inflammatory properties by blocking key enzymes and communication channels that induce inflammation. The release of pro-inflammatory mediators and proteins is inhibited, preventing the inflammatory response from worsening. It was suggested by a study that the ability of flavonoids to modulate inflammation may be contributed to by their preventative benefits against long-term illnesses such as cancer, heart disease, and neurological issues (45). It was reported by another study that that vivid colored flavonoid called Casticin can be found in wine, tea, flowers, stems, roots, bark, grains, vegetables, and fruits. Casticin is referred to as being used as an anti-carcinogen. The induction of apoptosis is suggested by the downregulation of target genes Bcl-xl and Bcl-2 via the activation of proapoptotic proteins Bid and Bax.

Kaempferol

Kaempferol, a flavonoid found in many fruits and vegetables, is linked to a lower risk of developing numerous malignancies, especially colon cancer, due to its ability to induce apoptosis, arrest the cell cycle, and downregulate the epithelial-mesenchymal transition (46). The presence of the flavonoid Kaempferol is noted in vegetables, black tea, green tea, onion, apples, and fruits. It is known to induce apoptosis in colon cancer cells. Activation of PARP and caspase-3, -7, and -9 is suggested by triggering caspase 8 through the Fas receptor via the FasL gene, leading to the induction of apoptosis in colorectal cancer cells.

Mechanism of Anti-inflammatory Photochemical

Cancer prevention can be aided by anti-inflammatory natural compounds derived from plants (47). This is achieved through various methods that inhibit the formation of cancer, such as the prevention of damage to DNA by reactive oxygen species, modulation of phase-I enzyme metabolism, elimination of reactive metabolites through phase-II conjugating enzymes, blocking the uptake of toxic substances, and enhancement of DNA repair. Antioxidant properties found in certain plant organs protect them from oxidative stress and cellular damage. Another way in which certain plant organs exhibit anti-cancer effects is through the process of apoptosis (48). Caspases are involved in the execution of apoptosis. The cleavage of the PARP-1 enzyme, which has DNA repair activity at the site of DNA damage, is a key indicator for the initiation of apoptosis. The increase in calcium levels, which were facilitated by the stressed endoplasmic reticulum, is proven to be vital for the activation of Bcl-xl (B-cell lymphoma—extra-large) and caspase 12. The activation of caspase 3 is triggered by the active compound via apoptotic protease-activating factor 1. Most of the 218 newly approved anticancer medications were derived from unaltered natural substances or their derivatives, rather than being synthesized. This is due to the fact that drug resistance, gastrointestinal irritation, bone marrow suppression, hair loss, and neurological malfunction can be caused by synthetic anti-cancer medicines. Natural products may be able to target specific signaling pathways implicated in cancer formation, in addition to having fewer side effects (49).

Anti-Inflammatory Suppressor Mechanism

The mechanism for suppressing inflammation requires a variety of sophisticated processes and methods to reduce the anti-inflammatory benefits of natural plant chemicals, in order to prevent tumor cell proliferation, stressed cells can be encouraged to undergo apoptosis or cell cycle arrest, or unregulated cell division can be allowed to occur. One significant mode of treatment involves the inhibition of pro-inflammatory enzymes that convert arachidonic acid into pro-inflammatory eicosanoids, such as lipoxygenase (LOX) and cyclooxygenase-2 (COX-2) (50). Natural substances such as curcumin, resveratrol, and green tea catechins have been demonstrated to suppress the expression and activity of these enzymes, reducing pro-inflammatory mediator synthesis. The expression and activity of these enzymes can be suppressed by natural substances such as curcumin, resveratrol, and green tea catechins, leading to a reduction in pro-inflammatory mediator synthesis. Plant-based compounds can inhibit the activation of transcription factors like NF-κB, which regulate gene expression linked to inflammation. The activation of transcription factors like NF-κB, which regulate gene expression linked to inflammation (51), can be inhibited by plant-based compounds. Polyphenols such as quercetin and epigallocatechin gallate can limit NF-κB activation by blocking upstream kinases such as IκB kinase. NF-κB activation can be limited by polyphenols such as quercetin and epigallocatechin gallate, which block upstream kinases such as IκB kinase. These pathways contribute to the anti-inflammatory properties of natural plant products, making them potential therapeutic agents for the treatment of inflammatory diseases and cancer prevention. The anti-inflammatory properties of natural plant products are contributed to by these pathways, making them potential therapeutic agents for the treatment of inflammatory diseases and cancer prevention.

Cell cycle

Antitumor medicines that can limit tumor cell proliferation and the cell cycle are considered critical for slowing cancer progression. Studies have focused on naturally occurring anti-inflammatory plant compounds that have been discovered to have anti-cell cycle effects by upregulating two CDK inhibitors, p21 and p27, and downregulating cyclin-dependent kinase 6 (CDK6), resulting in G0-G1 cell cycle arrest in breast cancer cells. Another study state that this discovery provides a realistic technique for the development of novel cancer medicines targeting the cell cycle to inhibit tumor growth and development (52). Resveratrol and grape seed proanthocyanidins, two polyphenols, have been shown to target critical cell cycle regulators, causing the arrest of the human cancer cell cycle. The expression of cyclins in human epidermoid carcinoma cells is specifically inhibited by grape seed proanthocyanidins (53). Similarly, in human

colon cancer cells, cyclin transcription is halted and cell cycle arrest is induced by resveratrol (54). It was found that the downregulation of the Wnt gene by resveratrol effectively suppresses the processes of metastasis, tumor growth, and tumor initiation. Therefore, it is suggested by the study that resveratrol is known to possess anticancer activity. As a result, the anticancer properties can be facilitated for a person by consuming 1 gm of resveratrol per day.

Inflammation

Pro-inflammatory proteins, such as chemokines and cytokines, are first increased before they are downregulated in response to an inflammatory response. However, as the response is triggered down, the expression of anti-inflammatory proteins is increased (Figure 1). The hierarchical regulation of inflammatory reactions is mediated by the transcription factor NF-κB, which is triggered by danger signals or stress (55, 56). The inducible pro-inflammatory enzymes COX-2 and iNOS have a profound impact on cancer genesis and progression. Overexpression of COX-2, in particular, can increase antiapoptotic proteins and activate PI3K/AKT. It is involved in inflammation, cancer, tissue remodeling, and cell growth regulation (57).

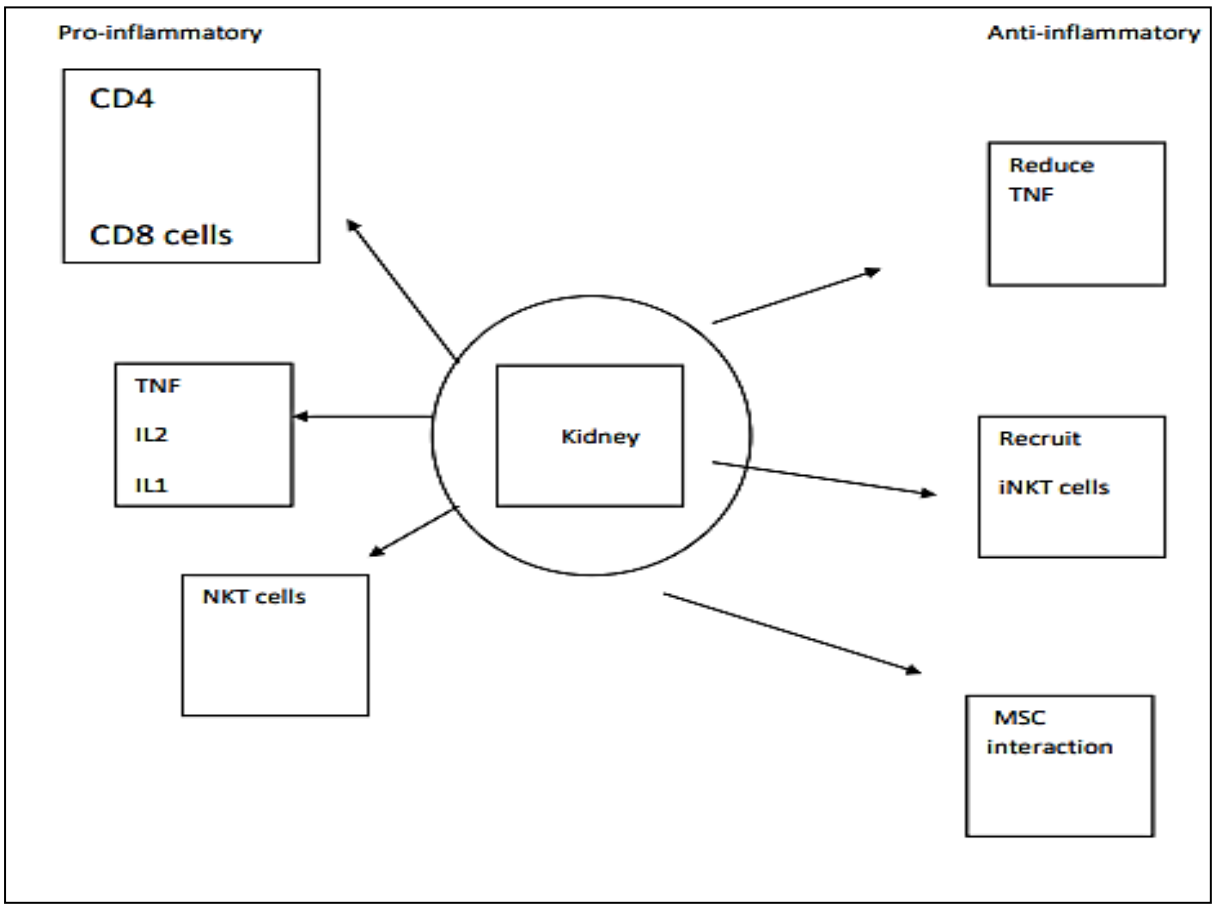

Figure 1: Pro-Inflammatory and Anti-Inflammatory Functions

EGCG, a polyphenol present in green tea, has been demonstrated to decrease COX-2 expression and activity in human breast and prostate cells, suggesting that it may be utilized as a potential cancer treatment in the future. Sulforaphane, a phytochemical found in cruciferous vegetables, has been shown to reduce AP-1 and therefore COX-2 production in human lung cancer cells (58). Similarly, tangeretin, a flavonoid found in citrus peels, has a similar effect through the activation of AKT and the inhibition of p38 MAPK and JNK. It was discovered that excellent NF-κB and MAPK pathway suppression activities were attributed to the chemical fisetin. The inhibition of MAPK was supported by the findings, which indicated a decrease in NF-κB-p65's nuclear translocation and phosphorylation of protein factors, and thus, the anti-inflammatory and anticancer properties of flavonols were suggested (59) (Figure 2). The potency of naturally occurring iNOS inhibitors to prevent cancer has been investigated in studies. Curcumin has been found to be a potent inhibitor

of iNOS and its upstream regulators, reducing NO generation by lowering macrophage protein expression and mRNA transcription. Other substances, such as gingerol, EGCG, and phenolphthalein isothiocyanate from winter cress, have been observed to lower iNOS expression, activity, or nitric oxide generation in macrophages, indicating potential anti-inflammatory and anti-cancer activities (60). Phytochemicals have long been utilized as chemotherapeutic medicines for the treatment of all types of cancer. The anti-colorectal cancer capabilities of phytochemicals are highlighted in Table 1.

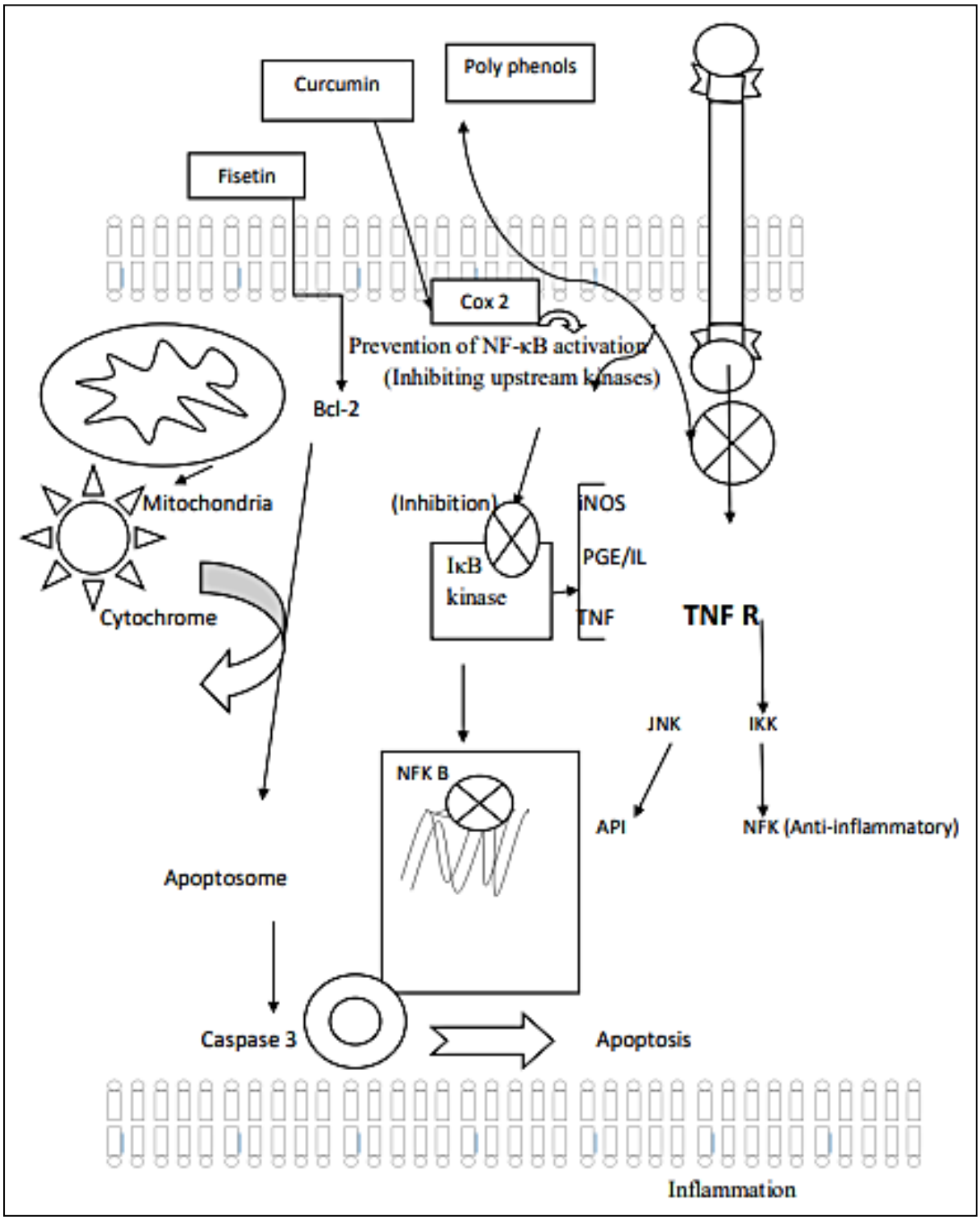

Figure 2: Schematic Representation of Metabolic Pathways of Phytochemical Compounds against CRC

Table 1: Anti-Colorectal Cancer Activity of Phytochemicals

Therapeutic element group	Therapeutic agent	Vegetable Source	Therapeutic Property	Activates	Literature
Flavonoids	Quercetin	Chilli, pepper, Onion,Spinach, Cherry, Broccoli, Asparagus, Lettuce, apples, Blueberries,	Apoptosis, Anti-inflammatory	caspases, AKT, COX-2, iNOS, p-AKT, MYC, ↓ ANXA1	(61-63)
Carotenoids	α-β Carotene (β-Cyptoxanthin), Lutein , Lycopene , Zeaxanthin	Carrot (α-β Carotene), Orange(β-Cyptoxanthin), cabbage, peas, , Tomatoes (Lycopene), Spinach (Lutein/Zeaxanthin)	Apoptosis, anti-inflammation, antioxidant	Caspases, Bcl-2, Bax, AKT, COX-2, iNOS, VEGF, cyclin D1, CDK, p21, p27,	(64-66)
Terpenoids	limonene Geranoil,	*Vitis vinifera, Citrus sinensis*	antiangiogenesis	caspases, p53, Bax, Bcl-2, Bcl-xL, and TNF-α	(67,68)
Poly phenols	Curcumin	Turmeric, Tea	peas, cabbage, orange	iNOS, survivin, STAT-3/-5, Bcl-2, Bax, p21, p53, ERK, COX-2, , IGF-1R, NF-κB, Her2, EGFR, A KT proteins, NRF2, β-catenin, NF-κB increased the production of intracellular ROS,	(69-71)
Isothiocyanates	Allyl isothicyanate Benzyl isothiocyanate, Phenethyl isothiocyanate, Sulforaphane, -C1, -B1,	Cress, mustard, kale, sprouts, brussels, cauliflower, turnips, broccoli, cabbage, vegetables , crucifereous, etc	HCT116 metabolic activity , inhibited HT-29, inhibition of angiogenesis activation of caspases, antiproliferation, and, anti-inflammation	COX-2, VEGF, iNOS, MMP-2/-9, p53, Bax, CDK, cyclin D, survivin, AP-1, NF-κB, Bcl2, , and AKT,	(72, 73)
Proanthocyanidins	Proanthocyanidins A2	Wine, beans, berries, cocoa, nuts,	anti-inflammation cell cycle arrest, antioxidant,	COX iNOS, AP-1, --9, MMP-2, NF-κB, PI3K/AKT, 2MAPK,	(74-76)
Naphthoquinone	Shikonin	Lithospermum erythrorhizon roots	Antiinflammatory	macrophage colony-stimulating factor, granulocyte, TNF-α, IL-1β-induced COX-2 activity, LPS	(77, 78)
Phenyl proponoid	Cinnamic aldehyde	Cinnamon	Antiinflammatory	induced-COX-2,	(79-82)

				inhibit NOX4 expressions; Reduce OS	
Flavonoid	Naringin	Grapes and Skin of organges	Antiinflammatory		(83, 84)
Isoflavone	Genistein	Soya bean	Antiinflammatory	Caspase 3, Caspase 9,	(85)
Alkaloids	Camptothecin	Chinese *Camptotheca acuminata*	anticancerous	Inhibit Topoisomearse 1	(86)
Phenols	Resveratrol	Peanuts and grapes	Anti-inflammatory of neurons	iNOS, IL-6, and TNF-α	(87)
Polypropo noids	Coumarins	*Peltophorum africanum*	Anti-inflammatory	Inhibition of NO	(88)
Polypheno ls	Catechins	*Camellia sinensis*	Anti tumour, antigiogenic, antioxidant, Caspase9, caaspase, 8, caspase 7, and caspase 3	MAPK JAK/STAT and P13/AKT,	(89, 90)
Anthaquin one	Emodin	Aloe vera	Anti-cancer	EMT genes, Wnt/β-catenin pathway	(91)
Diterpene	Carnosic acid	*Rosmarinus officinalis*	Anti-cancer	Nrf2/ARE pathw ay	(92)
Triterpeno id	Oleanolic acid	*Vitis vinefera*	Induce apoptosis on HCT116 cells	FOXO3a and Sirt6 expression	(93)
Flavonolig nan	Anthracin	*Chamaecyparis obtuse*	Induce apoptosis on HCT116 cells	JNK pathway activation	(94)
Phenol	Eugenol	Cloves	Induce apoptosis on	PI3K/AKT/mTOR	(95)
Steroidal lactones	Withanolides	*Withaniasomnifera*	Antiinflammatory	JAK pathway; MAP kinase signalling	(96)

↓ denotes down regulation

Several compounds are contained in cinnamon, including coumarin, cinnamic acid, cinnamic alcohol, and cinnamic aldehyde. Footpad edema in mice was reduced by cinnamic aldehyde, and COX-2 expression induced by carrageenan was decreased. PGE2 production in RAW264.7 cells was inhibited by cinnamic aldehyde, while LPS-induced COX-2 expression was also inhibited. TLR4-expressing HEK293 and RAW264.7 cells had their NF-κB activity lowered in response to LPS by applying cinnamic aldehyde. COX-2 activity generated by IL-1β in rat cerebral microvascular endothelial cells was inhibited by cinnamic aldehyde, with a minor effect (97). Naringin, a flavonoid molecule found in grapes and orange skin, reduces OS and inhibits NOX4 production (98). Genistein, an isoflavone molecule found in soya, activates caspase 9 and 3 and possesses anti-inflammatory properties (99). Resveratrol, a phenolic molecule found in peanuts, has been shown to reduce iNOS, IL-6, and TNF-α level (98). Preclinical investigations are currently being conducted on many phytochemicals to determine their anti-inflammatory and anti-cancerous effects on CRC. Their potential anti-CRC properties will need to be demonstrated through clinical investigations. Activation of initiator and executioner caspases by these bioactive chemicals can increase apoptosis and suppress cell cycle checkpoints,

among other processes, ultimately reducing tumor cell growth (100).

Conclusion

A wide range of phytochemicals is being investigated for their ability to treat cancer. Its potential anticancer effectiveness requires multiple mechanisms to be demonstrated. The phytochemicals of that group are commonly cited in Ayurvedic compositions. Polyphenols, flavonoids, terpenoids, carotenoids, proanthocyanidins, naphthoquinones, and cinnamic aldehyde are found in a wide range of plant species, including turmeric, garlic, grapes, carrots, nuts, *Lithospermum erythrorhizon*, and cinnamon, among others. Consequently, there is no new evidence of the effects of phytochemicals on colon cancer cells. The significance of phytochemical substances and how they can be used to cure cancer cells was investigated in this study. It was concluded that additional in vivo investigations on these phytochemical compounds are needed to demonstrate their anticancer activities.

Abbreviations

ADP-ribose: Adenosine di phosphate – ribose, AKT: Thymoma gene of AKR mouse. ANXA: Antiinflammatory protein, AP -1: Activating protein-1,Bak protein: BCL2 antagonist/killer (BAK) , Bax: (Bcl-2 Associated X-protein), Bcl-2/Bid: B-cell lymphoma 2/BH3 interacting domain, Bcl-xL: Bcell lymphoma-extra-large, BRAF mutations: B-Raf proto-oncogene serine/threonine-protein kinase, CCLs: Cancer cell lines, CDK4: cyclin-dependent kinase 4, CDK6: cyclin-dependent kinase 6, cGAS/STING : cyclic GMP–AMP synthase (cGAS)–stimulator of interferon genes (STING),CIMP: CpG island methylator phenotype, CIN: Chromosomal instability, COX: cyclooxygenase-2, CpG: unmethylated CG dinucleotides , Cyclin D:D-type cyclins, DLD-1:human colorectal carcinoma, DNA: Deoxy Ribonucleic acid, E- cadherin: epithelial-cadherin, EGCG: epigallocatechin gallate, EMT: epithelial to mesenchymal transition , ERK: extracellular signal-regulated kinases, 5- FU: 5-Flurouracil, FLA: focal laser ablation FLG: filaggrin gene, Fna C2: Fusobacterium nucleatum animalis clade 2, FOXO3a: orkhead box O-3a, Her2EGFR: Human epidermal growth factor receptor 2, IGF: Insulin-like growth factors, IGF-IR: Insulin-like growth factor-1 receptor, IL-6: interleukin-6, IL-8: interleukin-8, iNOS: inducible nitric oxide synthase, IκB kinase (IKK)I κB kinase, JAK pathway: Janus kinase-signal transducer and activator of transcription, JNK: c-Jun NH2-terminal kinase, KRAS: Kirsten rat sarcoma viral oncogene homologue, LOX: lipoprotein receptor-1, LPS-induced: LPS-induced expression of COX-2, COX-2: Cyclooxygenase-2, MACC1: Metastasis-associated in colon cancer-1, MAPK: mitogen-activated protein kinase, MMP-2: matrix metalloproteinase, MMP-2: Matrix metalloproteinase-2, MSC: mesenchymal stromal cells, MSI: Microsatellite instability, MSI-H: microsatellite instability-high, mTOR: mammalian target of rapamycin, MYC: gene, (NPS): Nanoparticles, NF-kB: Nuclear factor-kappa-B, NF-κB and MAPK: Nuclear factor-kappa-B Mitogen activated protein kinase, NO: Nitric Oxide, NOX4: NADPH oxidase 4, Nrf2 : nuclear factor-erythroid 2-related factor 2, ODC: ornithine decarboxylase, ODD : overall odds ratio, p21: wildtype activating factor-1/cyclin-dependent kinase inhibitory protein-1, p27: cell cycle regulator, p53: tumor suppressor gene p53, p-AKT: Phosphorylated AKT, PGE2: prostaglandin E, PI3K/: phosphoinositide 3-kinase, PI3K/AKT: phosphoinositide 3-kinase, POLE gene: Polymerase (DNA directed), epsilon, catalytic subunit, RAW264 7 cells macrophage cell line, Sirt6: Sirtuin 6 (SIRT6) is a member of the NAD + -dependent class III deacetylase sirtuin, Surviving STAT-3/-5: Signal transducer and activator of transcription , TGF-β: tumor necrosis factor alpha, TLR4: toll-like receptor 4 (TLR4), TNF -α : tumor necrosis factor alpha, Trail: tumor necrosis factor-related apoptosis-inducing ligand, VEGF: vascular endothelial growth factor,WHO: World Health organization, Wnt pathway: Wnt/β-catenin-dependent pathway and the β-catenin-independent pathway, Wnt/β: Wingless-related integration site (Wnt)/β-catenin.

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Author Contributions

Kalidoss Rajendran: wrote the manuscript, Sahana R. K: Edited the manuscript, Mariraj Murugan: collected the data, Muthukrishnan P: compiled the draft, Haania Ishaq: proof read and checked grammatical corrections, All authors revised and approved the final article.

Conflict of Interest

The authors declare that the work presented in this paper may not have been influenced by any of their known competing financial interests or personal relationships.

Ethics Approval

This is a review study, and none of the authors have conducted any experiments with human volunteers or animals.

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