JOURNAL OF NEUTRACEUTICALS AND HEALTH
Jul-Dec 2025, VOL. 3, ISSUE 2, pp. 3-12
https://doi.org/10.61577/jnh.2025.100007

RESEAPRO JOURNALS

REVIEW

OPEN ACCESS

Effects of nutraceuticals on inflammation and tumorigenesis: A review

Azime Irem Kuruhalila and Halit Tanju Besler

Department of Nutrition and Dietetics, Faculty of Health Sciences, Istanbul Aydın University, Istanbul, Turkey

ABSTRACT

Nutraceuticals are bioactive compounds that integrate the functional properties of nutrients and pharmaceuticals, offering notable benefits in promoting health, preventing diseases, and providing therapeutic solutions. Their capacity to influence biological pathways associated with chronic inflammation has garnered significant scientific attention. Chronic inflammation serves as a major contributor to carcinogenesis, driving processes such as cellular transformation, proliferation, invasion, metastasis, and angiogenesis. The therapeutic potential of nutraceuticals lies in their ability to target critical inflammatory pathways and transcription factors, including NF-κB and STAT3, which play pivotal roles in regulating inflammatory and tumorigenic processes. These compounds, encompassing polyphenols, vitamins, and other plant-derived bioactives, are also recognized for their antioxidative properties, which help mitigate oxidative stress, a key factor in the progression of chronic diseases. Telomere length serves as a molecular clock, measuring the number of cell divisions and playing a crucial role in cellular aging. Telomeres shorten with each cell division, leading to genomic instability and cellular aging. The enzyme telomerase helps maintain telomere length, crucial for delaying cellular senescence. Diets rich in omega-3 fatty acids, antioxidant vitamins, carotenoids, and polyphenols, such as the Mediterranean diet, can mitigate telomere shortening and promote genomic stability. Increased physical activity also positively influences telomere length, reducing oxidative damage and supporting healthy aging. By alleviating oxidative and inflammatory damage, nutraceuticals support healthy aging and the prevention of inflammation-related diseases. Given their multifaceted effects on cellular mechanisms, nutraceuticals emerge as promising candidates for advancing therapeutic and preventive strategies in modern medicine and nutrition. Their application in personalized and integrative approaches warrants further research to fully unlock their potential in clinical settings.

KEY WORDS

Nutraceuticals; Inflammation; Tumorigenesis; Cancer; Telomere integrity

ARTICLE HISTORY

Received 02 July 2025;
Revised 23 July 2025;
Accepted 11 August 2025

Introduction

Biologically active molecules are effective in the protection and development of health and the proper maintenance of normal physiological function. Nutraceuticals, which are biologically active molecules found in foods, are compounds that have similar properties to both nutrients and pharmaceuticals [1]. Although they are present in small amounts in foods, nutraceuticals are associated with many health benefits. In the current literature studies, nutraceuticals are promising therapeutic agents in many health problems such as atherosclerosis, hypertension, cardiovascular diseases, inflammation, diabetes, obesity, cancer, osteoporosis, arthritis and neurological disorders [1,2].

Nutraceuticals with various properties such as antioxidant, anti-inflammatory, antitumor and anticancer help to prevent diseases caused by these by acting on oxidative stress and inflammation. Nutraceutical compounds reduce inflammation by acting on various proinflammatory transcription factors such as nuclear factor κB (NF-κB) and signal transducer and activator of transcription factor 3 (STAT3), which are among the most important regulators of inflammation. Nutraceutical compounds reduce inflammation by acting on various proinflammatory transcription factors such as NF-κB and STAT3, which are among the most important regulators of inflammation [3]. Molecular targets of transcription factors of nutraceuticals on cytokines, growth factors and protein kinases are of great importance as they constitute a potential strategy for inflammation and cancer.

Telomeres, which play an important role in maintaining DNA stability, are structures necessary to prevent chromosomal fusion [4]. Telomere shortening comes to the fore in existing literature studies due to its association with various chronic diseases and cellular aging. Abrasions that can cause dysfunction on telomeres are important as they can be effective in the onset of the early stages of cancer [5]. This review paper aims to elucidate the connections between inflammatory molecules and transcription molecules that play a role in inflammation and therefore tumorigenesis by nutraceuticals targeting multiple cellular signaling and focus on the role of telomeres in aging.

Nutraceuticals

Nutraceuticals are defined as a food or food component that ensures medical and health benefits in the prevention and treatment of diseases [6]. The term nutraceutical, coined by Stephen DeFelice in 1989, is a combination of the words "nutrient" and "pharmaceutical" [7]. Nutraceuticals generally consist of modified or unmodified whole food, plant extracts alone or in combination, semi-or fully purified phytochemicals, and combinations of various phytochemicals [8].

Nutraceuticals are classified in different ways according to their properties such as food sources, chemical structures and mechanisms of action. Dietary fiber, probiotics, prebiotics, polyunsaturated fatty acids, antioxidant vitamins consisting of vitamins A, C and E, polyphenols and spices are the major

***Correspondence:** Dr. Halit Tanju Besler, Department of Nutrition and Dietetics, Faculty of Health Sciences, Istanbul Aydın University, Istanbul, Turkey, e-mail: halittanjubesler@aydin.edu.tr

groups that make up nutraceuticals. In addition, nutraceutical compounds whose health benefits have not been completed or completed are also examined under two groups, potential nutraceuticals and established nutraceuticals, respectively. A potential nutraceutical is becoming an established nutraceutical, with clinical data on its medicinal benefits being proven [2].

The term nutraceutical is often used misleadingly to functional foods, prebiotics, probiotics, herbal products, dietary supplements, medical foods [7,9]. Nutraceuticals are different from nutritional supplements, although they are administered in the same forms as dietary supplements, such as pills, tablets, capsules, or liquids.

Nutraceuticals act as cellular and functional modulators in the proper maintenance of physiological processes. Because of these health benefits, nutraceuticals help with cancer and inflammation and related health problems such as metabolic syndrome, obesity, diabetes, cardiovascular diseases and osteoporosis. Nutraceuticals, which are used as a promising treatment option in the prevention of diseases and health problems, also affect the modulation of proinflammatory response in the immune system [7].

Effects of Nutraceuticals on Inflammation

Inflammation

Inflammation, derived from the Latin word inflammatio, meaning "to set on fire," is an essential physiological process triggered by pathogen infections or tissue damage [3,10]. It is characterized by classic symptoms such as pain, redness, swelling, and increased temperature. While acute inflammation is a rapid immune response facilitating tissue repair and pathogen clearance, chronic inflammation arises from prolonged immune activity and unresolved tissue damage [10,11].

Chronic inflammation is marked by the persistent secretion of proinflammatory factors, including cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6), as well as chemokines, which disrupt cellular homeostasis. This process underlies several pathological conditions, including autoimmune diseases, metabolic syndromes, neurodegenerative disorders, and cancer [11].

In cancer, chronic inflammation fuels tumorigenesis by promoting genetic mutations, cell proliferation, and angiogenesis. Proinflammatory cytokines such as IL-6 and TNF-α create a tumor-supportive microenvironment, enhancing tumor invasion and metastasis. Studies indicate that up to 25% of cancers may originate from chronic inflammatory or infectious conditions, such as Helicobacter pylori in gastric cancer and hepatitis viruses in liver cancer [10].

The intricate relationship between inflammation and cancer underscores the importance of addressing chronic inflammation in disease prevention and management. Nutraceuticals, with their anti-inflammatory properties, offer a promising therapeutic strategy to disrupt these pathological processes.

Inflammation, molecular targets and tumorigenesis

Molecular connections between inflammation and chronic diseases are mediated by key molecules, including TNF-α, interleukins (IL-1β, IL-6, IL-8), cytokines, chemokines, STAT3, NF-κB, VEGF, COX-2, and 5-LOX [11-12]. Among these, IL-1β, IL-6, and IL-8, primarily secreted by macrophages, are central to inflammatory processes [10].

TNF-α, a pivotal cytokine, regulates immune responses and modulates signaling pathways that influence cell survival, proliferation, and metabolism. However, excessive TNF-α signaling is linked to chronic inflammation, promoting autoimmune disorders and cancer. It activates the IκBα kinase pathway, triggering NF-κB activation [10,12].

NF-κB serves as a critical molecular bridge between inflammation and cancer, regulating over 500 cancer-associated genes, including those driving antiapoptotic, proangiogenic, and proinvasive functions [3]. Its activation by stressors, such as cytokines, bacterial components, and radiation, underscores its role in tumor development [10]. Chronic inflammation, through mechanisms like cellular transformation, invasion, and angiogenesis, plays a central role in tumorigenesis [3].

Nutraceuticals target these inflammatory pathways, offering therapeutic potential in preventing and treating cancer. Spice-derived compounds modulate transcription factors, including NF-κB, STAT3, TNF-α, IL-1β, and IL-6, with NF-κB and STAT3 emerging as key players in both inflammation and cancer progression (Figure 1) [14,15].

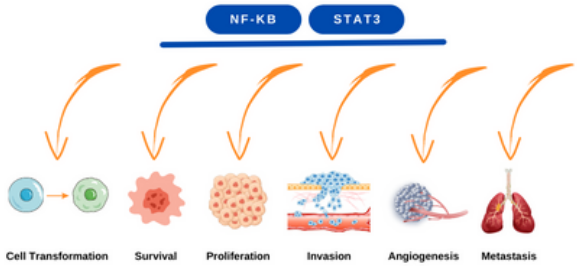

Figure 1. Roles of NF-κB and STAT3 in cellular transformation, cancer survival, proliferation, ınvasion, angiogenesis and metastasis.

Polyphenolic compounds and ınflammation

Polyphenols encompass diverse groups such as flavones, flavonols, flavanones, isoflavonoids, and anthocyanidins. Derived from secondary metabolites, polyphenols are abundant in vegetables and fruits, with flavonoids constituting the largest subgroup [16]. These compounds exhibit anti-inflammatory, antimutagenic, antiviral, free radical scavenging, and antioxidant properties. Their mechanisms of action include stimulating the immune system, inhibiting the cell cycle, reducing oxidative stress, enhancing detoxification enzymes, and inducing apoptosis, all of which contribute to their significant health benefits [17].

Flavonoids, as a major class of polyphenols, act on critical pathways to regulate inflammation and cancer progression. Transcription factors such as NF-κB and nuclear factor erythroid 2-related factor 2 (Nrf2) mediate the anticancer properties of polyphenolic compounds by modulating protein kinases like mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K). These kinases are pivotal in cancer cell proliferation and survival. Natural polyphenolic compounds, including resveratrol, quercetin, apigenin, luteolin, and genistein,have demonstrated the ability to induce apoptosis in various tumor cells [16].

https://doi.org/10.61577/jnh.2025.100007

Nutraceuticals and molecular targets

Nutraceuticals, including anethole, carnosol, caryophyllene, cinnamaldehyde, curcumin, ursolic acid, and sulforaphane, impact molecular pathways such as NF-κB, TNF-α, and STAT3. Compounds like allicin, apigenin, and piperine modulate cytokines (IL-1β, IL-6, IL-8), influencing inflammation and tumorigenesis [10].

Apigenin, abundant in parsley, celery, and thyme, exhibits anti-inflammatory and antioxidant properties, regulating cell cycles and promoting apoptosis. It shows therapeutic potential for inflammation, cancer, autoimmune, and neurodegenerative diseases [17]. Garlic-derived compounds, such as allicin and Z-ajoene, suppress proinflammatory cytokines (IL-1β, IL-6) while enhancing IL-10, an anti-inflammatory cytokine. They inhibit COX-2 activity, reducing STAT3 phosphorylation and nuclear translocation, highlighting the health benefits of dietary garlic [18]. Similarly, allyl isothiocyanate (AITC) from cruciferous vegetables demonstrates anti-inflammatory and anticancer effects by modulating mitochondrial dysfunction [19].

Cinnamon contains nutraceuticals like cinnamic acid and cinnamaldehyde with antioxidant and anti-inflammatory properties. Although nutraceutical compounds have been proposed to modulate inflammatory responses, clinical evidence remains limited. A randomized trial in patients with type 2 diabetes reported no significant changes in key inflammatory markers, including TNF-α, IL-6, and high-sensitivity C-reactive protein (hs-CRP), except for a significant reduction in nuclear factor kappa B (NF-κB) levels (P=0.02) [20,21]. Curcumin, the active compound in turmeric, blocks TNF-α signaling and NF-κB activation, reducing oxidative stress and promoting apoptosis. It is effective against cancer, metabolic syndrome, and neurodegenerative diseases [22,23].

Piperine, from black pepper, inhibits TNF-α and nitric oxide expression while suppressing leukotriene biosynthesis enzymes. Capsaicin, derived from chili peppers, acts on the Transient Receptor Potential Vanilloid 1 (TRPV1) receptor, thereby modulating immune responses. TRPV1 deficiency has been linked to increased proinflammatory cytokines (TNF-α, IL-1β), highlighting its therapeutic potential in inflammation and cancer (Figure 2)[12,24].

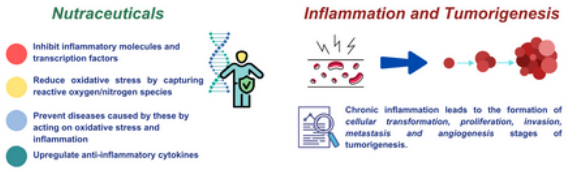

Figure 2. The role of nutraceuticals in ınflammation and tumorigenesis.

Multiple Targets of Nutraceuticals Cellular Signaling Pathways in Tumorigenesis

Cancer, the second leading cause of death worldwide, is predicted to account for 23.6 million new cases annually by 2030, according to the World Health Organization [25]. It is a multifactorial disease driven by intricate interactions among target molecules and signaling pathways [26]. Nutraceuticals have gained attention for their ability to influence these molecular targets, offering potential therapeutic strategies in cancer prevention and treatment.

Approximately 5-10% of cancers are attributed to somatic mutations, while 90-95% are linked to environmental factors, including diet (35%), tobacco use (30%), obesity (14-20%), infections (18%), and environmental pollutants (7%) [26]. These risk factors are closely associated with inflammation, a key driver of tumorigenesis. Pro-inflammatory lifestyle components, such as stress, obesity, and tobacco use, are recognized as contributors to cancer development.

The relationship between nutrition and cancer risk has become a central focus in research, with dietary interventions shown to alter epigenetic markers that regulate gene expression. Epigenetic changes, including modifications in tumor suppressor proteins like p53, are pivotal in cancer progression [10,27].

Nutraceuticals act on multiple cellular signaling pathways to inhibit tumor growth and inflammation. Key targets include transcription factors (NF-κB, STAT3, Nrf2, AP-1, PPARγ) and protein kinases (AMPK, VEGF, IGF-1R, HER2). These compounds modulate signaling cascades, preventing tumor progression and supporting anti-inflammatory mechanisms [26]. Oncogenic transcription factors such as NF-κB, STAT3, and MYC regulate genes involved in immune responses and cell proliferation. Modulating these factors in tumor cells halts growth or induces apoptosis, highlighting their potential as therapeutic targets [28].

NF-κB

NF-κB is a critical transcription factor that acts as a cellular stress responder and regulates genes involved in immunity, inflammation, cell proliferation, and apoptosis. Known as a key regulator of cellular homeostasis, its activity depends on multiple factors [29]. In cancer, NF-κB plays a significant role by controlling over 500 genes associated with cell survival, proliferation, invasion, angiogenesis, and metastasis. It also binds to the enhancer region of κB chains in B cells, suppressing apoptosis and contributing to tumorigenesis in various cancer types [26].

Nutraceutical compounds exert both direct and indirect effects on NF-κB modulation. Curcumin, one of the most extensively studied nutraceuticals, targets inflammatory cytokines, transcription factors, and apoptotic proteins. Specifically, it inhibits the expression of pro-inflammatory cytokines such as IL-1, IL-2, and IFNγ by suppressing NF-κB activity. Curcumin achieves this by blocking IκB phosphorylation, preventing the nuclear translocation of the NF-κB p65 subunit, and inhibiting AP-1 activation. These mechanisms highlight curcumin's potent anticancer properties [30].

Other nutraceuticals that target NF-κB include compounds like anethole, capsaicin, cardamom, diosgenin, and xanthohumol. Anethole inhibits NF-κB activation mediated by tumor necrosis factor, while its analogs, eugenol and isoeugenol, demonstrate similar inhibitory effects. These compounds collectively exhibit anticancer potential by inducing apoptosis and reducing tumor progression [26].

STAT3

Signal transducer and activator of transcription (STAT) proteins are transcription factors composed of modular domains [31,32]. The family includes STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6, mediating various intracellular signaling pathways [34]. STAT1 acts as a tumor suppressor, whereas STAT3 and STAT5 function as oncogenes by promoting cell cycle progression and inhibiting apoptosis. In contrast, STAT2, STAT4, and STAT6 primarily regulate normal cellular processes [31].

STAT3, a 770-amino-acid protein, features six essential domains: amino-terminal (NH2), helix-coil (CCD), DNA-binding (DBD), linker, SRC homology 2 (SH2), and carboxyl-terminal transactivation (TAD) domains. It plays a pivotal role in cell

https://doi.org/10.61577/jnh.2025.100007

proliferation, survival, differentiation, angiogenesis, oncogenic signaling, and immune response regulation, making it a critical cancer therapeutic target [32].

Among nutraceuticals targeting STAT3, curcumin from turmeric is notably effective. Curcumin interacts with molecular targets such as cytokines, transcription factors, adhesion molecules, cell cycle proteins, enzymes, and receptors in cancer cells. Menon et al. demonstrated that curcumin inhibits melanoma cell invasiveness and lung metastasis by suppressing matrix metalloproteinase-2 (MMP-2) activity [33]. Furthermore, curcumin blocks STAT3 signaling and the AKT/mTOR pathways, showing anticancer effects in Hodgkin lymphoma, cutaneous T-cell lymphoma, glioma, ovarian, endometrial, and head and neck cancers [26,33].

Capsaicin, the active compound in capsicum, also exhibits chemoprotective properties. It induces apoptosis by arresting the cell cycle and downregulating the IL-6/STAT3 pathway in glial tumor cells. Capsaicin enhances autophagic flow, critical for tumor cells resistant to apoptosis, and inhibits janus-activated kinase-1 (JAK-1) and c-Src activation, essential components of STAT3 signaling [34].

Other nutraceuticals, such as thymoquinone and ursolic acid, further demonstrate STAT3-targeting potential. Thymoquinone induces apoptosis in multiple myeloma cells by inhibiting STAT3 activation, while ursolic acid downregulates antiapoptotic genes (e.g., Bcl-2, Bcl-xL, survivin, and Mcl-1) regulated by STAT3, effectively reducing cancer cell proliferation [26].

The Effects of Nutraceuticals on Oxidant Stress

Free radicals are compounds produced during normal cellular processes in living organisms. While they play essential roles in physiological functions, their excessive accumulation can lead to toxic effects [35]. Reactive oxygen species (ROS), such as superoxide anion (O_2–), hydrogen peroxide (H_2O_2), hydroxyl radicals (OH), and singlet oxygen (O_2), and reactive nitrogen species (RNS), including nitroxyl anion, peroxynitrite, and nitrosonium cation, contribute to oxidative damage, including DNA damage [36,37].Oxidative stress occurs when ROS and RNS production exceeds the body's natural antioxidant defenses or when these systems are impaired. This imbalance is linked to cancer, cardiovascular diseases, neurodegenerative disorders, inflammation, and aging [35].

Antioxidant defenses are divided into endogenous and exogenous systems. Endogenous antioxidants include enzymes such as catalase (CAT), superoxide dismutase (SOD), glutathione peroxidase (GPx), and myeloperoxidase (MPO). Exogenous antioxidants, derived from dietary sources, include vitamins A, C, and E, as well as carotenoids and flavonoids, which neutralize free radicals and reduce their harmful effects [36].

Nutraceuticals' Health Benefits

Nutraceuticals, bioactive compounds found in foods, provide significant health benefits. Defined as "a food or substance that can be considered part of a nutrient with medical or health benefits and effects on diseases" nutraceuticals are formulated as nutritional supplements without regulatory classification and are intended for disease prevention or treatment [38]. These compounds contribute to biochemical processes and structural development due to their antioxidant, anti-aging, and anticancer properties. Furthermore, nutraceuticals enhance immune response, stimulate immunomodulators, promote phagocytosis, prevent hypersensitivity, and modulate autoimmune responses [37].

The health benefits of nutraceuticals are achieved through diverse mechanisms. They mitigate oxidative stress by neutralizing reactive oxygen and nitrogen species, chelating metal ions, enhancing antioxidant enzyme activity, and regulating mitochondrial function [37]. In addition to the body's endogenous antioxidants, nutraceuticals act as an exogenous antioxidant source, helping to maintain reactive species at manageable levels. Vegetables, fruits, nuts, and nutritional supplements are among the richest sources of antioxidant-containing nutraceuticals. Increasing dietary intake of these compounds is an effective strategy for preventing and reducing oxidative stress (Figure 3).

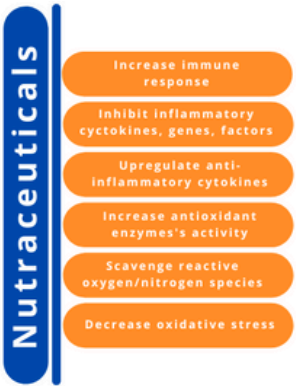

Figure 3. Health benefits of nutraceuticals.

Roles of Telomere in Aging

Telomere structure

Genome stability is essential for maintaining health [5]. Telomeres are critical structures that preserve DNA integrity and prevent chromosomal fusion [4]. First identified by McClintock and Muller in the 1930s, telomeres were named by Muller from the Greek words *telos* (end) and *meros* (part) [39].

Telomeres are composed of more than 2000 repeats of the "TTAGGG" sequence, comprising non-coding double-stranded DNA and guanine-rich single-stranded DNA at the ends of chromosomes [4]. These dynamic nucleoprotein structures act as biological clocks, regulating cell division by signaling pathways that determine the cell's lifespan. During each cell cycle, telomeres ensure the accurate replication of the genome while preventing chromosome ends from being misinterpreted as double-strand DNA breaks [4,5].

The telomere structure includes protein complexes such as the shelterin complex, the CST (CTC1-STN1-TEN1) complex, and related proteins [4]. The shelterin complex, consisting of six subunits: TRF1, TRF2, TPP1, POT1, TIN2, and RAP1 protects telomere ends from being recognized as DNA damage sites and regulates telomerase activity. The CST complex, composed of CTC1, STN1, and TEN1, complements these protective functions [4,39]. Together, these protein complexes safeguard telomeres by blocking DNA damage signals and regulating telomerase access and activity. Mutations in these complexes can disrupt the shelterin-telomere interaction, resulting in chromosomal instability, terminal fusions, and premature aging [39].

Telomere and aging

Aging is a biological process characterized by a progressive decline in tissue and organ function. This decline results from various cellular and molecular changes, including mitochondrial dysfunction, impaired proteostasis, altered intercellular communication, disrupted nutrient sensing,

https://doi.org/10.61577/jnh.2025.100007

epigenetic modifications, and DNA repair deficiencies. Such changes ultimately lead to telomere dysfunction and genomic instability [39].

Telomeres shorten with each cell division due to replication mechanisms, contributing to cellular aging and mitochondrial dysfunction [4]. Critically short telomeres on one or more chromosomes compromise genome integrity, accelerating cellular aging and tissue degeneration. Over time, these processes contribute to somatic aging and organ dysfunction [4,40].

During cell division, approximately 25–200 base pairs of telomeric DNA are lost in each cycle. This phenomenon, termed the "end replication problem" occurs because DNA polymerase cannot completely replicate the terminal domain of the double helix. For telomeres to maintain their function, a minimum repeat count of 500 base pairs is required, with at least 12.8 TTAGGG repeats necessary to prevent chromosomal end-to-end fusion. Telomere shortening ultimately limits cell proliferation through mechanisms like senescence and apoptosis, preventing uncontrolled growth [4].

Telomere length

Telomere length serves as a molecular clock, measuring the number of cell divisions and influencing cellular aging [5]. Telomerase, an enzyme that adds tandem RNA repeat sequences to the 3'-OH end of chromosomes, plays a crucial role in maintaining telomere length and ensuring proper replication [4]. According to the telomere theory, telomere shortening is a key trigger for cellular senescence and aging [39].

Shortened telomeres and telomere dysfunction are associated with several age-related diseases, including cardiovascular diseases, type 2 diabetes, metabolic syndrome, osteoporosis, myocardial infarction, cataractogenesis, neurodegenerative diseases, cognitive decline, and dementia [4,39,40]. Telomere length also acts as a tumor suppressor, and its dysfunction can initiate early cancer development by contributing to genomic instability [5].

In somatic cells, limited telomerase activity leads to telomere shortening and replicative senescence [4]. In contrast, cancer cells can bypass this limitation through the alternative lengthening of telomeres (ALT) mechanism, a telomerase-independent, recombination-mediated pathway. Approximately 5–10% of tumor cells utilize the ALT mechanism. Targeting telomerase activity or ALT pathways with inhibitors and antitumor agents represents a promising therapeutic approach for cancer [39].

Telomere length is influenced by lifestyle factors, including physical activity and nutrition. Increased physical activity is positively associated with longer telomeres. Similarly, diets rich in omega-3 (n-3) polyunsaturated fatty acids (PUFA), antioxidant vitamins A, C, and E, carotenoids like lutein and zeaxanthin, polyphenols, dietary fiber, and minerals -such as those found in the Mediterranean diet- can mitigate telomere shortening [4]. Diets high in antioxidants reduce oxidative stress and mitochondrial dysfunction while promoting endogenous antioxidant production. This has profound health benefits, particularly for maintaining telomere length and mitigating aging-related diseases.

Sirtuin 1: Molecular link between Telomere Function, Inflammation, and Tumorigenesis

Sirtuins (SIRTs) are a family of seven NAD^+-dependent deacetylase enzymes, designated Sirtuin 1 (SIRT1) through Sirtuin 7 (SIRT7) [41]. Among them, SIRT1 is a multifunctional protein involved in regulating critical cellular processes such as aging, energy metabolism, mitochondrial function, stress responses, and lipid homeostasis [41,42]. It contributes to systemic metabolic balance particularly by mediating communication between adipose tissue and the liver [42]. Additionally, SIRT1 has been shown to play regulatory roles in apoptosis, DNA repair, mitochondrial biogenesis, cellular differentiation, glucose-insulin regulation, neurogenesis, and circadian rhythm [41].

One of the key functions of SIRT1 is the deacetylation of both histone proteins (e.g., histone H4 lysine 16 (H4-K16), H3-K9, H1-K26) and several non-histone regulatory proteins including tumor protein p53 (p53), Forkhead box O1/3 (FOXO1/3), peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC-1α), and NF-κB, thereby modulating gene expression at the epigenetic level [41]. This mechanism plays a pivotal role in orchestrating aging, apoptosis, and DNA repair via transcription factors such as p53 and FOXO [42]. Through these functions, SIRT1 emerges as a potential therapeutic target in pathological conditions including tumor suppression, inflammation, and oxidative stress [43].

SIRT1 also interacts with aging-related genes such as FOXO1/3, Klotho, and p66Shc, modulating their expression and contributing to both metabolic homeostasis and the regulation of inflammatory responses. Thus, SIRT1 serves not only as an epigenetic regulator but also as a candidate therapeutic molecule in chronic inflammation and carcinogenesis [43].

Recent proteomic studies have further elucidated the broad regulatory impact of SIRT1 on cellular mechanisms. Plasma proteomic analyses have proven valuable in identifying early biomarkers of neuronal mitochondrial apoptosis in neurodegenerative diseases. Several regulatory molecules involved in these pathways -such as apelin, adiponectin, TGF-β, TNF-α, IGF-1, FGF21, HGF, and NGF- are associated with post-transcriptional regulation of SIRT1 via p53 [44].

Contemporary findings indicate that telomere shortening is not only linked to cellular aging and fibrosis but also to the suppression of SIRT1 expression. Activation of p53 under telomerase deficiency inhibits the expression of SIRT1 and other sirtuins through microRNAs, leading to mitochondrial dysfunction and progression of fibrotic processes. Conversely, supplementation with NAD^+ precursors such as nicotinamide mononucleotide has been shown to mitigate p53 activity, enhance mitochondrial function, and restore SIRT1 levels, thereby alleviating telomere-associated cellular damage. These results underscore the critical role of SIRT1 in maintaining telomere integrity [45].

Growing attention has been directed toward the influence of nutraceutical compounds -particularly polyphenols- on SIRT1 expression and activity. Resveratrol, a plant-derived polyphenol, has been characterized as a potent antioxidant and transcriptional activator of SIRT1. For instance, it has been reported that resveratrol partially suppresses β-glucan-induced IL-6 production in monocytes through SIRT1 activation [21]. However, the biological effects of nutraceuticals on SIRT1 may vary. A clinical trial involving daily supplementation of 3 grams of cinnamon for eight weeks in individuals with type 2 diabetes showed no significant changes in SIRT1 levels or in inflammatory markers such as NF-κB, hs-CRP, IL-6, and TNF-α [7]. These findings highlight the variability in SIRT1 modulation depending on the type of nutraceutical, dosage, and individual physiological context.

https://doi.org/10.61577/jnh.2025.100007

Given the integral role of SIRT1 in regulating aging, inflammation, tumorigenesis, mitochondrial function, and neurodegenerative pathways, pharmacological targeting of this protein is gaining substantial interest. Recent studies suggest that various nutraceuticals can enhance SIRT1 activity, contributing to telomere stability, suppression of oxidative stress, epigenetic regulation of transcription factors such as p53 and FOXO, and improved mitochondrial function. Therefore, SIRT1-targeted nutraceutical strategies may offer complementary benefits in the prevention and treatment of inflammation-driven chronic diseases, cancer, and age-associated neurodegenerative disorders.

Clinical trials related to nutraceuticals

Nutraceuticals, which play an active role in maintaining and modifying normal physiological functions, are effectively used to combat major health issues [2]. Defined as natural bioactive or chemical compounds, nutraceuticals not only provide nutritional benefits but also promote health, prevent diseases, and support treatment processes [1]. Studies have highlighted their potential as therapeutic agents for addressing cardiovascular diseases, atherosclerosis, diabetes, obesity, cancer, osteoporosis, arthritis, neurological disorders, and inflammation [1,2].

In elderly individuals, aging affects immune function and increases pro-inflammatory cytokines, contributing to the onset of diseases like cancer, diabetes, and arthritis. A case-control study evaluating the effects of nutraceuticals on inflammatory parameters in elderly individuals used a supplement containing *Lactobacillus acidophilus* (HA122), *Sambucus nigra*, arabinogalactans, vitamins C, E, and D, and zinc. After one month, improvements in IL-6, CRP, and lymphocyte levels were observed in elderly participants but not in younger individuals. These findings suggest that low-dose nutraceutical supplements may help reduce inflammation in the elderly [46].

Cinnamon

The effects of cinnamon supplementation on systemic inflammation are inconsistent in current studies. While cinnamon has shown benefits in chronic conditions with elevated C-reactive protein (CRP) levels, it has not significantly influenced CRP levels in diabetic patients. In a study investigating the effects of 600 mg cinnamon supplementation for 60 days on migraine attacks and inflammation, significant reductions in interleukin-6 and nitric oxide levels were observed in the intervention group compared to the control group [47].

A randomized, double-blind, controlled trial evaluated the effects of 3 grams of daily cinnamon supplementation for 8 weeks on NF-κB, Sirtuin 1 (SIRT1), and inflammatory markers in patients with type 2 diabetes. The results showed no significant changes in hs-CRP (P=0.29), TNF-α (P=0.27), IL-6 (P=0.52), and SIRT1 (P=0.51) levels, except for a significant reduction in NF-κB (P=0.02). Additionally, the placebo group showed no significant improvements except in hs-CRP levels (P=0.008). The study concluded that cinnamon supplementation does not significantly affect NF-κB, SIRT1, IL-6, TNF-α, or hs-CRP levels in type 2 diabetes patients [21].

Curcumin

Curcumin exhibits anticancer properties by modulating immune regulators, including COX-2, growth factors, protein kinases, NF-κB, STAT-3, and c-Jun N-terminal kinase (JNK) [23]. In a study investigating curcumin's effects on azoxymethane (AOM)-induced colorectal tumors in mice fed a high-protein diet (HPD), 30 female Balb/c mice were divided into three groups: a normal diet group (20% casein), an HPD group (50% casein), and an HPD group supplemented with curcumin (HPDC). The HPDC group demonstrated a 40% reduction in colorectal tumor incidence compared to the HPD group. Additionally, inflammatory markers such as COX-2 and nitric oxide synthase, plasma markers like TNF-α and nitric oxide, and other markers like short-chain fatty acids, fecal ammonia, and holonocyte proliferation rates were significantly lower in the HPDC group [48]. These findings suggest that curcumin, as a nutraceutical compound, may serve as a potential treatment for colon cancer by reducing colonic inflammation and proliferation.

Quercetin

Quercetin, a nutraceutical with antioxidant, anti-inflammatory, and anticancer properties, is found in various fruits, vegetables, and plants. It exhibits antitumor effects by influencing cell cycle progression, apoptosis, metastasis, and angiogenesis [49]. Quercetin targets key molecular pathways, including NF-κB, STAT3, p53, EGFR, and VEGF, which are critical in cancer development [50].

Recent studies suggest that quercetin's efficacy improves when combined with chemotherapeutic agents. For example, in prostate cancer, quercetin and green tea showed synergistic effects [51]. In ovarian cancer, quercetin combined with radiation therapy reduced tumor growth, upregulated p21, p53, and Bax, and downregulated Bcl-2. Additionally, quercetin enhanced cisplatin cytotoxicity by inhibiting STAT3 phosphorylation, leading to increased apoptosis in animal models [52].

Allyl isothiocyanate (AITC)

Allyl isothiocyanate (AITC) is a nutraceutical compound with notable anti-inflammatory properties, making it a potential therapeutic agent for various diseases. In a study on rats with non-alcoholic fatty liver disease (NAFLD), AITC significantly reduced hepatic steatosis and inflammation. These effects were attributed to the activation of the SIRT1 and AMP-activated protein kinase (AMPK) pathways and the inhibition of the NF-κB pathway. The findings suggest that AITC plays a beneficial role in improving liver health and reducing inflammation [19].

Resveratrol

Resveratrol is a nutraceutical compound known for its antioxidant, anti-inflammatory, antitumor, and anticancer properties, making it a promising therapeutic agent for cancer patients. Its anticancer effects are observed during the initiation, progression, and metastasis stages of carcinogenesis. Resveratrol has shown efficacy in treating various cancers, including lung, skin, hematological malignancies, and obesity-related cancers such as liver, pancreas, breast, prostate, and colorectal cancers [53].

In a study investigating its effects on drug and carcinogen-metabolizing enzymes in healthy individuals, daily supplementation with 1.0 g of resveratrol was found to modulate these enzymes, potentially inhibiting carcinogenesis. Another study evaluating resveratrol's impact on DNA methylation and prostaglandin expression in women at high risk of breast cancer reported that doses of 5 to 50 mg daily reduced methylation of the tumor suppressor gene RASSF-1. Additionally, in colorectal cancer patients, daily supplementation of 0.5 or 1.0 g of resveratrol achieved concentrations capable of exerting anticarcinogenic effects in the gastrointestinal tract [54].

https://doi.org/10.61577/jnh.2025.100007

Dietary Approach for Nutraceuticals Implementation

Nutraceuticals with many health benefits are divided into seven groups: those derived from dietary fiber, probiotics, prebiotics, polyunsaturated fatty acids, antioxidant vitamins, polyphenols and spices [2]. The use of nutraceutical compounds is increasing day by day, especially due to their therapeutic properties in diseases as cardiovascular diseases, hypertension, diabetes, cancer, osteoporosis and arthritis.

Dietary fiber

Dietary fiber consists of indigestible carbohydrates such as polysaccharides in plant-based foods [55]. Dietary fiber has proven effects on intestinal microflora, intestinal motility, body weight, abdominal adiposity, insulin sensitivity, chronic inflammation, and chronic diseases. Soluble dietary fiber affects the speed of digestion by delaying gastric emptying of the stomach, and is effective on obesity by creating a feeling of fullness. In addition, dietary fibers that increase insulin receptor binding and improve glycemic response have health-promoting effects in diabetes patients [2]. Dietary fibers also improve blood lipid profile by lowering LDL cholesterol.

Probiotics and prebiotics

Probiotics and prebiotics are nutraceuticals widely recognized for their extensive health benefits. The International Scientific Association for Probiotics and Prebiotics (ISAAP) defines probiotics as "live microorganisms that, when administered in adequate amounts, confer a health benefit on the host" [56]. Probiotics enhance immunity by modulating specific genes and influence gut-brain communication through gastrointestinal hormone regulation. For instance, Lactobacillus gasseri helps combat obesity by limiting adipose tissue expansion, while Lactobacillus casei, Lactobacillus acidophilus, and Bifidobacterium longum demonstrate hypocholesterolemic effects, reducing hypercholesterolemia [57]. Additionally, probiotics offer therapeutic potential for inflammatory diseases such as inflammatory bowel disease and Crohn's disease due to their anti-inflammatory properties.

Prebiotics, defined as "a substrate that is selectively used by host microorganisms and provides health benefits", are another vital category of nutraceuticals [58]. They help reduce cardiovascular risk factors, alleviate inflammation, support weight management, enhance mineral absorption, and protect against colon cancer [57].

Polyunsaturated fatty acids

Polyunsaturated fatty acids (PUFAs), which are essential fatty acids, are divided into two groups as omega-3 (n-3) and omega-6 (n-6) fatty acids. Omega-3 fatty acids consist of three fatty acids: α-linolenic acid (ALA), eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA). While DHA and EPA are generally found in oily fish like mackerel, salmon, tuna, trout, and herring, ALA is found in some nuts such as flaxseed, soybean, and walnuts [2].

PUFAs are effective on many cellular processes such as the fluidity of the cell membrane, cell signal, blood pressure, glucose level, nervous system, inflammation. Omega-3 fatty acids, which have a significant impact on brain development, also come to the fore with their anti-inflammatory properties. Omega-6 fatty acids are essential for normal blood flow. PUFAs have various roles in obesity, inflammation, cardiovascular diseases, cancer, osteoarthritis, autoimmune diseases, and aging [59].

Antioxidants vitamins

Another group of nutraceutical compounds is the antioxidants vitamins, which include vitamins A, C and E. Antioxidant vitamins have a significant effect on preventing oxidative stress and oxidative damage. These effects are due to free radical capture mechanisms. Antioxidant vitamins act both alone and synergistically to prevent oxidative reactions that cause various diseases like cardiovascular diseases, diabetes, cancer, neurodegenerative diseases. Tocotrienols, tocopherols, ascorbic acid known as vitamin C, and carotenoids transfer hydrogen atoms and scavenge singlet oxygen and other reactive oxygen species. Carotenoids like β-carotene, lycopene, lutein, and zeaxanthin are known as the most effective singlet oxygen quencher [2].

Polyphenols

Polyphenols are secondary metabolites generated by plants to protect them from photosynthetic stress and reactive oxygen species [2]. There are 8,000 different classes of polyphenols, including multiple subclasses such as flavonols, flavones, flavanones, flavan-3-ols, anthocyanins, stilbenes, phenolic acids, and lignans [2,60]. Polyphenols have a wide variety of effects in intracellular and intercellular signaling pathways and have roles in many biochemical and molecular mechanisms. Modulation of the synthesis of inflammatory mediators like TNF-α, IL-1β, IL-6, cytokines, regulation of fat metabolism, as well as some flavonoids increase insulin secretion, reduce apoptosis, insulin resistance, inflammation and oxidative stress [60]. Polyphenols are effective in various processes, including gene expression, platelet aggregation, and intercellular signaling. In addition, the fact that polyphenols possess antioxidant, anti-inflammatory, antimicrobial, and cardioprotective properties is significant for the prevention of several diseases [2].

Spice-derived nutraceuticals

Anti-inflammatory, antidiabetic, anticancer, antimutagenic, immune properties and cholesterol-lowering effects of nutraceutical compounds are important for human health. These nutraceutical compounds have regulatory effects on cardiovascular, respiratory, gastrointestinal, metabolic, neural and other systems [2]. Because of the benefits of spice-derived nutraceutical compounds on various health problems such as inflammation, cancer formation stages, cardiovascular diseases, diabetes, they are used as potential therapeutic agents in diseases.

Nutraceutical intake

The use of nutraceuticals is increasing to promote health and prevent disease. In addition to diet, nutraceutical compounds are taken into the body through supplements. The nutraceutical industry includes herbal/natural products, functional foods and dietary supplements [2].

Thanks to their anti-inflammatory and antioxidant properties, the most widely used nutraceuticals, which stand out with their benefits on chronic diseases and inflammation in general, are those obtained from fruits and vegetables [61]. With the acceleration of current literature studies, the importance of nutraceuticals in terms of human health draws attention. Therefore, interest in the health benefits of nutraceuticals continues to increase, with both dietary nutraceutical intake and nutraceutical supplements production increasing.

https://doi.org/10.61577/jnh.2025.100007

Conclusions

Nutraceutical compounds, which are bioactive molecules, are associated with many health benefits on human health. Nutraceutical compounds, which play a role as cellular and functional modulators in maintaining the homeostasis of physiological processes, have many health-promoting benefits just as antioxidant, anti-inflammatory, antitumor and anticancer. Nutraceuticals target inflammatory mediators and transcription molecules involved in chronic diseases like inflammation and cancer. Nutraceuticals have significant effects on cancer formation stages because they target multiple cellular signaling involved in tumorigenesis. The effect of nutraceutical compounds on molecular targets in cellular signaling pathways in inflammation and tumorigenesis is also beneficial on oxidative stress and chronic diseases associated with inflammation. Therefore, the usage of nutraceuticals as a therapeutic agent should be considered as a promising strategy in the prevention and treatment of various diseases, especially inflammation and cancer.

Disclosure Statement

No potential conflict of interest was reported by the authors.

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