

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



The Potential Role of Nutraceuticals in Inflammation and Oxidative Stress

Sevda Inan

Abstract

Nutraceuticals are defined as a food or food ingredients that prevent and treat diseases. They contain dietary supplements like proteins, vitamins and minerals, compound derived from natural sources. They have functions about delaying, preventing and treating chronic inflammatory diseases due to the presence of the phytochemicals. They have anti-inflammatory effects by inhibiting of the activation of NF- κ B, blocking the overexpression of tumor necrosis factor and interleukin-1, downregulation of the overexpression of cell adhesion molecules and inhibiting phospholipase A2, COX-2, lipoxygenase, iNOS, myeloperoxidase and inhibiting reactive oxygen species (ROS) generating enzyme activity and increasing ability to scavenge ROS. They have antioxidative role that can reduce the level of ROS and free radicals. They have effects on the process of lipid oxidation that inhibit or slow the formation of free alkyl radicals and cut off the free radical chain reactions.

Keywords: nutraceuticals, inflammation, oxidative stress, protective functions, disease

1. Introduction

In recent years, the consumption of natural products or functional foods are increased and enlarged segment of food industry. At the same time, Nutraceuticals are increased using as an alternative for pharmaceutical industry especially variety of diseases and cancers in humans and animals.

Firstly, nutraceutical is a term used by Stefane De Felice Nutraceuticals is defined as a food, bioactive products or food ingredients that prevent and treat diseases [1–4]. They are not drugs but they have pharmacologically active substance [2]. They contain dietary supplements like proteins, vitamins and minerals, compounds derived from natural sources. They provide health and medical benefits that delay, prevent and treat chronic inflammatory diseases due to the presence of the phytochemicals [1–4].

They have anti-inflammatory effects by inhibiting of the activation of NF- κ B, blocking the overexpression of tumor necrosis factor and interleukin-1, downregulation of the overexpression of cell adhesion molecules and inhibiting phospholipase A2, COX-2, 5-LOX, iNOS, myeloperoxidase and inhibiting ROS generating enzyme activity and increasing ability to scavenge ROS. They have antioxidative role that can reduce the level of ROS and free radicals. They have

effects on the process of lipid oxidation that inhibit or slow the formation of free alkyl radicals and cut off the free radical chain reactions. They have intracellular signaling pathway modular effects [2–4].

The foods including antioxidative nutraceuticals are fruits (grape, citrus, blueberries, strawberries, blackberries and crowberries), vegetables (tomato, beans, broccoli, beet, mushroom, corn, white cabbage, kale, cauliflower, spinach, garlic, onion, cacao beans and soybean), spices (rosemary, oregano and thyme), herbs (sage) and beverages (tea, wine) [4–6].

People's interest about nutraceuticals is increasing day by day due to various diseases. According to the global market data, China will be first nutraceutical market as lifestyle. The nutraceutical sector is affected by the stringent regulations and approval process of European Union. Due to the country, there are different names of laws on nutraceuticals. Nutraceuticals are using different definitions and terms including dietary supplement in USA, Natural Health Product in Canada, complementary medicines in Australia, food supplements in European Union and foods for special dietary in India [7].

With the increasing technology in the food, health and pharmaceutical sectors, the orientation to functional foods is increasing and the competition is accelerating. The sales of global market for nutraceuticals are expected to be US\$250 billion by 2018 [8].

When nutraceuticals are evaluated by consumers, the consumption of food has undergone changes in the past three decades. The easing of access to media and internet, increasing in scientific studies and obesity related diseases are increased to sale nutraceutical products by consumers. Between 2018 and 2025 years, the growth rate of this sector is assumed to exceed 9.7%. The countries including Brazil, China, India, South Korea, Poland and Mexico are increasing to use functional foods. The global market of nutraceuticals is assumed to be \$578.23 billion by 2025 at CAGR of 8.8% [9].

Inflammation is a protective response against the initial cause of cell injury. Inflammation is classified as acute and chronic. Acute inflammation is first response mechanism against infections, trauma, physical and chemical agents, which are induced wound healing. If this mechanism occurs persistent, it takes chronic phase [3, 10]. The process of inflammation contain vascular and cellular changes including of swollen, redness, local heating and loss of function. The permeability of capillaries is increased, exudate including the fluid and other elements leak into the body cavities. The inflammatory cells, leucocytes and other phagocytic cells migrate through the affected region. The lytic enzymes release from lysosomes of cells. During the inflammation, chemical mediators are synthesized proinflammatory cytokines (histamine, 5-hydroxytryptamine, bradykinin, leukotrienes and prostaglandins), selectins, integrins and immunoglobulins are stimulated for releasing [1]. Arachidonic acid metabolites including prostaglandins and leukotrienes are stimulated by the increasing expression of phospholipase A2. ROS are released from the inflammatory cells including neutrophils and macrophages. NADPH oxidase, xanthine oxidase and myeloperoxidase are seen increasing due to the ROS. The inflammatory cytokines, cell adhesion molecules and enzymes are regulated by the activation of the transcription factor NF- κ B [3, 11].

ROS generate intracellularly as natural by endogenous and exogenous sources. Endogenous ROS including superoxide, hydrogen peroxide and nitric oxide (NO) have functions in cell signaling and homeostasis [12]. ROS has functions in regulation of cell survival. At the moderate levels of ROS signaling support cell proliferation and survival. At the upper levels of ROS cause cell death [12, 13]. There is a relationship between ROS production and oxidative stress that play a role on redox signaling from the organelle to the cytosol to nucleus [12, 14].

ROS are present in different cancer types and age related diseases as neurodegeneration, inflammation, diabetes, vision and sensory loss [12]. ROS and reactive nitrogen species damage significant biological molecules which are lipids, DNA, essential cellular proteins. Oxidative stress is imbalance between the formation of free radicals and antioxidant defense mechanism [15, 16].

Enzymatic and nonenzymatic antioxidant systems which are superoxide dismutase, catalase, glutathione peroxidase, lipid soluble vitamin E, carotenes and water soluble vitamin C arrange between ROS and antioxidants [4, 17, 18].

Oxidative stress starts the oxidation of polyunsaturated fatty acids (PUFA), proteins, DNA and sterols. The oxidative stress reduce in the body with consumption of fruits and vegetables including high amounts of anti-oxidative nutraceuticals and for this reason, incidence of cancer and cardiovascular diseases decrease [4, 6]. According to the recent studies, there is a relationship between ROS and atherosclerosis, vasospasm, cancers, trauma, stroke, asthma, hyperoxia, arthritis, heart attack, age pigments, dermatitis, cataractogenesis, retinal damage, hepatitis, liver injury and periodontitis [4, 19, 20].

2. Nutraceuticals

2.1 Vitamin E

Vitamin E (alpha-, beta-, gamma- and delta-tocopherol, alpha-, beta-, gamma- and delta-tocotrienol) is quite effective antioxidant and beneficial aspects for rheumatoid arthritis [4, 21, 22]. Also, vitamin E has anti-inflammatory effects in animal recent studies [4, 23]. Tocopherols and tocotrienols have nonpolar structures and consist in the lipid phase. Tocopherols are member of biological membranes and. Tocopherols have antioxidants property that defend polyunsaturated fatty acids into the membrane and LDL [4, 24]. The anti-inflammatory and anti-oxidant effects of Vitamin E and its derivatives are summarized in **Table 1**.

Vitamin E and derivatives	Anti-oxidant and anti-inflammatory effects	References
(Review literature study), (randomized, double-blind placebo-controlled human study, 400 mg for 3 months), (The transgenic KRN/NOD mice, 0.268 mg for 6 weeks)	Effects on rheumatoid arthritis against the inflammation and oxidative stress	Lee et al. [4], Aryaeian et al. [21], Bandt et al. [22]
(Review literature study), (30 and 500 ppm for 30 days in old mice)	Inhibition of cyclooxygenase activity in macrophages	Lee et al. [4], Beharka et al. [23]
(Review literature study in elderly cardiovascular patients)	Decreases risk of cardiovascular disease, anti-cancer activity and decreases incidence of Alzheimer's disease	Meydani [24]
(Review literature study)	Changes the level cholesterol and blocks oxidation of LDL.	Lee et al. [4]
(Review literature study)	Alterations of cell membrane integrity, cell division and cell signaling pathways. Stimulates indirectly prostaglandin and cytokines, directly stimulates T cell function. Reduces incidence of infectious diseases including respiratory infections and asthma	Lewis et al. [25]

Vitamin E and derivatives	Anti-oxidant and anti-inflammatory effects	References
(Different doses, review literature study)	Prevents and treats a multitude of age related diseases. Ameliorates of lipid profile and modulates suppression of the senescence- associated secretory phenotype	Malavolta et al. [26]
(The randomized clinical trials, ranging doses 33-800 IU)	Effects lonely cardiovascular diseases by reducing myocardial infarction	Loffredo et al. [27]
(The clinical review literature study)	Preventive and therapeutic functions in cardiovascular diseases.	Jain et al. [28]
(The consumption of different doses, review of literature study in human)	Prevents various types of cancer, heart disease and chronic ailments	Shahidi [29]
(The ranging doses between 500 IU/kg for 4 weeks in rats, 600 mg/kg in rats, 45 and 60 mg/kg in rats)	Anti-oxidant roles by decreasing the distribution of free radicals and modulating plasmatic lipoproteins in traumatic brain injury related dementia	Dobrovolny et al. [30]

Table 1.
The effects of Vitamin E and its derivatives, relevant to anti-inflammatory and anti-oxidant activity.

2.2 Carotenoids

They are classified as xanthophylls and carotenes. The carotenes have hydrocarbon and xanthophylls have oxygen [2, 4]. Carotenoids including alpha- carotene, lycopene, lutein, zeaxanthin, beta-carotene and beta-cryptoxanthin have antioxidant effects [1, 4]. The anti-inflammatory and anti-oxidant effects of carotenoids are summarized in **Table 2**.

Carotenoids	Anti-oxidant and anti-inflammatory effects	References
(The literature review study)	Functions on cell growth, embryonic development, vision property and immune system. Modulates activity of intracellular communication by interaction with nuclear receptors like pregnant X- receptor or retinoic acid receptor	Lushchak [2], Ruhl [31]
(The literature review study), (The prospective study of older women between 55-69 ages)	Protective roles against rheumatoid arthritis, atherosclerosis, cataracts, age-related muscular degeneration and multiple sclerosis	Al-Okbi [1], Lee et al. [4], Cerhan et al. [32]
(The ranging numbers and amounts of cases and exposure, the epidemiological review study), (The prospective cohort study between 1986 and 1992, in cases of 812 prostate cancer), (The review study related with the consumption of foods including different amounts of carotenoids)	Decreases the expansion of cervical, colon, prostate, rectal, stomach and other different of cancer types	Giovannucci [33], Giovannucci et al. [34], Giovannucci [35]
(The literature review study)	Blocks the formation of oxidized products of LDL cholesterol in coronary heart disease	Weisburger [36]

Carotenoids	Anti-oxidant and anti-inflammatory effects	References
(25 and 50 mg/kg of body weight in mice for 3 days)	Antimutagenic effect	Polivkova et al. [37]
(Daily oral dose 10 mg/kg body weight and intraperitoneally 25 mg/kg body weight in female Wistar rats)	Neuroprotective activity	Sandhir et al. [38]
(Lycopene complex including 6% lycopene, 1.5% tocopherols, 1% phytoene and phytofluene, 0.2% beta-carotene for 10 days in rats at 6 mg/kg body weight)	Nephroprotective activity	Sahin et al. [39]
(The prospective randomized study in 159 primigravidas at the gestational time with the consumption of 2 mg oral lycopene daily for 77 women, placebo daily for 82 women)	Prevents preclampsia	Banerjee et al. [40]
(375 men and 576 women with hip fracture and nonvertebral fracture in elderly ages at different amounts of consumption of carotenoid and lycopene)	Decreases risk of hip fracture	Sahni et al. [41]
(The literature review study)	Anti-obesity functions by modulating insulin resistance and reducing blood glucose levels by regulation of cytokine expression from white adipose tissue	Gammone [42]
(In vitro research of 25 male Holstein calves in ages of 6–10 weeks and 3 Angus Heifers in ages of 8–30 weeks with doses of etinoic acid (1 µM) or β-carotene (8.3 µg/mL)	Promotes leukocyte apoptosis in bronchoalveolar lavage fluid and improves efferocytosis in macrophages	Duquette et al. [43]
(The review article study including animal and human in vitro researches)	Modulates intracellular signaling cascades, gene expression, and protein translation and blocks the translocation of nuclear factor κB to the nucleus. Inhibits Interleukin-8, prostaglandin E2 and oxidative stress damage by activating phase II and glutathione-S-transferases.	Kaulmann [44]
(The review article study)	Inhibits UV-induced cutaneous inflammation, pathologic keratinization, pigmentation and wrinkling	Imokawa [45]
(The intake of AIN-93G or AIN-93G + 10% Tangerine or red tomato powder for 35 weeks in mice)	Protects against the UVB-induced keratinocyte carcinoma.	Cooperstone et al. [46]
(The different amount of carotenoid content in commercial tomato hybrid Zebrino)	Cytoprotective functions by mitigating ROS production and protects against the glutathione depletion and lipid peroxidation	Del-Giudice et al. [47]
(The randomized double-blinded clinical trial study in 51 patients with beta-carotene fortified symbiotic food including 0.05 g beta carotene)	Decreases levels of insulin, triglycerides, VLDL-cholesterol, total/HDL cholesterol ratio, plasma nitric oxide and glutathione	Asemi et al. [48]

Carotenoids	Anti-oxidant and anti-inflammatory effects	References
(The doses of 20 and 40 mg/kg xanthophylls in hens and chicks)	Decreases inflammatory mediators and apoptosis in chick tissues including liver, duodenum and jejunum	Gao et al. [49]
(The review article study)	Modulates macrophage polarization and stops the progression of non-alcoholic fatty liver disease and provides liver homeostasis	Ni et al. [50]
(The review article study)	Neuroprotective functions against the Alzheimer's disease that prevents progression this disease and modulates of A β peptide production and accumulation, oxidative stress and secretion of pro-inflammatory mediator	Mohammadzade h Honarvar [51]
(59 young participants with the supplementation of 13 and 27 mg/day macular carotenoids)	Reduces stress, cortisol and symptoms of emotional and physical health.	Stringham et al. [52]
(The carotenoid derivatives and crystalline lycopene from tomato extract)	Prevents cancer and protects bone health by inhibiting of the nuclear factor kappa B activity.	Linnewiel-Hermoni et al. [53]
(The different amounts of intake carotenoid in this review article study)	Reduces variety types of cancer including oral cavity and laryngeal regions.	Leoncini et al. [54]

Table 2.
The effects of Carotenoids, relevant to anti-inflammatory and anti-oxidant activity.

2.3 Phenolic compounds, polyphenols

The polyphenols are phenolic compounds that are defined as a benzene ring bearing one or more hydroxyl groups attached to the ring. They are including plants, vegetables, fruit, vines, tea, coffee and microalgae [2]. The phenolic compounds are classified as simple phenols, benzoquinones, phenolic acids, acetophenones, phenylacetic acids, hydroxycinnamic acids, phenylpropens, coumarins, chromones, anthraquinones and flavonoids [4]. According to the recent articles, polyphenols have antioxidant [2, 4], anti-inflammatory [2, 55], anticancer [2, 56], antibacterial [2, 57], antiatherogenic [2, 58], antiangiogenic [2, 59], antimutagenic and free radical scavenging properties [4].

Flavonoids, which are water-soluble [3], are popular group of polyphenols and classified as flavones, flavonols, catechin or flavanols, anthocyanins and isoflavones. Flavonoids consist as free aglycones or with sugars connected the chemical structures to generate glycosides. Flavonoids have anti-inflammatory functions by inhibiting the enzymes responsible for production of phospholipase A2, cyclooxygenase and lipoxygenase [2, 3, 63]. The beneficial effects to health of phenolic compounds are listed below in **Table 3**.

2.3.1 Flavones

They are including apigenin, chrysin, baicalein, scutellarein and wogonin [2]. The anti-inflammatory and anti-oxidant effects of flavones are summarized in **Table 4**.

Polyphenols	Anti-oxidant and anti-inflammatory effects	References
(The review article study)	Anti-inflammatory effects	Lushchak et al. [2], Biesalski [55]
(The review article study)	Anti-cancer functions	Lushchak et al. [2], Fresco et al. [56]
(The review article study) (the commercial apple skin powder including 995.3 mg chlorogenic acid/100 g and 14.4 mg Trolox/g)	Anti-bacterial functions	Lushchak et al. [2], Du et al. [57]
(The interval of different age, dietary source of polyphenols and contents in this review article study)	Anti-atherogenic functions	Lushchak et al. [2], Rimbach et al. [58]
(The review article study)	Anti-angiogenic functions. Contributes formation of ROS by inhibiting enzymes or chelating trace elements	Lushchak et al. [2], Corradini et al. [59]
(The review article study)	Anti-mutagenic and free radical scavenging properties	Lee et al. [4]
(The serial review article study)	Modulates of intracellular communications in the phosphoinositide 3-kinase, Akt- protein kinase B, tyrosine kinase and protein kinase C signaling cascade	Lushchak et al. [2], Williams et al. [60]
(The rat kidney study with the different phenolic contents and amounts in foods)	Inhibits the angiotensin converting enzyme in cardiovascular system	Lushchak et al. [2], Actis-Goretta et al. [61]
(The review article study), (The 17 hypercholesterolemic male patients with the consumption of 40-90 g/day macadamia nuts for 4 weeks)	Decreases influence of inflammation, alters the gene expression of antioxidant enzymes and reduces the risk of cardiovascular disease and certain type of cancer	Al-Okbi [1], Lee et al. [4], Garg et al. [62]
(The review article study)	Anti-inflammatory functions	Chatterjee et al. [63]
(The review article study with different phenolic compounds activities and amounts)	Neuroprotective and anticonvulsive effects on brain tissue against the oxidative stress by binding to the benzodiazepine site on GABAA receptor	Diniz et al. [64]
(The randomized, controlled, double blind cross over human study, Olive oil including 80 mg phenolic compounds/kg, Olive oil including 500 mg phenolic compounds for 3 weeks)	Improves the proportions of IgA coated bacteria and plasma levels of C-reactive protein	Martin-Pelaez et al. [65]
(The review article study)	Regulates toll like receptor, inhibits cyclooxygenase, phospholipase A2 and anti-oxidant enzymes including xanthine oxidase	Yahfoufi et al. [66]

Table 3.
The effects of phenolic compounds, relevant to anti-inflammatory and anti-oxidant activity.

Flavones	Anti-oxidant and anti-inflammatory effects	References
(The review article study), (250 μ M quercetin (specific activity, 52.9 mCi/mM) for 10 min by injecting of <i>Xenopus laevis</i> oocytes)	Beneficial effects including as GLUT inhibitors in diabetes	Lee et al. [4], Kwon et al. [67]
(The review article study)	Cyclooxygenase inhibitory ability in cancer	Lee et al. [4], Kinghorn et al. [68]
(The treatment with 2.5–20 μ M apigenin in cell culture including human prostate cancer PC-3 and 22Rv1)	Anti-tumoral activity that inhibits of the p-IKK α , NF- κ B/p65, cell proliferation, invasion of prostat cancer cells	Shukla et al. [69]
(The study including phosphorylating five flavones and showing pancreatic cholesterol esterase inhibitory functions by IC ₅₀)	Acts as pancreatic cholesterol esterase inhibitor	Lee et al. [4], Peng et al. [70]
(The review article study)	Reduces neurodegeneration	Lee et al. [4], Gasiorowski et al. [71]
(The review article study), (Apigenin which is isolated from <i>Cordia dichotoma</i> bark, is received 5 mg/kg, p.o. in Male Swiss mice)	Treats colitis and reduces inflammatory enzymes	Lee et al. [4], Ganjare et al. [72]
(The review article studies)	Decreases the expression of tumor necrosis factor alpha and interleukin-6 in macrophages cells	Chatterjee et al. [63], Wu and Schauss [73]
(The review article study)	Anti-arthritic functions	Laev et al. [74]
(The review article study in vitro and in vivo)	Anti-inflammatory functions for neurodegenerative disease	Nabavi et al. [75]
(The review article study about anti-oxidant, anti-cancer, anti-tumoral activity, anti-inflammatory and hepatoprotective functions of dietary flavonoids)	Inhibits thromboxane synthesis in animal model and decreases iNOS and COX-2 expression	Xiao et al. [76]
(50 mg/kg of body weight doses of apigenin was injected intraperitoneally in Male C57BL/6J mice)	Immunomodulatory effects that reduces NF- κ B activity in the lungs and inhibits leukocyte infiltration	Cardenas et al. [77]
(1, 10, 25, 50, 75 and 100 μ M concentrations of flavonoids were added Murine C2C12 cell culture medium)	Protective effects on lipopolysaccharide related muscle atrophy	Shiota et al. [78]

Table 4.
The effects of flavones, relevant to anti-inflammatory and anti-oxidant activity.

2.3.2 Flavonols

They are protective functions from UV radiation [2]. They are including kaempferol, quercetin, myricetin, galangin and morin [2]. They have beneficial effects on different conditions and diseases related oxidative stress and inflammation. These effects are summarized in **Table 5**.

Flavonols	Anti-oxidant and anti-inflammatory effects	References
(At flavonoid concentrations of 10–70 $\mu\text{mol/L}$ were applied in HL-60, U937 and Jurkat cells)	Inhibits intracellular accumulation of ascorbic acid	Park et al. [79]
(The ranging content amounts of oolong tea leaves including 54 polyphenols were evaluated on the pancreatic lipase activity in vitro)	Inhibitory functions on pancreatic lipase with diabetes mellitus	Nakai et al. [80]
(At the concentrations of 0, 50, 100 and 250 μM of quercetin for 24–72 hours were added cell culture medium including mouse embryo 3T3-L1 cells)	Anti-oxidant activity on cell apoptosis	Hsu et al. [81]
(The oral treatment doses at 2.8 g/kg in male Wistar rats, aged 8–10 weeks)	Anti-oxidant and renoprotective effects in streptozotocin-diabetic rats	Liu et al. [82]
(The extracts of <i>Ficus carica</i> Linn. (Moraceae) leaves and fruits and <i>Morus alba</i> Linn. root barks (Moraceae) were given 50 and 150 mg/kg in adult female Swiss albino rats)	Hepatoprotective effects on tetrachloride-related oxidative stress and injury in rat liver tissue	Singab et al. [83]
(At the dose of 5 μM kaempferol was added cell culture medium including rat osteoblast-like UMR106 cells)	Regulates bone sialoprotein gene transcription and new bone formation	Yang et al. [84]
(At the doses of 50 and 100 mg/kg kaempferol were given orally in animal model study)	Regulates cyclooxygenase, inhibits production of nitric oxide	Mahat et al. [85]
(The review article study), (The double-blind study was given orally 4 x 500 mg quercetin in non-smoking, un-treated sarcoidosis individuals)	Decreases of oxidative stress and inflammation in sarcoidosis, colonic damage and allergic airway conditions	Chatterjee et al. [63], Boots et al. [86]
(The mice were fed Western diet including 0.05% quercetin for 18 weeks)	Modulates on accumulation and activation of immune cells and increases expression of mitochondrial gene in adipose tissue.	Kobori et al. [87]
(At the doses of 10 and 50 mg/kg quercetin were given intraperitoneally to the male Sprague Dawley rats)	Neuroprotective and anti-oxidant effects in subarachnoid hemorrhage, inhibits brain damage and edema.	Dong et al. [88]
(At the doses of 0 and 210 μM quercetin or taraxasterol were added cell culture medium including human umbilical vein endothelial cells)	Anti-atherosclerotic and cardioprotective effects against the oxidative stress and inflammation	Yang et al. [89]

Table 5.
The effects of flavones, relevant to anti-inflammatory and anti-oxidant activity.

2.3.3 Flavanones

They have important effects that regulate on the inflammatory process and oxidative stress. These beneficial effects are summarized in **Table 6**.

2.3.4 Catechin or flavanols

They are found in variety of fruits (apples, apricots, blackberries and grapes), red wine, black tea and cocoa [2]. For example; the long-term consumption of tea

Flavanones	Anti-oxidant and anti-inflammatory effects	References
(The review article study)	Inhibitory effects on carcinogenesis	Kinghorn et al. [68]
(At the concentrations of 5 and 25 μ M of chalcones and flavanones were given in the vitro study)	Regulate LDL oxidation in atherosclerosis	Miranda et al. [90]
(The review article study)	Have functions in anti-malarial chemotherapy	Kumar et al. [91]
(The review article study)	Anti-inflammatory effects	Kontogiorgis et al. [92]
(The review article study)	Anti-angiogenic effects	Mojzis et al. [93]
(At the treatment daily doses of 100 mg/kg naringenin were applied to the female BALB/c mice)	Decrease lung metastases in a breast cancer model	Qin et al. [94]
(At the dose of 50 mg/kg naringenin was applied to the adult male albino rats)	Anti-oxidative stress related hepatic damage in rats	Prabu et al. [95]
(At the concentration of 0.25 mmol of naringin derivatives was applied by agar dilution technique and direct contact assaying)	Anti-bacterial roles in pathogenic strains	Celiz et al. [96]
(At the doses of 50 mg/kg of quercetin and naringenin were applied to mice intraperitoneally)	Protect DNA in alloxan-induced diabetic mice	Orsolic et al. [97]
(At the doses of 30–200 μ mol/L were treated into the cell culture including macrophage cell line RAW 274.6 and BV2 microglia)	Inhibit synthesis of nitric oxide and expression of cyclooxygenase-2 in macrophages and microglia	Chao et al. [98]

Table 6.
The effects of flavanones, relevant to anti-inflammatory and anti-oxidant activity.

inhibits low grade inflammation [73]. The chronic consumption of dark chocolate reduces serum C-reactive protein concentrations in blood circulation [63, 73]. The other effects on inflammatory and oxidative stress are summarized in **Table 7**.

Catechin	Anti-oxidant and anti-inflammatory effects	References
(The review article including clinical and experimental studies)	Cardioprotective effects by inhibiting the NF- κ B initiated production of cytokines and adhesion molecule	Bhardwaj et al. [99]
(The review article study) (at the mixture of catechin, caffeic acid and resveratrol doses of 40 and 160 mg/kg body weight/day were given to the apoE KO mice for 8 weeks)	Anti-inflammatory and anti-atherogenic functions	Wu and Schauss [73], Norata et al. [100]
(The dentifrice including 1.0% green tea catechin was applied to the male Wistar rats)	Reduces gingival oxidative stress and periodontal inflammation	Maruyama et al. [101]
(After the massive hepatectomy, green tea extract catechins were applied to the male Wistar rats)	Anti-oxidative and anti-inflammatory effects on liver dysfunction with massive hepatectomy	Saito et al. [102]

Catechin	Anti-oxidant and anti-inflammatory effects	References
(The review article of clinical studies)	Prevents vascular problems related diabetes mellitus	Howes and Simmonds [103]
(At the double-blind randomized study was applied daily 200 mg flavanols for 28 male smokers)	Anti-inflammatory effects by decreasing expression of inflammatory genes in leukocytes and increases vascular health	Weseler et al. [104]
(At the randomized, placebo-controlled, double blind, crossover study was applied capsules including 1 g total catechin for 19 healthy men)	Cardioprotective effects by decreasing oxidation of low density lipoprotein and incidence of atherosclerosis	Suzuki-Sugihara et al. [105]
(The consumption of high flavanols chocolate for 4 weeks was applied to the overweight men between 45 and 70 ages)	Effects on endothelium related vasodilation. Increases leukocyte adhesion factors and vascular function	Esser et al. [106]

Table 7.
The effects of catechin or flavanols, relevant to anti-inflammatory and anti-oxidant activity.

3. Conclusion

Nutraceuticals are alternative or functional foods or ingredients that prevent or treatment of inflammatory and oxidative stress induced diseases. Nutraceuticals are cheaper and easier availability than prescription drugs. For this reason, consumer's demand has increased in recent years.

The effecting on pathogenesis and activity of diseases are also essential scientific subject for animal and human health. When the effects of nutraceuticals on oxidative stress and inflammatory related disease are discovered, usages of nutraceuticals in Pharmacology and scientific studies are seen huge growth. The relation between beneficial effects of nutraceuticals and diseases are required to research long-term multidisciplinary studies.

People are searching minimally processed food and want to benefit nutritional values and live healthy. For this reason nutraceutical market is growing day by day.

The aging, fast rising population, changing lifestyle and lifestyle induced diseases, healthcare research, increasing cases of cancer, economic and public problems are directed people to benefit better choices.

As a conclusion, nutraceuticals are important for nutrition of human and animal. The consumption of nutraceuticals is necessary to reduce effects of the oxidative stress and inflammation related diseases.

Conflict of interest

There is no conflict of interest for this chapter.

IntechOpen

IntechOpen

Author details

Sevda Inan

Department of Pathology, Faculty of Veterinary Medicine, Tekirdag Namik Kemal University, Tekirdag, Turkey

*Address all correspondence to: sevdainan@nku.edu.tr

IntechOpen

© 2019 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Al-Okbi SY. Nutraceuticals of anti-inflammatory activity as complementary therapy for rheumatoid arthritis. *Toxicology and Industrial Health*. 2012;1-12. DOI: 10.1177/0748233712462468
- [2] Lushchak V. Microalgae of the Chlorophyceae class: Potential nutraceuticals reducing oxidative stress intensity and cellular damage. In: Vanessa BV, Rocio OB, Ruth RS, Paola TM, Adelaida HG, Egdar CE, editors. *Oxidative Stress and Diseases*, Intech Open; 2012. pp. 581-610. DOI: 10.5772/2535
- [3] Watson RR, Preedy VR. Fruits, Vegetables, and Herbs. Bioactive foods in health promotion. In: Barve KH, Kulkarni YA, Gaikwad AB, editors. *Nutraceuticals as Therapeutic Agents for Inflammation*. 1st ed. Academic Press, Elsevier; 2016. pp. 121-147. DOI: 10.1016/B978-0-12-802972-5.00007-X
- [4] Lee J, Koo N, Min DB. Reactive oxygen species, aging, and antioxidative nutraceuticals. *Comprehensive Reviews in Food Science and Food Safety*. 2004; 3:21-33. DOI: 10.1111/j.1541-4337.2004.tb00058.x
- [5] Bravo L. Polyphenols: Chemistry, dietary sources, metabolism, and nutritional significance. *Nutrition Reviews*. 1998;56:317-333. DOI: 10.1111/j.1753-4887.1998.tb01670.x
- [6] Kaur C, Kapoor HC. Antioxidants in fruits and vegetables—The millennium's health. *International Journal of Food Science and Technology*. 2001;36: 703-725. DOI: 10.1046/j.1365-2621.2001.00513.x
- [7] Ganesh GNK, Ramachandran A, Suresh KR, Senthil V, Baviya Priyadharshini R. Nutraceuticals—A regulatory review. *International Journal of Drug Regulatory Affairs*. 2015;3(2):22-29. DOI: 10.22270/ijdra.v3i2.165
- [8] Stirling C, Kruh W. Nutraceuticals: The future of intelligent food. Where food and pharmaceuticals converge. KPMG: Cutting Through Complexity. 2015. Available from: <https://home.kpmg.com/content/dam/kpmg/pdf/2015/05/neutraceuticals-the-future-of-intelligent-food.pdf> [Accessed: 2018-12-09]
- [9] Jajodia S, Rawat DS, Sharma R. Indian Nutraceuticals Market. Current Scenario & Future Trends. Assocham India; 2018. Available from: <https://mrssindia.com/wp-content/uploads/2018/07/Nutraceuticals-Report-Final.pdf> [Accessed: 2018-12-09]
- [10] Kumar V, Abbas AK, Aster JC. *Inflammation and Repair Robbins Basic Pathology*. 10th ed. Philadelphia: Elsevier; 2018. pp. 57-59 ISBN: 978-0-323-35317-5
- [11] Huang MT, Ghai G, Ho CT. Inflammatory process and molecular targets for anti-inflammatory nutraceuticals. *Comprehensive Reviews in Food Science and Food Safety*. 2004;3:127-139. DOI: 10.1111/j.1541-4337.2004.tb00063.x
- [12] Kador PF. Topical applied nutraceutical antioxidant formulation reduces ocular oxidative stress. *Functional Foods in Health & Disease*. 2017;7(1):17-35. DOI: 10.31989/ffhd.v7i1.297
- [13] Trachootham D, Weigin L, Ogasawara MA, Del Valle NR, Huang P. Redox regulation of cell survival. *Antioxidants & Redox Signaling*. 2008; 10(8):1343-1374. DOI: 10.1089/ars.2007.1957

- [14] Murphy MP. How mitochondria produce reactive oxygen species. *The Biochemical Journal*. 2009;**417**(1):1-13. DOI: 10.1042/BJ20081386
- [15] Gupta RC. Nutraceuticals. In: Milatovic D, Zaja-Milatovic S, Gupta RC, editors. *Oxidative Stress and Excitotoxicity: Antioxidants from Nutraceuticals*. Academic Press; 2016. pp. 401-413. DOI: 10.1016/B978-0-12-802147-7.00029-2
- [16] Houston M. The role of nutrition and nutraceutical supplements in the treatment of hypertension. *World Journal of Cardiology*. 2014;**6**(2):38-66. DOI: 10.4330/wjc.v6.i2.38
- [17] Thomas MJ. The role of free radicals and antioxidants: How do we know that they are working? *Critical Reviews in Food Science and Nutrition*. 1995;**2-35** (1-2):21-39. DOI: 10.1080/10408399509527683
- [18] Wickens AP. Ageing and the free radical theory. *Respiration Physiology*. 2001;**128**(3):379-391. DOI: 10.1016/S0034-5687(01)00313-9
- [19] Cohen JH, Kristal AR, Stanford JL. Fruit and vegetable intakes and prostate cancer risk. *Journal of the National Cancer Institute*. 2000;**92**(1):61-68. DOI: 10.1093/jnci/92.1.61
- [20] Packer L, Weber SU. The role of vitamin E in the emerging field of nutraceuticals. In: Kramer K, Hoppe PP, Packer L, editors. *Nutraceuticals in Health and Disease Prevention*. New York: Marcel Dekker; 2001. pp. 27-43. DOI: 10.1093/ajcn/75.4.783
- [21] Aryaeian N, Shahram F, Djalali M, Eshragian MR, Djazayeri A, Sarrafnejad A, et al. Effect of conjugated linoleic acids, vitamin E and their combination on the clinical outcome of Iranian adults with active rheumatoid arthritis. *International Journal of Rheumatic Diseases*. 2009;**12**(1):20-28. DOI: 10.1111/j.1756-185X.2009.01374.x
- [22] Bandt MD, Grossin M, Driss F, Pincemail J, Babin-Chevaye C, Pasquier C. Vitamin E uncouples joint destruction and clinical inflammation in a transgenic mouse model of rheumatoid arthritis. *Arthritis & Rheumatology*. 2002;**46**(2):522-532. DOI: 10.1002/art.10085
- [23] Beharka AA, Wu D, Serafini M, Meydani SN. Mechanism of vitamin E inhibition of cyclooxygenase activity in macrophages from old mice: Role of peroxynitrite. *Free Radical Biology and Medicine*. 2002;**32**(6):503-511. DOI: 10.1016/S0891-5849(01)00817-6
- [24] Meydani M. Effect of functional food ingredients: Vitamin E modulation of cardiovascular diseases and immune status in the elderly. *American Journal of Clinical Nutrition*. 2000;**71**(6):1665S-1668S. DOI: 10.1093/ajcn/71.6.1665
- [25] Lewis ED, Meydani SN, Wu D. Regulatory role of vitamin E in the immune system and inflammation. *IUBMB Life*. 2018:1-8. DOI: 10.1002/iub.1976
- [26] Malavolta M, Pierpaoli E, Giacconi R, Basso A, Cardelli M, Piacenza F, et al. Anti-inflammatory activity of tocotrienols in age-related pathologies: A SASpected involvement of cellular senescence. *Biological Procedures Online*. 2018;**20**:22. DOI: 10.1186/s12575-018-0087-4
- [27] Loffredo L, Perri L, Di Castelnuovo A, Iacoviello L, De Gaetano G, Violi F. Supplementation with vitamin E alone is associated with reduced myocardial infarction: A meta-analysis. *Nutrition, Metabolism, and Cardiovascular Diseases*. 2015;**25**(4):354-363. DOI: 10.1016/j.numecd.2015.01.008
- [28] Jain AK, Mehra NK, Swarnakar NK. Role of antioxidants for the treatment of Nutraceuticals - Past, Present and Future cardiovascular diseases: Challenges and opportunities. *Current*

- Pharmaceutical Design. 2015;**21**(30): 4441-4455. DOI: 10.2174/1381612821666150803151758
- [29] Shahidi F, De Camargo AC. Tocopherols and tocotrienols in common and emerging dietary sources: Occurrence, applications, and health benefits. *International Journal of Molecular Sciences*. 2016;**17**(10). DOI: 10.3390/ijms17101745
- [30] Dobrovolny J, Smrcka M, Bienertova-Vasku J. Therapeutic potential of vitamin E and its derivatives in traumatic brain injury-associated dementia. *Neurological Sciences*. 2018; **39**(6):989-998. DOI: 10.1007/s10072-018-3398-y
- [31] Ruhl R. Induction of PXR-mediated metabolism by beta-carotene. *Biochimica et Biophysica Acta*. 2005; **1740**(2):162-169. DOI: 10.1016/j.bbadis.2004.11.013
- [32] Cerhan JR, Saag KG, Merlino LA, Mikuls TR, Criswell LA. Antioxidant micronutrients and risk of rheumatoid arthritis in a cohort of older women. *American Journal of Epidemiology*. 2003;**157**(4):345-354. DOI: 10.1093/aje/kwf205
- [33] Giovannucci E. Tomatoes, tomato-based products, lycopene, and Cancer: Review of the epidemiologic literature. *Journal of the National Cancer Institute*. 1999;**91**(4):317-331. DOI: 10.1093/jnci/91.4.317
- [34] Giovannucci E, Ascherio A, Rimm EB, Stampfer MJ, Colditz GA, Willett WC. Intake of carotenoids and retino in relation to risk of prostate cancer. *Journal of the National Cancer Institute*. 1995;**87**(23):1767-1776. DOI: 10.1093/jnci/87.23.1767
- [35] Giovannucci E, Clinton SK. Tomatoes, lycopene, and prostate cancer. *Experimental Biology and Medicine*. 1998;**218**:129-139. DOI: 10.3181/00379727-218-44277
- [36] Weisburger JH. Mechanisms of action of antioxidants as exemplified in vegetables, tomatoes and tea. *Food and Chemical Toxicology*. 1999;**37**(9-10): 943-948. DOI: 10.1016/S0278-6915(99)00086-1
- [37] Polivkova Z, Smerak P, Demova H, Houska M. Antimutagenic effects of lycopene and tomato Purée. *Journal of Medicinal Food*. 2010;**13**(6):1443-1450. DOI: 10.1089/jmf.2009.0277
- [38] Sandhir R, Mehrotra A, Kamboj SS. Lycopene prevents 3-nitropropionic acid-induced mitochondrial oxidative stress and dysfunctions in nervous system. *Neurochemistry International*. 2010;**57**(5):579-587. DOI: 10.1016/j.neuint.2010.07.005
- [39] Sahin K, Tuzcu M, Sahin N, Ali S, Kucuk O. Nrf2/HO-1 signaling pathway may be the prime target for chemoprevention of cisplatin-induced nephrotoxicity by lycopene. *Food and Chemical Toxicology*. 2010;**48**(10): 2670-2674. DOI: 10.1016/j.fct.2010.06.038
- [40] Banerjee S, Jeyaseelan S, Guleria R. Trial of lycopene to prevent pre-eclampsia in healthy primigravidas: Results show some adverse effects. *The Journal of Obstetrics and Gynecology Research*. 2009;**35**(3):477-482. DOI: 10.1111/j.1447-0756.2008.00983.x
- [41] Sahni S, Hannan MT, Blumberg J, Cupples LA, Kiel DP, Tucker KL. Protective effect of total carotenoid and lycopene intake on the risk of hip fracture: A 17-year follow-up from the Framingham osteoporosis study. *Journal of Bone and Mineral Research: The Official Journal of the American Society for Bone and Mineral Research*. 2009; **24**(6):1086-1094. DOI: 10.1359/jbmr.090102
- [42] Gammone MA, D'Orazio N. Anti-obesity activity of the marine carotenoid fucoxanthin. *Marine Drugs*.

2015;**13**(4):2196-2214. DOI: 10.3390/md13042196.

[43] Duquette SC, Fischer CD, Feener TD, Muench GP, Morck DW, Barreda DR, et al. Anti-inflammatory effects of retinoids and carotenoid derivatives on caspase-3-dependent apoptosis and efferocytosis of bovine neutrophils. *American Journal of Veterinary Research*. 2014;**75**(12):1064-1075. DOI: 10.2460/ajvr.75.12.1064

[44] Kaulmann A, Bohn T. Carotenoids, inflammation, and oxidative stress—Implications of cellular signaling pathways and relation to chronic disease prevention. *Nutrition Research*. 2014; **34**(11):907-929. DOI: 10.1016/j.nutres.2014.07.010.

[45] Imokawa G. Intracellular signaling mechanisms involved in the biological effects of the xanthophyll carotenoid astaxanthin to prevent the photo-aging of the skin in a reactive oxygen species depletion-independent manner: The key role of mitogen and stress-activated protein kinase 1. *Photochemistry and Photobiology*. 2018. DOI: 10.1111/php.13034

[46] Cooperstone JL, Tober KL, Riedl KM, Teegarden MD, Cichon MJ, Francis DM, et al. Tomatoes protect against development of UV-induced keratinocyte carcinoma via metabolomic alterations. *Scientific Reports*. 2017;**7**(1):5106. DOI: 10.1038/s41598-017-05568-7

[47] Del Giudice R, Petruk G, Raiola A, Barone A, Monti DM, Rigano MM. Carotenoids in fresh and processed tomato (*Solanum lycopersicum*) fruits protect cells from oxidative stress injury. *Journal of the Science of Food and Agriculture*. 2017;**97**(5):1616-1623. DOI: 10.1002/jsfa.7910

[48] Asemi Z, Alizadeh SA, Ahmad K, Goli M, Esmailzadeh A. Effects of beta-carotene fortified synbiotic food on

metabolic control of patients with type 2 diabetes mellitus: A double-blind randomized cross-over controlled clinical trial. *Clinical Nutrition (Edinburgh, Scotland)*. 2016;**35**(4):819-825. DOI: 10.1016/j.clnu.2015.07.009

[49] Gao YY, Jin L, Ji J, Sun BL, Xu LH, Wang QX, et al. Xanthophyll supplementation reduced inflammatory mediators and apoptosis in hens and chicks. *Journal of Animal Science*. 2016; **94**(5):2014-2023. DOI: 10.2527/jas.2015-9628

[50] Ni Y, Zhuge F, Nagashimada M, Ota T. Novel action of carotenoids on non-alcoholic fatty liver disease: Macrophage polarization and liver homeostasis. *Nutrients*. 2016;**8**(7). DOI: 10.3390/nu8070391

[51] Mohammadzadeh Honarvar N, Saedisomeolia A, Abdolahi M, Shayeganrad A, Taheri Sangsari G, Hassanzadeh Rad B, et al. Molecular anti-inflammatory mechanisms of retinoids and carotenoids in Alzheimer's disease: A review of current evidence. *Journal of Molecular Neuroscience*. 2017;**61**(3):289-304. DOI: 10.1007/s12031-016-0857-x

[52] Stringham NT, Holmes PV, Stringham JM. Supplementation with macular carotenoids reduces psychological stress, serum cortisol, and sub-optimal symptoms of physical and emotional health in young adults. *Nutritional Neuroscience*. 2018;**21**(4): 286-296. DOI: 10.1080/1028415X.2017.1286445

[53] Linnewiel-Hermoni K, Motro Y, Miller Y, Levy J, Sharoni Y. Carotenoid derivatives inhibit nuclear factor kappa B activity in bone and cancer cells by targeting key thiol groups. *Free Radical Biology & Medicine*. 2014;**75**:105-120. DOI: 10.1016/j.freeradbiomed.2014.07.024

[54] Leoncini E, Nedovic D, Panic N, Pastorino R, Edefonti V, Boccia S.

- Carotenoid intake from natural sources and head and neck cancer: A systematic review and meta-analysis of epidemiological studies. *Cancer Epidemiology, Biomarkers & Prevention*. 2015;**24**(7):1003-1011 DOI: 10.1158/1055-9965.EPI-15-0053
- [55] Biesalski HK. Polyphenols and inflammation: Basic interactions. *Current Opinion in Clinical Nutrition and Metabolic Care*. 2007;**10**(6):724-728 DOI: 10.1097/MCO.0b013e3282f0cef2
- [56] Fresco P, Borges F, Marques MPM, Diniz C. The anticancer properties of dietary polyphenols and its relation with apoptosis. 2010;**16**(1):114-134. DOI: 10.2174/138161210789941856
- [57] Du WX, Olsen CW, Avena-Bustillos RJ, Friedman M, McHugh TH. Physical and antibacterial properties of edible films formulated with apple skin polyphenols. *Journal of Food Science*. 2011;**76**(2):M149-M155. DOI: 10.1111/j.1750-3841.2010.02012.x
- [58] Rimbach G, Melchin M, Moehring J, Wagner AE. Polyphenols from cocoa and vascular health—A critical review. *International Journal of Molecular Sciences*. 2009;**10**(10):4290-4309. DOI: 10.3390/ijms10104290
- [59] Corradini E, Foglia P, Giansanti P, Gubbiotti R, Samperi R, Lagana A. Flavonoids: Chemical properties and analytical methodologies of identification and quantitation in foods and plants. *Natural Product Research*. 2011;**25**(5):469-495. DOI: 10.1080/14786419.2010.482054
- [60] Williams RJ, Spencer JP, Rice-Evans C. Flavonoids: Antioxidants or signalling molecules? *Free Radical Biology & Medicine*. 2004;**36**(7):838-849. DOI: 10.1016/j.freeradbiomed.2004.01.001
- [61] Actis-Goretta L, Ottaviani JI, Fraga CG. Inhibition of angiotensin converting enzyme activity by flavanol-rich foods. *Journal of Agricultural and Food Chemistry*. 2006;**54**(1):229-234. DOI: 10.1021/jf052263o
- [62] Garg ML, Blake RJ, Wills RB, Clayton EH. Macadamia nut consumption modulates favourably risk factors for coronary artery disease in hypercholesterolemic subjects. *Lipids*. 2007;**42**(6):583-587. DOI: 10.1007/s11745-007-3042-8
- [63] Chatterjee S, Jungraithmayr W, Bagchi D. Immunity and inflammation in health and disease. Emerging roles of nutraceuticals and functional foods in immune support. In: MJR H, editor. *Phytochemicals as Anti-Inflammatory Nutraceuticals and Phytopharmaceuticals*. Academic Press; 2018. pp. 363-388. DOI: 10.1016/B978-0-12-805417-8.00028-7
- [64] Diniz TC, Silva JC, de Lima-Saraiva SR, Ribeiro FP, Pacheco AG, de Freitas RM, et al. The role of flavonoids on oxidative stress in epilepsy. *Oxidative Medicine and Cellular Longevity*. 2015; **2015**:171756. DOI: 10.1155/2015/171756
- [65] Martín-Peláez S, Castañer O, Solà R, Motilva MJ, Castell M, Pérez-Cano FJ, et al. Influence of phenol-enriched olive oils on human intestinal immune function. *Nutrients*. 2016;**8**(4):213. DOI: 10.3390/nu8040213
- [66] Yahfoufi N, Alsadi N, Jambi M, Matar C. The immunomodulatory and anti-inflammatory role of polyphenols. *Nutrients*. 2018;**10**(11). DOI: 10.3390/nu10111618
- [67] Kwon O, Eck P, Chen S, Corpe CP, Lee JH, Kruhlak M, et al. Inhibition of the intestinal glucose transporter GLUT2 by flavonoids. *FASEB Journal*. 2007;**21**(2):366-377. DOI: 10.1096/fj.06-6620com
- [68] Kinghorn AD, Su BN, Jang DS, Chang LC, Lee D, Gu JQ, et al. Natural inhibitors of carcinogenesis. *Planta*

Medica. 2004;**70**(8):691-705. DOI: 10.1055/s-2004-827198

[69] Shukla S, Kanwal R, Shankar E, Datt M, Chance MR, Fu P, et al. Apigenin blocks IKK α activation and suppresses prostate cancer progression. *Oncotarget*. 2015;**6**(31):31216-31232. DOI: 10.18632/oncotarget.5157

[70] Peng G, Du Y, Wei Y, Tang J, Peng AY, Rao L. A new synthesis of fully phosphorylated flavones as potent pancreatic cholesterol esterase inhibitors. *Organic & Biomolecular Chemistry*. 2011;**9**(7):2530-2534. DOI: 10.1039/C0OB00640H

[71] Gasiorowski K, Lamer-Zarawska E, Leszek J, Parvathaneni K, Yendluri BB, Błach-Olszewska Z, et al. Flavones from root of *Scutellaria baicalensis* Georgi: Drugs of the future in neurodegeneration? *CNS & Neurological Disorders Drug Targets*. 2011;**10**(2):184-191. DOI: 10.2174/187152711794480384

[72] Ganjare AB, Nirmal SA, Patil AN. Use of apigenin from *Cordia dichotoma* in the treatment of colitis. *Fitoterapia*. 2011;**82**(7):1052-1056. DOI: 10.1016/j.fitote.2011.06.008

[73] Wu X, Schauss AG. Mitigation of inflammation with foods. *Journal of Agricultural and Food Chemistry*. 2012;**60**(27):6703-6717. DOI: 10.1021/jf3007008

[74] Laev SS, Salakhutdinov NF. Anti-arthritic agents: Progress and potential. *Bioorganic & Medicinal Chemistry*. 2015;**23**(13):3059-3080. DOI: 10.1016/j.bmc.2015.05.010

[75] Nabavi SF, Braidly N, Gortzi O, Sobarzo-Sanchez E, Daglia M, Skalicka-Woźniak K, et al. Luteolin as an anti-inflammatory and neuroprotective agent: A brief review. *Brain Research Bulletin*. 2015;**119**(Pt A):1-11. DOI: 10.1016/j.brainresbull.2015.09.002

[76] Xiao J, Capanoglu E, Jassbi AR, Miron A. Advance on the flavonoid C-glycosides and health benefits. *Critical Reviews in Food Science and Nutrition*. 2016;**56**(Suppl. 1):S29-S45. DOI: 10.1080/10408398.2015.1067595

[77] Cardenas H, Arango D, Nicholas C, Duarte S, Nuovo GJ, He W, et al. Dietary apigenin exerts immune-regulatory activity in vivo by reducing NF- κ B activity, halting leukocyte infiltration and restoring normal metabolic function. *International Journal of Molecular Sciences*. 2016;**17**(3):323. DOI: 10.3390/ijms17030323

[78] Shiota C, Abe T, Kawai N, Ohno A, Teshima-Kondo S, Mori H, et al. Flavones inhibit LPS-induced Atrogin-1/MAFbx expression in mouse C2C12 skeletal myotubes. *Journal of Nutritional Science and Vitaminology (Tokyo)*. 2015;**61**(2):188-194. DOI: 10.3177/jnsv.61.188

[79] Park JB, Levine M. Intracellular accumulation of ascorbic acid is inhibited by flavonoids via blocking of dehydroascorbic acid and ascorbic acid uptakes in HL-60, U937 and Jurkat cells. *The Journal of Nutrition*. 2000;**130**(5):1297-1302. DOI: 10.1093/jn/130.5.1297

[80] Nakai M, Fukui Y, Asami S, Toyoda-Ono Y, Iwashita T, Shibata H, et al. Inhibitory effects of oolong tea polyphenols on pancreatic lipase in vitro. *Journal of Agricultural and Food Chemistry*. 2005;**53**(11):4593-4598. DOI: 10.1021/jf047814+

[81] Hsu CL, Yen GC. Induction of cell apoptosis in 3T3-L1 pre-adipocytes by flavonoids is associated with their antioxidant activity. *Molecular Nutrition & Food Research*. 2006;**50**(11):1072-1079. DOI: 10.1002/mnfr.200600040

[82] Liu IM, Tzeng TF, Liou SS, Chang CJ. Beneficial effect of traditional Chinese medicinal formula

Danggui-Shaoyao-san on advanced glycation end-product-mediated renal injury in streptozotocin-diabetic rats. Evidence-Based Complementary and Alternative Medicine. 2012; Article ID 140103. DOI: 10.1155/2012/140103

[83] Singab AN, Ayoub NA, Ali EN, Mostafa NM. Antioxidant and hepatoprotective activities of Egyptian moraceous plants against carbon tetrachloride-induced oxidative stress and liver damage in rats. *Pharmaceutical Biology*. 2010; **48**(11):1255-1264. DOI: 10.3109/13880201003730659

[84] Yang L, Takai H, Utsunomiya T, Li X, Li Z, Wang Z, et al. Kaempferol stimulates bone sialoprotein gene transcription and new bone formation. *Journal of Cellular Biochemistry*. 2010; **110**(6):1342-1355. DOI: 10.1002/jcb.22649

[85] Mahat MY, Kulkarni NM, Vishwakarma SL, Khan FR, Thippeswamy BS, Hebballi V, et al. Modulation of the cyclooxygenase pathway via inhibition of nitric oxide production contributes to the anti-inflammatory activity of kaempferol. *European Journal of Pharmacology*. 2010; **642**(1-3):169-176. DOI: 10.1016/j.ejphar.2010.05.062

[86] Boots AW, Drent M, De Boer VC, Bast A, Haenen GR. Quercetin reduces markers of oxidative stress and inflammation in sarcoidosis. *Clinical Nutrition (Edinburgh, Scotland)*. 2011; **30**(4):506-512. DOI: 10.1016/j.clnu.2011.01.010

[87] Kobori M, Takahashi Y, Sakurai M, Akimoto Y, Tsushida T, Oike H, et al. Quercetin suppresses immune cell accumulation and improves mitochondrial gene expression in adipose tissue of diet-induced obese mice. *Molecular Nutrition & Food Research*. 2016; **60**(2):300-312. DOI: 10.1002/mnfr.201500595

[88] Dong YS, Wang JL, Feng DY, Qin HZ, Wen H, Yin ZM, et al. Protective effect of quercetin against oxidative stress and brain edema in an experimental rat model of subarachnoid hemorrhage. *International Journal of Medical Sciences*. 2014; **11**(3):282-290. DOI: 10.7150/ijms.7634

[89] Yang D, Liu X, Liu M, Chi H, Liu J, Han H. Protective effects of quercetin and taraxasterol against H₂O₂-induced human umbilical vein endothelial cell injury in vitro. *Experimental and Therapeutic Medicine*. 2015; **10**(4):1253-1260. DOI: 10.3892/etm.2015.2713

[90] Miranda CL, Stevens JF, Ivanov V, McCall M, Frei B, Deinzer ML, et al. Antioxidant and prooxidant actions of prenylated and nonprenylated chalcones and flavanones in vitro. *Journal of Agricultural and Food Chemistry*. 2000; **48**(9):3876-3884. DOI: 10.1021/jf0002995

[91] Kumar A, Katiyar SB, Agarwal A, Chauhan PM. Perspective in antimalarial chemotherapy. *Current Medicinal Chemistry*. 2003; **10**(13):1137-1150. DOI: 10.2174/0929867033457494

[92] Kontogiorgis C, Mantzanidou M, Hadjipavlou-Litina D. Chalcones and their potential role in inflammation. *Mini Reviews in Medicinal Chemistry*. 2008; **8**(12):1224-1242. DOI: 10.2174/138955708786141034

[93] Mojzis J, Varinska L, Mojzisova G, Kostova I, Mirossay L. Antiangiogenic effects of flavonoids and chalcones. *Pharmalogical Research*. 2008; **57**(4):259-265. DOI: 10.1016/j.phrs.2008.02.005

[94] Qin L, Jin L, Lu L, Lu X, Zhang C, Zhang F, et al. Naringenin reduces lung metastasis in a breast cancer resection model. *Protein & Cell*. 2011; **2**(6):507-516. DOI: 10.1007/s13238-011-1056-8

- [95] Prabu SM, Shagirtha K, Renugadevi J. Naringenin in combination with vitamins C and E potentially protects oxidative stress-mediated hepatic injury in cadmium-intoxicated rats. *Journal of Nutritional Science and Vitaminology (Tokyo)*. 2011;**57**(2):177-185. DOI: 10.3177/jnsv.57.177
- [96] Céliz G, Daz M, Audisio MC. Antibacterial activity of naringin derivatives against pathogenic strains. *Journal of Applied Microbiology*. 2011; **111**(3):731-738. DOI: 10.1111/j.1365-2672.2011.05070.x
- [97] Oršolić N, Gajski G, Garaj-Vrhovac V, Dikić D, Prskalo ZŠ, Sirovina D. DNA-protective effects of quercetin or naringenin in alloxan-induced diabetic mice. *European Journal of Pharmacology*. 2011;**656**(1–3):110-118. DOI: 10.1016/j.ejphar.2011.01.021
- [98] Chao CL, Weng CS, Chang NC, Lin JS, Kao ST, Ho FM. Naringenin more effectively inhibits inducible nitric oxide synthase and cyclooxygenase-2 expression in macrophages than in microglia. *Nutrition Research (New York, N.Y.)*. 2010;**30**(12):858-864. DOI: 10.1016/j.nutres.2010.10.011
- [99] Bhardwaj P, Khanna D. Green tea catechins: Defensive role in cardiovascular disorders. *Chinese Journal of Natural Medicines*. 2013; **11**(4):345-353. DOI: 10.1016/S1875-5364(13)60051-5
- [100] Norata GD, Marchesi P, Passamonti S, Pirillo A, Violi F, Catapano AL. Anti-inflammatory and anti-atherogenic effects of catechin, caffeic acid and trans-resveratrol in apolipoprotein E deficient mice. *Atherosclerosis*. 2007;**191**(2):265-271. DOI: 10.1016/j.atherosclerosis.2006.05.047
- [101] Maruyama T, Tomofuji T, Endo Y, Irie K, Azuma T, Ekuni D, et al. Supplementation of green tea catechins in dentifrices suppresses gingival oxidative stress and periodontal inflammation. *Archives of Oral Biology*. 2011;**56**(1):48-53. DOI: 10.1016/j.archoralbio.2010.08.015
- [102] Saito Y, Shimada M, Utsunomiya T, Imura S, Morine Y, Ikemoto T, et al. Green tea catechins improve liver dysfunction following massive hepatectomy through anti-oxidative and anti-inflammatory activities in rats. *Gastroenterology*. 2011;**140**(5):S-928. DOI: 10.1016/S0016-5085(11)63850-X
- [103] Howes MJ, Simmonds MS. The role of phytochemicals as micronutrients in health and disease. *Current Opinion in Clinical Nutrition and Metabolic Care*. 2014;**17**(6):558-566. DOI: 10.1097/MCO.0000000000000115
- [104] Weseler AR, Ruijters EJ, Driittij-Reijnders MJ, Reesink KD, Haenen GR, Bast A. Pleiotropic benefit of monomeric and oligomeric flavanols on vascular health—A randomized controlled clinical pilot study. *PLoS One*. 2011;**6**(12):e28460. DOI: 10.1371/journal.pone.0028460
- [105] Suzuki-Sugihara N, Kishimoto Y, Saita E, Taguchi C, Kobayashi M, Ichitani M, et al. Green tea catechins prevent low-density lipoprotein oxidation via their accumulation in low-density lipoprotein particles in humans. *Nutrition Research (New York, N.Y.)*. 2016;**36**(1):16-23. DOI: 10.1016/j.nutres.2015.10.012
- [106] Esser D, Mars M, Oosterink E, Stalmach A, Müller M, Afman LA. Dark chocolate consumption improves leukocyte adhesion factors and vascular function in overweight men. *FASEB Journal*. 2014;**28**(3):1464-1473. DOI: 10.1096/fj.13-239384