DOI: 10.26599/FSHW.2026.9251048

Contents lists available at SciOpen

Food Science and Human Wellness

journal homepage: https://www.sciopen.com/journal/2097-0765

China Food Publishing Co.

Food and Medicine Homology Substances in Cancer Management

Yimao Wu[1,2,†], Ruowei Sun[3,†], Jintao Liang[4,†], Gokhan Zengin[5,*], Meng-Yao Li[1,6,*]

[1]*Shanghai Cancer Institute, Renji Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China*

[2]*Second Clinical Medical College, Guangdong Medical University, Guangdong, China*

[3]*Department of Clinical Medical Sciences, Kangda College of Nanjing Medical University, Nanjing, China*

[4]*First Clinical Medical College, Guangdong Medical University, Zhanjiang, China*

[5]*Department of Biology, Science Faculty, Selcuk University, Konya, Turkey*

[6]*Shanghai Key Laboratory of Cancer Systems Regulation and Clinical Translation, Shanghai Jiading District Central Hospital, Shanghai, China*

ABSTRACT: Cancer remains a formidable global health burden, with conventional chemotherapy often limited by factors such as systemic toxicity, drug resistance, and challenges related to patient adherence. In this context, food and medicine homology (FMH) substances, rooted in the principles of Traditional Chinese Medicine, offer a distinctive therapeutic paradigm by integrating pharmacological efficacy with nutritional value. Defined by their low toxicity and suitability for long-term use, these substances present a compelling avenue for the development of safer and more integrative oncology strategies. This review provides the first systematic and comprehensive analysis of the role of these substances across the full spectrum of pan-cancer management, encompassing tumor prevention, adjunctive therapy, and postoperative nutritional support. At the mechanistic level, we elucidate their pleiotropic modes of action, including antioxidant activity through free radical scavenging and metal chelation, anti-inflammatory effects via modulation of key signaling pathways, immune enhancement, and direct antitumor activities. In addition, these substances function as effective adjuvants to chemotherapy and radiotherapy, enhancing therapeutic efficacy, reducing adverse effects, and helping to overcome drug resistance. By integrating molecular evidence, preclinical findings, and emerging clinical insights, this review bridges traditional knowledge with contemporary science, thereby laying a solid foundation for the clinical translation of these substances. It not only fills a critical gap in the systematic understanding of their application across diverse cancer types but also outlines a comprehensive framework for the development of safer and more effective integrative oncology strategies.

Keywords: Food and medicine homology, Pan-cancer, Cancer prevention, Cancer adjuvant therapy, Nutritional support, Clinical research

1. Introduction

Cancer poses a significant social, public health, and economic challenge globally. According to recent data from the International Agency for Research on Cancer (IARC), part of the World Health Organization (WHO)[1], cancer is the world's second leading cause of death, accounting for approximately one-sixth of all fatalities; this figure rises to nearly one-quarter when considering deaths related to non-communicable diseases (NCDs)[1,2]. The progression of cancers from precancerous lesions to malignant tumors is influenced by multiple factors, presenting serious threats to human health. Presently, surgery[3], radiotherapy, chemotherapy[4], targeted therapy[5], and immunotherapy[6] are the primary strategies employed in cancer treatment[7]. However, these methods have notable limitations in clinical practice,

†Authors contributed equally to this work.
***Corresponding author**
gokhanzengin@selcuk.edu.tr; limy@sioc.ac.cn

Received 1 December 2025
Received in revised from 23 December 2025
Accepted 16 March 2026

including poor responsiveness in some patients, treatment-related toxicities that significantly impact quality of life[8], and increasing instances of tumor resistance[9] that often result in treatment failure[10,11]. Consequently, the exploration of novel therapeutic or adjuvant approaches that can enhance the efficacy of radiotherapy and chemotherapy[12], mitigate toxic side effects[13], and overcome resistance has become an urgent scientific priority in contemporary oncology research[14–16].

The concept of “food and medicine homology” (FMH) represents a profound ancient wisdom that has been practiced in China for thousands of years, offering a promising new approach to address the challenges mentioned above[16]. As early as Huangdi Neijing, it was recorded that “medicine removes the disease, food follows accordingly,” which emphasized the synergy between food and medicine. In terms of cancer treatment, there are also precedents in ancient medical texts. A notable example is found in Zhang Zhongying's Jinkui Yaolue from the Eastern Han Dynasty, which describes the use of "Shengjiang Banxia Tang" to treat "a hard mass below the heart," a condition analogous to abdominal tumors and related symptoms in modern medicine. Both ginger and pinellia in this formula are recognized as FMH substances, providing historical evidence for their application in tumor-related conditions. Recently, Prof. Cong refined and articulated the definition of FMH substances, characterizing them as edible materials that possess both pharmacological activity and nutritional value, with the key attribute that their bioactive components are nontoxic and amenable to long-term human consumption[17]. This provides a theoretical basis for their application in long-term cancer prevention, treatment, and rehabilitation. Additionally, the rapid advancement of modern life sciences technologies, including spatial transcriptomics, single-cell multi-omics, organ models, and metabolomics, provides substantial technical support for elucidating the multi-component, multi-target anti-tumor mechanisms of FMH substances at the cellular, molecular, and spatiotemporal levels[18]. In summary, the deep historical foundation, clear theoretical definition, and strong modern technological support collectively establish a solid foundation for systematic modern scientific research on the anti-tumor effects of FMH substances.

The utilization of FMH substances in cancer prevention and treatment presents several significant advantages. Firstly, their widespread availability, cost-effectiveness, and high accessibility ensure that a majority of the population can benefit in the long term. Secondly, when compared to chemical drugs, FMH substances exhibit milder effects and lower toxicity, leading to improved patient prognosis and quality of life, thereby enhancing adherence. Mechanistically, these substances facilitate multi-target, multi-pathway synergistic regulation. their multi-component synergy effectively mitigates or delays the onset of tumor resistance. Notably, their intervention spans the entire spectrum of tumor progression: from pre-progression prevention, through direct or adjuvant treatment during progression, to post-treatment recovery, nutritional support, and immune system reconstruction. These unique advantages offer novel insights into the development of low-toxicity treatments for tumors[19].

While the potential of food-medicine homology substances in oncology is increasingly recognized, systematic reviews across multiple cancer types remain scarce. To address this gap, we comprehensively evaluate the scientific rationale and application value of these substances in cancer prevention and treatment.

Focusing on their dual pharmacological and nutritional functions, this review examines three key areas, namely tumor prevention, direct anti-tumor therapy, and adjuvant radiotherapy and chemotherapy. We cover molecular mechanisms underlying tumor growth inhibition as well as adjuvant benefits, including treatment sensitization, toxicity reduction, and reversal of drug resistance. Relevant clinical evidence is also analyzed to assess translational potential. To enhance clinical applicability, we categorize the application of these substances into three functional stages. The first stage is tumor prevention, which targets oxidative stress and chronic inflammation to block neoplastic initiation. The second stage encompasses direct and adjuvant treatment, aiming to suppress tumor growth, enhance therapeutic sensitivity, and overcome resistance. The third stage focuses on post-treatment recovery, prioritizing immune reconstruction and systemic homeostasis. It should be noted that the scope of this review extends beyond the officially published catalog of food and medicine homology substances. While this catalog serves as an authoritative benchmark, it is inherently subject to ongoing updates and continuous refinement. Accordingly, our discussion also incorporates three additional categories: firstly, substances that are not currently included in the catalog but strictly adhere to Prof. Cong's definition of FMH substances; secondly, materials explicitly identified in the academic literature as possessing such dual attributes; and thirdly, a select group of common foods widely recognized by the scientific community for their cancer-preventive potential. Through this expanded scope, the review aims to offer a more comprehensive and inclusive perspective on the application of medicinal and edible substances in oncology.

2. Application of FMH Substances in Tumor Prevention

2.1 Free Radical Scavenging and Antioxidant Processes

2.1.1 Mechanistic Elucidation

Free radicals, particularly reactive oxygen species (ROS) and reactive nitrogen species (RNS), are continuously generated in the body Under normal human metabolism, environmental pollution, radiation, and other factors[20]. Oxidative stress occurs When the accumulation of free radicals surpasses the body's clearance capacity. This stress can directly damage cellular DNA, proteins, and lipids, leading to gene mutations and cellular dysfunction. These events represent one of the key initiating steps in tumorigenesis[21,22]. Regarding the anti-cancer effects of antioxidants, there are still relevant controversies, which is a limitation of this article. However, for the sake of comprehensiveness, relevant content has still been compiled here.

2.1.2 Roles of FMH Substances

Numerous FMH substances are abundant in natural antioxidant components, which manifest their effects through various mechanisms. **Table 1** provides a comprehensive summary of the three primary antioxidant mechanisms associated with these substances. It includes representative materials, active components, action pathways, and related cancer types.

Table 1. Antioxidant Mechanisms of FMH Substances and Representative Examples Insertion Context with Descriptive Sentence

Active Component(s)	Source Plant(s)	Cancer Type(s)	Experiment Type(s)	Mechanism	Ref.
Eugenol	Clove	Leukemia Breast cancer Cervical cancer Colorectal cancer Melanoma Gastric cancer Lung cancer Prostate cancer Osteosarcoma Oral cancer	Cell (HL-60, MCF-7, HeLa, HT-29) Animal (Rats, Mice)	Dual nature: At low concentrations, antioxidant and free radical scavenger; at high concentrations, pro-oxidant inducing apoptosis, inhibits NF-κB, TNF-α	[23]
Curcumin	Turmeric	Cervical cancer	Cell (HeLa, SiHa, CaSki, C33A) Animal (BALB/c, C57BL/6, Swiss albino, NOD-SCID mice)	Induces ROS generation: Causes DNA damage, ER stress, mitochondrial apoptosis, inhibits COX-2 and NF-κB	[24]
Epigallocatechin gallate	Green tea	Prostate cancer Breast cancer Lung cancer Bladder cancer	Clinical (Prostate cancer pre-surgery) Cell (Prostate, Breast, Lung, Bladder)	Scavenges free radicals and activates Nrf2: Enhances antioxidant enzymes (SOD, CAT, GST) to protect normal cells and suppress tumor initiation	[25]
Daidzein	Soybean	Prostate cancer Breast cancer	Prostate cancer (Abiraterone-resistant) Breast cancer (early stage)	Scavenges free radicals, activates antioxidant enzymes (CAT, SOD, GPx)	[26]
Genistein	Soybean	Breast cancer Endometrial cancer Pancreatic cancer Colorectal cancer	Cell (Breast, Endometrial, Pancreatic, Colorectal)	Inhibits lipid peroxidation, activates Nrf2: Suppresses hydroxyl radical-induced lipid peroxidation, enhances cell antioxidant capacity	[27]
Carnosic acid	Rosemary	Leukemia Colorectal cancer Breast cancer Lung cancer Oral cancer Melanoma	Cell (HL-60, Caco-2, MCF-7) Animal (Xenograft, Hamster cheek pouch model)	Activates Nrf2/ARE antioxidant pathway: Induces Nrf2 protein accumulation, activates antioxidant enzymes (GPX1, SOD1), induces ROS-mediated mitochondrial apoptosis	[28]
Polysaccharides	Ganoderma lucidum Panax ginseng Lycium barbarum	Melanoma Breast cancer	Animal models (Melanoma, Breast cancer)	Activates immune cells (macrophages), enhances antioxidant enzyme activity to suppress tumors	[29]
Resveratrol	Grapes Peanuts Pistachios Berries	Colorectal cancer Prostate cancer Multiple myeloma	Clinical (Colorectal, Prostate, Myeloma) Animal models	Dual role: Antioxidant and pro-oxidant at low doses in tumors; induces autophagy by increasing oxidative stress biomarkers	[30]
[6]-Gingerol	Ginger	Bladder cancer	Cell (5637)	Pro-oxidant activity: Increases ROS, disrupts mitochondrial membrane potential, activates Caspase cascade and MAPK pathways, inducing apoptosis	[31]
Lycopene	Tomato Watermelon Guava Pink grapefruit	Gastric cancer	Cell (AGS)	Reduces ROS in cells and mitochondria, inhibits EGFR/Ras/ERK, p38 MAPK, NF-κB, and COX-2 expression, suppresses proliferation and induces apoptosis	[32]

(1) Direct Scavenging of Free Radicals

Direct elimination serves as the primary defense mechanism in antioxidant protection. This principle posits that antioxidant components found in food and medicinal substances, often abundant in active groups like phenolic hydroxyl groups, can swiftly donate an electron or hydrogen atom to unstable free radicals. This donation facilitates pairing and stabilization, effectively neutralizing the detrimental activity of these radicals and halting their chain reactions. The process metaphorically "sacrifices" itself to shield vital biological molecules within the body, such as DNA, proteins, and lipids, from potential harm. ROS, encompassing hydroxyl radicals, superoxide anion radicals, and hydrogen peroxide, are typical byproducts of cellular respiratory chain reactions. An overabundance of ROS can inflict cellular damage, resulting in protein and DNA degradation and contributing to various diseases[33–35]. Consequently, assessing the capability to scavenge hydroxyl radicals holds significant practical value. In this context, certain foods and medicinal substances have garnered attention, most notably clove, turmeric, and tea polyphenols, due to their demonstrated proficiency in scavenging.

Clove, the aromatic flower bud of Myrtaceae family, is botanically known as Syzygium aromaticum. Chaeib et al. analyzed the chemical composition of clove and identified eugenol (76.8%), β-caryophyllene (17.4%), α-humulene (2.1%) and eugenyl acetate (1.2%) as the main constituents[36]. Kumar Y et al. evaluated the antibacterial activity of clove at 1000, 1500 and 2000 ppm. Liu H et al. investigated the anticancer activities of clove in HT-29 cells and found that the ethyl acetate extract of clove (EAEC) and oleanolic acid (OA) from clove exhibited cytotoxicity against several human cancer cell lines[37]. The high phenolic content gives it a strong antioxidant capacity (AOC), including ferric reducing antioxidant power (FRAP), Trolox equivalent antioxidant capacity (TEAC) and oxygen radical absorbance capacity (ORAC) [22]. In tumor prevention, the aromatic hydroxyl group of eugenol acts as a potent free radical terminator. Many of the simple phenolic compounds have so far been proved very effective in seizing cancer cells growth due to their ability to induce cell cycle arrest, modulate reactive oxygen species (ROS) levels, hinder oncogenic signaling cascades that induce angiogenesis and apoptosis, and enhance the expression of tumor suppressor proteins such as p53[38]. Furthermore, preventing chronic inflammation is crucial to block tumorigenesis; normally, oxidized LDL (ox-LDL) binds to the LOX1 receptor and triggers a PCSK9-LOX1 positive feedback loop. This loop activates carcinogenic inflammatory cascades (IL-6, IL-8, and IL-1). By acting as a strong antioxidant, eugenol prevents LDL oxidation, thereby intercepting this inflammatory-driven cancer initiation at its source[39]. This antioxidant capacity also makes clove potentially useful for preventing therapy-induced malignant progression. For example, cisplatin combined with eugenol can specifically target ovarian cancer stem cells (OCSCs), preventing the acquisition of cisplatin resistance in ovarian cancer treatment. The synergistic mechanism of clove extract and cisplatin to target ovarian cancer stem cells and preventing drug resistance is shown in **Figure 1**. While genotoxic stress from cisplatin alone paradoxically enriched OCSCs and promoted a malignant resistant state, eugenol intercepted this oncogenic adaptation, significantly preventing the early stages of tumor cell proliferation and invasion in both in vitro and in vivo

models. The combination markedly reduced $CD44^+$ and $ALDH^+$ OCSC populations and suppressed their self-renewal capacity. Furthermore, eugenol antagonized the cisplatin-induced upregulation of drug efflux pumps, leading to increased intracellular cisplatin accumulation and efficacy. This was achieved through the inhibition of the NOTCH signaling pathway and downregulation of the key stemness factor Hes1. In SKOV3 and OV2774 cell lines, this combinatorial strategy effectively augmented the antitumor effect of cisplatin by targeting OCSCs, inhibiting NOTCH/Hes1 signaling, and reducing the expression of drug efflux pumps[40,41].

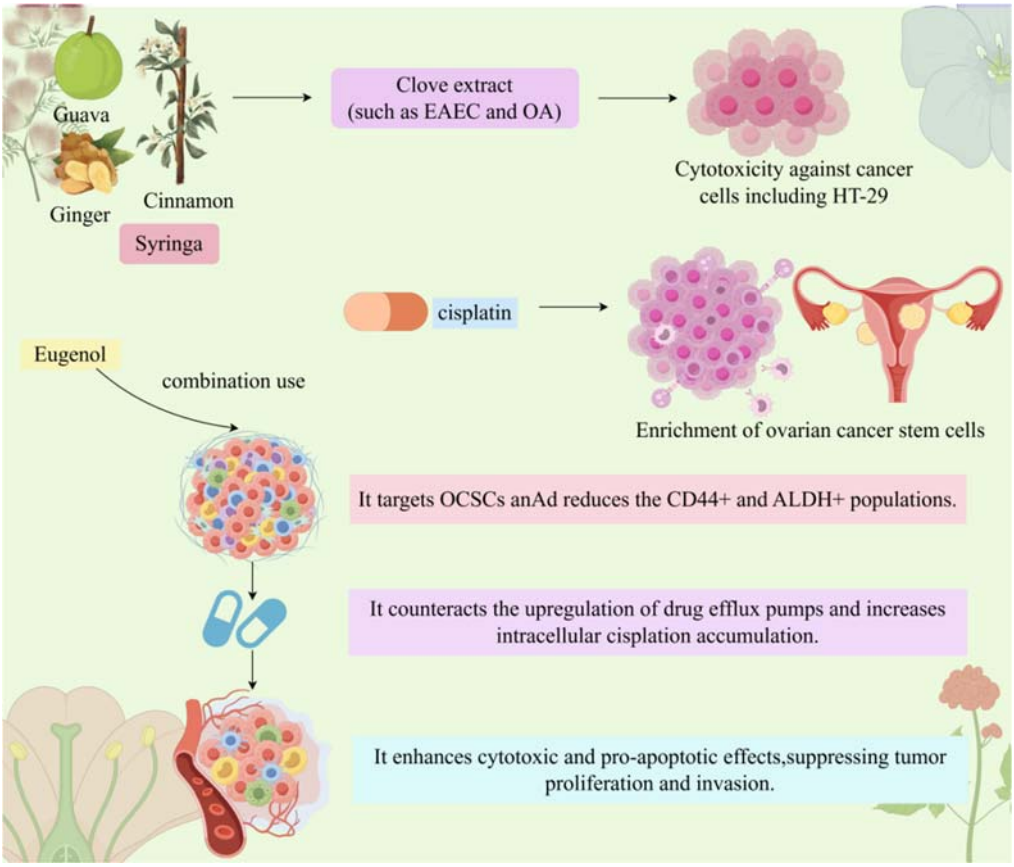

Figure 1. Clove Extract Enhances Cisplatin Efficacy by Targeting Ovarian Cancer Stem Cells and Reversing Drug Resistance. This figure illustrates the synergistic anti-ovarian cancer effect of clove extract (EAEC, OA) combined with cisplatin. Cisplatin alone enriches ovarian cancer stem cells (OCSCs) and induces drug resistance. Clove extract targets OCSCs, reducing $CD44^+$ and $ALDH^+$ OCSC populations and inhibiting their self-renewal ability. It also counteracts cisplatin-induced upregulation of drug efflux pumps, increasing intracellular cisplatin accumulation. Additionally, clove extract exhibits direct cytotoxicity against cancer cells and enhances cisplatin's cytotoxic and pro-apoptotic effects, significantly suppressing tumor proliferation and invasion. The combination of clove extract and cisplatin achieves synergistic anti-tumor efficacy by targeting OCSCs and reversing cisplatin resistance.

Curcumin, the main active ingredient extracted from turmeric (Curcuma longa), is widely used as a food additive and cosmetics. It has strong antioxidant, anti-inflammatory, and antimicrobial properties by effectively scavenging ROS[42]. As a free radical scavenger and hydrogen donor, curcumin exhibits both pro-oxidant and antioxidant activities and can chelate metal ions such as iron and copper, especially for iron[42,43]. Despite its low bioavailability, curcumin has broad biological activity and has shown potential in clinical trials for various diseases including multiple myeloma, pancreatic cancer[43]. In the context of prevention, curcumin serves as a chemopreventive agent that regulates signaling pathways like NF-κB and TGF-β to suppress the initial malignant transformation of normal cells and counteract the early pro-tumorigenic inflammatory environment[43]. Studies have also found that curcumin can inhibit

TNFα-induced LOX-1 expression and intracellular ROS production, prevent IκBα degradation and nuclear translocation of NF-κB, and promote eNOS phosphorylation and nitric oxide production to reduce oxidative stress and endothelial inflammation[44]. Its β-diketone structure gives it a strong ability to chelate metals, thereby inhibiting the Fenton reaction ($Fe^{2+} + H_2O_2 \rightarrow Fe^{3+} + \bullet OH + OH^-$) and reducing free radical generation[45]. Currently, numerous clinical trials have addressed the role of curcumin in advanced cancer treatment and supportive care. Following encouraging results in phase I–II trials, multiple phase III trials are underway for different indications to assess direct anti-cancer effects and novel formulations are being developed to improve bioavailability and enhance its use in supportive cancer care[44].

(2) Enhancement of the Body's Endogenous Antioxidant Enzyme System

The body's defense mechanisms against oxidative stress can be divided into two types: one is the direct elimination of ROS molecules; the other, more central pathway is to enhance the endogenous antioxidant enzyme system. This system activates related signaling pathways (such as Nrf2/ARE) and upregulates the expression and activity of a series of antioxidant enzymes, including superoxide dismutase (SOD), catalase (CAT), and glutathione peroxidase (GPx), thereby achieving body-driven, sustained, and efficient "endowed" defense[46,47]. Oxidative stress is an important pathophysiological basis in cancer. In cancer, elevated ROS induces genomic instability and drives tumor progression [48]. Both scenarios reflect an imbalance between pro-oxidation and anti-oxidation systems, involving dysregulation of redox-sensitive pathways such as Nrf2 and NF-κB, along with alterations in mitochondrial function that enhance adaptability in CSCs while increasing susceptibility in neurons[49,50]. Therefore, the NIK-NF-κB-JAG1-Notch1 axis can establish a tumor microenvironment that regulates the CSC population in basal-like breast cancer subgroups. Thus, targeting core pathways such as Nrf2/ARE to empower the body's own antioxidant capacity provides a potential strategy for alleviating oxidative damage in these diseases.

Activation or upregulation of superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and other enzymes in the body [51]. ROS scavenging is mediated by a variety of antioxidant enzymes, including SOD, CAT, ascorbate peroxidase (APx), monodehydroascorbate reductase (MDHAR), dehydroascorbate reductase (DHAR), glutathione reductase (GR), GPx, and peroxiredoxins (PRX) [47]. Elevated levels of reactive oxygen species (ROS) lead to genomic instability in cancer stem cells (CSCs) and promote tumor initiation and progression. Both situations involve disruption of the delicate balance between pro-oxidant and antioxidant systems, leading to chronic oxidative stress. Notably, CSCs and neurons exhibit alterations in redox-sensitive signaling pathways, including Nrf2 and NF-κB, which affect cell survival, proliferation, and differentiation. Mitochondrial dynamics further clarify these differences: enhanced CSC function supports adaptability and survival, whereas neuronal damage increases susceptibility. Understanding these shared mechanisms of redox imbalance induced by oxidative stress may provide insights for developing interventions that target hallmarks of aging and potentially alleviate or prevent both cancer and NDDs[48]. Unlike the "direct scavenging" passive defense, this is a more advanced and long-lasting "enhancement" defense strategy. These food and medicinal substances do not directly act as "targets" of free radicals but

activate endogenous antioxidant signal transduction pathways in human cells, upregulate the gene expression and activity of a series of endogenous antioxidant enzymes and phase II metabolic enzymes, which is equivalent to changing from "giving fish" to "teaching fishing", so as to improve the body's long-term resistance to oxidative stress.

The Nrf2/ARE signalling pathway is the central defense mechanism against oxidative and chemical stress. Under resting conditions, transcription factor Nrf2 binds to its cytoplasmic repressor Keap1 and is rapidly degraded through ubiquitin-proteasome pathway[52–54]. After ingestion of active components of FMH such as tea polyphenols or under oxidative stress, conformational changes in Keap1 result in release and stabilization of Nrf2, which then translocates into nucleus, binds antioxidant response elements (AREs) within genome, and initiates transcription and expression of multiple endogenous antioxidant enzyme genes including SOD, CAT, GPx and heme oxygenase-1 (HO-1) [55,56]. Among them, SOD serves as a first line of defense by converting superoxide anion ($O_2^{\bullet -}$) to hydrogen peroxide (H_2O_2); CAT further degrades H_2O_2 to water and oxygen; GPx reduces H_2O_2 and lipid hydroperoxides in presence of reduced glutathione (GSH), protecting cellular membranes; and HO-1 provides both antioxidative and anti-inflammatory effects, together forming a coordinated defense network[57].

China has a tea cultivation history of thousands of years and is the first country to discover, harvest, and consume tea. In recent years, large-scale cultivation has been carried out in tropical and subtropical regions. More than 400 types of tea belonging to 14 genera are cultivated in our native region. The six main types of Chinese tea are green tea, black tea, oolong tea, yellow tea, white tea, and dark tea. Tea contains polysaccharides, polyphenols, chlorophyll, β-carotene, various vitamins, caffeine, flavonoids, pyrroloquinoline quinone, proteins, amino acids, minerals such as calcium, iron, manganese, copper, magnesium, etc. Tea polyphenols (TPs) refer to the collective name of polyphenolic compounds contained in tea, which are rich in green tea and are the most abundant soluble components that bring health benefits to humans[58], including EGCG, ECG, EGC, and EC, among which epigallocatechin gallate (EGCG) is the most abundant[59]. TPs have strong antioxidant activity, and the reducing power of EGCG is about 100 times that of L-ascorbic acid. In addition, TPs also have antitumor, hypoglycemic, antiviral, anti-radiation, and antibacterial effects and can be used as adsorbents, so they are widely used in food processing and other fields[59]. Tea is a beverage consumed worldwide, and its health benefits are mainly attributed to its high content of polyphenols, especially tea polyphenols (TPs), accounting for 20%–30% of the dry weight. Among them, EGCG has the strongest biological activity, with significant antioxidant, anti-inflammatory, and antitumor effects[59–61].

Theaflavins (TFs), unique polyphenols in black tea, mainly theaflavin-3,3'-digallate, have anticancer, antioxidant, anti-inflammatory and neuroprotective activities[62–64]. The activation of Nrf2/ARE signaling pathway is One of the core mechanisms of tea polyphenols[65]. Under resting conditions, Nrf2 binds to Keap1 and is targeted for degradation[66,67]; when exposed to active components such as tea polyphenols, Keap1 undergoes a conformational change that facilitates nuclear translocation of Nrf2 and binding to AREs, thereby

initiating the expression of multiple endogenous antioxidant enzymes and phase II detoxification enzymes including SOD, CAT, GPx and HO-1, which systematically enhance the body's antioxidant defense capacity[67,68]. In addition to the Nrf2 pathway, EGCG can also inhibit the NF-κB pathway and MMP-9 activity, alleviate hyperglycemia-induced retinopathy and inhibit the formation of advanced glycation end products (AGEs). **Figure 2** shows the mechanism by which tea polyphenols enhance antioxidant defense and inhibit tumor progression through the Nrf2/ARE pathway. Due to their multiple roles in regulating oxidative stress, inflammation and metabolic pathways, tea polyphenols are considered functional components with potential anti-aging effects and the ability to delay age-related diseases[69,70].

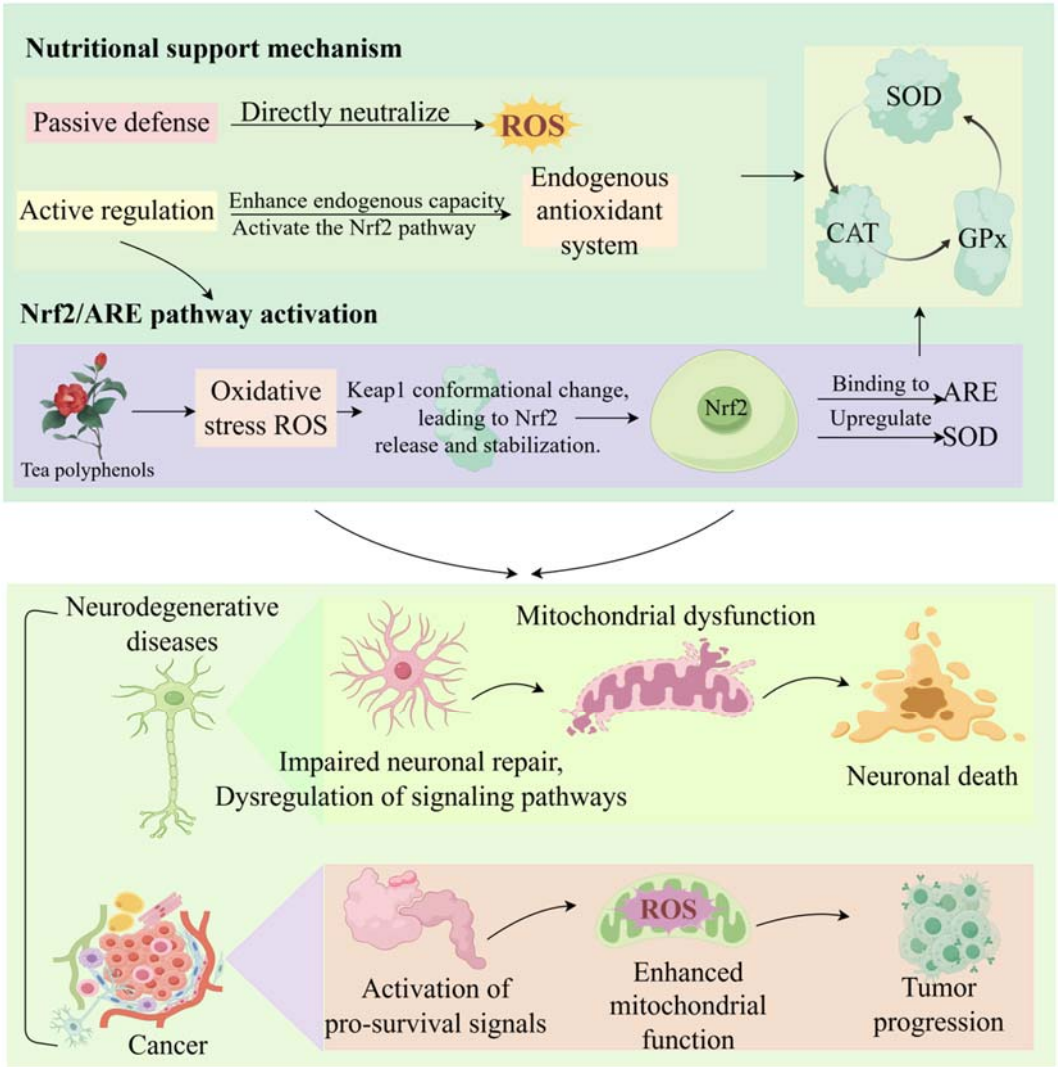

Figure 2. Tea Polyphenols Activate Nrf2/ARE Pathway to Enhance Antioxidant Defense and Inhibit Tumor Progression. This figure outlines the dual antioxidant defense mechanism of tea polyphenols and their anti-tumor effects. Under oxidative stress, tea polyphenols exert passive defense by directly neutralizing ROS. More importantly, they initiate active regulation: oxidative stress or tea polyphenols induce conformational changes in Keap1, leading to the release and stabilization of Nrf2. Activated Nrf2 translocates to the nucleus, binds to antioxidant response elements (AREs), and upregulates the expression of endogenous antioxidant enzymes (SOD, CAT, GPx). This enhances cellular antioxidant capacity, alleviating mitochondrial dysfunction and neuronal damage associated with neurodegenerative diseases. In tumor cells, tea polyphenols inhibit the activation of pro-survival signals and enhanced mitochondrial function induced by ROS, thereby suppressing tumor progression.

Human pharmacokinetic studies have shown that a daily intake of 700 mg theaflavins can achieve maximum plasma concentration and improve bioavailability[63,71,72]. Tea polyphenols are widely present in green tea, including EGCG, ECG, EGC, and EC, among which EGCG is the most abundant and biologically

active[67,68,73,74]. EGCG has strong antioxidant and anti-inflammatory effects and can inhibit MMP-9 activity and the NF-κB signaling pathway to alleviate hyperglycemia-induced retinal lesions and suppress AGEs formation[69]. As common dietary components, polyphenols can be oxidized into quinone metabolites, interact with Keap1, activate the Nrf2 signaling pathway, and upregulate intracellular antioxidant enzymes to enhance the body's defense against oxidative stress[67]. Ageing is a fundamental physiological process influenced by multiple biological and genetic pathways and it represents the major driver of age-related diseases such as diabetes, osteoporosis, cancer and neurodegenerative disorders including Alzheimer's and Parkinson's disease. Several mechanisms related to ageing have been intensively studied In modern research and significant progress has been made in the treatment of age-associated diseases. For effective and long-term interventions, nutritional therapy, especially with dietary polyphenols from natural sources, has been recognized. These dietary polyphenols (apigenin, baicalin, curcumin, EGCG, kaempferol, quercetin, resveratrol, and theaflavins) [75–77] target specific molecular and genetic pathways commonly involved in age-related diseases, including mitogen-activated protein kinase (MAPK) signalling, ROS production, NF-κB signalling in B cell activation, metal chelation, c-Jun N-terminal kinase (JNK) activity, and inflammation[22,78]. Polyphenols can slow down the ageing process and contribute to combatting age-related diseases, as demonstrated by clinical trials of certain dietary polyphenols in various conditions associated with ageing. In this context, polyphenols provide new insights into delaying ageing and reducing the incidence of classic age-associated diseases.

Cardamom, a spice derived from the seeds of plants in the Elettaria genus (specifically Elettaria cardamomum), is not only an important culinary ingredient but also holds significant medicinal value. Its potential extends beyond traditional uses, with Modern scientific research revealing its multifaceted role in "pan-cancer" prevention and treatment. The mechanisms involved form a comprehensive network that spans from prevention to adjunctive therapy. Chronic inflammation and oxidative stress are common underlying factors in the initiation and progression of malignant tumors. Cardamom's hexane and methanol extracts, rich in polyphenols, flavonoids, and terpenoids, have demonstrated significant free radical scavenging and metal-chelation activity in vitro. These compounds provide effective protection for cellular DNA, proteins, and lipids against oxidative damage, thereby establishing a primary defense system at the molecular level[79]. Furthermore, cardamom exhibits remarkable systemic anti-inflammatory properties. In lipopolysaccharide (LPS)- or carrageenan-induced inflammation models, cardamom significantly downregulated the expression of key proinflammatory mediators including COX-2, TNF-α, IL-6 and NF-κB[80]. It also reduced nitric oxide production by inhibiting inducible nitric oxide synthase, providing a molecular basis for blocking malignant transformation from chronic inflammation to cancer[81]. In addition to its underlying antioxidant and anti-inflammatory effects, cardamom further exerted its anticancer efficacy through direct intervention in tumor cell fate and immune surveillance regulation. green cardamom extract was confirmed as an effective apoptosis inducer that directly drove programmed tumor cell death via modulating apoptotic gene and protein expression with significant inhibition of tumor growth in a preclinical Ehrlich solid tumor model[82]. Notably,

it not only showed a synergistic antitumor effect but also increased mean survival time of tumor-bearing animals when combined with cyclophosphamide, suggesting its potential in chemosensitization.

In addition, its auxiliary value in tumor therapy is also reflected in its remarkable "toxicity reduction and efficiency enhancement" effect. Because of its strong reducing ability, it can effectively increase the levels of endogenous antioxidant defense systems (such as SOD, CAT, glutathione), so as to reduce oxidative damage caused by chemotherapy and protect liver and kidney functions[83,84]. Its active components such as cardamomin and indole-3-carbinol have been identified as potential intervention factors for epigenetics and overcoming drug resistance of tumor cells, providing new natural source solutions for clinical chemotherapy resistance problems[85]. In conclusion, cardamom with its multi-component and multi-target characteristics constructs a comprehensive anticancer network covering prevention (antioxidant/anti-inflammatory), intervention (induction of apoptosis/immunomodulation) and adjuvant therapy (reduction of toxicity/enhancement of efficacy/overcoming resistance). Its safety as part of daily diet provides a solid foundation for clinical application as cancer chemopreventive agent and therapeutic adjuvant. Future translational medical research should focus on isolation and identification of key active components, deeper analysis of signaling pathways and conduction of rigorous clinical trials to confirm effective dose and therapeutic efficacy in humans so that the great potential of this ancient spice can be translated into tangible clinical benefits.

The health benefits of cruciferous vegetables, such as broccoli, cabbage, cauliflower and kale are mainly attributed to their key active compound—sulforaphane. Sulforaphane is not directly present in these vegetables but is formed from its precursor glucosinolate, glucoraphanin, which is converted by the enzyme myrosinase when the vegetables are chewed and digested. The mechanism by which sulforaphane derived from cruciferous vegetables exerts antioxidant and multiple biological effects is shown in **Figure 3**. Studies have demonstrated that sulforaphane is one of the most potent Nrf2 signaling pathway activators among natural products. It activates Nrf2 through direct modification of specific cysteine residues on Keap1 protein, resulting in stabilization and release of Nrf2, which significantly upregulates a series of endogenous antioxidant enzyme expressions including SOD (superoxide dismutase), CAT (catalase), GPx (glutathione peroxidase) and HO-1 (heme oxygenase-1). This process enhances the body's overall antioxidant defense capacity[86–88]. In addition, sulforaphane is one of the most effective known natural anti-cancer compounds. It has a broad spectrum of anti-cancer activities against various cancer cells including breast cancer, prostate cancer, colon cancer, skin cancer, gastric cancer, bladder cancer and chronic myeloid leukemia. In addition, it also has potential anti-inflammatory, antihypertensive, cardioprotective, antidiabetic and anti-obesity effects as well as improving schizophrenia and autism symptoms. Recent studies have found that sulforaphane can inhibit the novel coronavirus, including the Delta and Omicron variants[89]. In terms of mechanism of action, sulforaphane can fight ferroptosis through AMPK-mediated Nrf2 activation, which plays an important role in diabetic cardiomyopathy[90]. However, Nrf2 exhibits a dual-edged sword effect; while it is beneficial in early

prevention, it may contribute to chemoresistance in advanced stages of cancer. Thus, the use of Sulforaphane requires careful consideration[91].

Currently, clinical research on Sulforaphane remains insufficient. A randomized controlled trial has suggested that Sulforaphane is a promising and safe therapeutic agent for various types of cancer. However, the study's methodological heterogeneity and clinical variability preclude the possibility of conducting a meta-analysis. Further, more in-depth clinical studies are needed to better understand its potential[92]. Another article highlights that the pharmacokinetic limitations of Sulforaphane, as well as individual patient variability, present significant challenges for its clinical translation[93].

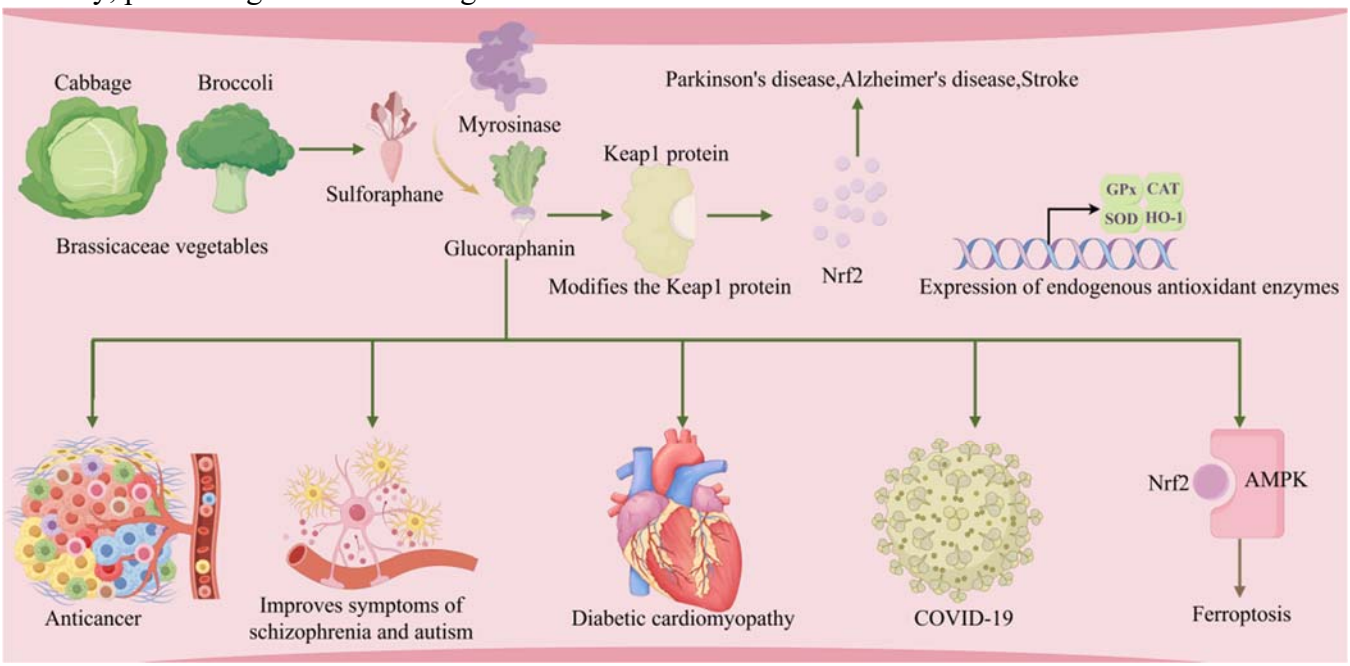

Figure 3. Sulforaphane from Cruciferous Vegetables Activates Antioxidant Defense and Exerts Multi-Potential Biological Effects. This figure outlines the mechanism of sulforaphane, a bioactive component in cruciferous vegetables (cabbage, broccoli), and its diverse biological functions. Sulforaphane is formed from glucoraphanin via myrosinase catalysis during vegetable chewing or digestion. It directly modifies cysteine residues on Keap1 protein, leading to the release and stabilization of Nrf2. Activated Nrf2 translocates to the nucleus, binds to antioxidant response elements (AREs), and upregulates the expression of endogenous antioxidant enzymes (SOD, HO-1, GPx, CAT), enhancing cellular antioxidant capacity. Additionally, sulforaphane activates the AMPK pathway to inhibit ferroptosis. These actions contribute to its multi-potential effects, including anticancer activity, improvement of symptoms in Parkinson's disease, Alzheimer's disease, stroke, schizophrenia, and autism, alleviation of diabetic cardiomyopathy, and inhibitory effects on COVID-19.

(3) Metal Ion Chelation

Chelating metal ions such as iron and copper to prevent their catalytic generation of additional free radicals represents a “preventive” antioxidant strategy. The aim is not to directly attack the free radicals themselves, but to remove the “catalyst” that generates them. metal ion homeostasis imbalance is one of the core pathological mechanisms underlying cancer initiation and progression, playing an important role in oxidative stress, signal transduction, and immune regulation. Iron metabolism disorders directly affect tumor cell proliferation[94]. Studies have shown that lysosomal acidification damage leads to iron depletion, which in turn alters mitochondrial metabolism and HIF signaling pathways, ultimately inhibiting cell proliferation. At the same time, calcium ion overload and ROS bursts in the tumor microenvironment constitute important features of immunosuppressive microenvironments. In response to this mechanism, metal ion chelation

strategies show promising anticancer potential. Plant-derived natural small molecules provide abundant lead compounds for regulating metal homeostasis. The introduction of nanotechnology further improves the precision of treatment[95] with the development of nanoparticles that combine both ROS scavenging and Ca^{2+} chelation functions[96]. The design of these nanoparticles can be directly applied to cancer therapy. The most groundbreaking advances come from the immune modulation aspect. Metallion-chelating nanostructures can activate the NLRP3 inflammasome and Ca^{2+}–NF-κB pathways, remodel dendritic cell function, reverse the immunosuppressive microenvironment, and thus restore the sensitivity of drug-resistant tumors to PD-1/PD-L1 inhibitors[97]. This represents a translation of metal ion regulation from basic mechanism research to practical cancer therapeutic strategies, providing a new paradigm for cancer prevention and treatment.

Soybean (Glycine max) as an important FMH substance, has multi-target biological potential in the prevention and treatment of cancer. The multi-target anticancer mechanism of soy isoflavones and rosemary active ingredients are shown in **Figure 4**. The core active ingredient, isoflavones (mainly genistein and daidzein), not only acts through the classic estrogen receptor regulation pathway but also chelates metal ions via its phenolic hydroxyl structure, inhibiting the Fenton reaction at its source and thereby exerting a "preventive" antioxidant and anticancer effect[98]. Large-scale prospective studies have confirmed that higher dietary intake of isoflavones can reduce the risk of various cancers such as breast cancer in women[99]. In addition, individual differences cannot be ignored; the ability of gut microbiota to metabolize isoflavones is an important regulatory factor. Studies have found that the lack of gut bacteria capable of effectively metabolizing isoflavones may worsen diseases, while a diet rich in isoflavones has been shown to significantly protect against central nervous system inflammation in experimental autoimmune encephalomyelitis models, suggesting its profound potential in regulating systemic immune-inflammatory networks[100]. It is important to note that the health effects of different components of soybean must be strictly distinguished: whole-soy products and their high-protein fractions exhibit anticancer potential, whereas refined soy lipid products are considered a risk factor for parenteral nutrition-associated liver disease[101]. Equol, a metabolite derived from isoflavones, exhibits the highest estrogenic and antioxidant activity. However, only about one-third to one-half of individuals are capable of producing it[102]. While studies suggest that soy is effective in cancer prevention[103], certain aspects remain characterized by unknown heterogeneity. In conclusion, soybean plays a multifaceted regulatory role in cancer prevention and treatment. Future translational research should focus on elucidating the exact dose–effect relationship of its active ingredients and transform this traditional crop into a modern tool for precision cancer prevention and adjuvant therapy based on individual genetic background and gut microbiota profile.

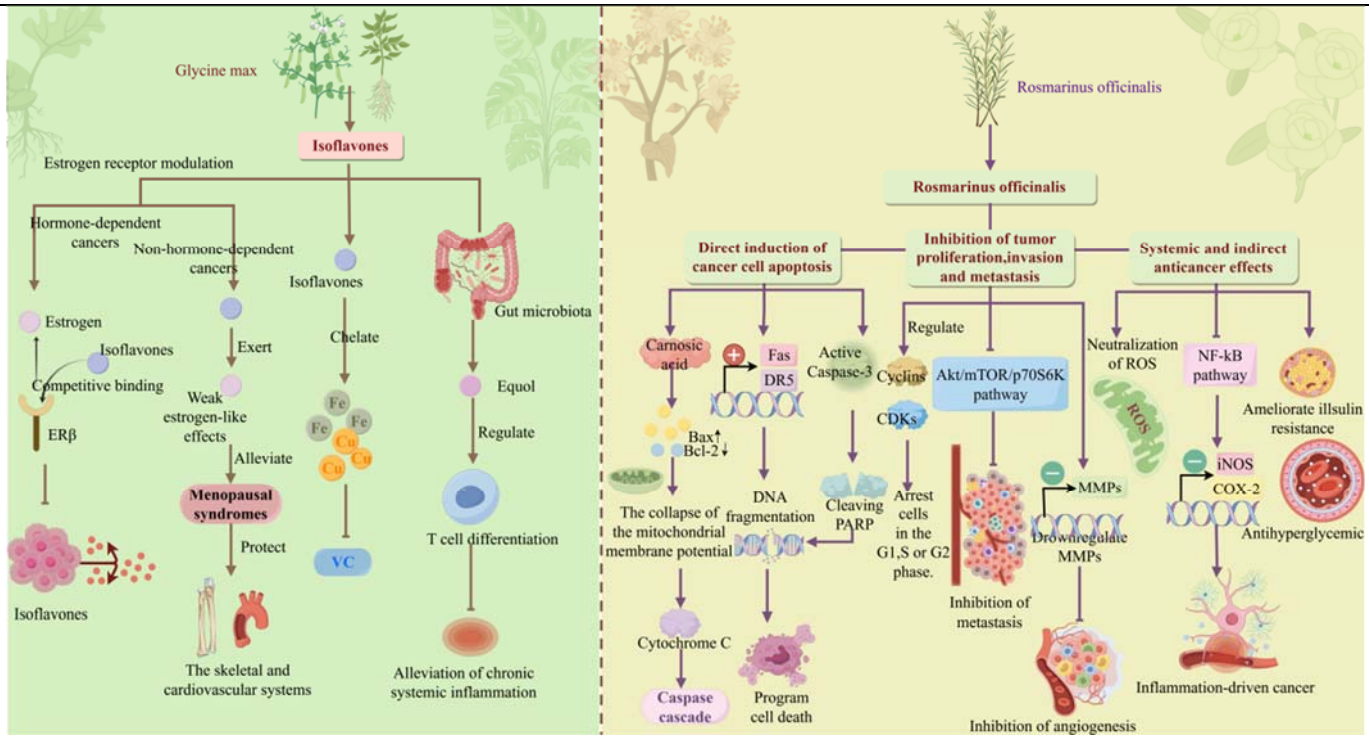

Figure 4. Multi-Target Anti-Cancer Mechanisms of Isoflavones and Rosemary Active Components. This figure details the anti-cancer effects of isoflavones (from Glycine max) and active components (e.g., carnosic acid from Rosmarinus officinalis). For isoflavones: in hormone-dependent cancers, they competitively bind to estrogen receptors (ERβ) to block estrogen-induced proliferation; in non-hormone-dependent cancers, they directly induce cancer cell apoptosis via the Fas/DR5-caspase-3 pathway, inhibit cyclins/CDKs to arrest cells in G1/S/G2 phases, and downregulate MMPs to suppress invasion and metastasis. They also chelate Fe^{2+} to neutralize ROS, regulate gut microbiota to produce equol, and alleviate insulin resistance. For rosemary components (carnosic acid): they activate the Bax-cytochrome C-caspase cascade, cleave PARP and DNA, inhibit the Akt/mTOR/p70S6K pathway, and downregulate COX-2/iNOS to block inflammation-driven cancer. Additionally, both substances exert systemic effects, such as protecting cardiovascular and skeletal systems and alleviating chronic inflammation.

Rosmarinus officinalis (rosemary), a medicinal plant belonging to the Lamiaceae family, has shown great promise in anticancer research. Studies have revealed that polyphenolic compounds found in rosemary, such as rosmarinic acid, carnosic acid, carnosol, and ursolic acid, exhibit anticancer properties through multi-target mechanisms. These active components can interfere with various stages of cancer progression, displaying dose-dependent effects without notable tissue or species specificity[104]. In numerous cancer models, including colorectal, breast, liver, gastric cancers, melanoma, and leukemia cells, rosemary extract has demonstrated significant tumor-suppressive capabilities. Its molecular actions encompass modulation of apoptosis, inhibition of angiogenesis, disruption of cell cycle progression, and suppression of metastasis[105]. The anticancer efficacy of rosemary is intricately linked to its robust antioxidant and anti-inflammatory attributes. Notably, the antioxidant potency of rosemary's acid derivatives in diverse lipid systems is markedly influenced by their lipophilicity, offering valuable insights for enhancing bioavailability. Additionally, rosemary holds considerable potential in addressing physiological disorders induced by biochemical, chemical, or biological agents[106]. In terms of neuroprotection, rosemary extract attenuates cerebral ischemia-induced blood–brain barrier disruption and brain edema by inhibiting the MAPK/NF-κB pathway and downregulating iNOS and COX-2 expression. Its antinociceptive effect involves GABAA receptors, TrpV1 channels, and the endogenous opioid system, showing synergistic effects with nonsteroidal

anti-inflammatory drugs[107,108]. Rosemary extract also disrupts bacterial biofilm architecture, compromises fungal membrane integrity and hyphal formation, and demonstrates significant inhibitory activity against various oral pathogens. In lead-induced hepatorenal toxicity, it exerts protective effects through restoration of endogenous antioxidant enzyme activities and reduction of lipid peroxidation[79,108,109]. Additionally, rosemary exhibits anxiolytic effects in anxiety models, potentially mediated by flavonoid-induced modulation of the GABAergic system and attenuation of neuroinflammation[106]. In the context of cancer chemoprevention and therapy, its extract exerts significant anti-proliferative effects on various cancer cells by inducing cell cycle arrest, including S phase retention, promoting apoptosis as evidenced by PARP cleavage, and suppressing key survival signaling pathways such as Akt/mTOR/p70S6K[110]. In addition to its direct anticancer effects, rosemary exhibits noteworthy metabolic regulatory properties. Both its extract and polyphenolic constituents have been shown to improve insulin resistance and exert antihyperglycemic effects, thereby indirectly modulating cancer risk associated with metabolic dysregulation[111]. From an application perspective, rosemary shows potential as a natural preservative, though further investigation into structure-activity relationships of its bioactive compounds is required[112]. Its therapeutic value for skin cancer treatment and localized delivery systems also merits exploration[113]. Although rosemary has been reported to have a wide range of beneficial effects, with bioavailability varying across different populations[114], rigorous and adequately powered clinical trials are still needed to clarify its primary therapeutic effects[115].

In conclusion, rosemary, as a FMH plant, has shown multifaceted potential in cancer prevention and treatment. Its synergistic effects from multiple active ingredients, multi-target mechanisms, and good safety make it a promising natural candidate for cancer chemoprevention strategies. Future research should focus on clinical translation to explore its practical application value in human cancer prevention and treatment.

Metal ion Chelation is a highly sophisticated and crucial antioxidant mechanism in FMH substances. By binding catalytically active free metal ions, it effectively eliminates a primary source of free radical amplification. This mechanism, in conjunction with "direct scavenging" and "enhancing endogenous systems," constitutes a comprehensive antioxidant defense system that operates synergistically. It blocks the source, immediately neutralizes, and provides long-term enhancement. This integrated system offers a robust molecular foundation for cancer prevention.

2.2 Inflammation and Inhibition of Inflammation-Cancer Transition

2.2.1 Mechanistic Elucidation

Chronic inflammation is recognized as the "seventh hallmark" of cancer. This Persistent inflammatory response generates ROS/RNS, stimulates cell proliferation, and inhibits apoptosis. Furthermore, it fosters a microenvironment that encourages cell proliferation, suppresses apoptosis, induces angiogenesis, and enhances invasion and metastasis. Numerous cancers, including liver, gastric, and colon cancer, originate from chronic inflammation, a process termed the "inflammation-cancer transition."

2.2.2 Mechanisms of Action of FMH Substances

They inhibit key inflammatory signaling pathways and reduce the production of pro-inflammatory factors, thereby blocking the inflammation–cancer transformation chain. The regulatory role of FMH substances in inhibiting inflammation-cancer transformation through multiple signaling pathways is shown in **Figure 5**. **Table 2** shows the core anti-inflammatory signaling pathways targeted by FMH substances as well as their representative materials, molecular mechanisms, and related cancer types.

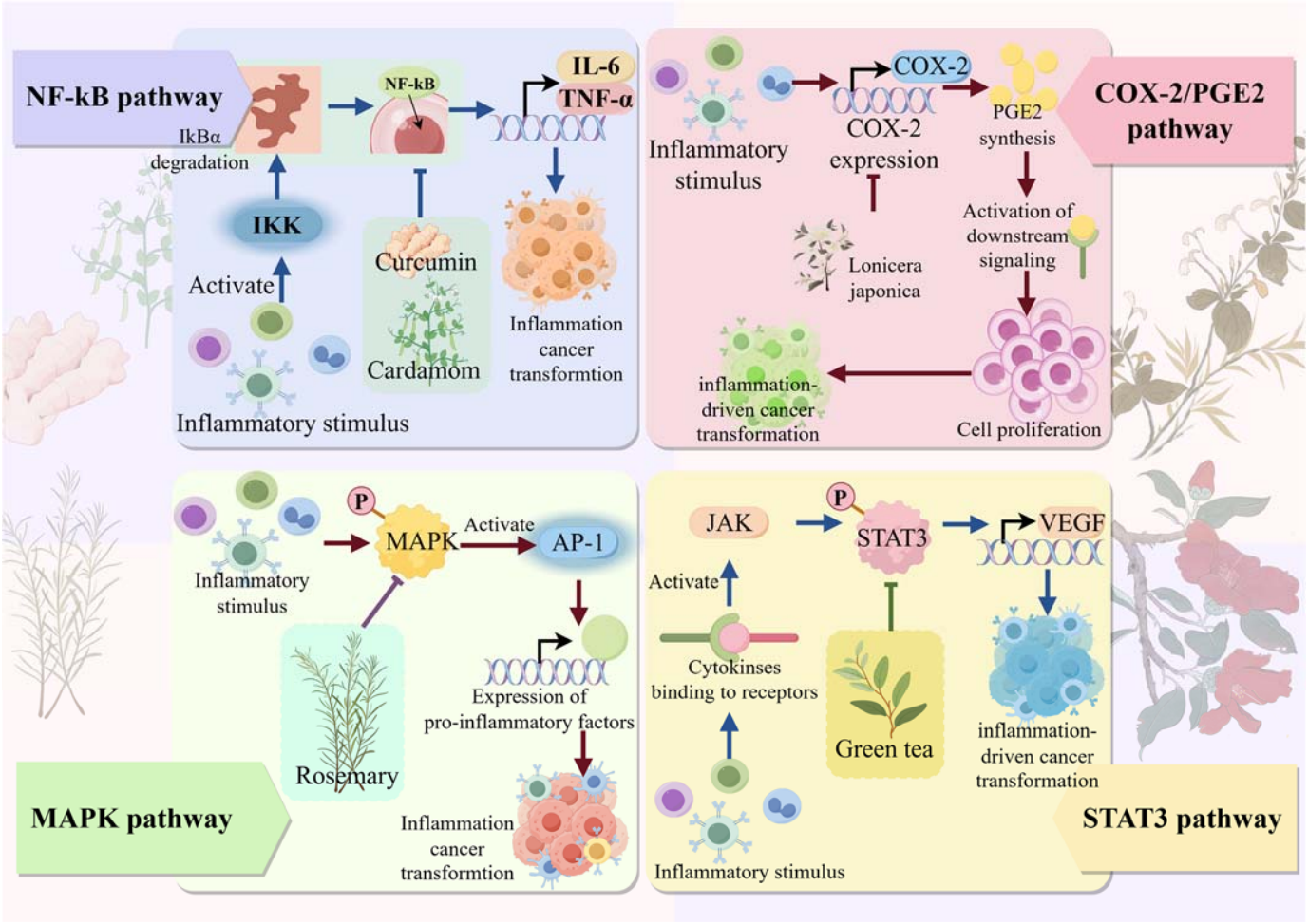

Figure 5. FMH Substances Inhibit Inflammation-Cancer Transformation via Multiple Signaling Pathways. This figure depicts how FMH substances block inflammation-driven cancer progression by targeting key inflammatory signaling pathways. Inflammatory stimuli (e.g., TNF-α) activate IKK, leading to IκBα degradation and nuclear translocation of NF-κB. NF-κB then upregulates the expression of pro-inflammatory factors (IL-6) and enzymes (COX-2), which promote PGE2 synthesis via the COX-2/PGE2 pathway, driving inflammation-cancer transformation. FMH substances including curcumin, Lonicera japonica, cardamom, green tea, and rosemary interfere with this process: curcumin inhibits NF-κB activation; Lonicera japonica target the COX-2/PGE2 axis; green tea and rosemary suppress the MAPK and STAT3 pathways. Additionally, inflammatory stimuli activate AP-1 via MAPK and STAT3 via JAK, promoting VEGF expression and cell proliferation; FMH substances block these downstream signaling cascades to inhibit inflammation-driven tumorigenesis.

Table 2. Anti-Inflammatory Mechanisms of FMH Substances and Representative Examples

Active Component	Source Plant(s)	Cancer Type(s)	Experiment Type(s)	Mechanism	Ref.
Terpenoids (Docetaxel, Tanshinone IIA)	Taxus Salvia miltiorrhiza	Gastric cancer Liver cancer	Clinical (Stage III gastric cancer patients, post-surgery) Cell (Gastric cancer stem cells, Bel-7402 liver cancer cells)	Tanshinone IIA induces ferroptosis by downregulating SLC7A11; Docetaxel enhances survival in Stage III patients	[116]
Polyphenols (Curcumin, Resveratrol, Quercetin)	Curcuma longa Grapes BerriesAcacia Onion Apple peel	Curcumin: Pancreatic cancer Gastric cancer Resveratrol: Lung cancer Prostate cancer Quercetin: Pancreatic cancer Breast cancer	Curcumin: Cell/Animal (Pancreatic, Gastric, Liver, Breast cancer) Resveratrol: Cell (Lung, Prostate) Quercetin: Cell (Pancreatic, Breast cancer)	Curcumin: Inhibits IL-6/JAK/STAT3, IL-1β/NF-κB pathways, suppresses EMT and angiogenesis in liver cancer. Resveratrol: Inhibits NF-κB, enhances antioxidant enzymes (SOD, CAT). Quercetin: Inhibits SHH, TGFβ/Smad, downregulates c-Myc, suppresses migration	[117]
EGCG	Camellia sinensis	Prostate cancer Breast cancer	Clinical (Prostate cancer pre-surgery, I/II stage breast cancer) Androgen-independent metastatic prostate cancer patients	Regulates prostate cancer biomarkers (Ki67), apoptosis (Bax/Bcl-2), and inflammation (NF-κB)	[118]
Diallyl Trisulfide	Garlic	Prostate cancer	Cell/Animal (PC-3 prostate cancer cells, Androgen-independent stage)	Induces Phase II detoxifying enzymes (GST, QR), inhibits Phase I enzymes, prevents carcinogenesis. Downregulates VEGFR-2, inhibits migration and angiogenesis. ROS-mediated induction of Bax/Bak expression	[119]
Sulforaphane	Broccoli	Prostate cancer Breast cancer	Prostate cancer (recurrence) Breast cancer (DCIS)	Inhibits NF-κB signaling, reduces COX-2 expression, and lowers pro-inflammatory cytokines (IL-8, TNF-α), intervening in multistage carcinogenesis	[120]
Piperine	Piper nigrum Piper longum	Breast cancer	Cell/Animal (4T1, MDA-MB-231, MCF-7, Mouse xenografts)	Inhibits NF-κB activation, reduces TNF levels, suppresses MMP-2, MMP-9, migration, and inflammation	[121]
Capsaicin	Capsicum(Red Peppers)	Prostate cancer	Cell/Animal (LNCaP, PC-3, DU-145, Mouse xenografts)	Inhibits proteasome activity, prevents IκBα degradation, blocks NF-κB nuclear translocation, reduces TNF-α induced inflammation, suppresses cancer cell survival and proliferation	[122]

(1) Inhibition of the NF-κB Signaling Pathway

The NF-κB pathway represents a critical mediator of inflammation, which, when activated, orchestrates the upregulation of numerous pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6.

Curcumin, a well-known inhibitor of the NF-κB signaling pathway, plays a crucial role in modulating inflammatory responses. As the primary dietary polyphenol found in turmeric, curcumin exhibits significant anti-cancer potential within the context of FMH substances. A key mechanism through which it exerts its effects is by inhibiting the NF-κB signaling pathway, which is frequently overactivated in various cancers, thereby promoting inflammation, cell proliferation, and survival. Research indicates that curcumin can directly interfere with the nuclear translocation of NF-κB or interact with its regulatory proteins, leading to the downregulation of pro-inflammatory factors and anti-apoptotic genes, thus inhibiting tumor progression[75–77]. Furthermore, the multi-target nature of curcumin enables it to co-regulate oxidative stress and metabolic disorders, further enhancing its functional value in cancer prevention and treatment. In summary, curcumin, as a natural NF-κB inhibitor, offers both theoretical support and practical prospects for slowing cancer progression and improving age-related pathological conditions.

(2) Inhibition of the COX-2/PGE2 Pathway

Cyclooxygenase-2 (COX-2) and its metabolite, prostaglandin E2 (PGE2), are pivotal in inflammation and tumorigenesis. Within multiple malignancies, the COX-2/PGE2 signaling axis has emerged as a central mechanism facilitating tumor immune evasion and progression. In breast cancer, this pathway orchestrates immune suppression via EP receptors, altering the tumor microenvironment by attracting tumor-associated macrophages, myeloid-derived suppressor cells, and regulatory T cells. Simultaneously, it diminishes the activity of T cells and natural killer (NK) cells[123]. Investigations into colorectal cancer have demonstrated that the COX-2–PGE2–EP4 cascade amplifies PD-1 expression in T cells and macrophages through the PI3K–Akt–NFκB pathway. This directly curtails T cell proliferation, cytotoxicity, and macrophage phagocytic capabilities, fostering immune evasion[124]. In glioblastoma, the interplay between the COX-2/PGE2 pathway in tumor cells and glioma-associated macrophages/microglia establishes a reinforcing loop, bolstering tumor growth, invasion, and angiogenesis via cytokine modulation[125]. Collectively, these findings underscore the promising prospects of targeting the COX-2/PGE2 axis to counteract tumor-induced immune suppression and augment treatment outcomes, particularly through the use of EP4 receptor antagonists in combination with immune checkpoint inhibitors. Additionally, they offer fresh insights into the anti-cancer properties of conventional non-steroidal anti-inflammatory drugs.

Flavonoids-rich herbs such as Lonicera japonica can inhibit the expression of key inflammatory mediators, including cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) Lonicera japonica (Honeysuckle) is a traditional Chinese medicinal herb that has long been used for anti-inflammatory and detoxification therapies. Flavonoids and terpenoids in honeysuckle have been identified as major bioactive constituents, which exert inhibitory effects on COX-2 in an in vitro model[126]. In recent years, its anti-inflammatory mechanisms have been explored in various disease models, especially cancer-related

inflammatory pathways. Although studies regarding the direct role of Lonicera japonica through COX-2/PGE2 in pan-cancer are limited, several studies have revealed that honeysuckle can indirectly affect COX-2/PGE2 expression by regulating key inflammatory signaling pathways. The water extract of honeysuckle leaves significantly inhibited the production of pro-inflammatory mediators including iNOS, NO, IL-1β, and TNF-α in LPS-induced BV2 microglial cells[127]. Mechanistically, this extract inhibited JNK phosphorylation and IκBα degradation, thereby modulating MAPK and NF-κB pathways, both of which are known core regulators of COX-2 transcription activation. Thus, Lonicera japonica may indirectly suppress COX-2 expression and PGE2 synthesis via blockade of these upstream signals[127].

Furthermore, studies have shown that Lonicera japonica extract (the same genus as honeysuckle) can alleviate oxidative stress and inflammation by upregulating the Nrf2 pathway, and activation of Nrf2 can negatively regulate COX-2[128,129]. In conclusion, Lonicera japonica may exert anti-inflammatory and potential anticancer effects in a pan-cancer context through multi-target regulation of the COX-2/PGE2 axis, including inhibiting MAPK/NF-κB pathways and activating Nrf2. However, direct experimental evidence still needs to be further explored. In conclusion, Lonicera japonica may exert anti-inflammatory and potential anticancer effects in a pan-cancer context through multi-target regulation, potentially involving the COX-2/PGE2 axis via inhibition of MAPK/NF-κB pathways and activation of Nrf2. However, direct experimental evidence confirming this specific mechanism is still required.

2.3 Providing Nutrition to Enhance Immunity and Improve the Body's Ability to Eliminate Tumor Cells

2.3.1 Mechanism Description

The human immune system, encompassing both innate immunity and adaptive immunity, serves as vigilant sentinels that detect and eradicate transformed cancer cells. However, during states of malnutrition or immune dysregulation, these sentinels become compromised, diminishing their capacity to effectively identify and neutralize tumor cells. This impairment allows for unchecked tumor growth and evasion from immune surveillance.

2.3.2 The Role of FMH Substances

Unlike chemical drugs that strongly activate the immune system, FMH substances moderately regulate immune balance through a 'strengthening healthy qi and consolidating root' approach. **Table 3** provides an overview of their immunomodulatory effects, which include enhancing immune cell function, regulating cytokines, and offering nutritional support.

Table 3. Immunomodulatory Effects of FMH Substances and Representative Examples

Active Component(s)	Source Plant(s)	Cancer Type(s)	Experiment Type(s)	Mechanism	Ref.
Codonopsis pilosula polysaccharide	Codonopsis pilosula	Melanoma	Animal/Cell (C57BL/6 tumor-bearing mice, B16 melanoma cells, RAW264.7 macrophages)	Reprograms macrophage polarization from M2 (pro-cancer) to M1 (anti-cancer), increases IL-1, IL-6, iNOS, and TNF-α levels, reduces tumor CD68+ macrophages, synergizes with dacarbazine	[130]
Vitamins (VC)	Citrus fruits Berries Vegetables	Breast cancer Non-small cell lung cancer Glioblastoma	Clinical (53 IIA–IIIB stage breast cancer, 39 metastatic cancer patients, late-stage NSCLC and GBM)	Enhances immune cell activity and epigenetic regulation, promotes T cell infiltration, stabilizes Treg function via TET-dependent DNA demethylation, increases NK and γδT cell proliferation, enhances response to anti-PD-1 therapy	[131]
Retinoic acid	Vitamin A animal liver, fish oil carotenoids green vegetables	Nasopharyngeal cancer Melanoma	Clinical/Animal/Cell (65 NPC patients, B16-F0 melanoma mice, human NPC xenografts)	Reverses immune exhaustion by targeting γδT cells, inhibits Tim-3 expression, activates NF-κB, enhances IFN-γ, TNF-α secretion, improves T cell cytotoxicity	[132]
Polysaccharides (Ganoderma lucidum, Astragalus)	Ganoderma lucidumAstragalus membranaceus	Colon cancer Sarcoma Melanoma	Ganoderma lucidum: HT-29 colon cancer cells; Lachnum: S180 sarcoma mice; Astragalus: metastatic melanoma mice	Ganoderma lucidum: Polarizes TAMs from M2 to M1; Lachnum: Enhances M1 polarization via TLR4-NF-κB; Astragalus: Enhances PD-L1 antibody efficacy, suppresses melanoma metastasis	[133]
Lycium barbarum L. polysaccharide	Lycium barbarum L.	Liver cancer	Animal/Cell (H22 tumor-bearing BALB/c mice, DC2.4 dendritic cells, H22 cells)	Enhances dendritic cell (DC) function, inhibits ER stress, reduces lipid accumulation in DCs, upregulates MHC II, CD80, CD86, increases TNF-α, and boosts CD8+ and CD4+ T cell proliferation	[134]
Lentinan	Lentinula edodes (Shiitake mushroom)	Lung cancer Gastric cancer Colon cancer	Clinical (Late-stage lung cancer, gastric cancer, colorectal cancer)	Activates Dectin-1 receptor to enhance macrophages, T cells, and NK cells, modulates cytokine balance, downregulates PD-L1, increases CD4+/CD8+ ratio, improves chemotherapy outcomes	[135]
Curcumin	Curcuma longa	Pancreatic cancer	Clinical (25 late-stage pancreatic cancer patients)	Remodels immune-suppressive tumor microenvironment, inhibits Treg infiltration, promotes M1 polarization of macrophages, enhances CTL and NK cell activity, reduces NF-κB and p-STAT3 in peripheral monocytes	[136]
Berberine	Berberis vulgaris	Colon adenoma prevention Late/Metastatic lung cancer	Clinical (Colon adenoma patients), Animal (Lewis lung cancer mice), Cell (NSCLC cells like H460, A549)	Metabolic and immune checkpoint reprogramming, blocks PD-L1, restores T cell function, reduces Treg and MDSCs, promotes M1 polarization of TAMs	[137]
Piperlongumine	Piper longum	Hepatocellular carcinoma	Cell (Human peripheral blood T cells, liver cancer cells)	Dual-regulation (pro-oxidant/immune suppression): Induces apoptosis via ROS and ER stress, suppresses T cell activation and enhances Treg differentiation at non-cytotoxic concentrations	[138]

(1) Providing Basic Nutrition and Immune Substrates

A diet abundant in proteins, vitamins C and A, and trace elements like zinc and selenium provides the nutritional foundation required for the effective proliferation, differentiation, and functional activity of immune cells.

(2) Activating Immune Cells

Enhancing the cytotoxic activity of natural killer (NK) cells, promoting the phagocytic ability of macrophages, and regulating the ratio of T lymphocyte subpopulations (e.g., increasing the CD4+/CD8+ ratio).

(3) Regulating Cytokines

Promoting the secretion of cytokines with anti-tumor effects (e.g., interferon-γ, interleukin-2/IL-2). The immune system is the body's primary defense mechanism for monitoring and eliminating tumor cells. When immune function is compromised, mutated cells are more likely to evade surveillance and develop into tumors.

FMH substances such as Poria cocos and Lentinus edodes are rich in bioactive polysaccharides. These components not only provide basic nutritional support in pan-cancer treatment, but also exert synergistic antitumor effects by regulating the immune microenvironment. Studies have shown that Poria cocos polysaccharide (PCP) can activate macrophages, T lymphocytes and other immune cell subset groups, regulate key cytokine networks such as IL-6, TNF-α, etc., reshape the immune homeostasis of tumor microenvironment, and enhance the body's antitumor immune response[139]. At the same time, it has been further confirmed that Lentinus edodes polysaccharide is used in functional foods to improve intestinal immunity and systemic energy metabolism, providing immune nutrition substrate for cancer patients[140]. The above mechanism reveals the potential value of FMH substances as immune metabolic regulators in integrated cancer treatment, and provides a theoretical basis for the development of new nutritional immunotherapy. In addition, prescription analysis based on data mining shows that Poria cocos is often combined with Astragalus membranaceus and Atractylodes macrocephala, which tonify deficiency, remove dampness and promote blood circulation, and work together to enhance immune response, which provides a theoretical basis for the integration of traditional Chinese and Western medicine in the comprehensive treatment of cancer[141]. These mechanisms not only support the core role of polysaccharides in nutritional immunology, but also open up new directions for the development of new adjuvant cancer therapy.

Chinese yam and coix seed, as quintessential food and medicinal substances, are abundant in active components such as proteins, amino acids, and polysaccharides. These components not only possess significant nutritional value but also exhibit intricate mechanisms in cancer prevention and treatment by modulating immunity and directly inhibiting tumor growth. The immune-enhancing properties of Chinese yam and coix seed constitute a primary antitumor mechanism[142]. Research indicates that the polysaccharides derived from Chinese yam markedly elevate the spleen index in immunosuppressed mice, stimulate lymphocyte proliferation, and augment macrophage phagocytic activity, thereby fortifying cellular immune

responses. Their non-starch polysaccharides (NSPs) have been verified to prompt the secretion of pivotal cytokines like IL-6, TNF-α, and IFN-γ in splenic lymphocytes, thus amplifying antitumor immune surveillance through the adjustment of Th1/Th2 equilibrium[143]. Conversely, Coix seed predominantly influences humoral immune modulation. Its polysaccharides bolster specific antibody reactions by elevating serum hemolysin levels and boosting the concentration of immunoglobulins, including IgG. The combined effects of these two substances can ameliorate the immunosuppressive milieu within the tumor microenvironment, setting the stage for subsequent therapeutic interventions.

The antitumor properties of coix seed are notably significant, with its extracts, such as coix seed oil, being incorporated into the Kanglaite injection for adjunctive clinical therapy. Mechanistic research indicates that lipids from coix seed can impede the division and migration of endothelial cells, effectively obstructing tumor angiogenesis. Furthermore, these lipids induce a cell cycle arrest in the G2/M phase of tumor cells, diminishing the proportion of cells in the DNA synthesis phase and thereby inhibiting proliferation. Both Chinese yam and coix seed contain triterpenoid and polysaccharide components that modulate signaling pathways like AMPK/mTOR and NF-κB. This modulation synergistically promotes tumor cell apoptosis and suppresses the expression of proteins associated with metastasis.

(4) Gut microbiota regulation and metabolic reprogramming

Recent studies have found that coix seed intervention significantly improved gut microbial dysbiosis caused by high-humidity environment, increasing the abundance of beneficial bacteria such as Akkermansia spp. and Lactobacillus spp. and decreasing the levels of opportunistic pathogens such as Shigella spp. The regulatory mechanism of FMH substance on gut microbiota–inflammation axis to prevent inflammation-cancer transition was shown in **Figure 6**. This microbial remodeling was accompanied by normalization of sphingolipid metabolic pathways, reduction of proinflammatory cytokine (TNF-α, IL-6, IL-17) release, and indirect inhibition of tumor-associated chronic inflammation. Dietary fiber and polysaccharide in Chinese yam also acted as prebiotics to maintain intestinal barrier integrity and reduce endotoxin translocation, thereby creating a stable environment for systemic immunity[144–147].

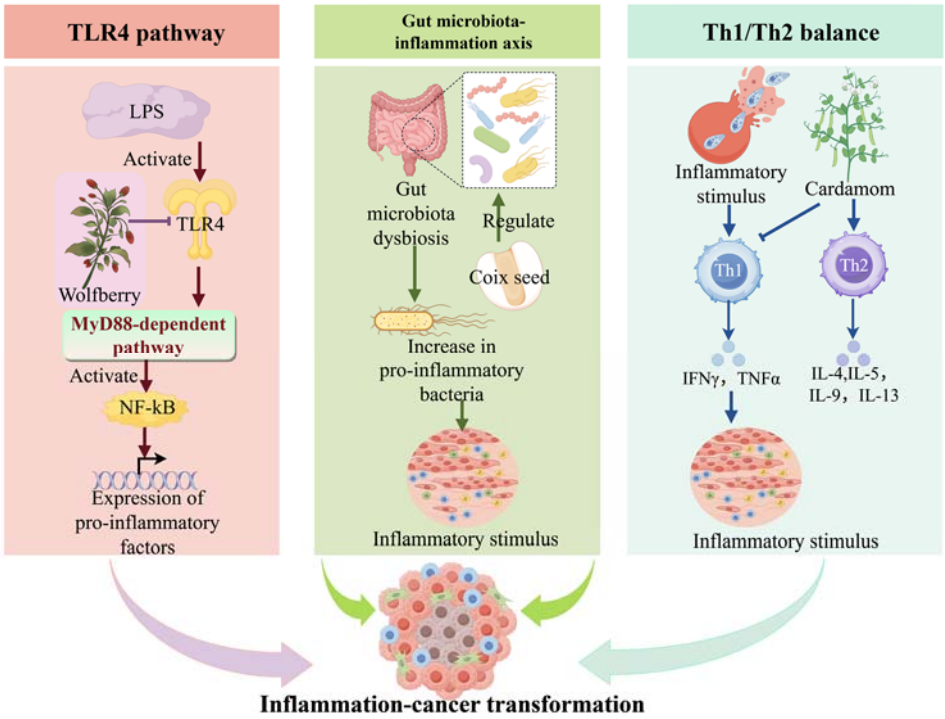

Figure 6. FMH Substances Regulate Gut Microbiota-Inflammation Axis to Block Inflammation-Cancer Transformation. This figure illustrates how FMH substances (coix seed, cardamom, wolfberry. Gut microbiota dysbiosis leads to increased pro-inflammatory bacteria, which release LPS. LPS activates the TLR4-MyD88-dependent pathway, triggering NF-κB nuclear translocation and upregulating pro-inflammatory factor expression. Simultaneously, inflammatory stimuli activate the iNOS pathway, increasing NO production and inducing DNA damage, thereby promoting inflammation-cancer transformation. FMH substances intervene at multiple nodes: they restore gut microbiota balance (reducing pro-inflammatory bacteria), inhibit TLR4/NF-κB signaling to reduce pro-inflammatory factor secretion, and regulate Th1/Th2 balance (modulating IFN-γ, TNF-α, IL-4, IL-5, IL-9, IL-13 levels).

In summary, Chinese yam and coix seed, via their bioactive constituents such as proteins, amino acids, and polysaccharides, establish a comprehensive antitumor mechanism that encompasses both localized immune activation and systemic metabolic modulation. These components not only furnish the requisite substrates for immune cell proliferation and antibody production but also directly modulate tumor-associated signaling cascades and ameliorate the tumor microenvironment, underscoring their significant potential in cancer prevention and therapeutic interventions.

Dioscorea opposita and coix seed, as representative medicinal foods, are rich in high-quality proteins and essential amino acids, which not only provide essential raw materials for immune cell proliferation and antibody synthesis but also exhibit multifaceted mechanisms in cancer treatment. Studies have shown that dioscorea polysaccharides can regulate the Th1/Th2 balance and promote the secretion of cytokines such as IL-6, TNF-α, and IFN-γ, thereby enhancing antitumor immune surveillance[143,148]. The active components of coix seed demonstrate more direct antitumor properties. Its unique coixol component and coix seed oil have been developed into the anticancer drug Kanglaite, which exerts an antiproliferative effect by inducing tumor cell cycle arrest and inhibiting angiogenesis[149]. Notably, both substances show synergistic potential in regulating the tumor microenvironment. Coix seed extract can remodel the gut microbiota, increasing the abundance of beneficial bacteria such as Akkermansia spp. and Lactobacillus spp., while correcting sphingolipid metabolism disorders, which in turn lowers serum levels of pro-inflammatory cytokines (TNF-α, IL-6, IL-17) and alleviates tumor-associated chronic inflammation[150]. Furthermore, nanodelivery systems based on coix seed oil (such as the TET-CTM/L complex) can effectively open a “normalization window” in

tumor vasculature, promoting deeper penetration of anticancer components and offering new insights for the design of multicomponent traditional medicine nanoparticle drug delivery systems[151]. These findings collectively reveal that D. opposita and coix seed form a multitarget regulatory network in cancer prevention and treatment through immune modulation, direct antitumor effects, metabolic reprogramming, and improved drug delivery.

Jujube (Ziziphus jujuba) has been demonstrated to have applications in tissue engineering and wound healing, which are closely related to its antioxidant components such as flavonoids and polyphenols. Its role in tumor immune regulation also gradually attracted attention. Notably, trace elements rich in jujube including Fe and Zn play a key role in maintaining the homeostasis of immunity. Fe is an essential cofactor for lymphocyte proliferation and activation, involved in regulating T cell differentiation and NK cell cytotoxicity. The deficiency of Fe can lead to impaired immune function and affect anti-tumor immune response. Zn stabilizes T cell receptor signaling, regulates dendritic cell function and maintains thymic microenvironment to ensure the effectiveness of immune surveillance. In pan-cancer, disturbance of Fe and Zn metabolism is common in various malignant tumors and can promote immune escape of tumors. Therefore, dietary supplementation with jujube or its active ingredients may enhance the function of immune cells by correcting the imbalance of trace elements, thereby remodeling the tumor microenvironment and providing a potential strategy for adjuvant anti-tumor therapy[152].

Goji berry (Lycium barbarum), integrating traditional efficacy with modern pharmacological research, has garnered increasing attention for its active components, especially trace elements like iron and zinc, in modulating the tumor immune microenvironment. Iron, a crucial cofactor in immune cell metabolism and function, is directly involved in T-cell activation, mitochondrial respiration, and macrophage polarization. Zinc is central to maintaining the integrity of T-cell receptor signaling, regulating the activity of inflammation-related transcription factors such as NF-κB, and promoting interferon production. In pan-cancer contexts, tumor-associated ferroptosis and disorders of zinc metabolism are prevalent in advanced malignancies, contributing to T-cell exhaustion and diminished immune surveillance. Goji polysaccharides, the primary active constituents of goji berries, not only possess immunomodulatory and antioxidant properties but may also synergistically replenish essential trace elements like iron and zinc. This could rectify metabolic imbalances in immune cells, bolster the cytotoxicity of $CD8^+$ T cells and NK cells, and counteract the immunosuppressive functions of myeloid-derived suppressor cells, thereby remodeling the antitumor immune response[153]. Such mechanisms offer a theoretical foundation for employing goji berry and its derivatives as complementary strategies in tumor immunotherapy, although further prospective studies are warranted to validate its clinical potential[154].

3. FMH Substances in Cancer Treatment

3.1 Direct Inhibition of Tumor Progression by FMH Substances

3.1.1 Pharmacological Mechanisms

Numerous FMH substances contain active components capable of inhibiting the proliferation signaling pathways of tumor cells. **Table 4** provides a comprehensive overview of the direct antitumor mechanisms associated with these substances, which include the inhibition of proliferation, induction of apoptosis, and suppression of metastasis, along with their corresponding representative materials and targeted pathways.

Table 4. Direct Antitumor Mechanisms of FMH Substances and Representative Examples

Active Components	Source Plant(s)	Cancer Type(s)	Experiment Type(s)	Mechanism	Ref.
Curcumin	Curcuma longa (Turmeric)	Colon cancer, Prostate cancer, Glioblastoma, Breast cancer	Clinical (Colon cancer, mCRPC, Glioblastoma, Breast cancer)	Inhibits proliferation, migration, and promotes apoptosis by targeting NF-κB, EGFR, PI3K/Akt/mTOR, Wnt/β-catenin, JAK/STAT-3 pathways; converts Tregs to Th1 cells; reduces DNA oxidative damage and COX-2 in colorectal cancer.	[155]
Curcumin	Curcuma longa (Turmeric)	Pancreatic cancer, Colon cancer, Prostate cancer, Breast cancer	Clinical (Pancreatic cancer, FOLFOX for liver metastasis); Cell/Animal (PC-3, MDA-MB-231)	Regulates PI3K/Akt/mTOR, Wnt/β-catenin, JAK/STAT pathways; induces apoptosis by restoring mutant p53 (Y220C) and activating Caspase-3; inhibits metastasis and EMT.	[156]
Allicin	Allium sativum (Garlic)	Liver cancer, Colon cancer, Stomach cancer	Clinical (Stomach cancer, pre-surgical); Cell/Animal (HCT-116, HepG2)	Induces apoptosis via ROS-mediated mitochondrial damage; inhibits STAT3 nuclear translocation, VEGF, and HIF-1α to prevent angiogenesis. Inhibits telomerase and ODC1 activity to block cell proliferation.	[157]
Diallyl disulfide	Allium sativum (Garlic)	Stomach cancer, Leukemia	Clinical (Stomach cancer, long-term garlic use); Cell/Animal (PC-3, HL-60)	Inhibits proliferation via CDK1 and Cyclin B1 downregulation, induces G2/M arrest, inhibits Ras and Src/Fak/Integrin signaling; reduces angiogenesis by upregulating E-cadherin and blocking EMT.	[158]
Diallyl disulfide	Allium sativum (Garlic)	Colon cancer	Cell/Animal (HT-29, HCT116, SW480, SW620)	Induces apoptosis and inhibits proliferation by downregulating PI3K/Akt pathway and upregulating TRIM21, leading to ubiquitination and degradation of POU2F1, causing DNA damage.	[159]
Genistein	Glycine max (Soybean)	Breast cancer	Animal (Ovariectomized obese mice); Cell (E0771, 4T1, EMT-6)	Inhibits metastasis and proliferation, modulates microenvironment by activating PPAR-γ, degrading NF-κB, and inhibiting Wnt3a/β-catenin signaling; reduces pro-inflammatory factors (TNF-α, IL-6).	[160]
Ginsenoside Rg3	Panax ginseng (Red ginseng)	Lung cancer	Cell (A549, H460)	Promotes apoptosis by generating ROS, induces mitochondrial apoptosis (cleaved caspase-3, PARP); activates PINK1-Parkin mitophagy pathway, inhibits proliferation and colony formation.	[161]
Ginsenoside Rh2	Panax ginseng (Ginseng)	Colon cancer	Cell/Animal (HCT116, HCT15, DLD1; HCT116 xenograft)	Downregulates Axl signaling and PI3K/Akt/mTOR, MAPK/ERK cascades; inhibits metastasis by reversing EMT, upregulates E-cadherin, reduces N-cadherin and vimentin; induces apoptosis by blocking G0/G1 phase and activating p53.	[162]
Sulforaphane	Cruciferous vegetables (Broccoli, Broccoli sprouts, Radish)	Prostate cancer, DCIS (Breast)	Clinical (Recurrent prostate cancer, DCIS)	Inhibits NF-κB signaling, suppresses inflammation, reverses epigenetic changes via HDAC inhibition, induces G1/S and G2/M arrest, activates Caspase pathways for apoptosis.	[163]
Epigallocatechin 3-gallate (EGCG)	Camellia sinensis (Green tea)	Prostate cancer, Breast cancer, Melanoma, Colon cancer, Leukemia	Clinical (Prostate cancer, Breast cancer); Cell (Melanoma, Colon cancer, Leukemia)	Induces apoptosis by activating Caspase-3/9, alters Bcl-2 family ratios, inhibits proliferation and migration, blocks VEGF, EGFR, STAT3, ERK1/2, NF-κB pathways, enhances immune killing in lung cancer by downregulating PD-L1.	[164]
Capsaicin	Genus Capsicum (Chili pepper)	Prostate cancer	Cell/Animal (Androgen-independent prostate cancer cells: LNCaP, PC-3, DU-145; PC-3 xenograft)	Induces apoptosis via p53, p21, and Bax expression; inhibits proliferation by suppressing PSA expression; blocks NF-κB nuclear translocation and inflammation-related survival signals by inhibiting proteasome activity.	[165]
Isoliquiritigenin	Licorice (Glycyrrhiza uralensis), Shallot, Bean sprouts	Non-small cell lung cancer	Cell (HCC827, H1650, H1975, A549); Animal (H1975 xenograft)	Directly targets EGFR (wild-type and L858R/T790M mutations), inhibits Akt1 and ERK2 activity, induces Bim expression and reduces Bcl-2 to promote apoptosis.	[166]

(1) Inhibition of Tumor Cell Proliferation

Curcumin, a natural polyphenol with extensive medicinal and culinary history, demonstrates multi-target regulatory capabilities in cancer prevention and treatment. When applied during the active treatment phase, curcumin transitions into a therapeutic disruptor that inhibits pathways like NF-κB and STAT3 to directly arrest the proliferation of established tumor cells by downregulating Cyclin D1. This action prevents tumor cells from advancing from the G1 to the S phase, thereby impeding proliferation. Central to its mechanism is the potent suppression of aberrant activation in key carcinogenic pathways, including NF-κB and STAT3, resulting in marked downregulation of Cyclin D1. Such interference disrupts the standard regulation of the G1/S checkpoint, obstructing the phosphorylation of the retinoblastoma protein and the subsequent release of E2F transcription factors. This effectively hinders the critical transition from the G1 to the S phase, ultimately curtailing cell proliferation[167–170]. This process mirrors the function of tumor suppressors like p16INK4A. Supporting evidence spans from the LKB1-ARK5-p21 axis's modulation of p53 to various miRNAs orchestrating G1/S phase arrest, emphasizing the significance of targeting the G1/S transition in thwarting tumor growth. Moreover, the fluctuating patterns of NAD+/NADH ratios during the cell cycle suggest an intricate link between metabolic conditions and cycle control. Curcumin's engagement with this network underscores its potential in cancer therapeutic strategies. Curcumin effectively reverses the Warburg effect by inhibiting the mTOR-HIF1α axis, which downregulates key rate-limiting enzymes such as PKM2, thereby disrupting the tumor’s energy supply[171]. Additionally, it reprograms pro-cancer M2 macrophages to anti-cancer M1 macrophages by inhibiting the MAO-A/STAT6 pathway, thus reshaping the immunosuppressive microenvironment into an immune-activated state, which synergistically suppresses tumor progression[172].

Garlic (Allium sativum), a traditional medicinal and culinary agent, derives its anticancer properties from organic sulfur compounds (OSCs), notably allicin and its derivatives such as diallyl disulfide (DADS). These bioactive constituents are synthesized when fresh garlic undergoes mechanical disruption (e.g., mashing or chopping), with the conversion of alliin to allicin being catalyzed by alliinase. It is important to note that thermal processing denatures this enzyme, thereby diminishing allicin formation[173,174]. Garlic demonstrates multifaceted mechanisms in oncogenesis prevention and therapy. Allicin and its metabolites provoke mitochondrial dysfunction and oxidative stress, leading to substantial reactive oxygen species (ROS) production. This ROS surge subsequently activates caspase-3/8 and prompts cytochrome c release, culminating in the initiation of the mitochondrial apoptosis pathway within tumor cells. Concurrently, these compounds modulate critical signaling cascades to impede tumor growth: they inhibit the MEK-ERK cascade downstream of EGFR/Ras, obstructing proliferative signal transduction; and they also target pivotal survival and inflammation-associated pathways like PI3K/Akt and NF-κB, thereby curtailing cell viability, suppressing the inflammatory milieu, and hindering tumor invasion. At the cellular regulatory level, these OSCs can induce G1/S or G2/M phase arrest, a process underpinned by the inhibition of cyclin proteins (e.g., Cyclin D1) and the activity of cyclin-dependent kinase (CDK) complexes[175,176]. Furthermore,

epidemiological evidence indicates that prolonged garlic consumption is linked to a decreased risk of certain gastrointestinal cancers. Despite the challenges presented by allicin's instability and metabolic properties affecting its bioavailability, innovative technologies like nanodelivery systems are being explored to improve its targeted delivery efficiency and stability. Collectively, these insights suggest that the organic sulfur compounds found in garlic have a comprehensive role in both the prevention and treatment of cancer, achieved through mechanisms such as inducing oxidative stress, modulating various signaling pathways, and interfering with cell cycle progression.

Soybeans are rich in isoflavones, particularly genistein, which are natural compounds with plant estrogenic activity that offer diverse effects in cancer chemoprevention. This property arises from their structural similarity to endogenous estrogens, allowing them to competitively bind to estrogen receptors. This results in bidirectional regulatory impacts across various tissues: in hormone-dependent cancers, such as certain breast cancers, genistein counteracts the proliferative signals of endogenous estrogens, effectively inhibiting tumor cell growth and survival. Beyond this hormonal pathway, genistein also demonstrates anticancer properties through non-hormonal mechanisms, including inhibition of tyrosine kinase activity, disruption of cell cycle progression (e.g., inducing G2/M phase arrest), and promotion of tumor cell apoptosis[177,178]. Such multifaceted actions underscore the intervention potential of soy isoflavones in pan-cancer contexts, establishing a scientific foundation for their role in nutritional oncology.

(2) Induction of Cell Apoptosis

The major polyphenolic bioactive compound in green tea, EGCG, has demonstrated a core mechanism of action in pan-cancer models by triggering apoptosis through the mitochondrial pathway and thus inhibiting tumor growth. The molecular mechanisms by which green tea EGCG exerts anticancer effects via apoptosis induction and proliferation inhibition are shown in **Figure 7**. Its molecular interference starts with remodeling the balance within the Bcl-2 protein family by specifically upregulating pro-apoptotic proteins such as Bax and Bak while downregulating the levels of anti-apoptotic proteins like Bcl-2 and Bcl-xL. This imbalance causes damage to the mitochondrial membrane potential, prompting the release of cytochrome c into the cytosol, which in turn activates caspase-9 and its downstream effector caspases (e.g., caspase-3), ultimately initiating the classical intrinsic apoptotic program. Notably, EGCG-induced apoptosis is cell context dependent. For example, in laryngeal squamous carcinoma, EGCG acts through a p53-mediated mitochondrial pathway but may also involve caspase-independent death modalities. In addition, EGCG suppresses pro-survival signaling pathways such as PI3K/Akt/mTOR, synergistically enhancing its pro-apoptotic effects. It also inhibits telomerase activity and hTERT expression, further restricting the unlimited proliferative capacity of cancer cells[179,180]. These multitarget effects make EGCG a promising natural compound for use in cancer chemoprevention and adjuvant therapy.

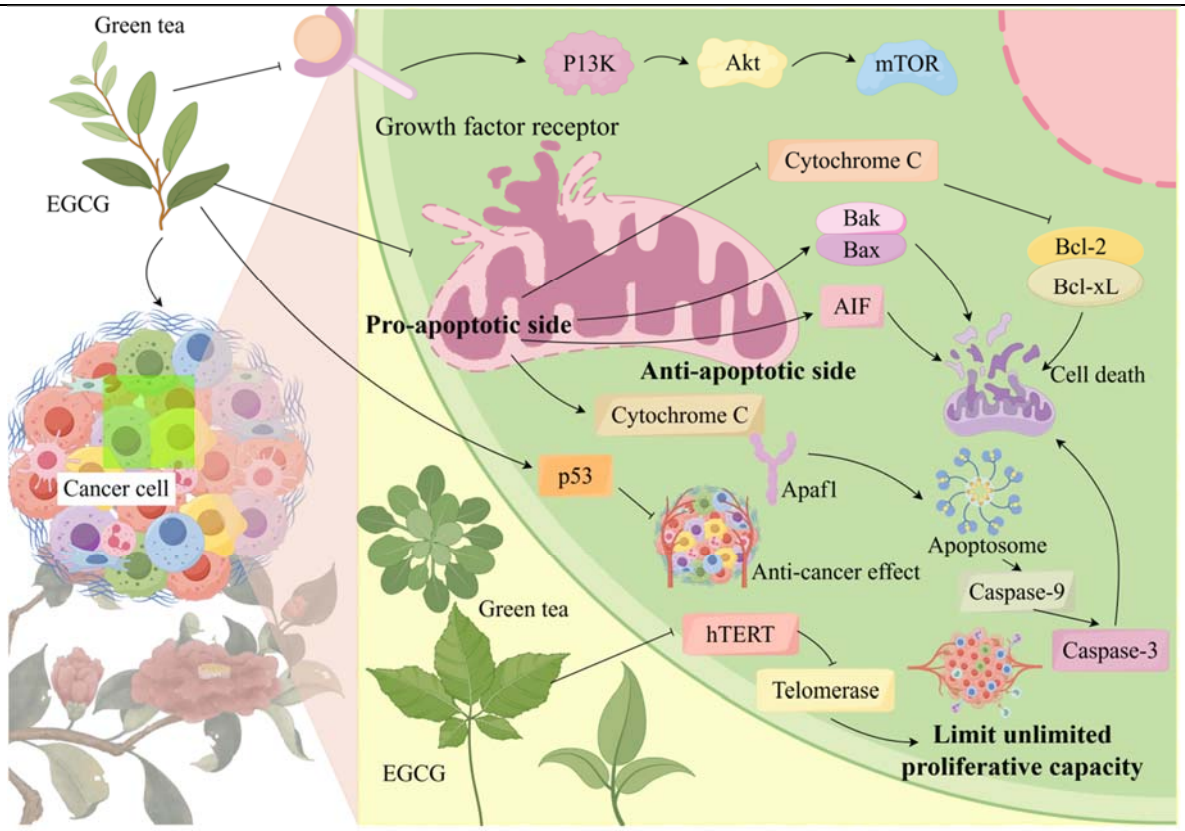

Figure 7. EGCG from Green Tea Induces Cancer Cell Apoptosis and Inhibits Unlimited Proliferation. This figure illustrates the dual anti-cancer mechanisms of epigallocatechin gallate (EGCG), the key active component in green tea. First, EGCG regulates the balance of Bcl-2 family proteins: it upregulates the expression of pro-apoptotic proteins (Bak, Bax) and downregulates anti-apoptotic proteins (Bcl-2, Bcl-xL). This imbalance disrupts mitochondrial membrane potential, triggering the release of cytochrome C and apoptosis-inducing factor (AIF) from mitochondria. Cytochrome C forms an apoptosome with Apaf-1 and activates caspase-9, which further activates caspase-3 to initiate the mitochondrial apoptotic cascade. Second, EGCG inhibits the expression of human telomerase reverse transcriptase (hTERT), reducing telomerase activity and limiting the unlimited proliferative capacity of cancer cells. Additionally, EGCG blocks the PI3K/Akt/mTOR signaling pathway activated by growth factor receptors, further suppressing cancer cell survival and proliferation.

Ginsenoside Rg3 and Rh2, active constituents of ginseng, demonstrate pivotal mechanisms in inducing tumor cell apoptosis through dual pathways across various cancers. Their functions extend beyond merely activating the death receptor-mediated extrinsic apoptotic pathway; they also modulate the equilibrium of Bcl-2 family proteins, triggering mitochondrial inner membrane permeabilization. This results in the release of cytochrome c and subsequent activation of the caspase cascade, characteristic of the intrinsic apoptotic pathway. In the BGC-823 gastric cancer model, both Rh2 and Rg3 independently induce apoptosis and display pronounced synergistic effects when combined with paclitaxel (PTX) within a liposomal drug delivery system, further suppressing tumor cell proliferation. The collaborative mechanism between ginsenosides Rg3/Rh2 and paclitaxel in promoting gastric cancer cell apoptosis and inhibiting angiogenesis is illustrated in **Figure 8**. Additionally, Rg3 has been verified to have standalone anti-angiogenic properties, indirectly impeding tumor growth and metastasis by interfering with the tumor neoangiogenesis network[181,182]. These multifaceted, multi-pathway synergies underscore the pharmacological foundation of ginsenosides Rg3 and Rh2 in cancer chemoprevention and adjunct therapy.

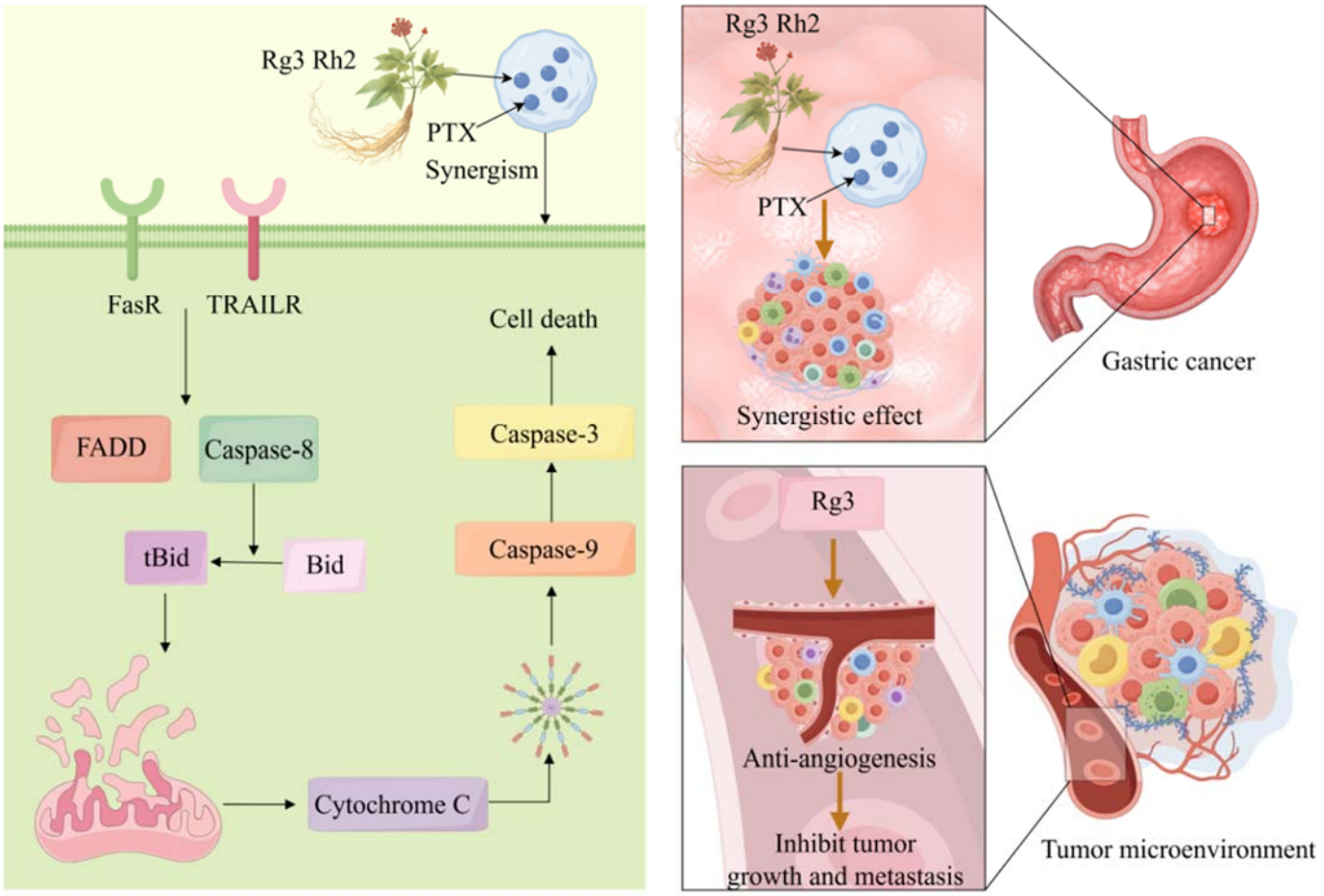

Figure 8. Ginsenosides Rg3/Rh2 Synergize with Paclitaxel to Induce Gastric Cancer Cell Apoptosis and Inhibit Angiogenesis. This figure depicts the synergistic anti-gastric cancer effects of ginsenosides (Rg3, Rh2) and paclitaxel (PTX). Rg3 and Rh2 induce apoptosis through dual pathways: they activate the extrinsic pathway (FasR/TRAILR-FADD-caspase-8-caspase-3) and the intrinsic mitochondrial pathway (regulating Bcl-2 family, releasing cytochrome C to activate caspase-9-caspase-3). When combined with PTX in a liposomal delivery system, Rg3/Rh2 exhibit significant synergism, further enhancing gastric cancer cell (BGC-823) apoptosis and proliferation inhibition. Additionally, Rg3 independently exerts anti-angiogenic effects by disrupting the tumor neoangiogenesis network, indirectly inhibiting tumor growth and metastasis.

(3) Regulation of Cell Cycle

Resveratrol, a naturally occurring polyphenolic compound found in plants such as grapes and mulberries, demonstrates multi-target anti-cancer properties across various cancer types. Unlike its preventive role, the therapeutic application of Resveratrol focuses on aggressive tumor suppression by regulating cell cycle checkpoints to arrest malignant proliferation at the G1 or S phase. This action is facilitated through both p53-dependent and independent pathways: resveratrol markedly enhances the expression of cyclin-dependent kinase inhibitors, notably p21, and the tumor suppressor protein p53. This upregulation impedes the activity of cyclin-CDK complexes, obstructing the G1/S phase transition. The dual pathways through which resveratrol induces cell cycle arrest and apoptosis in tumor cells are illustrated in Figure 9. In studies on ovarian cancer, Ma et al. observed that resveratrol halts A2780 cells in the G0/G1 phase by downregulating the ILK/β-catenin signaling pathway[183]. Similarly, in breast cancer models, Wang et al. verified its influence on epithelial-mesenchymal transition via POLD1 expression modulation. It is noteworthy that resveratrol's ability to arrest the cell cycle exhibits pronounced time- and concentration-dependent effects. These phenomena have been consistently reported in diverse cancer models, encompassing colorectal, pancreatic,

and lung cancers. Given its capacity for cross-cancer cell cycle modulation, induction of apoptosis (for instance, via the Bax/Bcl-2 axis), inhibition of immune evasion within the tumor microenvironment, and reversal of chemotherapy resistance, resveratrol emerges as a promising natural anti-cancer agent.

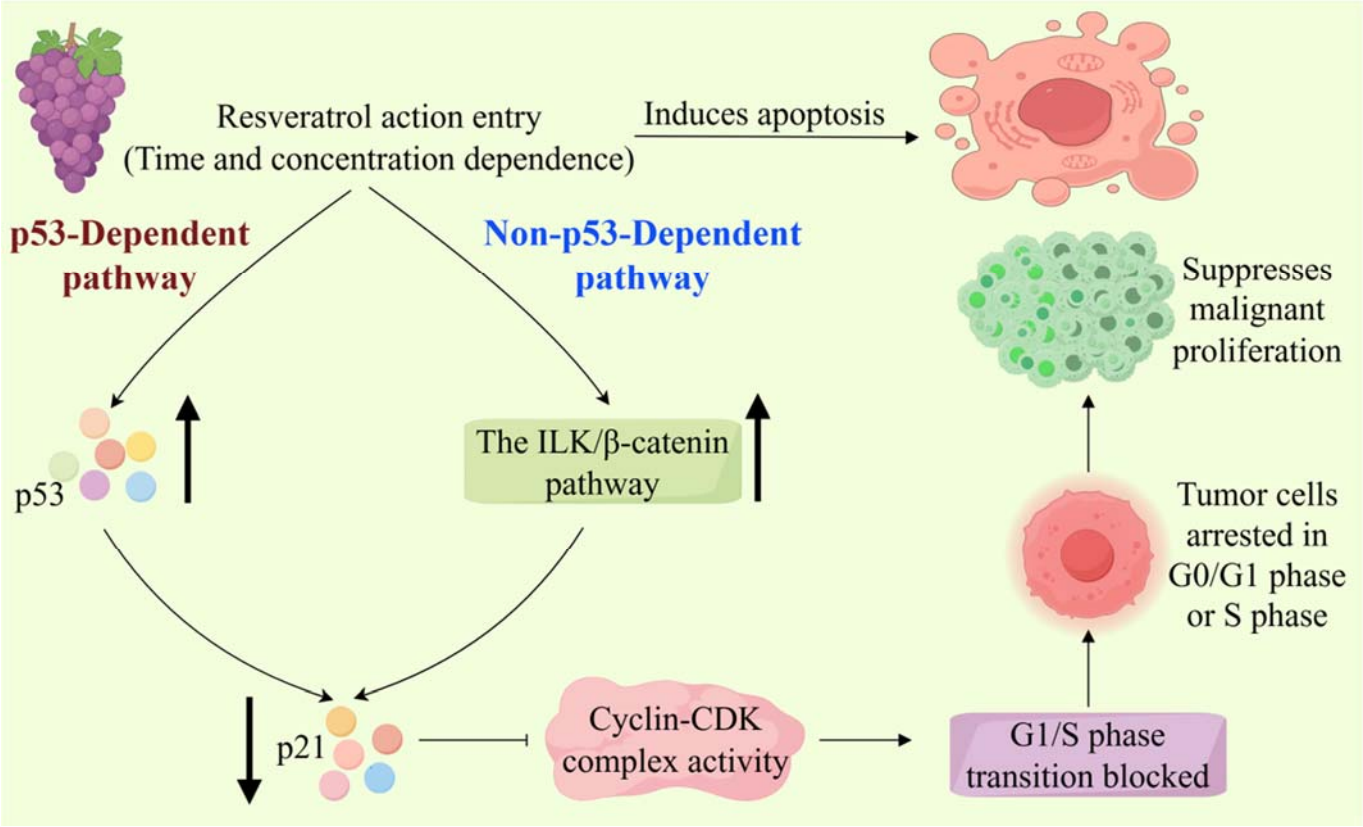

Figure 9. Resveratrol Induces Cell Cycle Arrest and Apoptosis in Tumor Cells via p53-Dependent and Independent Pathways. This figure illustrates the anti-proliferative and pro-apoptotic mechanisms of resveratrol, which exhibit time and concentration dependence. Resveratrol acts through two pathways: in the p53-dependent pathway, it upregulates p53 expression, leading to G1/S phase arrest by blocking cyclin-CDK complex activity. In the non-p53-dependent pathway, it inhibits ILK/β-catenin complex activity, arresting tumor cells in G0/G1 or S phase. Additionally, resveratrol induces tumor cell apoptosis through these pathways, suppressing malignant proliferation and exerting anti-cancer effects.

(4) Inhibition of Invasion and Metastasis

Shiitake (Lentinula edodes) and its active ingredient, shiitake mushroom polysaccharides, have unique immune regulation effects in cancer treatment. Although their direct cytotoxicity is limited, studies have confirmed that they can inhibit tumor progression and metastasis through various mechanisms. Among them, the new shiitake-derived polysaccharide MPSSS can induce myeloid-derived suppressor cells (MDSCs) to differentiate into M1-like macrophages, thereby reducing the MDSC population and its immunosuppressive function in the tumor microenvironment, ultimately inhibiting tumor growth[184]. The mechanism by which the mushroom polysaccharide MPSSS remodels the tumor microenvironment and inhibits tumor progression is shown in **Figure 10**. In addition, shiitake mycelium polysaccharides can effectively downregulate the expression of long non-coding RNA MALAT1, which may play an important role in inhibiting advanced glycosylation end products from inducing endothelial cell activation, thus potentially interfering with the metastatic microenvironment of tumors[185]. Basic research also suggests that fermentation extracts of special strains such as C91-3 can induce apoptosis in many tumor cells including A549, S180, and H22[183], and there is evidence that its active substances may affect the adhesion ability of tumor cells. These results together

outline a profile of shiitake mushroom polysaccharides as multitarget immune regulators capable of remodeling the tumor microenvironment and interfering with the process of metastasis, suggesting promising therapeutic potential for pan-cancer therapy.

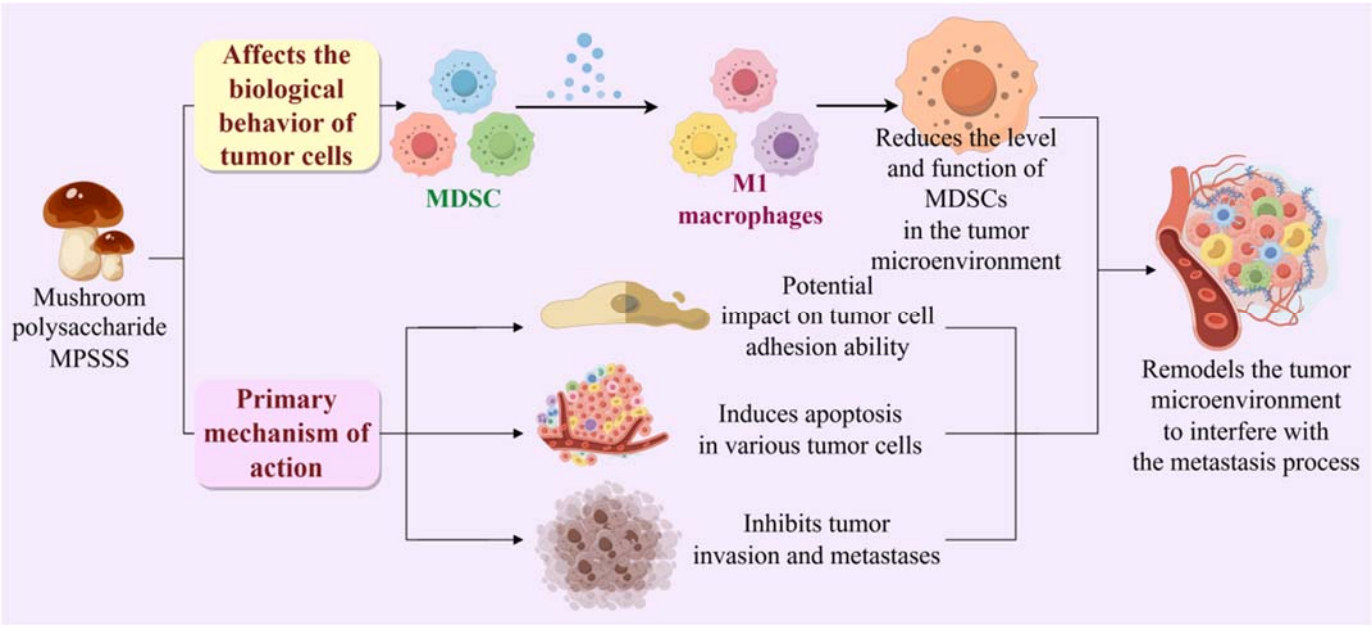

Figure 10. Mushroom Polysaccharide MPSSS Remodels Tumor Microenvironment and Inhibits Tumor Progression. This figure outlines the anti-tumor mechanisms of mushroom polysaccharide MPSSS. MPSSS induces the differentiation of myeloid-derived suppressor cells (MDSCs) into M1-like macrophages, reducing MDSC abundance and its immunosuppressive function in the tumor microenvironment. It directly induces apoptosis in various tumor cells and potentially impairs tumor cell adhesion ability. By remodeling the tumor microenvironment (regulating MDSCs and macrophages) and interfering with the metastatic process (inhibiting invasion and metastasis), MPSSS exerts comprehensive anti-tumor effects.

3.1.2 Nutritional and Immune Mechanisms

(1) Nutritional Support

In the realm of supportive cancer therapy, food-derived medicinal substances such as Chinese yam, dates, and coix seeds have gained prominence. These substances, abundant in polysaccharides, amino acids, and trace elements, offer more than just basic nutrition; they synergistically alleviate cancer-related fatigue and cachexia through various mechanisms. Research indicates that yam polysaccharide CYP-PLGA nanoparticles, formulated via emulsification-evaporation techniques, can influence the tumor immune microenvironment to exert anti-tumor effects[186]. Furthermore, date polysaccharides exhibit notable antioxidant and immunomodulatory properties[187]. Clinical studies have demonstrated that date syrup enhances appetite and quality of life in tuberculosis patients[188], a finding pertinent to cancer patients as well. Such natural compounds aid in rectifying negative nitrogen balance and preserving muscle mass, thereby providing a foundation for patients to sustain physical health and better withstand anti-tumor therapies. Their significance extends beyond mere nutritional supplementation to encompass immune modulation and metabolic enhancement, fostering an internal milieu favorable for recovery. This approach melds traditional knowledge with contemporary science, delivering holistic support for cancer patients undergoing treatment.

(2) Immune Regulation

Lingzhi (Ganoderma lucidum), a traditional medicinal fungus, exhibits a comprehensive mechanism of immune regulation in tumor therapy via its active component, Lingzhi polysaccharides. Research has established that these polysaccharides can simultaneously activate both innate and adaptive immune responses by augmenting macrophage phagocytosis, bolstering natural killer (NK) cell cytotoxicity, and triggering cytotoxic T lymphocyte (CTL) activation. This results in the formation of a synergistic anti-tumor immune network. Concurrently, there is a notable secretion of pivotal cytokines, including interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α), which are instrumental in altering the tumor's immune-tolerant microenvironment. Moreover, its bioactive constituents have been found to amplify the effectiveness of 5-fluorouracil in colorectal cancer models[189], reinforcing the breadth of its immune-regulatory capacities. Collectively, these insights emphasize that Lingzhi polysaccharides, through their multifaceted immune activation pathways, markedly boost the body's capacity for immune surveillance and tumor cell elimination, offering robust scientific validation for its incorporation into pan-cancer immunotherapeutic approaches.

Goji berry (Lycium barbarum), a key tonic herb in traditional Chinese medicine, has shown great potential for tumor immune regulation through its active ingredient, Goji polysaccharides. Studies have found that Goji polysaccharides can precisely regulate the core of the immune response by promoting dendritic cell maturation, which is a critical step in linking innate and adaptive immunity. Mature dendritic cells effectively present tumor antigens, thereby triggering and amplifying specific T-cell responses, including the proliferation and functional differentiation of CD4+ helper T cells and CD8+ killer T cells. This mechanism has been confirmed in many experiments: Goji polysaccharides inhibit the NLRP3/NF-κB pathway to reduce inflammation and oxidative stress[190] and activate the PI3K/AKT/Nrf2 signaling pathway to improve metabolic status[191], creating an environment favorable for effective T-cell activation and function within the tumor microenvironment. In particular, the promotion of dendritic cell maturation is a crucial step in eliciting potent antitumor immune responses[192]. Therefore, Goji polysaccharides provide a solid scientific basis for their inclusion in tumor immunotherapy strategies by enhancing antigen presentation and T-cell-mediated specificity immunity.

3.1.3 FMH Reshaping the Tumor Microenvironment and Metabolic Reprogramming

In terms of glycolysis inhibition, both curcumin and resveratrol exhibit potent metabolic regulatory capabilities. Curcumin can directly inhibit the activity of key metabolic enzymes such as hexokinase 2 (HK2), pyruvate kinase M2 (PKM2), and lactate dehydrogenase A (LDHA) by downregulating the expression of HIF-1α. It also blocks the function of glucose transporter 1 (GLUT1) and monocarboxylate transporters (MCTs), effectively reversing the Warburg effect and cutting off the energy supply and synthetic precursors of tumor cells[193]. Resveratrol has been shown to reduce glycolytic levels in pancreatic stellate cells (PSCs) within the stroma by inhibiting the miR-21 signaling pathway, thereby decreasing lactate secretion[194].

In remodeling the tumor microenvironment (TME), these compounds can regulate immune and stromal cells within the TME[195]. Berberine, the principal component of berberine, plays a central role in reshaping the immune microenvironment by effectively inhibiting the STAT3 signaling pathway. This leads to the

repolarization of immune-suppressive M2-type macrophages (TAMs) into anti-tumor M1-type macrophages, reducing the release of IL-10 and TGF-β, while enhancing antigen presentation[196,197]. Furthermore, berberine induces GSDME-mediated pyroptosis via the mitochondrial pathway, releasing immunostimulatory signals, promoting dendritic cell (DC) maturation, and recruiting CD8+ T cell infiltration, thus converting the tumor microenvironment from "cold" to "hot"[196,197]. Resveratrol, on the other hand, blocks the "reverse Warburg effect" in stromal cells, disrupting the metabolic coupling that delivers nutrients from stromal cells to cancer cells.

In summary, bioactive compounds derived from food and medicine intervene through multiple targets: they not only inhibit tumor cell nutrient uptake at the metabolic level but also improve the acidic and immunosuppressive microenvironment spatially. These synergistic effects collectively suppress tumor growth, invasion, and metastasis.

3.2 FMH Substances in Adjuvant Chemoradiotherapy

3.2.1 Sensitizing Effects

Curcumin, a natural polyphenolic compound, has garnered significant attention for its chemo-sensitizing effects in cancer treatment. This compound effectively counteracts the survival mechanisms of tumor cells induced by chemotherapy drugs through precise regulation of the key NF-κB signaling pathway. Research indicates that curcumin significantly inhibits the activation of the NF-κB pathway triggered by commonly used chemotherapy agents such as 5-fluorouracil (5-FU) and oxaliplatin, thereby preventing the upregulation of anti-apoptotic proteins and enhancing chemotherapy-induced apoptosis in tumor cells. In colorectal cancer models, curcumin has demonstrated an ability to inhibit epithelial-mesenchymal transition (EMT), thereby reducing tumor cell migration and invasion[198]. Remarkably, curcumin also exhibits synergy with immune checkpoint inhibitors, bolstering anti-tumor immune responses by restoring the T cell stimulatory activity of dendritic cells[199]. Additionally, studies on pancreatic cancer have shown that exosomes derived from curcumin-treated tumors display significant anti-tumor activity[200]. These multifaceted mechanisms collectively provide a theoretical foundation for the use of curcumin as a chemo-sensitizer and support its incorporation into combination chemotherapy strategies, although its bioavailability remains a critical factor to optimize for clinical application.

Soy isoflavones, particularly their active component genistein, demonstrate unique sensitizing effects in tumor radiotherapy. The primary mechanism of action involves the precise inhibition of critical DNA repair enzymes within tumor cells, such as topoisomerase II and tyrosine protein kinases. This significantly impairs the tumor cells' ability to repair DNA damage induced by radiation. Following radiation-induced DNA double-strand breaks, genistein disrupts key repair pathways, including non-homologous end joining and homologous recombination. This leads to the accumulation of damaged DNA, ultimately driving tumor cells towards apoptotic death. This molecular-level intervention in DNA repair mechanisms effectively counteracts the inherent radioresistance of tumor cells, offering an innovative strategy for enhancing radiotherapy efficacy. Despite its biosynthesis being finely regulated by transcription factors such as MYB[201], genistein

encounters challenges in clinical translation due to bioavailability issues. Nevertheless, as a natural radiation-sensitizing agent, soy isoflavones present a promising adjuvant approach in comprehensive cancer treatment.

3.2.2 Detoxifying Effects

(1) Reducing Gastrointestinal Toxicity

Ginger (Zingiber officinale), a natural antiemetic, has been widely recognized in clinical studies for its role in tumor supportive therapy. Its active components, gingerols, zingiberene and gingerones exert their effects through multiple mechanisms to alleviate chemotherapy-induced nausea and vomiting (CINV). They Not only directly act on the central and peripheral emetic reflex pathways by inhibiting 5-HT3 and muscarinic M3 receptors but also regulate gastrointestinal motility to relieve digestive symptoms[202]. Clinical evidence shows that ginger preparations at daily doses as high as 2 g significantly control vomiting episodes with good safety profiles[202]. Notably, the combination of ginger and curcumin further enhances anti-inflammatory effects via activation of the Nrf2/HO-1 pathway, providing a new dimension in controlling inflammation-related nausea[81]. This multi-pathway mechanism of action makes ginger an ideal adjunctive therapy for CINV patients who experience insufficient efficacy or adverse reactions from conventional antiemetic drugs. Its value in improving the quality of life of cancer patients goes beyond traditional herbal remedies, making it an indispensable adjunct in integrative medicine.

Within the realm of tumor supportive therapy, traditional medicines such as hawthorn (Crataegus pinnatifida) and dried tangerine peel (Chenpi), known for their ability to strengthen the spleen and regulate qi, are gaining recognition due to their modern pharmacological mechanisms. Research indicates that the flavonoid components in hawthorn can effectively modulate digestive function by inhibiting the activity of α-glucosidase and α-amylase, thereby significantly delaying the rate of starch hydrolysis[203]. This not only aids in maintaining blood glucose homeostasis but also mitigates common postprandial bloating symptoms experienced by cancer patients. The volatile oils and flavonoids present in dried tangerine peel stimulate the secretion of digestive fluids and regulate gastrointestinal motility, directly alleviating cancer-related anorexia and early satiety. The Active components produced during its solid-state fermentation process further demonstrate its potential for multi-dimensional regulation of gastrointestinal function[204]. The combined effects of these substances can effectively rectify gastrointestinal dysfunction within the tumor microenvironment, thereby supporting the maintenance of baseline nutritional status by enhancing nutrient intake efficiency. This metabolic regulatory strategy, which is based on improving digestive function, provides a scientific basis for the incorporation of traditional Chinese medicine into comprehensive tumor supportive treatment.

(2) Reducing Cardiotoxicity

Astragaloside, a key active component of Astragalus membranaceus, demonstrates significant cardioprotective properties in the context of tumor therapy. Its mechanism for protecting against anthracycline drug-induced cardiotoxicity, such as that caused by doxorubicin, has been substantiated through

experimentation: it reinstates myocardial redox balance, markedly diminishes ROS levels, and impedes mitochondrial membrane potential decay, thereby mitigating oxidative stress damage[205]. At a molecular level, astragaloside modulates the miR-375/PDK1/AKT signaling axis to curtail doxorubicin-induced apoptosis in myocardial cells[206]. Remarkably, this compound also enhances myocardial energy metabolism, preserves myocardial cell contractile function, and alleviates diastolic dysfunction induced by doxorubicin[207]. This multifaceted protective mechanism not only offers a cardioprotective strategy for cancer patients undergoing anthracycline chemotherapy but also ensures the integrity and efficacy of chemotherapy regimens by reducing the risk of cardiotoxicity. This underscores the significant auxiliary value of active compounds in traditional Chinese medicine in comprehensive cancer therapy.

(3) Reducing Neurotoxicity

Cinnamon (Cinnamomum verum), which has antibacterial properties, contains active ingredients such as cinnamaldehyde, eugenol, benzoic acid, benzaldehyde and cinnamic acid. These components endow cinnamon with antimicrobial and neuroprotective effects. Cinnamon nanoparticles can generate ROS to induce oxidative stress in bacteria[208]. In tumor supportive therapy, cinnamon and its active ingredients have the potential to regulate chemotherapy-induced peripheral neurotoxicity. Studies have shown that cinnamaldehyde, the main active ingredient of cinnamon, can alleviate the neurotoxicity induced by chemotherapeutic drugs such as oxaliplatin through multiple pathways. It significantly inhibited the expression of inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2), reduced the levels of pro-inflammatory mediators such as nitric oxide and prostaglandin E2, thereby alleviating inflammation in the dorsal root ganglia and peripheral nerves[209]. This anti-inflammatory effect combined with its antioxidant mechanism counteracts the oxidative damage caused by oxaliplatin[210]. Although duloxetine and other drugs are still the main treatment options for neurotoxicity[211], the multi-target action characteristics of cinnamon's active ingredients provide new intervention strategies for preventing and improving chemotherapy-related peripheral neuropathy, especially by regulating neuroinflammation, which may bring dual benefits of maintaining the intensity of chemotherapy dosage and improving patients' quality of life.

(4) Protecting Bone Marrow Function

Donkey-hide gelatin (Ejiao) and Angelica sinensis (Danggui), traditional herbs known for their blood-tonifying properties, are increasingly recognized in modern pharmacology for their potential role in tumor supportive therapy. Research indicates that these herbs can mitigate chemotherapy-induced bone marrow suppression through multifaceted mechanisms. The renowned formulation, Siwu Decoction, which includes Angelica sinensis and Rehmannia glutinosa among other ingredients, markedly enhances hematopoietic stem cell proliferation and differentiation. This leads to elevated levels of leukocytes, erythrocytes, and platelets in peripheral blood. The underlying mechanisms encompass the modulation of the bone marrow microenvironment, enhancement of mitochondrial function, and rectification of metabolic imbalances, collectively safeguarding hematopoietic stem cells from chemotherapy-induced damage[212]. It is noteworthy that the blood-tonifying efficacy of Angelica sinensis is considerably amplified post-processing.

its active constituents stimulate the secretion of hematopoietic factors and modulate associated signaling pathways, thereby expediting the recovery of hematopoiesis[213]. Such comprehensive regulatory influence on the hematopoietic system offers robust scientific substantiation for incorporating donkey-hide gelatin and Angelica sinensis as adjuncts in tumor treatment, underscoring their distinct benefits in addressing chemotherapy-associated hematologic toxicity.

As traditional blood-nourishing medicines, Donkey-hide gelatin (Ejiao) and Angelica sinensis (Danggui) are increasingly being validated for their value in cancer supportive therapy through modern pharmacology. Studies have shown that both can improve chemotherapy- and radiotherapy-induced bone marrow suppression via multitarget mechanisms. The classic formula Siwu Decoction (containing Angelica sinensis, prepared Rehmannia, etc.) significantly promotes the proliferation and differentiation of hematopoietic stem cells and increases peripheral blood leukocytes, erythrocytes, and platelets. Its underlying mechanism involves regulating the bone marrow microenvironment, improving mitochondrial function, and correcting metabolic disorders, thereby protecting hematopoietic stem cells from damage caused by chemotherapeutic agents[214]. Notably, the blood-nourishing effect of Angelica sinensis is significantly enhanced after processing because its active ingredients can promote the secretion of hematopoietic factors and regulate related signaling pathways, accelerating the recovery of hematopoiesis[215]. This multidimensional regulation of the hematopoietic system provides a scientific basis for using Ejiao and Danggui as adjunct therapies in cancer treatment, highlighting their unique advantages in managing treatment-related hematological toxicity.

3.2.3 Reversing Drug Resistance

Curcumin, a natural polyphenol derived from the rhizome of Curcuma longa, has been widely confirmed as one of the critical agents in reversing multidrug resistance (MDR) in cancer research[216,217]. Its core mechanism involves effectively antagonizing the drug efflux pump function mediated by the overexpression of P-glycoprotein (P-gp). P-gp, an ATP-dependent transmembrane transporter, actively pumps out a variety of chemotherapeutic drugs (such as paclitaxel, doxorubicin, etc.) from the cell, directly leading to a decrease in intracellular drug concentration and treatment failure[218,219]. Curcumin counteracts this resistance through a dual strategy: at the molecular level, it downregulates the expression of P-gp; at the functional level, it competitively binds to P-gp's drug-binding pocket or ATP-binding site, directly inhibiting its efflux activity. This inhibitory effect has been validated in various resistant tumor models, including leukemia CCRF-CEM/ADR5000 cells, cervical cancer KB-V1 cells, and osteosarcoma MNNG/HOS/MTX cells, as evidenced by a significant increase in intracellular accumulation of chemotherapy drugs and the restoration of chemotherapy sensitivity[220,221]. Notably, to overcome the challenges of curcumin’s poor water solubility, rapid metabolism, and low oral bioavailability, novel delivery systems (such as PLGA nanoparticles conjugated with anti-P-gp antibodies) have demonstrated outstanding targeting and enhancement capabilities[6,222,223]. These advancements have solidified curcumin’s position as a promising MDR reversal agent in pan-cancer therapy. The main polyphenolic component in green tea extract, epigallocatechin gallate

(EGCG), has shown potential as a multidrug resistance modulator in pan-cancer treatment. EGCG enhances the efficacy of conventional chemotherapy drugs by inhibiting the activity of P-glycoprotein (P-gp) and multidrug resistance-associated protein 1 (MRP1). Studies have shown that although EGCG is not a substrate of P-gp, it acts as a natural P-gp inhibitor by competitively binding or modulating the ATPase function to reduce chemotherapeutic drug efflux such as anthracyclines and taxanes, thereby increasing intracellular drug accumulation[224]. In addition, EGCG and its methylated metabolites were confirmed as MRP1 and MRP2 substrates but significantly increased drug retention in cancer cells when co-administered with chemotherapeutics through MRP inhibition. For example, sevenfold higher EGCG accumulation was observed in MDCKII/MRP1 cells in the presence of inhibitors, which further enhanced cytotoxicity[225]. This dual inhibition not only overcomes multidrug resistance but also cooperates with JAK/STAT and apoptotic pathway modulation to promote cancer cell death, providing a combination strategy for pan-cancer treatment[226]. Although preclinical data support its sensitizing effects, further clinical trials are needed to optimize EGCG delivery and verify its safety and efficacy.

When integrated with contemporary chemoradiotherapy, substances derived from FMH demonstrate synergistic effects, including 'sensitization, toxicity reduction, and multidrug resistance reversal'. This offers a safer and more efficacious comprehensive treatment approach for oncology patients. Table 5 delineates the three primary adjuvant effects of these substances in chemoradiotherapy and elucidates their underlying mechanisms.

Table 5. Adjuvant Effects of FMH Substances in Chemoradiotherapy

Active Components	Source Plant(s)	Cancer Type(s)	Experiment Type(s)	Mechanism	Ref.
Flavonoids	Celery (Apium graveolens), Parsley (Petroselinum crispum), Hops (Humulus lupulus)	Colon cancer	Cell (HCT116, HT-29, T84), Animal (Syrian hamster model)	Chemosensitization and reduction of toxicity: Synergizes with 5-FU by inhibiting p38 MAPK and NF-κB, inducing apoptosis; alleviates chemotherapy side effects such as mucositis and neuropathic pain.	[227]
Astragaloside IV	Astragalus membranaceus (Astragalus)	Leukemia	Cell (K562), Animal (TBI mouse model)	Radio-sensitization and bone marrow protection: Activates AMPK/PGC1α to enhance mitochondrial function and hematopoiesis post-radiation, improving blood cell counts.	[228]
Dietary Citrulline	Citrullus lanatus (Watermelon)	Colon cancer	Rat Ward colon tumor model	Muscle protein synthesis: Activates mTORC1 to counteract chemotherapy-induced muscle wasting, though no improvement in chemotherapy efficacy was observed.	[229]
Lentinan	Lentinula edodes (Shiitake mushroom)	Colon cancer, Melanoma	Mouse subcutaneous xenograft (MC38, B16F10)	Enhances CAR-T therapy: Promotes memory T cell differentiation, reduces exhaustion (TIM-3), and reprograms tumor-associated macrophages (TAMs) to M1 phenotype.	[230]
Diallyl Trisulfide	Allium sativum (Garlic)	Stomach cancer	Cell (BGC-823), Mouse xenograft	Enhances cisplatin efficacy: Induces G2/M arrest and activates p38/JNK, induces apoptosis; inhibits Nrf2/Akt pathway to reduce drug resistance.	[231]
Resveratrol	Berries, Nuts, Red wine	Colon cancer, Melanoma	Cell (CT26, B16F10)	Radiosensitization: Increases ROS under radiation, reduces mitochondrial potential, depletes glutathione, enhances radiation-induced apoptosis.	[232]
Piperine	Piper longum (Long pepper), Piper nigrum (Black pepper)	Colon cancer, Melanoma	Cell (CT26, B16F10)	Radiosensitization: Enhances ROS generation, disrupts mitochondrial function, activates Caspase cascade, promotes apoptosis in response to radiation.	[232]
Phenylethyl Isothiocyanate	Nasturtium officinale (Watercress)	Breast cancer	Cell (MCF-7)	Radiosensitization: Depletes glutathione, disrupts redox balance, increases DNA damage under radiation, enhances radiotherapy effectiveness.	[233]
β-Elemene	Curcuma wenyujin (Turmeric)	Glioblastoma	Clinical (GBM patients), Cell (U87-MG, T98G)	Dual sensitization (chemotherapy + radiotherapy): Inhibits ATM, AKT, ERK pathways, interferes with DNA repair, enhances radiosensitivity and chemosensitivity, induces apoptosis.	[234]
β-Carotene	Various fruits and vegetables	Breast cancer, Head and neck cancer	Clinical (Prevention study), Cell (P-gp/MRP1/BCRP resistant lines)	MDR reversal: Enhances chemotherapy effectiveness by inhibiting P-glycoprotein (P-gp) and BCRP, improving paclitaxel and doxorubicin efficacy against resistant cells.	[235]
Capsaicin	Capsicum (Chili pepper)	Cholangiocarcinoma	Cell (QBC939, SK-ChA-1, MZ-ChA-1), Mouse xenograft	Autophagy inhibition to enhance sensitivity: Activates PI3K/AKT/mTOR, inhibits protective autophagy, increases 5-FU-induced apoptosis and reduces tumor volume.	[236]
Indole-3-Carbinol	Cruciferous vegetables (e.g., Broccoli, Cabbage)	Ovarian cancer, Primary peritoneal cancer, Cervical cancer, Prostate cancer	Clinical (Ovarian cancer, ongoing), Cell (OVCAR5), Animal (xenograft)	Chemosensitization: Synergizes with Bortezomib, induces G2-M arrest, disrupts ER stress, downregulates drug resistance genes, sensitizes cancer cells to cisplatin/carboplatin.	[237]

4. Application of FMH Substances in Post-Treatment Recovery and Immune Enhancement

4.1 Promoting Body Repair

Dangqi-Qi Decoction, composed of Codonopsis pilosula and Astragalus membranaceus, focuses on the rehabilitation stage rather than direct cytotoxicity, aiming to replenish energy and mitigate the physiological exhaustion induced by intensive surgery and chemotherapy. Research indicates that polysaccharides from Codonopsis significantly enhance the antitumor efficacy of dendritic cell vaccines by promoting antigen presentation and T-cell activation, thereby altering the immune status of the tumor microenvironment[238]. Polysaccharides from Astragalus act as key immune adjuvants, activating macrophages and natural killer cells, upregulating interferon-γ and other Th1 cytokine secretions, and fostering an immune response conducive to antitumor effects. In patients undergoing tumor surgery, this combination therapy effectively mitigates cancer-related fatigue and metabolic disorders by regulating the SIRT3/SIRT1/PGC-1α signaling pathway and improving oxidative stress conditions[239]. The mechanism encompasses multi-target regulation: active components in Codonopsis, such as Mannose-B, modulate cell differentiation processes[240], offering gastrointestinal protection and anti-aging benefits[241]. Meanwhile, unique acetylene components in Astragalus regulate the inflammatory network, jointly preserving immune homeostasis. Grounded in the traditional concept of "replenishing qi and solidifying the foundation," these pharmacological effects offer scientific validation for immune function reconstruction during the perioperative phase of cancer treatment, underscoring the distinctive contribution of traditional Chinese medicine to integrated cancer care.

Five Red Decoction, a traditional food therapy formula, exhibits unique metabolic support value in tumor supportive therapy. This formula employs the synergistic effects of key ingredients such as red beans and jujube to provide a multi-target intervention strategy for cancer-related anemia. Research indicates that jujube polysaccharides have significant immune-regulatory and antioxidant properties, which aid in restoring the function of the hematopoietic microenvironment and improving anemic conditions[187]. Within the tumor microenvironment, chemotherapy drugs and malignant consumption often result in iron metabolism disorders and erythropoietin resistance. The natural plant compounds found in Five Red Decoction may regulate the hepcidin-ferroportin axis, enhance iron utilization efficiency, and stimulate the differentiation of erythroid progenitor cells. This nutritional intervention model not only supplies essential amino acids, trace elements, and vitamins for bone marrow hematopoiesis but also provides functional regulation of hematopoietic stem cells and progenitor cells through the synergistic effects of multiple components. Consequently, it alleviates anemia symptoms while supporting patients' overall physical condition and enhancing their quality of life, thereby highlighting the distinctive role of traditional food therapy in contemporary integrated cancer treatment[242].

Cistanche-Shaoyao Pigeon Soup aids in the recovery of kidney function and warming yang for convalescent patients. Cistanche deserticola, a traditional tonic herb, exhibits multi-target potential in tumor supportive therapy[243,244]. Studies indicate that the primary active components of Cistanche, phenylethanoid glycosides (including echinacoside and acteoside), have neuroprotective and antioxidant properties and influence the tumor microenvironment. A Network pharmacology analysis indicates that the combination of Cistanche and Epimedium can impact the expression of key genes such as TP53, VEGFA, and AKT1 by modulating the PI3K-AKT signaling pathway, HIF-1 signaling pathway, and T-cell receptor signaling pathway. This interaction contributes to antitumor effects, promotes osteoblast differentiation, and induces osteoclast apoptosis in breast cancer bone metastasis models. Additionally, the immunomodulatory functions of Cistanche may enhance the immune status of cancer patients, and its hormone-like regulatory effects might be significant in alleviating certain endocrine-related tumor symptoms[243,244]. These diverse pharmacological actions provide scientific backing for the use of Cistanche in comprehensive cancer treatment, particularly in modulating bone and immune microenvironments, meriting further investigation.

4.2 Activation and Enhancement of Immunity

In the post-treatment recovery phase, Ganoderma lucidum polysaccharides prioritize immune system reconstruction rather than direct tumor killing, boosting antitumor surveillance and reversing the immune exhaustion caused by standard oncology therapies**.** Central to this process is the activation and polarization of macrophages towards the antitumor M1 phenotype. This transformation is mediated by the TLR4 receptor-dependent activation of the NF-κB and MAPK signaling pathways, which in turn promotes the secretion of pro-inflammatory cytokines while downregulating the expression of anti-inflammatory cytokines. Concurrently, these polysaccharides have the capacity to reconfigure the tumor microenvironment, counteracting the pro-tumor phenotype of tumor-associated macrophages and effectively modulating adaptive immune responses. This results in the normalization of CD4+/CD8+ T cell ratios, heightened B cell activity, and elevated immunoglobulin levels. Intriguingly, Ganoderma lucidum polysaccharides also augment the effectiveness of traditional chemotherapy agents by inhibiting EGFR-mediated signaling pathways, thereby amplifying cisplatin-induced apoptosis in tumor cells[245–247]. These collective mechanisms underpin the molecular foundation for the use of Ganoderma lucidum polysaccharides as an adjunct in tumor immunotherapy, substantiating its application in comprehensive cancer supportive treatment.

Lycium barbarum polysaccharides exhibit multi-target regulatory potential in tumor immunotherapy, with the core mechanism being the enhancement of antitumor immune responses through regulation of the dendritic cell–T cell axis. Studies have shown that Lycium barbarum polysaccharides promote dendritic cell maturation and antigen presentation, thereby triggering specific T cell immunity[192]. At the tumor microenvironment level, it alleviates inflammation and oxidative stress by inhibiting the NLRP3/NF-κB signaling pathway[246] while improving metabolic status via the PI3K/AKT/Nrf2 pathway[191], creating favorable conditions for effector T cell function. This dual regulation of both innate and adaptive immunity enables Lycium barbarum polysaccharides to effectively enhance the body’s immune surveillance and

clearance of tumor cells, providing a molecular basis for their integration into tumor immunotherapy strategies.

5. Clinical-Related Research

5.1 Clinical Practice of Nutritional Support

In the realm of pan-cancer treatment, nutritional support has transitioned from a supplementary role to a central component of comprehensive therapeutic strategies. This shift is grounded in the global Leadership initiative on malnutrition (GLIM) standards and enriched by individualized nutritional interventions derived from traditional Chinese medicine (TCM). The mechanisms of these interventions extend beyond mere nutritional supplementation. Research indicates that such integrated nutritional support can enhance clinical outcomes in cancer patients through multifaceted mechanisms. Accurate nutritional diagnosis and targeted interventions initially decrease the occurrence of treatment-related adverse events, ensuring the seamless execution of anti-cancer therapies. Crucially, by optimizing the body's nutritional status and energy metabolism, this approach augments patients' physical well-being and functional capacities, establishing a robust physiological foundation for enduring intensive anti-cancer treatments. At the molecular level, suitable nutritional interventions might alter the metabolic state of the tumor microenvironment, thereby influencing cancer cell energy provision and signal transduction. Randomized controlled studies in patients with gastrointestinal malignancies have demonstrated that the combination of GLIM-based differentiated dietary tables and TCM dietary therapy significantly improves nutritional status, physical condition, and overall quality of life. This integrated intervention may indirectly enhance anti-tumor immune responses and increase tumor cell sensitivity to therapeutic drugs by addressing cancer cachexia-related metabolic disorders. Consequently, integrating GLIM standards with TCM dietary therapy into individualized nutritional support strategies offers multifaceted clinical benefits in pan-cancer treatments. It establishes a metabolic foundation for patients to better tolerate standardized treatments and potentially boosts anti-cancer efficacy by modulating the tumor's metabolic microenvironment. Ultimately, this approach achieves the dual objectives of enhancing quality of life and improving clinical outcomes. Such an integrative medicine model provides novel insights and evidence for cancer nutrition therapy.

5.2 Clinical Potential of Specific Components

A recent pivotal study underscores the crucial role of dietary fatty acids in modulating tumor immunity. This research demonstrates that oleic acid, a monounsaturated fatty acid prevalent in olive oil and avocado, markedly bolsters the anti-tumor immune response of γδ-T cells. Conversely, palmitic acid, present in palm oil and animal fats, manifests immunosuppressive effects. At the mechanistic level, oleic acid upregulates the expression of genes associated with effector functions in γδ-T cells via epigenetic modulation, thereby amplifying their capacity to detect and destroy tumor cells. Intriguingly, clinical data analysis substantiates that elevated levels of oleic acid in peripheral blood correlate positively with improved therapeutic outcomes from immune checkpoint inhibitors, offering a molecular rationale for integrating nutritional strategies with

immunotherapy[248]. This groundbreaking investigation advocates for increased dietary intake of oleic acid to augment the anti-tumor surveillance capabilities of γδ-T cells, establishing a scientific precedent for immune-nutritional approaches in comprehensive cancer treatment. Central to this is the interplay between cellular metabolism and epigenetic regulation: Oleic acid acts as a signaling molecule, influencing cell membrane fluidity and lipid raft configurations, which in turn optimizes the assembly and signal transduction efficacy of γδ-T cell receptors (γδTCR). At the molecular level, oleic acid metabolites function as co-factors for histone-modifying enzymes, thereby modulating chromatin accessibility and facilitating the transcriptional activation of effector molecules such as interferon-γ (IFN-γ) and granzyme B. Furthermore, oleic acid stabilizes the mitochondrial membrane potential, which enhances oxidative phosphorylation metabolism in γδ-T cells, providing them with the energy required for sustained anti-tumor functions. This multifaceted regulatory mechanism positions oleic acid as a promising clinical immune-metabolic modulator, presenting novel targets for tumor immunonutrition therapy[249].

5.3 Clinical Research Challenges and Directions

FMH substances exhibit significant auxiliary therapeutic value in pan-cancer treatment due to their unique multi-target and low-toxicity mechanisms. Unlike traditional chemotherapy drugs that directly destroy tumor cells, these substances primarily exert anti-tumor effects through indirect pathways such as immune modulation, metabolic reprogramming, and epigenetic modifications. Research indicates that bioactive components, including polysaccharides from Lycium barbarum (goji berry) and Ganoderma lucidum (reishi mushroom), enhance anti-tumor immune responses by regulating the dendritic cell-T cell axis and tumor-associated macrophage polarization states. Similarly, components like Coix lacryma-jobi (job's tears) lactone interfere with key signaling pathways, such as PI3K/Akt/mTOR, to alter the tumor metabolic microenvironment. these natural compounds also show considerable potential in reversing tumor drug resistance, owing to Their multi-component nature which allows them to target multiple resistance-related pathways simultaneously, thereby increasing sensitivity to conventional chemotherapy drugs. Furthermore, FMH substances can improve the body’s anti-tumor immune status by modulating the gut microbiome-immune axis.

Although clinical studies specifically focusing on FMH substances are still relatively limited, and their single-agent antitumor effects are weaker compared to traditional chemotherapy, their excellent safety profile and multiple mechanisms of action make them promising adjuncts in cancer therapy. Future research needs to be more rigorous, utilizing innovative models like patient-derived organoids[250] (PDOs) and patient-derived xenografts[251] (PDXs), to further validate the clinical value of these substances in pan-cancer treatment[252–254]. The core mechanism of antitumor action of FMH substances lies in their multicomponent, multitarget synergistic action model[255]. At the molecular level, various active components in these substances can simultaneously target multiple aspects such as immune cell function modulation, tumor microenvironment remodeling, and epigenetic regulation. For example, polysaccharide components primarily activate innate immunity via pattern recognition receptors like Toll-like receptors, enhancing the maturation

and function of antigen-presenting cells; while small molecules inhibit histone deacetylases and other epigenetic regulators, altering the gene expression profile of tumor cells. This multilayered network of action not only directly suppresses tumor progression but also enhances the efficacy of existing immunotherapy and chemotherapy by improving the immunosuppressive state of the tumor microenvironment. Importantly, the low toxicity of FMH substances to normal tissues makes them particularly suitable for long-term use, which is crucial for the management of malignant tumors requiring continuous treatment. Despite this, more high-quality studies are needed to support their clinical translation[256].

6. New Technologies for the Application of FMH Substances in Cancer Treatment

In the use of FMH substances for cancer treatment, bioavailability is a major challenge limiting their clinical application. Many FMH compounds have poor solubility and bioavailability, which restricts their absorption and therapeutic effects in the body. To enhance efficacy, researchers have employed various strategies to address this issue, such as using nanotechnology or formulation innovations to improve the solubility and stability of FMH components. Additionally, drug delivery systems allow for the targeted release of FMH substances within the tumor microenvironment, boosting their anti-cancer effects while minimizing toxicity to healthy tissues. These advancements in technology open up new possibilities for the clinical application of FMH substances.

6.1 Cutting-Edge Technology for Mechanism Analysis

A research team from the Chinese Academy of Agricultural Sciences has pioneered a polymerase-driven DNA molecular computation diagnostic platform. This innovative method offers insights into the mechanisms of FMH bioactive components in pan-cancer treatment. Leveraging machine learning, the platform screens cancer-specific microRNAs and assigns them diagnostic weight values, thereby constructing a high-precision molecular classifier[257,258]. Notably, the platform elucidated the molecular mechanism through which allicin and curcumin impede the growth of non-small cell lung cancer (NSCLC) by modulating the expression of specific miRNAs. The findings indicate that these natural bioactive compounds markedly influence key signaling pathways, including TGF-β and PI3K-Akt. They orchestrate the expression networks of various oncogenes and tumor suppressor genes, facilitating multi-tiered regulation of tumor proliferation, apoptosis, and metastasis. This miRNA-centric regulatory approach not only presents novel targets for NSCLC intervention but also underscores the potential of FMH components in pan-cancer therapy[259]. Instead of directly inducing cytotoxicity, this method refines the gene expression profile, offering more precise tumor intervention[260]. Such research paves the way for a systems biology perspective on the anti-cancer properties of natural compounds.

6.2 Nanotechnology and Formulation Innovation

In the realm of pan-cancer therapeutics, FMH bioactive components present a novel strategy for enhancing the therapeutic index of conventional chemotherapy agents through molecular self-assembly into nanostructures and our recent research discusses this field in detail[261,262]. Natural compounds such as

polyphenols and saponins, replete with functional groups, can autonomously assemble into nanoparticles, micelles, or vesicles via molecular interactions including hydrogen bonding, π-π stacking, and hydrophobic forces[263–265]. These self-assembled systems derived from natural products not only adeptly encapsulate hydrophobic chemotherapeutic agents, bolstering their solubility and stability, but also augment tumor-specific accumulation due to the enhanced permeability and retention (EPR) effect, markedly diminishing off-target toxicity to healthy tissues. Research indicates that these self-assembled nanostructures demonstrate superior biocompatibility in systemic circulation and can discharge active constituents in response to specific cues within the tumor microenvironment, such as variations in pH and enzymatic activity, facilitating intelligent drug delivery[266]. Remarkably, certain FMH components inherently exhibit immunomodulatory or sensitizing attributes, producing a synergistic anti-tumor impact alongside chemotherapy drugs[267,268]. This collaboration mitigates the adverse effects of traditional chemotherapy while substantially elevating overall treatment efficacy[269,270]. Such an approach ingeniously marries the multi-target potential of natural products with the precision delivery paradigm of nanomedicine, heralding a fresh avenue for pan-cancer interventions.

7. Conclusion

This review provides a comprehensive synthesis of the role of FMH substances in pan-cancer prevention, treatment, and post-therapy recovery. It highlights their unique advantages, including multi-component, multi-targeted regulation and high safety. The core mechanisms are systematically elaborated upon: antioxidant effects through free radical scavenging, enhancement of endogenous enzymes, and metal ion chelation; inflammation inhibition by targeting key pathways such as NF-κB and COX-2/PGE2; immune modulation via nutrient supply and activation of immune cells; direct tumor suppression through arresting proliferation, inducing apoptosis, and inhibiting metastasis; and adjuvant benefits in chemoradiotherapy, including sensitization, toxicity reduction, and reversal of drug resistance. The review integrates preclinical mechanistic studies with emerging clinical evidence, underscoring the translational potential of FMH substances while acknowledging current challenges like limited large-scale clinical trials and bioavailability issues. It emphasizes the significance of modern technologies, such as nanodelivery systems and omics, in advancing FMH research. Ultimately, this work establishes a reference point for the clinical application of FMH substances, showing considerable potential for inclusion in mainstream cancer treatments. This paves the way for innovative, personalized, and safe cancer treatment strategies.

Ethical Approval and Consent to participate

Not applicable.

Consent for publication

All the authors declare no conflicts of interest and are published uniformly.

Data availability

The datasets used and analyzed during the current study available from the corresponding author on reasonable request.

Declaration of competing interest

The authors declare no competing interests.

Funding

No funding support is involved.

Reference

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