8 Anti-Inflammatory Nutrients and Nutraceuticals for Active and Healthy Aging

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Abstract

Inflammaging is the continuation of a mild chronic asymptomatic inflammation over a long time in the body, followed by clinical symptoms of aging as the result. This process underlies many diseases associated with aging, including cancers, diabetes, and diseases with cognitive decline. There is a variety of anti-inflammatory agents to help prevent or ameliorate the process. Best and most frequent natural sources that contain anti-inflammatory agents are the food and herbs, out of which there are some dietary supplements manufactured as well.

Major anti-inflammatory components in food include certain amino acids, vitamins, and minerals, and most importantly, polyunsaturated fatty acids. As it is hard to precisely separate food from edible herbs—since some herbs are a part of the daily diet—the great family of polyphenols is discussed as the major anti-inflammatory in herbs, despite their existence in what is called food, as well. The molecular mechanisms of the most frequent and effective agents and their role in the prevention of certain diseases related to inflammaging are discussed. And finally, briefly categorized tables are composed, to compare the sources of the compounds in more detail.

Keywords

Inflammaging · Neuroinflammation · Polyunsaturated fatty acids · Polyphenols · Flavonoids

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S. M. Nabavi et al. (eds.), *Nutrients and Nutraceuticals for Active & Healthy Ageing*,
https://doi.org/10.1007/978-981-15-3552-9_8

8.1 Inflammation

Inflammation is a process occurring in response to an infection or injury in the body. It involves many specific cell pathways and cytokine release that cope with the unusual cells; and it may come to production of cells or factors that might cause pathological conditions themselves, this is associated with the incapability of the immune system to distinguish self from non-self (Fasano 2012). This is where the inflammation can be potentially harmful. If the underlying cause of inflammation is not removed, the inflammatory processes will continue until they fall into a chronic inflammatory state.

Inflammaging refers to the condition in which a prolonged, low-grade inflammation is triggered and continued for a part of a life span, which is in this term, the aging span. It is at first subclinical, with no notable symptoms, but it will eventually show up with diseases, the predominant ones being cancers, and diseases related to cognitive decline as well as diabetes and other metabolic disorders. Table 8.1 overviews the common diseases and symptoms of inflammation. Franceschi et al. have described and discussed the pathophysiology associated with inflammaging in their review (Franceschi and Campisi 2014). As proposed by them, there are six main sources to inflammaging:

1. the damaged cells and macromolecules (which should have been eliminated but accumulated); these could mimic a possible inflammatory state as they appear pathogenic to the immune system.

Table 8.1 Common diseases associated with inflammaging

Neurologic and cognitive disorders	Alzheimer's Disease Parkinson's Disease Multiple Sclerosis Bipolar Mood Disorder Major Depression Disorder General Anxiety Disorder
Metabolic disorders	Diabetes Dyslipidemia
Cancers	Gastric cancer Colorectal cancer Pancreatic cancer Hepatocellular carcinoma Bladder cancer Prostate cancer
Eye and vision	Cataract Macular degeneration
Joint and skeletal	Arthritis
Cardiovascular diseases	Hypertension Ischemic heart diseases and atherosclerosis
Pulmonary diseases	Infection Lung cancer

2. products of the bacteria of the normal flora. Along with aging, the ability of the intestinal cells to prevent leakage to the inner tissues decreases, which allows more pathogenic molecules to be introduced to the immune system.
3. persistently senescent cells, because they produce high amounts of proinflammatory cytokines
4. Increased activation of the coagulation system
5. Immunosenescence; As adaptive immunity declines with aging, the innate immune system increases its activity, which does not possess the specificity of the adaptive immunity.
6. Dysregulation in the complement pathway, a cause for many degenerative diseases associated with aging

One of the most significant changes in chronic inflammation is the imbalanced ratio of proinflammatory to anti-inflammatory cytokines. Cytokines are the dominant factors in inducing or suppressing the inflammation. The mechanisms involved are generation of molecules with the ability to eliminate the undesired, such as ROS, or the iNOS protein; producer of NO, which plays an active role in inflammation in the neurons, joints, and lung (Sharma et al. 2007). Abundant ROS can cause DNA damage and genome instability, thereby inducing cancer. It also promotes tumor proliferation, angiogenesis, and survival (Wu et al. 2014). NF-κB is a protein activated by proinflammatory stimuli such as viruses, cytokines, oncogenes, toll-like receptors, etc. This protein is also tumorigenic as it mediates cell proliferation and angiogenesis (Wu et al. 2014). Moreover, the ROS, NO, cytokines, and prostaglandins are the main actors in inducing inflammation in the CNS, following different proteinopathies, which stand for the neurodegenerative state caused by over activated microglia (Glass et al. 2010).

During the subclinical period of *inflammaging*, lifestyle intervention, including exercise and healthy diet, contribute to prevent or delay the progression of inflammation.

Healthy diet, such as Mediterranean pattern, has been recognized as one of the best approaches to ameliorate the inflammatory status, due to the high amount of the bioactive compounds that have been found to be efficient in treatment of inflammation; some of them are also used as supplements or nutraceuticals. Many vitamins and minerals fall into this category; however, they are mainly taken by the normal daily diet. It is only of importance that necessary considerations be taken regarding the changes in the need for vitamins and minerals, especially those with an anti-inflammatory role, in the elderly.

8.2 Food

Poor nutrition contributes to many chronic aging diseases, including cardiovascular diseases, diabetes and most importantly, cancer. It is known what a poor diet might consist of; however, what exactly a “rich” or healthy diet might mean, varies upon

individuals, for the beneficial and detrimental sides of the constituents might be difficult to describe. Subsequent studies at the end of the twentieth century focused on diets rich in plants and fruits, as they showed a promise to prevent cancer. These studies had focused on the radical scavenging and antioxidant characteristics of the natural constituents, including polyphenols, flavonoids, and tannins.

Dominant contents that a diet covers, which could influence the inflammatory state are vitamins, minerals, amino acids, and beneficial fats, i.e. long chain fatty acids.

8.2.1 Vitamins and Minerals

Vitamins and minerals are essential to the diet at any age; however, their amount of intake changes during aging. Some of them, such as Zinc, Folate, vitamin B12, Calcium, and vitamin D have an anti-inflammatory activity. It is only recommended that vitamins and minerals should be taken within the normal dosage range as they are normally found in a rich and healthy diet. Main mechanisms are charted in Table 8.2.

8.2.2 Amino Acids

Amino acids have a variety of functions in the body. Some have antioxidant and anti-inflammatory effects. Most effective ones are *Arginine*, *Glutamine*, *L-carnitine*, *Tryptophan*, *Creatine,* and *Taurine*. A number of in vivo studies evaluated their efficacy as a supplement/nutraceutical in reducing inflammation. Main mechanisms are charted in Table 8.3, in vivo studies in Table 8.4 as well.

Table 8.2 Main anti-inflammatory mechanisms of the vitamins/minerals

Vitamin/ mineral	Anti-inflammatory mechanism	Ref.
Vitamin B12	May inhibit the inflammatory mediators	Hosseinzadeh et al. (2012)
Folate	Through folate receptor beta on activated macrophages	Poh et al. (2017)
Calcium	Major role is through calcium sensing receptors, which promote inflammatory response in deficiency of calcium	Hendy and Canaff (2016)
Zinc	Modulation of NF-κB, regulation of inflammatory cytokines	Gammoh and Rink (2017)
Vitamin D	Might reduce inflammatory markers specially NF-κB, modulates lymphocytes and immunoglobulins	de Carvalho and Ribeiro (2017)

Table 8.3 Main anti-inflammatory mechanisms of the amino acids

Amino acid	Anti-inflammatory mechanism	Ref.
Arginine	Suppresses T cell function	Raber et al. (2012)
Glutamine	Activates MKP-1 and inhibits NF-κB and MAPK	Kim et al. (2015)
L-carnitine	Inhibits NF-κB	Koc et al. (2011)
Tryptophan	Suppresses T cell function	Santhanam et al. (2016)
Creatine	Reduces inflammatory mediators, including TLRs and NF-κB	Riesberg et al. (2016)

8.2.3 Omega-3 Fatty Acids

Omega-3 fatty acids are polyunsaturated fatty acids (PUFA), having their last pi bond between C3 and C4. Most active biological omega-3 acids include eicosapentaenoic acid (EPA, 20:5n-3), docosapentaenoic acid (DPA, 22:5n-3), and docosahexaenoic acid (DHA, 22:6n-3). Omega 6 fatty acids are characterized by a double bond between the C6–7. These fatty acids have a major role in preventing the inflammation.

It is thought that PUFAs will integrate into the membrane of many cells, including immune cells, e.g. macrophages, lymphocytes, and neutrophils. This integration stands for the fatty acid composition, when responding to the inflammatory stimuli, i.e. the more (PUFA) in the membrane of the cells, the more they will be involved in the eicosanoid cascade (Calder 2015). This hypothesis has been proved in several studies (Healy et al. 2000; Faber et al. 2011; Thies et al. 2001; Kew et al. 2003). By an inflammatory trigger, phospholipase A2 will release the ARA from the membrane; however, it is clear that by a decreased amount of ARA, the omega-3 fatty acids will substitute the ARA, and stand as substrates for the COX and LOX enzymes. This has been further detailed below.

The cascade of biological inflammatory response involves two main pathways. The N-3 pathway results in the production of PGE3 (anti-inflammatory), the n-6 produces Dihomo-gamma-linolenic acid, which, if interrupted by the environmental factors, will be the substrate for the production of PGE1 (anti-inflammatory). But when continued, it produces Arachidonic acid, the primary substrate for COX, LOX, and CYP450 enzymes, responsible for PGE2 and leukotriene production (inflammatory). The two pathways are linked to same enzymes (mostly elongase and desaturase); but what determines the predominant pathway, will be the availability of the nutrients needed for each equation, as well as the metabolic environment (Mahan et al. 2017). Hence, a well-thought diet will have to make sure of adequate intake of n-3 fatty acids, and the supplements and minerals supporting the PGE1 and PGE3 production Table 8.5.

Table 8.4 Studies on the anti-inflammatory effects of amino acids

Target group	Amino acid	Study	Dosage	Duration	Outcome	Ref.
Animals	Taurine	Rats with liver injury	200 mg/kg/day	Single dose	Decreased inflammatory factors and liver transaminases significantly	Liu et al. (2017)
	L-carnitine	Albino mice	100 or 300 mg/kg/day	5 days	Reduced microglial activation and increased BDNF concentration	Kazak and Yarim (2017)
Humans		Healthy obese women	2 g/day	8 weeks	Therapy alone did not change the inflammatory markers	Rafraf et al. (2015)
		Patients with coronary artery diseases	1000 mg/day	12 weeks	Levels of inflammation markers were significantly reduced	Lee et al. (2015)
	Glutamine	Patients with abdominal malignancies treated with radiotherapy	30 g/day	From 3 days before radiotherapy until end of treatment	Decreased the inflammation caused by radiation	de Urbina et al. (2017)
	Creatine	Young athletes	0.3 mg/kg	7 days	Inhibited the increase of inflammatory markers after exercise	Deminice et al. (2013)

Table 8.5 Common herbs to prevent or fight inflammation

Herb	Content	Indications and dosage	Safety profile
Agrimony (*Agrimonia eupatoria*)	Catechin tannins Flavonoids (quercetin, Kaempferol, apigenin, luteolin) Procyanidins	No pharmacologic data available on the dosage (European medicine agency, committee on herbal medicinal products EMA/HMPC/680595/2013 n.d.) Cannot be recommended as a nutraceutical	No pharmacologic data available on the safety profile of systemic chronic and subchronic use (European medicine agency, committee on herbal medicinal products EMA/HMPC/680595/2013 n.d.) Cannot be recommended as a nutraceutical
Arnica (*Arnica montana*)	Sesquiterpene lactones Short-chained fatty acids: Acetic acid and isobutyric acid Flavone and flavonol glycosides	Approved by the commission E for rheumatism No oral dosage range	Classified by the US Food and Drug Administration as unsafe because of its toxicity It should not be taken orally
Brewer's yeast (*Saccharomyces cerevisiae*)	Mannans, glucans Group B vitamins	No indications reported regarding inflammaging A study of 500 mg daily for 12 weeks on rhinitis, has reported improvement, with no side effects (Moyad et al. 2009)	Classified as GRAS
English plantain (*Plantago lanceolata*)	Iridoids: Rhinantin, catalpol Flavonoids: Apigenin, luteolin Tannins: Aesculetin Salicylic acid	A polyherbal formulation containing plantago psyllium reduced blood glucose and serum lipids in 30 DM2 patients (Zarvandi et al. 2017). However, there isn't enough data on dosage and period of use for diabetes or hyperlipidemia (Ota and Ulrih 2017) A study on 18 PD patients proved benefits on levodopa pharmacokinetic profile, administering 3.5 g TDS of plantago husk (Fernandez-Martinez et al. 2014)	It contains allergenic substances and antigens, thus can result in flu-like symptoms and anaphylactoid reactions
Fenugreek (*Trigonella foenum-graecum*)	Saponins, known as graecunins (glycosides of diosgenin) Flavones: Vitexin, vitexin glycoside, quercetin Amino acids: Isoleucine,	Cholesterol lowering effect (with no significant change on HDL profile) (Valette et al. 1984; Singhal et al. 1982; Hannan et al. 2003; Stark and Madar 1993; Thompson Coon and Ernst 2003; Yadav et al. 2004; Sauvaire et al. 1991; Gupta et al. 2001)	No special adverse reactions, except for a probable hypoglycemia

(continued)

Table 8.5 (continued)

Herb	Content	Indications and dosage	Safety profile
	4-hydroxyisoleucin Sapinogens: Diosgenin, smilagenin, sarsasapogenin, tigogenin, neotigogenin, gitogenin, neogitogenin	Antidiabetic effect, seen especially with the amino acid 4-hydroxyisoleucine. The mechanism is through rising plasma insulin, either secretion, or synthesis The anti-inflammatory effects are proved on animals (Sur et al. 2001). In a 21-day trial on rats, the concentration of inflammatory mediators was decreased on fenugreek mucilage; the effects were concluded to be higher than that of indomethacin (Sindhu et al. 2018). Thus, the plant carries a promising anti-arthritic property. However, literature lacks clinical data The plant exerts its anti-inflammatory effects On neurological diseases as a neuroprotective, antidepressant, antianxiety as well as a modulator on cognitive functions (Sharma et al. 2017; Zameer et al. 2017)	
Flax (*Linum usitatissimum*)	Unsaturated fatty acids mainly ALA and linoleic acid Lignans: Secoisolarciresinol diglucoside	It has shown cholesterol lowering effect (Lucas et al. 2002; Kaul et al. 2008; Edel et al. 2015; Torkan et al. 2015) By the EMA, it is only approved for its mucilage effects and constipation relief	The US Food and Drug Administration has NOT classified flaxseed [oil] as GRAS. However, it does allow up to 12% (weight) flaxseed in food
German chamomile (*Matricaria recutita*)	Volatile oil: (−)-alpha-bisabolol (levomenol), bisabolol oxide A, bisabolol oxide B, bisabololone oxide A, chamazulenespathulenol Flavonoids: Apigenin, luteolin, chrysoeriol, apigenin-7-O-glucoside, apigenin glucoside acetate, quercetin, isorhamnetin, patuletin	On scopolamine-induced memory impaired rats, the drug has improved the neuroinflammation through modulation of the cholinergic system and antioxidant activity in the hippocampus (Ionita et al. 2018) A study on type-2 DM patients, has reported reduction in glycemic index with the extract (Zemestani et al. 2016) A clinical trial has proved that the extract can be a safe and effective treatment for moderate cyclic mastalgia (Saghafi et al. 2018)	No special side effects reported with the studies mentioned (Zemestani et al. 2016; Saghafi et al. 2018; Mao et al. 2016)

	Hydroxycoumarins: Umbelliferone, herniarin Mucilages: Rhamanogalacturonane	A study has proved long-term use of chamomile extract to improve moderate to severe GAD symptoms, but not the rate of relapse (Mao et al. 2016) The study consisted of two phases. Phase 1 was defined as 12 weeks of open-label treatment with chamomile extract 500 mg TDS for 12 weeks; and phase 2 double-blind randomized trial, in which patients were divided into two groups, receiving either the extract or placebo for 26 weeks in substitution No established pharmaceutical use by EMA by 2011 (EMA/HMPC/55843/2011 n.d.)	
Oats (*Avena sativa*)	Fiber (beta-gluacan), manganese, selenium, phosphorous, tryptophan, thiamine, and vitamin E (mainly as alpha-tocopherol) Unsaturated triglycerides enzymes: Lipase, lipoxygenase, superoxide dismutase	A study has shown reduction in need for laxatives and increased bioavailability of vitamin B12, as well as maintaining body weight in the elderly at nursing homes who received oat bran in addition to food (Sturtzel et al. 2010) Many, but not all, trials show reductions in LDL-cholesterol using beta-glucan (Cugnet-Anceau et al. 2010; Liatis et al. 2009b; Hallikainen et al. 2006; Chen et al. 2006; Queenan et al. 2007). Oat fiber can decrease cholesterol levels modestly. Eight grams per day (Chen et al. 2006) of the soluble fiber or 3 g/day of beta-glucan (Liatis et al. 2009b; Maki et al. 2010) has been recommended in the studies. The study reports 5 mg/dL decrease in LDL upon addition of 3 g/day of beta-glucan to American diet (Maki et al. 2010)	Classified as GRAS by US Food and Drug Administration (FDA) when taken as food. Safety and efficacy of dosages higher than those found in food are unproven
St. John's wort (*Hypericum perforatum*)	Flavonoids: Isoquercetin, quercetin, phenols	It shows anti-inflammatory effects by inhibition of arachidonic acid release and inflammatory-cytokine production (Panossian et al. 1996) SJW extracts exhibit neuroprotection, improve cognitive function as well as decreasing Amyloidβ plaques (Hofrichter et al. 2013; Cao et al. 2017) Mild antidepressive effects in elderly (Ng et al. 2017;	May result in photosensitivity and allergic reactions Its vast interactions profile with drugs may limit its consumption

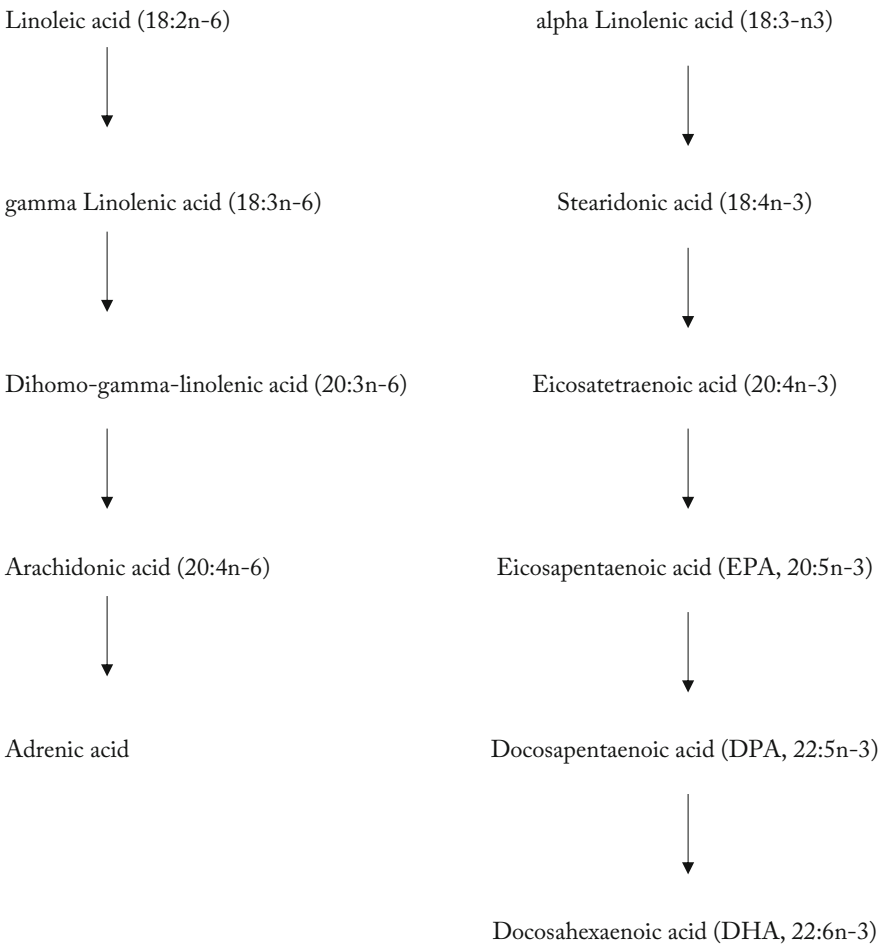
(continued)

Table 8.5 (continued)

Herb	Content	Indications and dosage	Safety profile
		Apaydin et al. 2016) Has shown antiaging effects on mice receiving 135 mg/kg/day for 4 weeks of the lyophilized extract (Mohammadirad et al. 2013)	
California peppertree (*Schinus molle*)	Volatile oil: Alpha-phellandrene, beta-phellandrene, limonene Flavonoids: Kaempferol, myricetin, quercetin Resins Mucilages	Because of its anti-inflammatory effects, might be effective in rheumatism, however, pharmacological data lack	No pharmacological data available on the use as a nutraceutical A study on rats reported safety in dosages used as an insecticide (Ferreroa et al. 2007)
Cape Aloe (*Aloe ferox*)		Purgative and laxative (van Wyk and Smith 2008; Hutchings et al. 1996; Grace et al. 2008; Chen et al. 2012; Cock 2015) Rheumatoid arthritis Topically used to treat erythema Available in forms of capsule, cream, gel	No pharmacological data available
Sage (*Salvia officinalis*)	Essential oil Flavones Phenolic acids Phenylpropanoid glycosides (martynoside) Terpenes and terpenoids: Camphor, thujone	It has shown memory enhancement in animals and human clinical trials. (doses of 300 and 600 mg) (Kennedy et al. 2006; Scholey et al. 2008; Kennedy and Scholey 2006) Might be used to treat Alzheimer's disease (333 mg) (Akhondzadeh and Abbasi 2006; Akhondzadeh et al. 2003) Topically used to treat erythema	Its thujone and camphor are recognized as neurotoxic when taken at higher doses Lima et al. (2004)
Strawberry (*Fragaria vesca*)	Tannins Flavonoids: Anthocyanin Quercetin	Reduces NF-κB activity, upregulates endothelial NOS activity (Basu et al. 2014) There are no enough data on established clinical use of the herb (Basu et al. 2014; EMA/HMPC/432276/2015 n.d.)	Might cause allergic reactions due to allergens Strawberries raise the plasma level of potassium, which might result in renal stones in prone patients Great care must be given in patients with heart failure

Turmeric (*Curcuma longa)*	Curcumin Monoterpenes Sesquiterpenes	Anti-hyperlipidemia Antitumor	GRAS Contraindicated in patients with bile duct obstruction, liver disease, gallstones and any bile-related disease
Ginseng (*Panax ginseng)*	Terpenoids: Sapogenins, oleanolic acid Group B vitamins	Corticosteroidal activity Clinical data shows: Enhanced cognitive performance, hypoglycemic activity, cancer prevention, enhanced quality of life, immunomodulatory effects	The long-term safety has not been established, but it is better not to be used in long term. Scientifically unproven data suggest preventing the use of Ginseng when under hormone therapy or receiving stimulants like coffee or antipsychotics, as well as ADHD patients and those with anxiety or mania

Not all the contents of a plant are mentioned, only the ones related to an anti-inflammatory effect
Not all the medicinal and other uses are mentioned, only those related to inflammaging
The contents are taken from Gruenwald et al. (2007)



Apart from the role of Omega-3 fatty acids in enhancing the lipid profile, their role in the prevention of Arachidonic acid-derived products will induce the hypothesis of preventing inflammation caused by 2-series prostanoids, such as rheumatoid arthritis (RA). Some clinical trials have reported anti-inflammatory effects of omega-3 rich diets in the RA (Kremer et al. 1985, 1987; Cleland et al. 1988).

8.2.3.1 Dosage Considerations

There seems to be a threshold for the anti-inflammatory responses of n-3 fatty acids (Calder 2015). Based on a trial, an intake of more than 2 grams per day of DHA + EPA is needed to trigger the effects (Calder 2015; Rees et al. 2006). On the other hand, it is also important not to go beyond a maximum border of daily intake, this will suppress the arachidonic acid production, affecting the balance of the two pathways (Mahan et al. 2017).

8.2.3.2 Omega3 Fatty Acids in RA

A number of clinical trials supported omega-3 supplementation alongside rheumatoid medications. A trial on almost 700 patients with early RA suggests that taking higher amounts of omega 3 a year before the initiation of *disease modifying antirheumatic drug* (DMARD), might yield to better outcomes of the drug therapy (Lourdudoss et al. 2017). Level of omega-3 is also associated with the inflammatory/refractory pain of early RA patients receiving methotrexate for 3 months (Lourdudoss et al. 2018). A study evaluated the rate of concomitant need to analgesics after consumption of 3.6 g of EPA and 4.2 g of DHA daily for 12 weeks (Rajaei et al. 2016). They reported an improved disease state as well as a reduction in need for analgesics.

8.2.3.3 Omega3 Fatty Acids in Cardiovascular Diseases

Omega-3 can impact the cardiovascular system through several mechanisms. They are capable of decreasing blood cholesterol and triglyceride, preventing vessel stiffness and atherosclerosis. Omega-3 can relax the smooth muscle of the veins, which will enhance vasodilation. They also promote endothelial function. With their antioxidant activity besides their anti-inflammatory effects, they are considered key nutrients in cardiovascular complications of aging. Several studies have evaluated their role as nutrients in cardiovascular system (Pase et al. 2015; Casanova et al. 2017; Colussi et al. 2017).

8.2.3.4 Omega 3 Fatty Acids and Neuroinflammation

There are plenty of data on the role of omega-3 in preventing cognitive decline or maintaining metabolic status in neurodegenerative diseases. Both anti-inflammatory and antioxidant activity of omega-3 are the main mechanisms for these effects. Moreover, long-term metabolic imbalances like dyslipidemia are risk factors for the Alzheimer's disease, which could be modulated with omega-3 supplementation.

The major neuroprotective role of omega-3 is their lipid balancing property that is discussed in studies, rather than an antioxidant activity. As amyloid precursor protein (APP) and the secretases are integrated into the lipid bilayer of the cells, lipid balance will be of importance (Grimm et al. 2017). Although trials suggest positive changes in memory function and cognition, there is no definite conclusion (Grimm et al. 2017; Shinto et al. 2014; Samieri et al. 2017; Külzow et al. 2016). Yet, as omega-3 is generally regarded as safe (GRAS), a usual and safe daily intake could be recommended, both as prevention or supplementation of an Alzheimer's or Parkinson's disease (AD or PD) patients (Taghizadeh et al. 2017).

8.2.4 Immunomodulating Polysaccharides

There are many natural compounds who influence the immune system, especially the innate one. Beta-glucans are polysaccharides based on glucose monomers found in the cell walls of bacteria and fungi. They can be taken orally as dietary fiber or supplement, and are well-known for their cholesterol lowering effects and

immunomodulation (Liatis et al. 2009a; Behall et al. 2004). A low dose of 3 g/day of beta-glucan (available as supplements) seems to be effective in mildly reducing cholesterol (Bashir and Choi 2017). Their anti-inflammatory effects are widely used in respiratory conditions like asthma and respiratory tract infections (RTI), which is not necessarily related to aging (Bashir and Choi 2017; Sarinho et al. 2009; Talbott and Talbott 2009, 2012).

8.2.5 Chondroitin and Glucosamine

Glucosamine and chondroitin are dietary supplements used in osteoarthritis because of their cartilage building property. As osteoarthritis is a condition with which mostly elderly cope, these compounds could play a role in healthy aging. However, two reviews over their efficacy have reported no significant benefit from consumption of the supplements in treating osteoarthritis (Henrotin et al. 2012; Runhaar et al. 2017). However, as they report that more data is needed to confirm the (in) effectiveness, they could still be recommended due to the low adverse effect profile.

Their anti-inflammatory effects are carried out through inhibiting NF-κB. A trial of 18 healthy overweight individuals measured some inflammatory biomarkers, including C-reactive protein (CRP), after 30 days of 1500 mg glucosamine and 1200 mg chondroitin consumption per day (Navarro et al. 2015). 23% decrease in serum CRP was reported, and the authors concluded that this supplementation may lower systemic inflammation. However, the data still lack in this area and more trials have to be run to further investigate the effects.

8.3 Polyphenols

There are a variety of chemical compounds found in herbs and natural sources that have an anti-inflammatory role. Phenols and polyphenols are a wide group of compounds, having an anti-inflammatory activity along with antiseptic and antioxidant activities, including the simple salicylic acid, rosmarinic acid, and the complex phenolic glycosides. Phenols contain one aromatic ring, while polyphenols have more than one. They might either be unconjugated or bound to a saccharide molecule, and less often, to lipids, amino acids, etc. These compounds have been widely discussed in Chap. 7.

8.3.1 Tannins

The term “tannin” refers to phenolic substances used in tanning (dyeing brown) leather and textiles. However, the concentration of these polyphenols is too low to make them functional for conversion into leather.

Tannins are most used to tighten up loose or damaged tissues, as in burns, varices or diarrhea (to dry excess secretions). Tannins are subdivided into two major groups. Proanthocyanidin groups or condensed tannins and ellagic acid-derived.

8.3.2 Flavonoids

Flavonoids are the most common polyphenols. They are known with a 6-3-6 (no. of the ring carbons) structure. The middle ring stands for the division of the family into chalcones, anthocyanins and proanthocyanidins, dihydrochalcones, flavonones, flavonols, flavones, flavonols, and isoflavones. Many flavonoids have anti-inflammatory effects. Their mechanisms will be discussed further in the current chapter.

Fruits have an abundant amount of flavonols and proanthocyanidins. Citrus family contains further types of flavonoids like flavonones and flavones. Vegetables are rich sources of flavonols, especially quercetin, which is a great anti-inflammatory agent. Celery and lettuce contain falvones.

8.3.3 Quercetin (Meletin/Sophretin)

Quercetin is a flavanol, belonging to the flavonoid's family. It is a well-known anti-inflammatory molecule that exerts its effects via inhibiting the NF-κB, resulting in prostanoid synthesis, cytokine production, and iNOS expression (Comalada et al. 2005; Morikawa et al. 2003). It is also thought to be a neuroprotective, preventing neuronal cells from inflammatory injuries (Chen et al. 2005). Together with its antioxidant effects, the molecule could be effective against cognitive impairment, especially in neurodegenerative diseases, where taupathy and Beta-amyloidosis are the problems, i.e. AD. A study on murine models of AD shows that quercetin can decrease Beta-amyloid and taupathy in the hippocampus and amygdala (Sabogal-Guáqueta et al. 2015). Shen et al. have proved a reduction in the rate of tau protein hyper phosphorylation induced by okadaic acid in vitro (Shen et al. 2018). Furthermore, in another AD mouse model, mitochondrial function was improved, as well as beta-amyloid plaque reduction, proved by higher levels of ROS and ATP in hippocampus mitochondria (Wang et al. 2014). Quercetin increased the AMPA protein kinase significantly, suggesting a mechanism by which it improves cognition.

The issue over this molecule is the pharmacokinetic profile. Quercetin undergoes significant first pass elimination and thus a high proportion of it is lost. Moreover, further in vivo data is needed to confirm the bioavailability of the drug to the brain, as the molecule can barely pass the blood–brain barrier (BBB) (Babaei et al. 2018).

Javadi et al. have studied the effects of 500 mg/day of quercetin for 8 weeks on women with rheumatoid arthritis. Quercetin could significantly reduce inflammatory markers and clinical symptoms, i.e. pain in the morning and after activity and the early morning stiffness (Javadi et al. 2017).

8.3.4 Isoflavonoids

Phytoestrogens are substances with estrogenic activity, though not steroids in structure, and they include isoflavones, coumarins, stilbenes, and lignans. "Isoflavonoid phytoestrogens" are extensively used and studied, due to their contribution in human health. They are commonly referred to as isoflavonoids. The most common types of isoflavonoids, Genistein (4′,5,7-trihydroxyisoflavone), daidzein (4′,7- dihydroxyisoflavone), and glycetein (4′,7-dihydroxy-6-methoxyisoflavone) are found in the soy. They are mostly referred to as antioxidants, anti-inflammatory, and antitumor agents, due to their estrogenic activity. The antioxidant characteristics are discussed in Chap. 7.

8.3.5 Actions of Isoflavonoids in Human Health

8.3.5.1 Cancer and Chronic Inflammatory Disease Prevention

Genistein is an estrogen agonist. By binding to the conventional nuclear estrogen receptor, it can mimic estrogenic effects. Moreover, there has recently been interest in its effects on G protein-coupled estrogen receptor (GPER), one of the massive study areas in breast cancer. This receptor is activated by estrogens (and probably other similar ligands) and its activation leads to phosphorylation of mitogen-activated protein kinases/extracellular signal-regulated kinases (MAPKs/ERK) pathway, involving the adenylate cyclase and phospholipase C, and will be continued through insulin-like growth factor-1 receptor (IGF-1R) and epidermal growth factor receptor (EGFR) (Kuo et al. 2010; Madeo and Maggiolini 2010; Maggiolini et al. 2004; Meyer et al. 2011; Prossnitz and Barton 2011). This can be a way to estrogen's anti-inflammatory and antitumor activity (Blasko et al. 2009; Rettew et al. 2010), and as the receptor can be found on microglia, its effects on the nervous system. This might stand for the mechanism that genistein can modulate the inflammatory response of microglia, as it is demonstrated in a recent study by Du et al. (Du et al. 2018).

By the stimulation of microglia by the antigen, interleukin (IL)-1β, tumor necrosis factor (TNF)-alpha, and IL-6 are the major mediators produced, in which MAPKs signaling pathway, i.e. ERK, p38, and Jun N-terminal kinase (JNK) are involved. They are responsible for the release of inflammatory mediators, including NO (by iNOS) and TNF-α. Du et al.'s study on BV2 microglia demonstrated that genistein could inhibit the MAPK pathway (Du et al. 2018). Microglial stimulation will also free NF-κB, via the TLR4, and results in its nuclear translocation (Reed-Geaghan et al. 2009). NF-κBs are regulators of the immune response. They are one of the first signals activated by immunogens. ROS, heavy metals, infections, interleukins, and TNF are of the mediators that can induce their response. The NF-κB will then bind to the promoter region of these inflammatory mediators. Many studies involving the NF-κB pathway use the LPS of Gram-negative bacteria for stimulation. NF-κBs are both involved in acute and chronic inflammations, including diseases like the rheumatoid arthritis, as well as in memory and neural survival.

8.3.5.2 NF-κB and Inflammation

A study on the molecular effects of genistein reported several mechanisms through which genistein can exert anti-inflammatory effects (Jeong et al. 2014). Genistein could block the nuclear translocation of the NF-κB and thereby regulate the inflammatory response, by reduction of the reactive oxygen species. It also attenuated the production of TNF-alpha and IL-1β generation in LPS-stimulated microglia and thus the neuroinflammation. The study further declares that genistein can also inhibit both Cox-2; resulting in inhibition of inflammatory prostaglandins (PGE2), and iNOS, resulting in lower NO production.

A recent study evaluated the anti-inflammatory effects of 8-odthohydroxydaidezin (8-OHD), an analogue of genistein, on the same cell line (BV2 microglia), and compared them with genistein (Wu et al. 2018). The results demonstrated better effects with the 8-OHD rather than genistein in preventing NO production, through downregulation of iNOS expression. It was also proved that 8-OHD could more effectively reduce the ROS released by LPS-activated microglia. However, in COX-2 inhibition, genistein could be slightly more effective.

These anti-inflammatory mechanisms contribute to genistein effects on preventing breast cancer and chronic inflammatory diseases, such as R.A. There are some synthetic agents found as GPER agonists, without feminizing effects; however, genistein's function on other estrogen receptors, including its effects on the reproductive system, has been approved as it is used in menopausal symptoms.

8.3.5.3 Prevention of Cognitive Decline

Overactivation of microglia in chronic neuroinflammation can result in neural damage and degeneration, the highly believed etiology of neurodegenerative disorders. Mechanisms are discussed further.

8.3.5.4 NF-κB and Memory

Based on the anti-inflammatory effects of estrogen, it is hypothesized that it is able to attenuate neurodegeneration (GDNF contributes to estrogen-mediated protection of midbrain dopaminergic neurons n.d.; The possible role of estrogen and selective estrogen receptor modulators in a rat model of Parkinson's disease n.d.; Estradiol protects dopaminergic neurons in a MPP+ Parkinson's disease model n.d.). Studies have proved the role of TLR4 and the NF-κB in the inflammation in neurodegeneration, suggesting an increase in their amount or activity, since TLR4 is able to recognize Amyloidβ (Okun et al. 2009; Liao et al. 2011; Frank et al. 2009). A study has confirmed that genistein could reverse the inflammatory effects of Amyloidβ, i.e. decreasing the production of IL-1β and iNOS in vitro (Zhou et al. 2014). In the study, cells treated with Amyloidβ showed a significant increase in NF-κB and TLR4 production, and genistein could reverse the signs by downregulating the expression of TLR4 and NF-κB (refer to NF-κB and inflammation).

Studies report that GPER activation, associated with the modulation of microglial activity, will yield to the neuroprotective effects on DA nigral neurons (Bessa et al. 2015; Bourque et al. 2012; Mendes-Oliveira et al. 2017; Zhao et al. 2016). In the study, DA neural loss by LPS-induced microglia was treated with GPER agonist,

which will result in reduced NO and phagocytic activity; the pathway that is normally stimulated via the 17-β estradiol (estrogen). Moreover, blockade of GPER resulted in reduction of phagocytic activity and iNOS gene expression. Estrogen exerts its anti-inflammatory effects via the classical estrogen receptors (ER alpha and beta) too; in fact, agonizing their receptors also attenuate microglial NO production. However, the study utilized the synthetic agonists/antagonists (G1/G15), with neither feminizing effects nor difficulty passing the BBB. It has been proved that genistein can easily pass the BBB, (Mozolewski et al. 2017) but its effects on the reproductive system, might make it not so compatible as a long-term nutraceutical treatment, except for proper cases such as postmenopausal women. A recent review has proposed that polyphenols may be potentially beneficial to develop new drugs against neuroinflammation by targeting the TLR4 pathway (Rahimifard et al. 2017).

8.3.5.5 Lipid Profile and Cardiovascular Effects

Genistein can reduce the Apo lipoprotein B secretion from hepatocytes. Microsomal triglyceride transfer protein (MTP) is an essential molecule for lipoprotein assembly, which helps transfer esterified cholesterol (EC), triglyceride (TG), and phospholipid (PL) to the recently produced apolipoprotein-B (ApoB) molecules. It is thus essential for the release of ApoB. Genistein reduces both the expression and activity of MTP in the cell (Borradaile et al. 2002), meaning that in long-term use, it might be able to keep MTP at lower concentrations, resulting in lower release of VLDL and chylomicrons. It has been also demonstrated that both genistein and daidzein can decrease the rate of LDL-receptor expression and activity, which will result in higher LDL re-uptake. Genistein can also inhibit Acyl-coenzyme A (CoA): cholesterol acyltransferases (ACATs) which will prevent cholesterol from getting esterified and apolipoproteins from getting assembled. This will reduce the lipoprotein secretion, a mechanism close to 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors.

Cardioprotective effects of estrogen, especially ERβ receptor agonists, including genistein are well-known (Kararigas et al. 2014; Hsieh et al. 2015; Fliegner et al. 2010; Pedram et al. 2013). After an ischemic heart crisis, reperfusion will cause an inflammatory condition, maintained by accumulation of the leukocytes. This is triggered by some inflammatory cytokines, including TNF-a, which will increase the expression of Intracellular adhesion molecule-1 (ICAM-1) (also known as CD54) production, a factor for the leukocytes' intercellular adhesion. Genistein can attenuate the expression of ICAM-1, by reducing TNF-α in a dose dependent manner. Thus, it is considered as a leukocyte-endothelium interaction inhibitor, resulting in the improved atherosclerotic condition (Kayisli et al. 2013).

8.3.5.6 Menopausal Symptoms and Osteoporosis

There has been a huge load of data on the estrogen-mimicking effects of genistein. It is a full agonist of ERβ, and this receptor is a negative inhibitor of ER alpha. Thus, genistein and phytoestrogens act through anti-growth properties, whereas ERalpha has pro-growth effects. Phytoestrogens are capable of ameliorating vasomotor

symptoms, depressive moods, osteopenia, and vaginosis and could probably be taken in proper doses for months or years. There is also some clinical evidence that it might be effective in osteoporosis (Kayisli et al. 2013). However, data regarding vaginal atrophy still lack (Le Donne et al. 2011; Manonai et al. 2006).

8.3.5.7 Potential Adverse Effects

There might have been some concern about the feminizing effects of isoflavonoids; however, many studies do not approve reproductive problems or infertility, neither in pediatrics nor in adults. In fact, it is suggested that infants who are breastfed from mothers whose diets are soy-rich, have lower incidences of cancer, with respect to the adults with a soy-rich diet (Franke et al. 1999). A study has reported no special feminizing effects on male (Mitchell et al. 2001).

As isoflavonoids are substrates for thyroid peroxidase, high-dose isoflavonoid might be thought as an inducer of hypothyroidism. However, a recent clinical trial on almost 400 postmenopausal women who took up to 54 mg/day of genistein over 2–3 years, reported no significant decline in thyroid hormones (Bitto et al. 2010). As long as iodine storage is sufficient, no potential harm might threat thyroid conditions (Marini et al. 2012; Bruce et al. 2003).

8.3.5.8 Dietary Intake and Herbal Sources

Although there are many soy-based supplements available in the market, it is recommended to consume soy-rich diets instead, as a nutraceutical, as not to lose the other components in the plant, that would enhance the efficacy, or cause synergism. Moreover, this approach will ensure a safe amount of intake rather than supplements.

Genistein is mostly found in leguminosae plants; beans, peas, and peanuts as ones found in the normal human diet. In some fruits, flavonols are mostly found in the skin, and thus peeling will substantially reduce the intake. Other herbs containing flavonoids can be found in Table 8.3.

8.3.6 Cannabinoids

Cannabis smokers are less capable of recovering from fungal and bacterial infections. This is because the major cannabinoid found in cannabis, delta9-tetrahydrocannabinol (THC) decreases the production of proinflammatory cytokines, acting like an immunosuppressant. THC is a lipid soluble substance that will instantly distribute to different tissues, including the brain.

Cannabidiol (CBD) is a non-psychoactive cannabinoid that has anticonvulsive, sedative, anti-inflammatory, and hypnotic effects. It is thought to have a neuroprotective role in ischemic conditions. However, a systematic review has reported that it is not possible to conclude any efficacy out of it, regarding its effects on neurodegenerative disorders (Lim et al. 2017). Moreover, cannabinoids do not show any effects of note on the conditions rumored to be effective; i.e. multiple sclerosis (MS) (Sexton et al. 2014), anorexia in cancer or acquired

immunodeficiency syndrome (Whiting et al. 2015), chemotherapy-induced nausea and vomiting (Whiting et al. 2015), and the pain related to cancer or rheumatism (Häuser et al. 2017).

8.4 Taken Together

Prevention of inflammation could be beneficial at any age. Many of the substances mentioned in the chapter are able to confront inflammation through several pathways, preventing cancers, diabetes dyslipidemia, atherosclerosis, etc. However, the dosage range and long-term use data for many of them still lack, and especially those thought to have effects on neurological disorders, have not proven favorable changes on the outcome. Nevertheless, most of them, including long chain PUFAs, vitamins, minerals, and isoflavonoids are regarded as safe within the normal consumption range; thus, taking a safe daily portion of them is recommended. Anti-inflammatory herbs are mostly not safe to be taken long-term daily, but per case and in courses of time. The daily intake limit for herbs shall be taken into consideration as well as their possible interactions' profile with medications, which is a part of the life of many elderlies.

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