Chapter

Dietary Regulation of Keap1/Nrf2/ARE Pathway: Focus on Acai Berries and Pistachios and Cashews as Natural Food Sources

Rosanna Di Paola, Salvatore Cuzzocrea, Roberta Fusco and Marika Cordaro

Abstract

Inflammation is a biological reaction to oxidative stress in which cell starts producing proteins, enzymes, and other substances to restore homeostasis, while oxidative stress could be intrinsically a biochemical imbalance of the physiologically redox status of the intracellular environment. The nuclear factor erythroid 2-related factor 2 (Nrf2)/antioxidant response element (ARE) pathway, which controls the transcription of numerous antioxidant genes that protect cellular homeostasis and detoxification genes that process and eliminate all toxic compounds and substances before they can cause damage. The Nrf2 pathway is the heart of the daily biological response to oxidative stress. Transient activation of Nrf2 by diet can upregulate antioxidant enzymes to protect cells against oxidative stress inducers. In this chapter, we summarize the effects of some novel foods in the regulation of the Nrf2/ARE pathway and its cellular mechanisms.

Keywords: food, oxidative stress, inflammation, diet, Nrf2

1. Introduction

A diet rich in fruits and vegetables has numerous positive effects on the body. In fact, in recent years, research has turned its attention to substances of natural origin: these are rich in essential nutrients with potential therapeutic actions. Nutrients include mainly: vitamins, minerals, fiber, fatty acids, flavonoids, anthocyanins, and carotenoids; the presence of these mainly gives it antioxidant, anti-inflammatory, antimicrobial, antiproliferative, hypoglycemic, cholesterol-lowering, neuroprotective, and cardioprotective action [1]. Recently, the consumption of dried fruits and by-products has gained special attention, among them we can mention in these chapter Cashews, Acai berries, and Pistachios. These components give it anti-inflammatory, antioxidant, antimicrobial, antiproliferative, and astringent actions thanks to the presence of nutrients and substances with different therapeutic actions that give them mainly action against inflammation and oxidative stress as demonstrated in

several studies both in vivo and in vitro. Additionally, we briefly discuss the two main molecular pathways involved: NF-E2-related factor 2 (Nrf2) for oxidative stress and NFkB for inflammation (**Figure 1**).

1.1 Nrf2

Nrf2 is one of the most important regulators that shields cells from ROS and xenobiotics that play a key role against the production of antioxidant and detoxifying enzymes [2, 3]. Nrf2 shields cells against stressors such as xenobiotics in food, radiation, reactive oxygen species (ROS), and endogenous chemicals. As a result, activating the Nrf2 pathway may be a viable chemoprevention method [4]. ROS act as a second messenger in cellular communication, but they can alter natural components as lipids, proteins, and DNA, having a detrimental effect on the biological system [5]. Nrf2 is a member of basic leucine zipper genes (bZIP) that are universally expressed in a variety of tissues and cell types and have a conserved structural domain known as a cap'n'collar domain. The leucine zipper region basic's portion is in charge of DNA binding, whereas the acidic area is necessary for transcriptional activation. The heterodimerization of Nrf2 with other bZIP proteins is required for ARE-mediated transcriptional activation [6]. Keap1, an E3 ubiquitin ligase substrate adaptor that is redox-sensitive, controls how much Nrf2 is present inside the cell [7]. Keap1 interacts to Nrf2 in the cytoplasm when the body is not under stress, promoting ubiquitination and proteasomal destruction of Nrf2. The ubiquitin E3 ligase activity of the Keap1-Cul3 complex decreases with exposure to chemicals (typically electrophiles) or ROS, and Nrf2 is stabilized. As it builds up in the nucleus, stable Nrf2 activates the target genes [8]. Under oxidative stress, free freshly produced Nrf2 translocates to the nucleus and heterodimerizes with one of the small Maf (musculoaponeurotic fibrosarcoma oncogene homolog) proteins. The Nrf2-Keap1 association is resolved in a dose-dependent manner. The enhancer sequences known as antioxidant response elements (AREs), which are found in the regulatory regions of Nrf2 target genes. Nrf2 coordinates the expression of several genes, including not only genes encoding antioxidant enzymes but also a series of genes involved in various processes

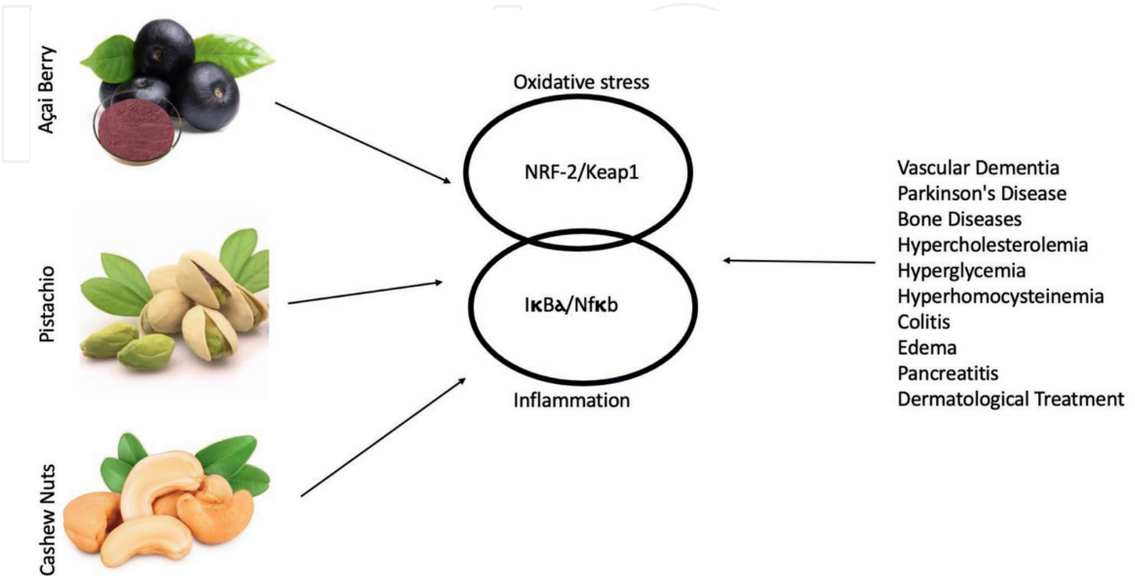

Figure 1.
Açai berry, pistachio, cashew nuts regulation of oxidative stress and inflammation.

including respiratory, cerebrovascular, and neurodegenerative diseases [9–11]. In **Figure 2**, the mechanism of action of Nrf2 is clearly demonstrated. Briefly, (1) Nrf2 is sequestered to the cytoplasm through binding with Keap1 and continually shuttled to the proteasome for degradation. (2) After a response to external stressors, Keap1 cysteine residues are oxidized and Nrf2 serine (Ser) 40 is phosphorylated by protein kinase C (PKC). (3) Nrf2 is then able to translocate into the nucleus and bind to ARE responsive genes in order to increase or decrease their expression. (4) Subsequently, a delayed response to external stressors causes the phosphorylation of GSK-3β by tyrosine (Tyr) kinases. (5) GSK-3β then activates Src kinases, allowing for their translocation into the nucleus. (6) These Src kinases phosphorylate Nrf2 Tyr568, which allows for nuclear export, (7) ubiquitination, and degradation of Nrf2. (8) However, if the insulin receptor signaling is initiated, GSK-3β activity is inhibited. (9) Keap1 is also able to regulate Nrf2 activity through sequestration with PGAM5 to the mitochondria [12].

Multiple genes are impacted by Nrf2 that encode proteins serving as redox balancing agents, detoxifying enzymes, stress response proteins, and metabolic enzymes [6]. Examples of antioxidant detoxification enzymes induced by Nrf2 include heme oxygenase 1 (HO-1) and manganese-dependent superoxide dismutase (Mn-SOD) [13]. Nuclear HO-1 interacts with Nrf2 under oxidative stress, preventing GSK3-mediated phosphorylation along with ubiquitin-proteasomal destruction and extending its accumulation in the nucleus. The preferential transcription of phase II detoxifying enzymes such NQO1 and glucose-6-phosphate dehydrogenase (G6PDH), a regulator of the pentose phosphate pathway, depends on this control of Nrf2 post-induction by nuclear HO-1 [14]. Moreover, the SODs are a family of antioxidant enzymes that catalyze the dismutation of superoxide free radical anions, which are generated during a variety of metabolic activities and lead to the creation of oxygen and hydrogen peroxide molecules. Copper-zinc SOD (Cu, Zn-SOD) and MnSOD, the two primary forms of SODs, are located in the cytoplasm and mitochondria, respectively [15]. It was demonstrated that Nrf2-mediated upregulation of antioxidant

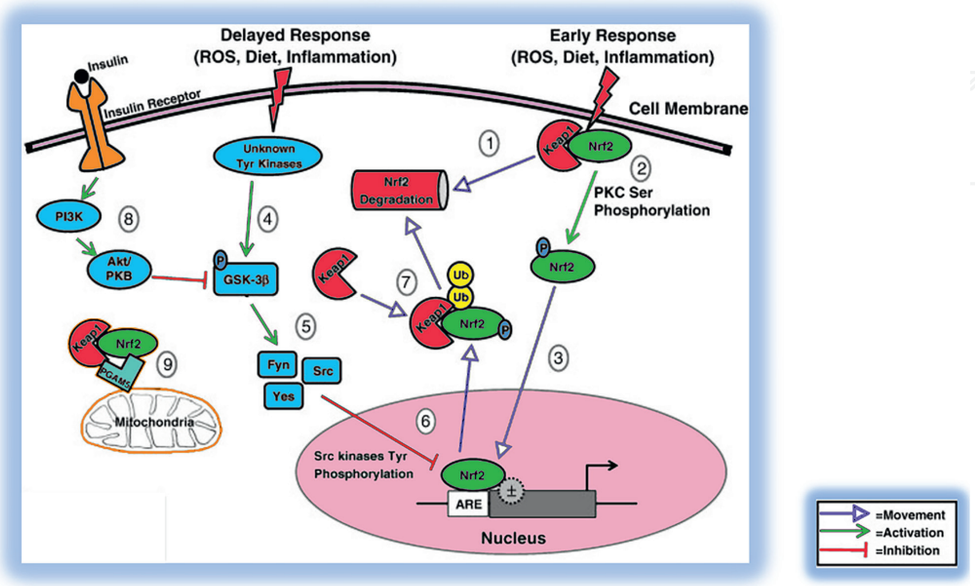

Figure 2.
Schematic diagram of Nrf2 regulation.

Class	Source	Mechanisms of Nrf2 induction	Reference
Isothiocyanates	Cruciferous vegetables	• Keap1-cys151 • Activation of ERK1/2 and Akt kinase • Acceleration of Nrf2 protein synthesis • De-methylation of Nrf2 promoter	[22–27]
Phenols	Ginger	• De-methylation of Nrf2 promoter • Binding with cysteine residue of Keap1	[28–30]
Organosulfur	Garlic	• Keap1- Cys288 • Inducing ROS production • Activation PI3K/Akt/Nrf2	[29–31]
Polyphenol	Tea	• Activation of the p38 MAPK and the ERK1/2 signaling pathways • Dissociation of Nrf2 from Keap1 and Increasing the nuclear translocation Activation of ERK1/2 and PI3K/Akt	[32–35]
Isoflavone	Lupin, fava beans, soybeans, kudzu, coffee and psoralea	• Increasing keap1 S-nitrosylation and enhancing DNA-binding activity of Nrf2 • Increasing PI3K activity	[36, 37]

Table 1.
Selected Nrf2 activators present in diet.

enzymes as GSTs and MnSOD would act to minimize oxidative-stress-induced damage [16].

1.2 Nrf2 and NF-κB

To maintain the physiological balance of cellular redox state and to control the cellular response to stress and inflammation, it is hypothesized that Nrf2 and NF-κB signaling pathways work in concert. NF-κB is a complex protein system constituted by transcription factors that regulate the expression of genes influencing innate and adaptive immunity, inflammation, oxidative stress responses, and B-cell development. NF-κB proteins can be divided into two classes according to whether they include or lack a transactivation domain. Since p50 and p52 lack the transactivation domains that RelA (p65), RelB, and c-Rel possess. Heterodimerization with the Rel proteins is necessary for them to activate transcription [17]. Nrf2/ARE signaling plays a crucial role in the protection against oxidative stress and is responsible for the maintenance of homeostasis and redox balance in cells and tissues. In contrast, NF-κB is also a redox-regulated transcription factor, which regulates inflammatory responses and cellular injury [18]. Firstly, Nrf2 inhibits oxidative-stress-mediated NF-κB activation by decreasing the intracellular ROS levels. Furthermore, Nrf2 prevents the IκB-α proteasomal degradation and inhibits nuclear translocation of NF-κB [19]. Studies suggest that Nrf2 counteracts the NF-κB-driven inflammatory response by competing with transcription co-activator cAMP response element (CREB) binding protein (CBP) [20, 21]. Histones are acetylated by the CBP-p300 complex, which also makes DNA accessible for the construction of the transcriptional machinery.

Additionally, the Nrf2 and p65 non-histone proteins, as well as others, have their lysine residues acetylated by the CBP-p300 complex. Since, CBP also preferentially interacts with p65, the overexpression of p65 limits the availability of CBP for Nrf2 interaction; accordingly, knockdown of p65 promotes Nrf2 complex formation with CBP (**Table 1**) [38].

2. Açai berry

The Açaí berry is a little, spherical fruit (about the size of a grape) that is green while immature and turns dark purple when it is fully developed. It comes from the Açaí palm, a native of Central and South America that also thrives in marshes and flood plains in addition to the Amazon region. Açaí berries are eaten fresh or juiced as food. The juice can be used as a natural food colorant and is commercially employed in jelly, syrup, ice cream, liquors, energy drinks, and a range of other beverages [39]. Açaí juice is viscous and contains 5.9% fats and 2.4% protein. The apple pulp has 12% fats and 4% protein. Vitamins A, C, and E, calcium, phosphorus, iron, and thiamine are among the nutrients. The Açaí berries of the *Euterpe oleracea* plant are thought to be a source of bioactive substances, particularly anthocyanins and unsaturated fatty acids, which are known to have health-promoting properties. These berries may help to reduce metabolic stress and inflammation while enhancing antioxidant protection. Orientin, isoorientin, vanillic acid, as well as the anthocyanins cyanidin-3-glucoside and cyanidin-3-rutinoside, are only a few of the polyphenolic components having antioxidant capabilities found in acai extracts. Acai pulp is rich in proanthocyanins and total phenolics, but also contains trace amounts of anthocyanins. Industrially processed samples have a significant percentage of proanthocyanidins, but naturally occurring anthocyanins are significantly enriched (20 times more). The unprocessed Açai pulp extracts reduced the expression of pro-inflammatory genes such as interleukin-1, cyclooxygenase-2, nitric oxide synthase, and interleukin-6 and dramatically inhibited the generation of nitric oxide, which has been linked to proanthocyanidins in the initial inflammatory response [40]. These chemicals' existence is mostly associated with their anti-inflammatory, antiproliferative, antioxidant, and cardioprotective properties [41]. Açai can be used to treat certain diseases due to its anti-inflammatory and antioxidant effects, acting at the level of the Nrf2 pathway. It has also been shown that Açai may act on different pathways; for example, according to some studies, it goes to act on peroxisome proliferator-activated receptors (PPARs) α and γ, going to decrease the transcription of various genes, including pro-inflammatory, pro-oxidants, and those affecting lipid metabolism genes. Another pathway that goes to modulate is that of Nf-kB, going to decrease the production of pro-inflammatory cytokines. For example, the fruit has been used to treat Vascular Dementia (VaD), which is the secondary most frequent reason for inherited biological cognitive impairment [42]. VaD is caused by an oxidative stress increase, which might cause cognitive decline brought on by aging and neurological diseases. Since oxidative and inflammatory stressors may reduce synaptic plasticity and memory by resulting in dendritic modification and cell death, important brain regions such as the hippocampus should be more susceptible to these situations. Additionally, the expression of microtubule-associated protein 2 (MAP-2) and α-Tubulin, two significant neuronal markers of well-being, is altered in the brain of VaD patients [43, 44]. Furthermore, it has been demonstrated that impaired autophagy alters protein

"quality control," accumulates unwanted proteins and organelles in brain cells [45]. In this study, Açai Berry was useful to conteract VaD alterations in the brain. Açaí berries can also mitigate Parkinson's disease progression, which is the second most prevalent neurological condition in people over 65 [46]. Recent studies have revealed that the Nrf2/ARE signaling cascade is the most likely target for therapeutic therapy, despite advancements in our understanding of the pathophysiology of PD [47]. The oral administration of Açaí berries has shown an important decrease of ROS and an increase of Nrf2 expression. Also, in this study, the authors observed a significantly improvement in both motor and non-motor deficits, histological alteration, pro-inflammatory cytokine release, neutrophilic infiltration, and lipid peroxidation limiting dopaminergic neuronal death [48]. Some studies, additionally, have shown Açai berries' anti-inflammatory properties in a model of co-culture between Caco-2 and RAW 264.7 macrophages, which has the potential to prevent intestinal inflammatory diseases, due to anthocyanin improved Tight Junction barrier integrity and reduce gastrointestinal inflammation by preventing the expression of cytokines, especially IL-6, IL-8, and PGE2 through inhibition of COX-2 [49]. Açai barriers can also be used for anti-inflammatory treatment of bone diseases such as periodontal disease are triggered by chronic inflammation causing the upregulation of osteoclastogenesis. This in turn shifts the bone remodeling process toward increased bone resorption [50]. Inflammatory cytokines have been associated with bone destruction, having a role in the regulation of the expression of the receptor activator of nuclear factor kappa B (RANK) and receptor activator of nuclear factor kappa B ligand (RANKL), which is a vital step in the activation of osteoclastogenesis [51]. Açai-berry extract (ABE) on the reduction of osteoclast formation and resorptive activity of RANKL-induced osteoclast precursor cells. Moreover, ABE also modulated the secretion of several inflammatory cytokines during osteoclastogenesis and osteoclast activity [52]. Açai seeds, according to some studies, regulate NF-κB and Nrf2/ARE pathways protecting lung against acute and chronic inflammation [53]. Moreover, studies have shown the cytotoxic effect of Açai seeds against the MCF-7 breast cancer cell line. This effect is given by the ability to induce ROS synthesis inside these cells. But also, it induces morphological changes and reduces cells viability, due to flavonoids content [54]. In high-fat mice, Açai seed extract reduces the activation of the renin-angiotensin system, oxidative stress, and inflammation in the white adipose tissue [55]. Acai seed prevented the body weight rise brought on by the heart failure diet, which was correlated with the diminution of adipocyte area and the accumulation of visceral fat, indicating that the diminution of adipose mass may contribute to the acai seed-mediated decrease in body weight. These advantageous effects of acai seed were also connected to a significant decrease in the serum levels of total cholesterol (TC), triglycerides (TG), very low-density lipoprotein (VLDL), and low-density lipoprotein (LDL), indicating a favorable impact of Açai seed on the altered lipid profile [56]. The pulp of Açai can be used, for example, to mitigate colitis-associated colon carcinogenesis, which is one of the most common cancers in the modern world. A lesion caused by acute inflammation was characterized microscopically by a coagulative necrosis process and had macroscopic signs of necrosis. According to the phytochemical tests, the lyophilized acai pulp (AP) utilized in the in vivo trial included significant amounts of the phytonutrients cyanidin 3-rutinoside (C3R) and cyanidin 3-glusoside (C3G). Additionally, the concentration of anthocyanins may range between açai samples utilized in various research. Cells' ability to move slightly less after receiving acai pulp treatment [57, 58].

3. Pistachios

Pistachios originate in West Asia and are traded in the Mediterranean, Europe, and the East. The only species that produces edible nuts is *Pistacia Vera* L. (Pistacio), which is a member of the Anacardiaceae family [59]. The fact that pistachio plants can grow in a variety of soil types and survive dryness is crucial for sustainability because semi-arid regions require vital water consumption. The pistachio fruit is an edible drupe with a thin, soft coating. The endocarp, which is covered with a fleshy, thin hull that is light green in color with red undertones, is inedible. In comparison to other nuts, pistachios contain a high concentration of compounds that have antioxidant and anti-inflammatory properties [60]. Nuts have positive health effects on a variety of metabolic conditions, including hypercholesterolemia, hyperglycemia, hyperhomocysteinemia, and everything else that goes along with them. Pistachios has a high nutritional content and is consumed frequently over the world because it has significant nutritional properties and offers many health advantages [60]. One of the foods that must be included in a nutritious and balanced diet is the eating of nuts. Protein, fiber, monounsaturated fatty acids, minerals, and vitamins are all present in excellent amounts in pistachios, but they are also a good source of carotenoids, phenolic acids, flavonoids, and anthocyanins (**Table 2**).

Lutein, zeaxanthin, and a variety of other bioactive phenolic compounds found in pistachios help to improve endothelial function, glycemic management, and antioxidant and anti-inflammatory activity. The highest concentrations of potassium, tocoferol, and phytosteroids can be found in citrus fruits [61, 62]. Lipophilic extracts from the peel and kernel of raw shelled pistachios contain fatty acids, phytosterols, and tocopherols, according to phytochemical study. These polyphenols in pistachios have strong antioxidant action. Gallic acid and other phenolic chemicals, such as phenol acids, flavonoids, stylibenes, and tannins, have one or more aromatic rings and hydroxyl groups [63–65]. As a great source of phenolic compounds, pistachios have strong antioxidant properties that can block ROS, preventing the oxidation of biological macromolecules [66]. The activity of the various pistachio nut components was evaluated in a number of in vitro and in vivo investigations, and the various lipophilic (carotenoids, tocopherols, and chlorophyll) and hydrophilic extracts were

Macronutrient and energy content	**g/100 g**
Protein	20.2
Total lipid	45.3
Saturated fatty acids	5.9
Monounsatured fatty acids	23.3
Polyunsaturated fatty acids	14.4
Carbohydrate, by difference	27.2
Fiber, total dietary	10.6
Sugars, total	7.66
Starch	1.67
Energy	2340 kJ

Table 2.
Macronutrients content in 100 g of Pistacio. Source: U.S. Department of Agriculture Food Data Central 2019.

compared [67]. The hydrophilic extract exhibits higher antioxidant activity than the lipophilic components in the kernel, and this activity has been observed to block the metal-dependent and independent lipid oxidation of bovine liver microsomes in a dose-dependent manner [68]. Human low-density lipoprotein (LDL) has also been shown to oxidize less when exposed to copper [60]. Compared with the kernel, the tegument of the pistachio contains a higher level of antioxidant activity. By combining lipophilic and hydrophilic extracts with macrophages that have been stimulated by lipopolysaccharide (LPS), this was proven [69]. The hydrophilic tegument extracts shows stronger inhibition by subsequently reducing nitric oxide (NO) production. The extracts markedly decreased ROS formation. According to the findings of this in vitro study, the tegument extract had a higher concentration of phenolic compounds and hence had more antioxidant activity. In mature adipocytes, these fractions greatly decreased lipid accumulation. Additionally, it has been proposed that the antiproliferative properties of pistachios contribute to their anticancer properties. The growth of LT97 colon adenoma cells has been shown to be inhibited by pistachio fermentation supernatants in vitro in a dose-dependent manner [66]. Additionally, pistachio fermentation supernatants have been shown to increase antioxidant activity, which promotes the expression of catalase (CAT), which lessens DNA damage brought on by hydrogen peroxide (H_2O_2) [70]. According to the findings of these investigations, roasting pistachios may alter their phytochemical composition and improve biological activity [71]. The gut microbiota, a complex ecology that varies according to anatomical location, is another crucial area of study in science. Obesity, type 2 diabetes, and other illnesses can sometimes cause the microbiota to become out of balance and enter a state of dysbiosis [72, 73]. Diet also plays a significant part in this. According to a study comparing the intake of almonds and pistachios on treated volunteers, the consumption of pistachios was able to change the microbiota's composition more than almonds [74]. According to studies on the microbiome, eating pistachios in moderation can help the body's microbiota get back into balance by boosting the population of helpful bacteria and lowering acute inflammatory conditions. In fact, pistachio supplementation has been found to repair the intestinal microbiota in diabetic rats on a high-fat diet. Drug resistance is a widespread issue, and novel treatments are the focus of current research. Because they include bioactive substances that can be employed as antimicrobials and antivirals, plant extracts play a significant role in medicine. Bactericide properties of raw, salted, roasted pistachios have been demonstrated. Additionally, the effectiveness of a Pistacia Vera metabolic extract against staphylococcal infections has been demonstrated. Pistachios contain polyphenols, which can be extracted alone or combined with other medications to make a potent alternative to antibiotics [75]. Additionally, polyphenols have antiviral properties. Pistachios contain polyphenols, which can be extracted alone or combined with other medications to make a potent alternative to antibiotics. Additionally, polyphenols have antiviral properties. This has been shown to prevent replication of Herpes Simplex Virus Type 1 (HSV-1). Pure polyphenol extracts were used to treat the condition, which inhibited the expression of many viral proteins and the creation of viral DNA [76]. It is important to keep in mind that pistachio component quantities can differ depending on genotype, pre- and post-harvest circumstances, and storage [77]. Numerous experimental models have been used to examine the anti-inflammatory properties of pistachio components in acute inflammatory states such paw edema [78–81], LPS inflammation [69], and chronic inflammation models such as colitis [82]. By contrasting raw, shelled pistachios with salted and roasted pistachios, the therapeutic effects of pistachios were discovered in an experimental animal model of

paw edema generated in rats. In contrast to roasting, which results in a 60% drop-in antioxidant activity, eating raw shelled natural pistachios has been shown to result in reduced nitrate protein production [68, 82, 83]. A diet with a balanced intake of pistachios has been demonstrated to enhance serum concentrations of tocopherol, lutein, and carotene. In addition, pistachio consumption has been proven to decrease oxidized LDL concentrations in randomized trials of healthy patients and hypercholesterolemic subjects [84]. Malondialdehyde (MDA), a by-product of lipid peroxidation, was reduced, and blood antioxidant potential was improved by eating pistachios [85]. Numerous studies have demonstrated the critical role played by bioactive components in mastic oil produced from Pistachio Lentiscus in the treatment of ulcerative colitis, where inflammation and oxidative stress play a significant role. Myeloperoxidase (MPO) activity was dramatically decreased by flavonoids and other bioactive substances [86]. Mastic oil therapy reduces the inflammatory response of ulcerative colitis, which is mediated by cytokines such as TNF- and IL-6. These research studies sought to emphasize the critical function of the pistachio's bioactive components and the potential significance of including them in a nutritious, well-balanced diet [87, 88]. In particular, Nrf2 pathway plays a significant role in antioxidant activity. When there is a redox imbalance, this pathway becomes less active, which depletes the body's supply of antioxidant enzymes. The release of pro-inflammatory cytokines can also activate the NF-B signaling pathway, which results in decreased Nrf2 pathway activity and oxidative stress conditions. Inflammatory response and oxidative stress are modulated, according to a study done after the extraction of polysaccharides from *Pistacia vera* L. Pistachio polysaccharides decreased inflammation and oxidative stress by boosting antioxidant production through the Nrf2 pathway and attenuating the NF-kB pathway [89, 90]. The positive effects of bioactive substances are dose-dependent, it should be noted. Additionally, research has been done on the therapeutic effects of pistachios in experimental models of neurodegenerative diseases for cognitive problems [91]. In particular, lutein and zeaxanthin improved cellular communication required for light processing and the growth of neural circuits in the visual system, which helped improve memory and motor performance when pistachios were supplemented [92]. The anti-inflammatory and antioxidant properties of pistachio bioactive components are dose-dependent, it should be noted. By preventing the cellular aging phenomenon brought on by inflammation and oxidative stress, their balanced consumption in the diet might enhance quality of life.

4. Cashew

Cashew (*Anacardium occidentale L.*) is a tree that originates in Brazil, but with the exploration has also spread to Asia and Africa. Cashew is a perennial plant belonging to the family of the Anacardiaceae: these plants have a considerable height, the trunk is irregular and short, the leaves evergreen elliptical oblate, while flowers are small with sepals and petals gathered in a panicle. The cashew fruit consists of an accessory fruit and a true fruit. The accessory fruit is called cashew apple and, when it reaches full maturity, is a kidney-shaped drupe, inside of which is the cashew nut surrounded by a double shell. From the cultivation of this plant, the fruit is used: both cashew apple and cashew nut; but more recently also a by-product, the cashew nut shell liquid [93–95]. The cashew nut has remarkable nutritional properties due to its various components: lipids including polyunsaturated and monounsaturated

fatty acids; amino acids including glutamic acid, aspartic acid and leucine; minerals such as calcium, potassium, and magnesium. Cashew apple is rich in sugars and minerals; the cashew nut shell liquid is rich in phenols and has antimicrobial properties. In addition, cashew by-products have several properties: the cashew skin extract is a good antioxidant; instead, the bark is rich in tannins and has astringent, anti-inflammatory, hypoglycemic, antibacterial, and antimutagenic properties. Also in cashews other molecules with possible therapeutic effects are: saponins, catenins, tannins, carotenoids, and anthocyanins. With regard to the therapeutic applications of cashew, several studies have shown that its molecules grant it different actions reason why different therapeutic effects are being evaluated recently. Foremost among them, the anacardic acid is an antimicrobical agent, particularly it acts against Gram-positive bacteria; another application of anacardic acid is such as antitumoral agent, in fact has been shown to act by blocking the HAT enzyme: this is an enzyme involved in the acetylation of histones [96]. Furthermore, some studies have highlighted how anacardic acid induces autophagy and apoptosis. Certainly among the most studied therapeutic applications today are the antioxidant and anti-inflammatory effects of cashew nuts [97]. The anti-inflammatory effects of cashew are due to its interaction with the transcriptional factor NFkB, specifically there is inhibition of this pathway, resulting in a decrease in proinflammatory cytokines. Antioxidant effects are due to action on several factors: the anacardic acid acts on lipid peroxidation and lipoxygenase [98]; in addition, polyphenols and flavonoids have antioxidant action as they modulate oxidative balance and also have been seen to act on the Nrf2 pathway, promoting its translocation into the nucleus resulting in the synthesis of cytoprotective enzymes such as NADPH quinone dehydrogenase NQO-1 and HO-1. Additionally, the modulation of Nrf2 pathway influences other important molecular pathways and mechanism: such as NLRP3 and apoptosis. Several studies have been conducted in recent years to evaluate the effects of cashew nut consumption, and these have yielded positive effects in the treatment of various diseases. In in vitro studies, the activity of cashew nuts on the human microbiota was evaluated: the effects obtained induce a change in metabolic activity with potential prebiotic activities [99]; the cashew apple juice contains gluco- oligosaccharides that promote the growth of the microbiota [99] . In vivo studies included different experimental protocols going to investigate various pathologies. Among neurodegenerative diseases, a study has been done on Parkinson's disease: the pathology has been induced by rotenone in male rats, and then they were treated with anacardic acid; analyses have shown that there is a decrease in oxidative stress, specifically there is modulation of mitochondrial respiration and superoxide dismutase [100]. In in vivo study was evaluated two aspects of cashew nuts: antioxidant and anti-inflammatory action in different model of inflammatory disease: such as colitis, edema, and pancreatitis. In colitis model, the pathology was induced intrarectally through injection of dinitrobenzene sulfonic acid (DNBS); subsequently, the cashews were administrated orally. Findings have shown that cashew nut consumption inhibits the inflammatory pathway NFkB and activates the expression of antioxidants such as superoxide dismutase [97]. The pancreatitis was induced in CD1 mice by cerulein; in this case, the cashew acts on Nrf2 pathway and on NRLP3 pathway: Nrf2 translocates into the nucleus by inducing the synthesis of cytoprotective enzymes such as HO-1 hemeoxygenase and superoxide dismutase; instead the cashew acts on NRLP3 reducing its levels resulting in decreased pro-inflammatory cytokines. These effects are probably due to its components such as flavonoids and polyphenols [101]. The edema was induced by

carrageenan injection in male rats, and the results showed that the administration of cashew reduced edema formation and induced the endogenous antioxidants activity; and also in this study is shown the analgesic effect [102]. The antioxidant and anti-inflammatory action of cashew nuts is evaluated also in multi-organ pathology such as Hyperhomocysteinemia [103, 104]. Among the cardiovascular diseases considered was ischemia/reperfusion injury, in this model demonstrated that the consumption of cashew acts on lipid peroxidation, tissue myeloperoxidase activity, and reactive oxygen species generation: inducing a decrease of levels; also there is a decrease of pro-inflammatory cytokines and an increase of antioxidant activity. In addition, studies have shown that cashew consumption reduces the risk of cardiovascular disease: probably because of its concentration of fatty acids, which also have a hypolipidemic action [105, 106]. Other studies have shown that not only cashew nut consumption has therapeutic effects but also its derivatives such as extracts. The leaf extract of Anacardium has an anti-inflammatory and bronchodilatory action: this is shown by in vivo studies on animal model. In this case, the effects are due to a derivative present in the extract, oleamide [107]. In the dermatological field, there is some evidence to suggest a possible application of cashews as a dermatological treatment as well, but extensive studies have not yet been conducted [108]. Certainly the in vitro and in vivo studies carried out demonstrate action on inflammation and oxidative stress, particularly cashews modulate important pathways, such as Nrf2 and NFkB. The latest studies instead are also focusing on the anticancer effect, and this food might have evaluated antiproliferative action on cancer cells [109].

5. Conclusion

It has been increasingly clear in recent years how nutrition may affect the prevention and/or treatment of several chronic diseases. Based on the food ingredients that can have positive effects on health, a balanced and diverse diet is advised. For instance, antioxidant chemicals can fight free radicals directly or indirectly by boosting cellular endogenous antioxidant defenses, such as by activating Nrf2. Resveratrol, catechin, and allicin are a few chemical substances found in the human diet that have strong biological effects and may be good for cardiovascular health. They also prevent ROS damage by upregulating phase II detoxifying enzymes and raising levels of cellular glutathione. Açai berries, cashew nuts, and pistachios are some of the bioactive ingredients of the diet that are covered in this chapter. Since the majority of studies are in vitro or in animals, and it is unknown how far these doses can be extrapolated to be effective in humans, it is not yet possible to establish safe and effective doses for supplementation, taking into account all the studies that have been discussed in this chapter. The usage of food ingredients does, however, seems to have the benefits of relatively low toxicity, a wealth of resources, and low cost. Therefore, "nutritional therapy" emerges as a crucial method for preventing and/or treating a variety of diseases, enhancing the welfare of people, and trials to determine their efficacy should be carried out.

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Conflict of interest

The authors declare no conflict of interest.

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