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MiniReview

Brief Challenges on Medicinal Plants: An Eye-Opening Look at Ageing-Related Disorders

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Abstract: Several studies have reported that nature-derived antioxidants may prevent free radicals over-production and therefore control the onset and prevent the exacerbation of different kinds of diseases caused by oxidative stress and redox-derived stressors, including ageing, fundamentally by suppressing the oxidative by-products-mediated degradation. Naturally derived antioxidants exert their anti-ageing action via a panoply of signalling systems, many of which engaging reactive oxygen and nitrogen species scavenging, with the Nrf2/Keap1-ARE system and improving the many survival genes and functions (such as the pathway mTOR/Foxo/SIRT1) able to slow cellular senescence. Most of the research in this field has evaluated the regulative effects and even pathways of herbal extracts with antioxidant property in the ageing process, and various age-related disorders such as cardiovascular disease, ischaemia-reperfusion injury, coronary and myocardial circulatory perfusion, peripheral vascular resistance, and even neurodegenerative disorders are prevented plant phytochemicals often via their antioxidant potential. A much more complex ability to interact with survival functions makes these compounds successfully active in preventing ageing-related disorders. This report aimed to discuss in more detail some selected medicinal plants including *Allium sativum*, *Aloe vera, Crataegus spp.*, *Cynara scolymus*, *Eleutherococcus senticosus*, *Ginkgo biloba*, *Hippophae rhamnoides*, *Panax ginseng*, *Rosmarinus officinalis*, *Schizandra chinensis, Vitis vinifera* and seaweeds in the prevention of ageing-related pathologies. A systematic overview of the relevant information in the antioxidant function of the many herbal products reviewed here for the control of the ageing process is proposed, to provide a new horizon on the design of anti-ageing herbal medicines.

Destructive and progressive modifications in one or more tissues lead to organs impairment function and consequently to ageing, which over time cause disease and in last instance death [1]. The ageing process is an unavoidable pathway directly influenced by lifestyle, genetic and environmental factors [2], and a process that briefly involves the acceleration of destructive modifications over time, both at the cellular and molecular levels [3]. Moreover, ageing process is also correlated with immune system dysfunction, nervous system impairment and apoptosis [4]. Different studies have found that the induction of apoptosis is related to a decrease in glutathione (GSH) levels and elevated oxidative stress in brain and liver tissues [4,5]. In fact, the relationship of apoptosis with ageing and cellular senescence is much more complex and can highlight some of the anti-ageing effects described for phytochemicals [6]. The oxidation process is a natural and pivotal process of the body, besides to be also destructive, as it can bear noxious damage. Cells produce, in a continuous manner, free radicals and reactive oxygen (ROS) and nitrogen (RNS) species as part of the metabolic processes [7]. Those molecules are unpaired electrons released by biochemical processes in the body, which are formed when the body uses oxygen to metabolize nutrients (i.e., fats and carbohydrates). However, they can also be produced due to stress, radiation, infections and smoking exposure [8–12]. Considered extremely harmful to the body, these highly reactive molecules favour the appearance of numerous damages in organic biomolecules (i.e. nucleic acids, lipids and proteins), induce DNA changes, which in turn affect the organic homeostasis of the body, and can lead to several oxidative stress-related disorders, such as cardiovascular and other degenerative disorders, and even cancer [13,14]. Moreover, oxidative stress reflects an imbalance between the antioxidant system and oxidants in the

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body [5]; that is, it can also impair cell membranes function and consequently induce irreversible damages, which culminates with cell death and/or triggering of age-related chronic diseases, such as Alzheimer's, Parkinson's, arthritis, atherosclerosis, osteoporosis, dementia, cardiovascular diseases and cancer [15]. The mechanism underlying ROS scavenging involves not only detoxifying enzymes but also the much more complex signalling pathway Nrf2/Keap1/ARE. Usually, this master tuner of oxidative stress is related to further cell sensors, such as the hypoxia-inducible factor (HIF-1α), which activates a broad panoply of genes against the hypoxic injury, being this activity regulated by the intracellular oxygen sensors prolyl hydroxylases (PHDs) [16]. Cells possess at least three different isoforms of PHDs, that is PHD 1–3. The PHD-1 gene silencing induces hypoxic tolerance and shift cell function to reprogramme mitochondrial oxygen consumption, through decreasing ROS production also in hypoxic mitochondria [16]. When the antioxidant machinery should be activated to remove ROS, the nuclear factor-erythroid 2 p45-related factor 2 (Nrf2) via the intracellular sensor Kelch-like ECH-associated protein 1 (Keap1) regulates the basal and inducible expression of numerous antioxidant stress genes. The transcription factor Nrf2 (NF-E2-related factor 2) plays a vital role in maintaining cellular homeostasis, especially upon the exposure of cells to chemical or oxidative stress, through its ability to regulate the basal and inducible expression of a multitude of antioxidant proteins, detoxification enzymes, and xenobiotic transporters. The activity of Nrf2 is primarily regulated via its interaction with Keap1 (Kelch-like ECH-associated protein 1), which directs the transcription factor for proteasomal degradation. Phytochemicals are also good activators of the Nfr2 activity [17–19], and this ability makes phytochemicals able to prevent cell ageing-related disorders [20–23]. In this sense, the indirect antioxidant activity of natural products resulting in the production cytoprotective proteins (phase 2 enzymes) and endogenous direct antioxidants seems to be more important than their direct antioxidant activity.

The improvement of life expectancy and the delay of ageing process have deserved special relevance since ancient times but recently gained pivotal attention, being the maintenance of health and well-being of human individuals crucial. In fact, numerous studies have emphasized that free radicals and ROS/RNS over-production represent a suitable environment for the development of age-related diseases [24,25]. Furthermore, it has also been shown that reduced levels of antioxidant molecules or even a limiting bioavailability of antioxidant enzymes improves oxidative stress, leading to cellular destruction [26,27]. The different multifaceted aspects of ageing and cellular senescence are intriguing targets for multiple natural substances coming from plants, due to their well-known pleiotropism. Their activity targets not only the complex antioxidant and enzyme-mediated ROS and RNS scavenging system, but also many other pathways involved in energy balance and ageing, such as AMPK/mTOR/Foxo-1/sirtuin 1 system [28,29]. The antioxidant activity achieved by eliciting antioxidant enzymes or even acting directly on biological nucleophiles may also explain, to some extent, the anti-inflammatory and cytotoxic activity of these compounds. Over the years, an increasing interest in the use of natural substances, including some questions related to the safety of synthetic compounds, has been highlighted, which encourages the development of more and increasingly detailed studies through using plant-derived resources [30,31]. The assessment of the bioactive potential of natural products, namely herbal products and its derived preparations, has also received increasing attention, as some of them were already considered excellent anti-ageing agents and health promoters [32]. Plants and animals have complex antioxidant systems, which act as effective protectors against invaders or even slow down the oxidation induced by multiple chemical substances. Commonly known as endogenous antioxidants, enzymes such as superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), and numerous non-enzymatic antioxidants, including vitamins C and E, beta-carotene, ubiquinone, trace elements zinc and selenium, GSH, lycopene, lutein and flavonoids, are among the most prominent and efficient ones [33]. However, with the magnitude of oxidative stress reactions, endogenous antioxidants are limiting, and therefore, other alternatives need to be found to improve and even to complement the organic protection.

There are two sources of antioxidants: antioxidative enzymes are mainly found in and around cells, while exogenous antioxidants have been primarily obtained through fruits and vegetables, nuts, berries, red wine, green tea and ultimately dietary supplements [34,35]. The activity of many of these plant-derived natural products is to tune the existing interplay between the mitochondria-endoplasmic reticulum (ER)-proteasome with cell ability in controlling apoptosis/autophagy and survival functions [36]. On the other hand, some of the major chronic diseases related to ageing such as arthritis, atherosclerosis, osteoporosis, cardiovascular diseases and dementia are linked to inflammation, and therefore, inflammatory processes may be considered a potential pathway, is triggering molecular modifications and worsening pathological processes, in which flavonoids are major anti-inflammatory molecules, able to inhibit the pro-inflammatory role of NF-κB [37,38]. Although several studies have been performed in this field, a general overview elucidating the most efficient and promissory plant-derived phytochemicals with anti-ageing abilities is still relatively restricted [2]. Thus, the objective of the present report was to provide an extensive knowledge regarding the different possibilities based on the use of medicinal plants for anti-ageing purposes (table 1). The different roles of bioactive constituents were also included as also their contributive role in ageing regulation.

Medicinal Plants for Ageing: Which Ones?

Herbal remedies have been again more readily accepted than the synthetic alternatives by worldwide consumers, after a period in which natural resources became secondary [39]. Herbal formulations comprise an ancient practice being even considered the first choice for treating adaptive and functional ageing-related disorders [40]. It is tempting to speculate that herbal preparations might be effectively used in the field of

Table 1.

Selected medicinal plants with active anti-ageing properties.

Plants	Parts used and main components	Therapeutic effects	Mechanisms of action	References
Allium sativum Liliaceae (Garlic)	**Bulbs.** Diallyl sulphide (DAS), Allyl methyl disulphide (AMDS), Allyl methyl trisulphide (AMTS), Diallyl disulphide (DADS), Diallyl trisulphide (DATS), Diallyl tetrasulphide (DATTS), 2-vinyl-[4H]-1,3-dithiin (2-VDT), 3-vinyl-[4H]-1,2-dithiin (3-VDT), alkaloids, flavonoids (quercetin, rutin, kaempferol), cardiac glycosides, terpenes, steroids and resins	Antioxidant, antimicrobial, antidiabetic, anticarcinogenic, antimutagenic, anti-atherosclerotic and anti-inflammatory effects	Hypolipaemic activity	[3,57–60,65,83]
Aloe vera Aloeaceae (Aloe)	**Leaves.** Naringin, hesperetin, chrysin, apigenin, kaempferol, quercetin, ellagic acid and phenolic acids	Anti-ageing and microcirculatory stimulant effects and wound healing effect	Inhibitor of thromboxane A2, stimulation of macrophages and fibroblasts activity and prevention of prostaglandin E2	[95,98]
Crataegus spp Rosaceae (Hawthorn)	**Leaves, flowers, fruits.** Hesperetin, apigenin, vitexin, eriodictyol-7-glucuronide, luteolin-7-*O*-glucuronide, chlorogenic acid, catechins, naringenin, quercetin and epicatechin	Prevention of ischaemia-reperfusion injury, cellular antioxidant function, improvement of coronary and myocardial circulatory perfusion, reduction in peripheral vascular resistance and anti-inflammatory activity	Prevention of plasma lipids elimination, maintenance of mitochondrial antioxidant status, decrease Kreb's cycle enzymes, improvement of membrane permeability for calcium and inhibition of phosphodiesterase	[52,53,113,114, 120,121]
Cynara scolymus Asteraceae (Artichoke)	**Leaves.** Luteolin, cynaroside, cynarine and chlorogenic acid	Prevention of atherogenesis in cultured endothelial cells and monocytes and inhibition of oxidative LDL	Antioxidant activity, inflammatory mediators	[130,131,134]
Eleutherococcus senticosus Araliaceae (Siberian ginseng)	**Root.** Phenolic acids (gallic acid, *trans-p*-coumaric acid, *cis-p*-coumaric acid, 3-OH-cinnamic acid, *cis*-ferulic acid), kaempferide, morin, quercetin, apigenin and catechins	Inflammatory disorders, anaemia, and rheumatoid arthritis	Anti-ageing, antistress, scavenger of ONOO−	[52,146,147]
Ginkgo biloba Ginkgoaceae (*Ginkgo biloba*)	**Leaves.** Kaempferol. quercetin and isorhamnetin	Cerebral insufficiency and peripheral arterial disease in elderly, antiarrhythmic on cardiac reperfusion-induced arrhythmias, and prevention of mobile phones-induced oxidative stress	Antioxidant activity, lipid peroxidation inhibition	[148,152,156,157]
Hippophae rhamnoides Elaegnaceae (Sea buckthorn)	**Fruits.** Epicatechin, catechin, rutin, kaempferol, quercetin, naringenin and ellagic acid	Immunomodulatory, anti-inflammatory, anti-atherogenic, antistress, cardioprotective and wound healing effects	Antioxidant activity preventing DNA damage	[170,171,178]
Panax ginseng Araliaceae (Chinese ginseng)	**Root.** Catechins, isoflavones, ginsenosides, kaempferol and polyacetylene.	Neuroprotective in several disorders: Alzheimer's disease (AD), Parkinson's disease or Huntington's diseases models	Anti-inflammatory, antioxidative, antidiabetic, anticancer	[32, 191–200]

(continued)

holistic gerontotherapeutics, that is, therapeutic management, carefully designed to retard the sudden drop in performance, quite frequently after the sixth decade of life. Herbal medicine often retrieves its ability to prevent pathology from folk traditions, and a long, millenarian empirical expertise, but, anyway, modern pharmacology appears to assess and confirm some of these beliefs. Currently, traditional herb remedies have gained special relevance, up to the point that has been considered potential candidates for the management and even treatment of chronic and ageing-related diseases [41–43]. Taking into

Table 1. (continued)

Plants	Parts used and main components	Therapeutic effects	Mechanisms of action	References
Rosmarinus officinalis Lamiaceae (Rosemary)	**Leaves.** 6′'-O-(E)-feruloylhomoplantaginin, 6′'-O-(E)-feruloylnepitrin, 6′'-O-(E)-p-coumaroylnepitrin, 6-methoxyluteolin 7-glucopyranoside, luteolin 3′-O-beta-D-glucuronide, luteolin 3′-O-(3′'-O-acetyl)-beta-D-glucuronide, kaempferol, luteolin, genkwanin, and ladanein, 1-O-feruloyl-beta-D-glucopyranose, 1-O-(4-hydroxybenzoyl)-beta-D-glucopyranose, rosmarinic acid, carnosic acid and carnosol	Neurological disorders associated with inflammation	Antispasmodic, anti-inflammatory, antinociceptive, hepatoprotective, diuretic, anti-ageing	[52, 202–211, 215–216, 221–222]
Schizandra chinensis Schisandraceae (Magnolia vine)	**Fruits.** Proanthocyanidins, quercetin, isoquercitrin, quercitrin, rutin, phenolic acids and lignans	Hepatoprotective from oxidative damage, stimulation of caspase-dependent apoptosis in human cancer cells, alleviate cognition disorders and attenuate oxidative brain damage and alleviates non-alcoholic fatty liver	Suppression of lipid peroxidation, antioxidant, antibacterial, cytotoxic, anti-inflammatory	[223–238]
Seaweeds	**Full seaweed.** Phlorotannins, hydroxybenzoic acid, hydroxycinnamic acid, ferulic acid, phloroglucinol, gallic acid, chlorogenic acid, caffeic acid, myricetin and quercetin	Liver diseases, swelling, cysts, phlegm and enlarged thyroid glands	Antioxidant (radical scavenging and singlet oxygen quencher)	[239–248]
Vitis vinifera Vitaceae (European grapevine)	**Fruits.** Resveratrol, quercetin, and kaempferol	Prevention of ageing and cardiovascular disease	Antioxidant, neurodegenerative disease preventive	[249–266]

account such examples, it is convenient to highlight the results of several studies, which suggests that 'anti-ageing herbs' exert multifunctional effects and can protect the whole body through different mechanisms [44]. Further, other lines of research have also reported that those matrices are potential candidates to prevent and/or even to treat multiple ageing-related neurological disorders [32,45]. In fact, most of the currently available chemical drugs derive, directly or indirectly, from natural compounds, playing therefore a great contribution to drug discovery and development [46–48]. Many of these herbs and their main active principles (flavonoids) are shown in fig. 1.

Major Medicinal Plants Used in Medication System as Anti-Ageing Agent

The World Health Organization (WHO) reported that at least three-quarter of the world population uses medicinal herbs for their health care. Actually, remarkable research papers about medicinal plants deal with pharmacognosy, chemistry, pharmacology and clinical therapeutics of Ayurveda and Chinese therapeutic systems [49]. Current knowledge demonstrated that the main factors of inflammatory processes could occur via dysregulated gene expression under the age-related oxidative stress as well as through induction of redox-sensitive transcription factors. Important agents contributed to the inflammatory pathways are those of age-related up-regulation, such as NF-κB, IL-1β, IL-6, TNF-α, cyclooxygenase-2, adhesion molecules and inducible NO synthase [37,50,51].

Allium sativum *L. (English name: Garlic; Family: Alliaceae).* Garlic is considered an active and efficient anti-ageing agent [52–56]. A direct influence of garlic on atherosclerosis was already discussed [57–60], and their anti-atherosclerotic effect attributed to its hypolipaemic activity [61]. Experimental and clinical data have demonstrated that garlic reduces blood cholesterol levels [62–64], dementia and risk of heart disease [65], homocysteine levels [66], hypertension [64,67], as well as inflammation [68]. Ajoene (4,5,9-trithiadodeca-1,6,11-triene 9-oxide) is the main active principle of garlic. Its anti-inflammatory potential has been reported as inhibiting the *quorum sensing* (QR) system of some bacteria, such as *Pseudomonas aeruginosa,* which use this mechanism to synchronize the expression of specific genes involved in pathogenicity [69]. The role of garlic as an anti-ageing natural product has been particularly stressed in recent years [70–73]. In fact, the major effect of garlic on

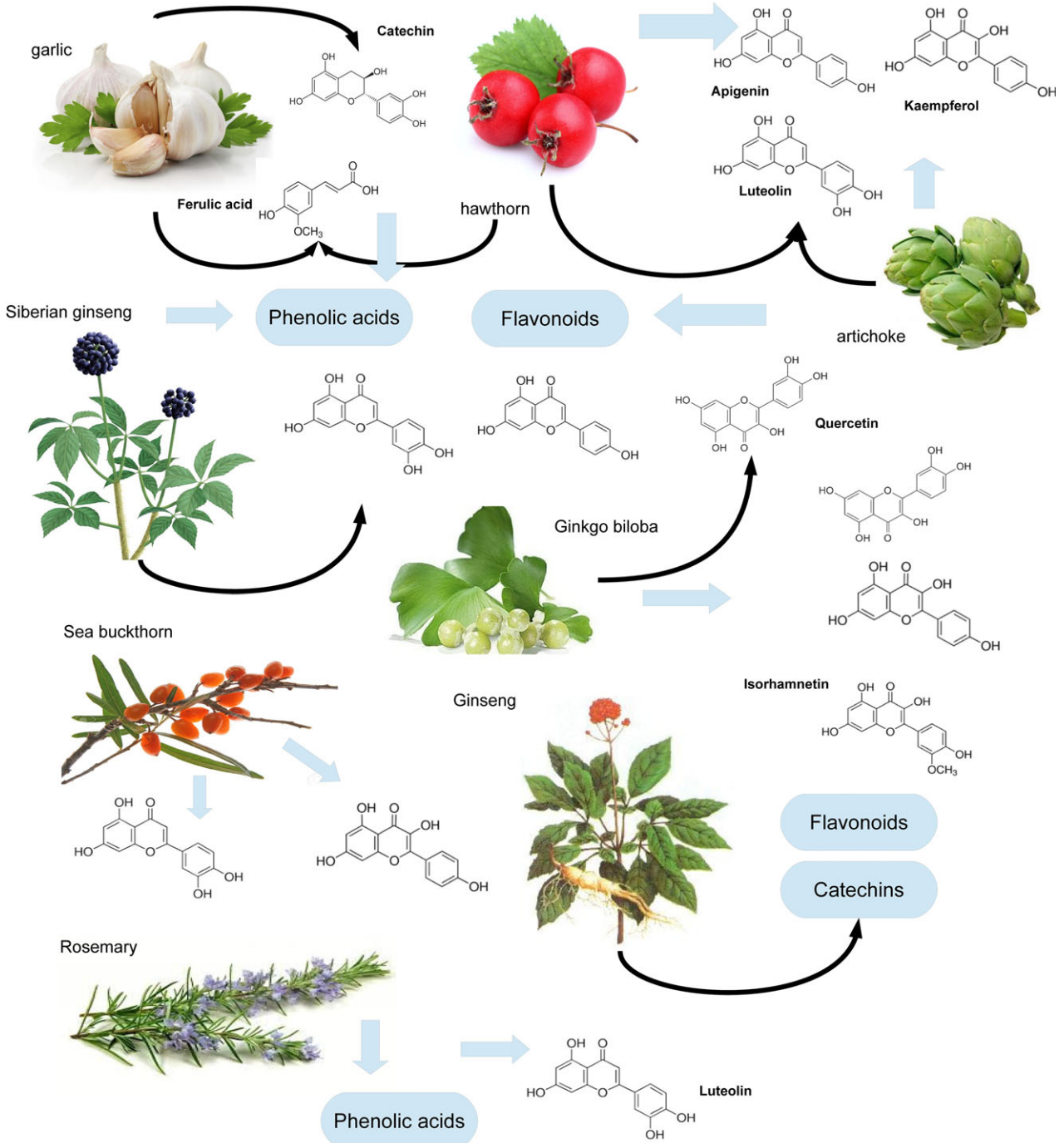

Fig. 1. The main flavonoids contained in different medicinal plant extracts. Quite almost of these sources are rich in luteolin, which is present in most of the indicated plants, besides quercetin, catechins and apigenin. Black curve arrows indicate the major isolated flavone-derived compounds and blue arrows the major phytochemical classes.

ageing-related disorder has been demonstrated in both atherosclerosis and inflammation.

Besides their activity in bacteria, garlic also exerts a beneficial effect on further disorders related to ageing, such as atherosclerosis. Treatment during 4 years with a standardized garlic-based drug, such as 900 mg garlic powder (Kwai®), could decrease 5–18% volume of atherosclerotic plaques in femoral and carotid arteries [74]. The association between increased age and the volume of plaque showed an elevation between 50 and 80 years, which garlic treatment reduced by 6–13% over 4 years. Therefore, using garlic, the volume of plaque remained practically constant for the age span of 50 and 80 years [75]. The activity of many allyl sulphides in garlic might give insight on its activity towards DNA. For

example, both diallyl sulphide and diallyl disulphide inhibit the DNA damage induced by aflatoxin B1 in rat hepatocytes, increasing gene expression repair and hepatocyte viability, enhancing intracellular glutathione-S-transferase (GST) [76]. The effect of these allyl sulphides has been reported to modulate oxidized LDL (ox-LDL)-mediated adhesion on endothelia by leucocytes via protein kinase A (PKA) and protein kinase B (PKB) signalling pathways [77].

A meta-analysis carried out by Silagy *et al.* [78] reviewed the effects of *Bulbus Allii sativi* on lipoproteins and serum lipids. Sixteen of the 25 randomized controlled trials they reviewed were selected, which provide data for 952 individuals [78]. Of these studies, 14 were parallel group trials, and two were crossover studies. Twelve of these studies were double-blind, two were single-blind, and two were open-label studies. Those studies investigated the efficacy of garlic prepared in different formulations including in dried powder (600–900 mg), raw form (10 g), oil form (18 mg) or aged garlic extracts with the median duration of therapy of 12 weeks. In summary, an average of 12% reduction in total cholesterol upon receiving garlic supplementation in either powder or non-powder form was observed, while 13% reduction in serum triglycerides was observed in groups receiving garlic supplementation in powdered form [78]. The clinical data reported by Silagy and Neil [78] in the meta-analysis well supported the notion that garlic therapy is effective in lipid-lowering action. Moreover, similar results of potential lipid-lowering for preparations of dry garlic powder have been reported in other studies [79–81]. Thus, a daily dose of 600–900 mg garlic powder proved to be effective to significantly decrease triglyceride and serum cholesterol levels [79,82]. Another study showed that garlic extract exerted neuroprotective effects on cognitive dysfunction and neuroinflammation through decreasing the activation of microglia and IL-1β to basal levels [83]. Numerous biological effects of garlic, including antimicrobial, antioxidant, antidiabetic, anticarcinogenic, antimutagenic, anti-atherosclerotic and immunomodulatory activities have been recently documented, and many of them are related with ageing-dependent disorders [3,84,85]. Garlic as well-known medicines worldwide could be administered in the public herbal medication [86].

Aloe vera *(L.) Burm.f. (English names: Barbados Aloes, Bitter Aloe, Curacao Aloe; Family: Aloaceae).*

The *Aloe vera* plant possesses very interesting anti-ageing and microcirculatory stimulant effects [52]. Components of *Aloe vera* have been recently analysed [87]. One of its major components, emodin, has been reported to inhibit type 2 diabetes-dependent neuropathic pain in rat models by decreasing the excitatory transmitting activity of the P2X3 receptor in the dorsal root ganglia [88]. Clinical studies demonstrated that preparation and administration of aloe vera gel could stimulate wound healing [89]. Previous studies have revealed that aloe vera gel was able to prevent progressive dermal ischaemia due to several kinds of trauma, including burns, electrical injury, intra-arterial drug abuse and frostbite [90–92]. An *in vivo* study using aloe vera gel demonstrated a thromboxane A2 inhibitor effect that could suppress the progression of tissue damage induced by thromboxane A2 [93,94]. Besides that, there are also several other mechanisms that have been increasingly proposed to elucidate the mechanism of action of aloe vera gel in wound healing, such as providing hydration, insulation and protection, as well as stimulating the compliment linked to polysaccharides [95,96]. Moreover, aloe vera gel was also able to promote wound healing mediated through *in vivo* stimulation of macrophages and fibroblasts activity. It is known that the activation of fibroblast has been associated with enhancement of collagen and proteoglycan synthesis, subsequently to support tissue repair [95,97]. Based on the currently available literature, approximately 75 potentially active ingredients were already proposed to be responsible for the observed effects; among them are vitamins, enzymes, minerals, sugars, lignin, saponins, salicylic acids and amino acids [96,98]. Wound healing is one of the possible concerns in repairing trauma during ageing. Furthermore, some of the active principles have been identified as polysaccharides, which are composed of several monosaccharides, predominantly mannose [96,99,100]. As the main sugar component in aloe vera gel, mannose 6-phosphate has been suggested to play an important role in the wound healing properties of the gel. Studies reported that mannose 6-phosphate enhances fibroblasts activity through binding to the growth factor receptors present on the surface of cells [95]. Similarly, mucopolysaccharides isolated from *Aloe vera* was also found to improve the anti-ageing effect through induction of fibroblast activity that makes elastin and collagen fibres more strengthful, resulting in less wrinkled and more elastic skin [101]. Aloes exert their anti-ageing effects mainly through the modulation and scavenging of ROS contents [102,103]. Aloe-derived emodin exerts its antioxidant and pro-apoptotic effect (e.g., in cancer cells) via the Nfr2-mediated signalling [104]. Also, it was reported that *Aloe vera* extract could induce considerable improvements in decreased CAT, SOD, GSH, GPx and glutathione-*S*-transferase levels in liver and kidney of diabetic rats, suggesting their immunomodulatory and antioxidant effects [105,106]. For certain aspects, *Aloe vera*'s antioxidant activity seems to be strictly correlated with their anti-inflammatory, free radicals- and superoxide radical-scavenging effects, that is through reducing the production of prostaglandin E2 from arachidonic acid, inactivation of different transcription factors and even the activity of several enzymes, such as cyclooxygenase and lipoxygenase [98]. Besides, the antioxidant potency of polysaccharides from *Aloe vera* against doxorubicin (DOX)-induced myocardial oxidative stress in albino Wistar rats has also been shown, thus reporting insightful data about the cardiovascular disorders often related to aged individuals [107]. *Aloe vera* gel and latex have shown to present therapeutic effects and health management benefits, through exerting antitumour, antioxidant and anti-inflammatory activities. This activity enables *Aloe vera* extracts to exert potential benefits on many ageing-related ailments such as type 2 diabetes [108], Alzheimer's disease (AD) [109,110], cardiovascular disease and stroke [111,112].

Crataegus *spp. (English name: Hawthorn; Family: Rosaceae).*

The antioxidant activity of methanolic extracts from flowers and fruits of the genus *Crataegus* spp. was demonstrated in several stages of development [113]. *Crataegus* extracts are also able to reduce the levels of plasma lipids, such as total cholesterol, triacylglycerides, as also LDL and VLDL fractions [114,115]. An alcoholic extract from *Crataegus oxyacantha* L. (AEC) was found to exert similar cardioprotective effects as captopril. AEC increased the activity of antioxidant enzymes in mitochondria and prevented the decrease of Krebs's cycle enzymes induced by isoproterenol in rat heart. Pre-treatment of AEC also successfully inhibited the increase in heart mitochondrial lipid peroxides, preventing mitochondrial lipid peroxidative damages [114,116]. The cardiotropic effect of *Crataegus* spp. mainly derives from its ability to increase membrane permeability for calcium as also through inhibition of phosphodiesterase with the subsequent increase in intracellular cAMP concentrations, culminating with the increase of coronary and myocardial circulatory perfusion and reduction in peripheral vascular resistance [52,53]. A Japanese clinical trial involving 80 patients giving fruits and leaves from *Crataegus* spp. highlighted the clinical improvement observed in cardiac function, dyspnoea and oedema. On the other hand, a German clinical study including 60 patients with stable angina pectoris receiving 60 mg hawthorn three times a day showed increased coronary perfusion and economized myocardial oxygen consumption [52]. *Crataegus oxycantha* extract has shown to exhibit promising effects in preventing ischaemia-reperfusion injury. *Crataegus* extract (100 mg/kg b.w.) significantly reduced creatine kinase activity and infarct size in an *in vivo* rat model of acute myocardial infarction [114]. The study further elucidated that *Crataegus* extract was capable of attenuating the phosphatase and tensin homolog (PTEN) activities, chromosome deletions, up-regulation of phospho-Akt and c-Raf levels in the heart. The experimental research suggests that *Crataegus* extract prevents apoptosis caused by myocardial ischaemia-reperfusion through regulation of HIF-1 and Akt signalling pathways [114,117]. In a study carried out by Hwang *et al.* (2017), a mixture of *Panax ginseng* Meyer and *Crataegus pinnatifida* (GC) could exert protective activities against skin ageing in human dermal fibroblasts (HDF) under UV-B irradiation through elevating the expression of procollagen type I and decreasing the secretion of matrix metalloproteinase-1 [118]. Also, the cellular antioxidant activity of *C. pinnatifida* (Chinese hawthorn) was reported as being derived from the interaction between phenolic compounds with other phytochemicals [113,119,120]. Moreover, the anti-inflammatory activity of extracts from *Crataegus azarolus* L. seems to be regulated by their remarkable antioxidant activities, through preventing pro-inflammatory cytokines production, as well as by increasing the secretion of anti-inflammatory cytokines [121]. In another study, it was also demonstrated that the microcapsules containing procyanidins from hawthorn bark, as also the extract of procyanidins exerted valuable antioxidant and anti-inflammatory activities, suggesting their future application in dietary and pharmaceutical products, and even as ingredients for functional foods formulation [122]. Moreover, hawthorn extract exerted prominent effects on alveolar bone loss and periodontal inflammation, through modulation of total oxidant status, oxidative stress index and total antioxidant status, in rats with systemic periodontal disease [123]. As many edible or pharmaceutical plants, also *Crataegus* genus is widely used in many ageing-related disorders, such as diabetes [124], brain damage following stroke [125] and cardiovascular function [126,127].

Cynara scolymus *L. (English name: Artichoke; Family: Asteraceae).*

Artichoke (*Cynara scolymus* L.) is a Mediterranean edible vegetable, which is known to be rich in natural antioxidants, among them hydroxycinnamic acids, vitamin C and flavones [128,129]. The herbal formulation from this plant is commonly indicated as primary health care for different purposes [130]. It was reported that artichoke exerted a considerable improvement in GPx activity in erythrocytes from a rat model [128]. Also, artichoke could decrease the levels of 2-aminoadipic semialdehyde, a biomarker of protein oxidation present in plasma proteins and haemoglobin [128]. Zapolska-Downar *et al.* [131] demonstrated that artichokes exerted protective actions against oxidative stress-resulted through oxidative LDL and inflammatory regulators in preventing atherogenesis in cultured monocytes and endothelial cells. The study showed that both aqueous and ethanolic extracts from artichoke at 50 μg/mL inhibited oxidative stress-induced by oxidative LDL in 15% and 29%, respectively. Therefore, it was suggested that artichoke extract can be a potent therapeutic factor for atherosclerosis by lowering the rates of LDL oxidation [131]. On the other hand, biosynthesis of cholesterol from ^{14}C-acetate in primary cultured rat hepatocytes in a concentration-dependent biphasic manner could be inhibited by a dried aqueous extract from artichoke leaves (ratios 4.5:1), being observed a moderate control (around 20%) from 0.007 to 0.1 mg/mL and greater inhibition at 1 mg/mL (80%) [132,133]. Moreover, the replacement of ^{14}C-acetate with a ^{14}C-mevalonate largely prevented the inhibitory effects of the extracts, indicating inhibition of the activity of hydroxyl-methyl-glutaryl-CoA-reductase (replacement of an acetate substituent with mevalonate was followed by tracing radionuclides ^{14}C activity) [133]. Thus, the induction of hydroxyl-methyl-glutaryl-CoA-reductase activity through insulin was easily inhibited by the extract [133]. In past reports, Gebhardt *et al.* [134] found that cynaroside and its aglycone luteolin were the main responsible constituents present in extract for enzyme inhibition. These data seem to be confirmed in very recent reports [135]. The effects of dried aqueous extract from artichoke leaves were evaluated by two randomized, controlled clinical trials on the cholesterol concentrations in 187 patients [136,137]. The first study comprised a randomized, double-blind, placebo-controlled pilot study involving 44 healthy volunteers, and assessed the effect of a crude extract on cholesterol levels. The study was conducted by assigning randomized patients to receive either 640.0 mg of the extract or a placebo three times daily for

12 weeks [138]. No significant effects on serum cholesterol were found; however, in the subgroup analysis, significant cholesterol-lowering effects were observed in individuals with a total cholesterol level of >210 mg/dL ($p < 0.022$) [136]. The second study evaluated the efficacy and safety of a dried aqueous extract of fresh artichoke by placebo-controlled investigation (25–35:1) [137]. Patients received either 1800 mg of artichoke extract as coated tablets, each containing 450.0 mg extract, or a placebo. One hundred and forty-three hypolipoproteinaemia patients with initial total cholesterol >7.3 mmol/L (>280 mg/dL) administered 1.8 g of a dried extract of leaf per day or the placebo for 6 weeks. A statistically significant effect of dry artichoke extract on the changes in total cholesterol and low-density lipoprotein cholesterol was observed at the end of treatment when compared to the placebo ($p = 0.0001$). The patients treated with the extract previously shown to experience reductions in total cholesterol levels by 18.5%, while only 8.6% reduction was observed in the placebo group after 6 weeks of treatment [137]. The decrease in low-density lipoprotein cholesterol by 63% was also observed in the group treated with the extract while only 22.9% reduction in the placebo group. The ratio of low-density lipoprotein to high-density lipoprotein showed a decrease of 20.2% in the group that received the extract and 7.2% in the group that received placebo. No drug-related adverse effects were reported [137]. Based on the latest findings, the investigation of antioxidative phytochemicals from artichoke has gained growing attention not only for their recognized health-promoting activities but also due to the high contents of caffeoylquinic acids and flavones present in capitula and leaves [129].

Eleutherococcus senticosus *(Rupr. & Maxim.) Maxim. (English names: Siberian Ginseng, Eleuthero; Family: Araliaceae).*

Siberian ginseng is a highly valued woody medical product, usually as a herbal shrub from the Araliaceae family with a long history of use (by the Chinese population for over 2000 years) [139]. It contains different kinds of saponins such as noroleanane, oleanane, lupane and 3,4-secolupane types, according to the aglycone structure [140]. This medicinal plant material exhibits noticeable anti-ageing effects [52], but adaptogenic and antistress effects of *Radix Eleutherococci* have also been related to metabolic control of energy, tissue proteins and nucleic acids [141]. The intraperitoneal administration of a fluid extract from the roots (1.0 mL/kg body-weight) enhanced the anabolic activity in male rats [95]. Meanwhile, intragastric administration in mice of butanol extract from roots (170 mg/kg b.w., daily, 6 days/week for 6 weeks) enhanced the activity of oxidative enzymes and SOD in skeletal muscle, which consequently improved the rates of aerobic metabolism [142,143]. Moreover, the roots of *E. senticosus* are a natural source of flavonoids (hyperin, rutin, afzelin, quercetin and kaempferol), phenols such as eleutherosides (lignans, coumarins and phenylpropanoids derivatives), phenolic and triterpenic acids, and even anthocyanins [144,145]. The extracted compounds from fruits mainly contain phenolic acids, eleutherosides (eleutherosides B and E), flavonoids, as well as essential oil; also, dried fruits are a rich source of Ca, Mg, Mn, Zn and Cu [144]. Flavonoids (quercetin, quercitrin and rutin) have been mainly identified in leaves [144]. It has also been reported that Siberian ginseng is an effective scavenger of peroxynitrite ($ONOO^-$), while to a Siberian ginseng MeOH extract was found the maximum ferric reducing antioxidant power (FRAP) [146]. Also, it has been utilized in the treatment of anaemia, inflammatory disorders and rheumatoid arthritis [147].

Ginkgo biloba *L. (English names: Gingko, Maidenhair tree; Family: Ginkgoaceae).*

Ginkgo is one of the oldest tree living species, widely applied for therapeutic purposes in modern pharmacology. It is reported to be effective in the treatment of peripheral arterial disease and cerebral insufficiency in elderly [148,149]. Ginkgo has been demonstrated to improve concentration and memory deficits induced by peripheral arterial occlusive disease [150]. With the approval by the European Commission, ginkgo can be used to relieve symptoms caused by organic brain dysfunction, such as tinnitus (vascular origin) and vertigo (vascular origin). Ginkgo is also able to enhance blood flow and decrease neutrophil infiltration, and therefore, it could be beneficial for ischaemic dementia [151]. It has shown that membrane is stabilizing and antioxidant activity of ginkgo may increase the tolerance of cerebral hypoxia [53,152].

The standardized ginkgo leaf extracts are among the herbal preparations that have undergone most extensive clinical investigation. The effects of ginkgo extract in dementia have been clinically tested mostly in trials involving patients with cognitive deficiency, AD and/or multi-infarct dementia [153]. *Ginkgo biloba* extract (EGb 761) is prepared from dried ginkgo leaves and has a standardized content of 22–27% flavonol glycosides and 5–7% terpene trilactones. This extract is used internally as a treatment for peripheral vascular and cerebral diseases, as well as to alleviate some of the ailments associated with ageing, including dizziness, ringing in the ears and short-term memory deterioration [150]. So far as is known, the extract has only minimal side effects, even after prolonged use [154,155]. Moreover, it has also been demonstrated that EGb 761 displays an interesting effect as antiarrhythmic on cardiac reperfusion-induced arrhythmias due to their antioxidant activity [156]. Ginkgo could also prevent the mobile phones-induced oxidative stress, through preservation of the activity of antioxidant enzymes in brain tissue of rats [157]. Clinical use of *G. biloba* has been shown to effectively improve the symptoms due to insufficient cerebral blood flow, such as concentration and memory difficulties, absentmindedness, confusion, reduced physical performance, tiredness, depressive mood, lack of energy, anxiety, tinnitus, dizziness and headache [158]. Further, ginkgo has been shown to improve the vasoregulation effects by increasing the blood flow in arteries, capillaries and veins. Besides that, ginkgo has also shown to exert rheological effects, metabolic effects,

including minimizing disturbances of neurotransmitters, increasing the tolerance to anoxia and preventing membrane damage induced by free radicals [95]. On the other hand, Zhou and Qi [152] revealed that *G. biloba* extract EGb-761 could attenuate the cerebral ischaemia-induced neuronal damage by long-term pre-treatment in aged mice. Furthermore, it was reported high antioxidant and lipid peroxidation inhibitory effects to *G. biloba* leaf essential oil in various radical-scavenging models [159]. Moreover, and not least important to point out is that it has been revealed that polyphenols are one of the main chemical constituents identified in *G. biloba* leaves with antioxidant activities [160]. The analytical composition of *G. biloba* extracts allowed recent authors to retrieve compounds, such as bilobalide, ginkgolides A, B, C, quercetin, kaempferol, isorhamnetin, rutin hydrate, quercetin-3-beta-D-glucoside and quercitrin hydrate [161]. Many of them are classical flavonoids, which enable this extract to be active in many ageing-related disorders [162–164].

Hippophae rhamnoides *L. (English name: Sea Buckthorn; Family: Eleagnaceae).*

Hippophae rhamnoides, commonly called as sea buckthorn, is the unique nitrogen-fixing deciduous shrub, native from Europe and Asia [165] and widely used for its medicinal and nutritional properties [166,167]. All the plant parts contain more than 190 bioactive substances, including flavonoids, phenols, carotenoids, vitamins (A, E, K, C, B1, B2, B9), pigments, fatty acids (ω3, ω 6, ω 7, ω 9), organic acids, tocopherols, terpenes, sterols, tannins, minerals and other trace elements with antioxidant properties [168,169]. The variability in antioxidants, flavonoids and phenolics present in sea buckthorn seeds was observed across nine Himalayan populations' underlines, highlighting the determinant effect of geographical location and genetic factors to the chemical composition and subsequent identification of the health-promoting responsible compounds [170]. Leaves, seeds and fruits of sea buckthorn have shown to exhibit diverse therapeutic and pharmacological effects, including antioxidant, anti-inflammatory, immunomodulatory, anti-atherogenic, cardioprotective, wound healing and antistress properties [171]. It strengthens sight and inhibits sclerosis and ageing process [52]. In fact, sea buckthorn leaf alcoholic extract demonstrated a good ability to up-regulate antigen presentation of macrophages in aged mice, exhibiting their immune-boosting and anti-ageing effect [171,172]. Preparations of sea buckthorn are widely known for their cardioprotective effects, which are well documented in Tibetan traditional medical literature [173]. Some studies in human and animals have been carried out to evaluate the effect of flavonoids from sea buckthorn in cardiovascular diseases. In fact, some flavonoids are well known to have positive ionotropic effects, namely being able to improve the functioning of cardiovascular system [174]. Flavonoids extracted from sea buckthorn leaves and fruits, known as total flavonoids of Hippophae (THF), are a group of compounds containing seven kinds of flavonoids. Among them, isorhamnetin and quercetin were the main components, both exhibiting protective effects on myocardial ischaemia and reperfusion, tumours, oxidative injury and ageing process [171,175]. On the other hand, alcoholic leaf extract and seed oil provided significant protection against hypobaric hypoxia-stimulated through transvascular fluid leakage in the lungs and brain of rats, through reduction in vascular endothelial growth factor (VEGF) expression [176]. Moreover, the pre-treatment with seed oil enhanced the hypoxic tolerance as shown by the elevated survival time and hypoxic gasping time, and declined plasma catecholamine levels [171,176]. Hypoxic stress significantly enhances the levels of malondialdehyde free radical production, accompanied by a marked decrease in antioxidants levels, such as GSH, GPx and SOD. Thus, in pre-treated animals with *H. rhamnoides,* seed oil significantly reduced malondialdehyde content and production of free radicals [177]. In *C*-6 glioma cells hypoxia models, alcoholic leaf extract of *H. rhamnoides* had similar effects: the exposure of cells to hypoxia for 12 hr significantly increased the cytotoxic effect and coupled with depolarization of mitochondrial transmembrane potential [178]. The increase in nitric oxide (NO) and ROS production and an increase in DNA damage were also observed during hypoxia. Simultaneously, pre-treated cells with alcoholic leaf extract of *H. rhamnoides* at a concentration of 200 mg/mL significantly blocked the induced cytotoxicity, ROS production, maintained the antioxidant levels, restored mitochondrial integrity and prevented the occurrence of DNA damages induced by hypoxia [179]. Free radicals have been associated with the development of atherogenesis through oxidative processes [175]. In fact, sea buckthorn is rich in polyunsaturated fatty acids (PUFA), as well as lipophilic and aqueous antioxidants. It was even found that antioxidants present in sea buckthorn juice ameliorate the main risk factors for coronary heart disease (LDL oxidation, plasma lipids, plasma soluble cell adhesion, platelet aggregation and protein concentration) in humans [175,180]. The decrease in NO production induced by lipopolysaccharides (LPS), the secretion of pro-inflammatory cytokines, inducible nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) expression corroborates the anti-inflammatory properties of the methanolic fraction obtained from sea buckthorn, containing tannins, proteins and carbohydrate groups. Therefore, sea buckthorn seems to be an immunomodulator which might even be effectively administered as a therapeutic remedy for inflammatory disorders [181]. Also, it was also shown that sea buckthorn extract could protect oropharyngeal mucositis in rats induced by methotrexate (MTX), through gene expression, biochemical and histopathological tests, proposing this plant as an inexpensive and effective natural product in controlling oropharyngeal damages induced by MTX [182]. Clinical studies performed using sea buckthorn showed their efficacy in cold stress, as anti-hyperlipidaemic and even positive modulatory effects on mental and general health status [183,184]. In a double-blind clinical trial, 128 ischaemic heart patients were treated with total flavonoids from sea buckthorn at 10 mg each time, three times daily, for 6 weeks; a decrease in total cholesterol levels and angina, and an improvement in cardiac function among the patients that were given sea buckthorn were observed

[185]. Not least interesting to highlight is that no harmful effects of flavonoids from sea buckthorn were shown in renal and hepatic functions. Besides, the mechanism of action seems to be through decreasing the stress of cardiac muscle tissue and by modulation of inflammatory mediators [185]. In laboratory animal mouse models, sea buckthorn flavonoids were capable of declining the formation of pathogenic thromboses [171,185,186]. Moreover, flavonoid-enriched seed extract could reduce high-fat-diet-induced obesity, hypertriglyceridaemia and hepatic triglyceride accumulation in C57BL/6 mice [187]. Therefore, it was revealed that this pathway regulates the expression of both PPARγ and PPARα genes, and suppresses adipose tissue inflammation. Total flavones from *H. rhamnoides* could prevent myocardium from ischaemia via decreasing *Bax* protein expression, increasing *Bcl-2* expression and inhibiting cardiomyocyte apoptosis [188]. Moreover, total flavones from *H. rhamnoides* could also reduce serum and heart advanced glycation, and the content of end products [189]. Some simple sea buckthorn-based formulas have been used to treat cardiovascular diseases, by improvement cardiac function and correcting blood circulation [185]. An immunohistochemical method was even used to assess the inhibitory actions of total flavonoids from sea buckthorn on the induction of NF-κB through stretching cultured cardiac myocytes [190]. The results supported that the blockage of NF-κB activation might be a potential access to the improvement in myocardial function, and therefore, using sea buckthorn, it would be better assessed the treatment of hypertension and chronic cardiac insufficiency [190].

Panax ginseng *Meyer (English name: Ginseng; Family: Araliaceae).*

Ginseng roots have been used for more than 2000 years and recognized as a valuable ethnomedicinal herb in many Asian countries, such as Japan, China and Korea [191]. Moreover, ginseng is being extensively consumed both as a preventive and therapeutic agent, against different kinds of diseases due to their prominent anti-inflammatory, antioxidative, antidiabetic and anticancer effects [192]. Their traditional use has been divided into two main categories: short-term – to improve the levels of histamine, the healing process, stress resistance, vigilance and work efficiency in healthy individuals; and long-term – to improve well-being in debilitated and degenerative conditions especially associated with old age [52,53,153]. Also, ginsenoside Rc, one of the main protopanaxadiol-type saponins extracted from *Panax ginseng* is well known for their anticancer, anti-inflammatory, antiobesity and antidiabetic activities. On the other hand, it was revealed that their anti-inflammatory effects pass through suppressing TANK-binding kinase, 1/IκB kinase (TBK1), ε/interferon regulatory factor-3 (IRF-3) and p38/ATF-2 signalling [193]. As a matter of fact, more than 28 ginsenosides were already extracted from ginseng and might be associated with a broad range of therapeutic actions at a level of central nervous system (CNS), cardiovascular and endocrine systems. Noteworthy, ginseng has also been found to increase metabolism and immune function and to exert anti-ageing and antistress activities [194]. It was also proved that several ginsenosides act as non-organ-specific tumour suppressors as also improve the learning and memory abilities in patients with AD [194]. In another study, the anti-inflammatory activities of Korean red ginseng (KRG)-derived components were evaluated, namely water extract (KRG-WE), saponin fraction (KRG-SF) and non-saponin fraction (KRG-NSF); the obtained outcomes indicated that all of them exerted anti-inflammatory properties, mainly through suppression of interferon regulatory transcription factor 3 (IRF3) pathway [195]. It is well known that both ginsenosides and ginseng exert protective action against various neurodegenerative diseases on different stages of pathogenesis and even symptoms. It was demonstrated in previous studies that ginseng efficiently attenuates pathological changes in cellular and animal models with AD, Parkinson's disease (PD) or even Huntington's diseases [196]. The beneficial effects of ginseng on AD have been demonstrated both in human and animal studies. In a Korean open-label trial, patients with AD who had a dose of 9 g KRG/day in a period of 12 weeks demonstrated significant improvement in clinical test performance. In the ginseng group, the obtained scores for mini-mental state examination (MMSE) and AD assessment scale (ADAS) were significantly higher than those of the control group during the 12 weeks of ginseng consumption, and even after discontinuing ginseng intake, a decline was observed [32,33,196]. Furthermore, it has been observed in several PD models that ginseng exert neuroprotective effects, through multiple mechanisms, including as an antioxidant, attenuates activation of caspase-3, suppresses activation of stress kinases and may promote cell survival through elevation of NGF mRNA expression [32]. Moreover, it may also protect neurons in different disease stages; it interferes with stress kinase signalling pathway and attenuates activation of caspases, considered to be upstream and downstream events in the apoptosis cascade, respectively; it also inhibits *N*-methyl-D-aspartate (NMDA) receptor and therefore may slow down the progression of neurodegeneration [32,192,197]. Overall, ginseng is a well-known 'anti-ageing herb' due to its multidisease stage intervention properties and multiple protective mechanisms [32].

In another study, the *in vitro* antioxidative and anti-inflammatory effects of BIOGF1K, a compound K-rich fraction isolated from the root of Panax g*inseng,* were accessed, being observed a significant suppression of IKKβ and TBK1, involved respectively, in the transcriptional regulation of NF-κB and IRF3 [198]. Moreover, the microbial transformation of ginsenoside Rb1, Re and Rg1 increased their anti-inflammatory properties via lipopolysaccharide-stimulated murine RAW 264.7 macrophages and even xylene-induced acute inflammatory model of mouse ear oedema [199]. Further, in another study, it was shown that pre-treatment with total saponins extracted from ginseng remarkably inhibited NO production through suppression of iNOS expression. Moreover, saponins extracted from ginseng considerably decreased IL-1β production both in LPS-induced TNF-α and in LPS-induced RAW 264.7 cells. It was reported that NF-κB could be translocated

from the cytosol to the nucleus, while the pre-treatment with saponins from ginseng could stimulate the sequestration of NF-κB in the cytosol, through the inhibition of κB degradation, and therefore suggest that saponins extracted from ginseng could be promising therapeutic agents for the treatment of inflammatory diseases associated with macrophage activation [200].

Rosmarinus officinalis *L. (English name: Rosemary; Family: Lamiaceae).*

Rosmarinus officinalis, commonly known as rosemary, belongs to the Lamiaceae family. It is a woody perennial native plant from the Mediterranean countries, generally spread in the European region. Hydroalcoholic extracts of rosemary have been identified by the European Food Safety Authority as safe [201], and therefore, their administration is licensed as a natural preservative and antioxidant in foods. Rosemary is used worldwide for several purposes, due to its useful properties such as antispasmodic [202], anti-inflammatory [203], antinociceptive [204], hepatoprotective [205] and diuretic [206], directly connected with the active constituents present in leaf extracts [207]. The most commonly identified compounds are monoterpenes (essential oils), diterpenic phenols (carnosol, carnosic acid, rosmanol, isorosmanol and epirosmanol), triterpene acids and flavonols (oleanolic acid, ursolic acid and betulinic acid) and phenolic acids (rosmarinic acid) [207–210]. Carnosic and rosmarinic acids, as well as carnosol, are the most important and potent antioxidant compounds present in rosemary, being useful as protectors against free radicals [211–214]. Besides, the hydroalcoholic extract of rosemary leaves could inhibit the activity of acetylcholinesterase (AChE) and butyrylcholinesterase (BChE), leading to an improvement of impaired memory in rats [215]. Also, rosemary polyphenols increased cholinergic activities in PC12 cells due to PI3K/Akt and ERK1/2 pathways [216,217]. Therefore, cholinergic activities of rosemary extracts play an important contribution in pain signalling via cholinergic system regulation [218]. The selective regulators of α7 [219] and α9α10 [220] nAChR subtypes could alleviate nerve trauma-stimulated pain in rats and inhibit nervous system derangement that underlies neuropathies. Moreover, this plant also exhibits anti-ageing effect [52], acting the diterpenoids carnosic acid, carnosol, rosmanol and epirosmanol as efficient inhibitors of superoxide anion production in the xanthine/xanthine oxidase system. At concentrations of 3–30 μM, these diterpenes completely inhibited mitochondrial and microsomal lipid peroxidation induced by NADH or NADPH oxidation. Further, carnosic acid also protects red cells against oxidative haemolysis. Therefore, these phenolic diterpenes have shown to be effective in protecting biological systems against oxidative stress [213,221]. Finally, the ethanolic extract from rosemary and specifically rosmarinic acid are well recognized to be effective in inflammatory disorders and pain relief, mainly through regulation of neuroinflammation, suggesting their potential application in different neurological disorders associated with inflammation [222].

Schizandra chinensis *Baill (English name: Schisandra; Family: Schizandraceae).*

Schizandra is a plant species whose fruits have been widely used in traditional and modern Chinese medicine [223]. Its fruits present a rich chemical composition, in which dibenzo [a,c]cyclooctadiene lignans are the most important components [224]. The plant material has a potent anti-ageing activity being applied in PD [154,223]. Both schisandrol and schisandrin B, at 1.0 mmol/L, inhibited gossypol-induced superoxide anion generation in rat liver microsomes [224]. Specifically, schisandrin B suppressed *in vitro* lipid peroxidation induced by carbon tetrachloride in hepatocytes, while schisandrol scavenged oxygen radicals in human neutrophils, induced by tetradecanoylphorbol acetate [82,225]. Furthermore, treatment with schisandrol, schisandrin C and schisandrin B, at 1.0 mmol/L, inhibited lipid peroxidation in rat liver microsomes [82]. The release of glutamate pyruvate transaminase (GPT) and lactate dehydrogenase was also reduced, thereby increasing hepatocyte viability and integrity of hepatocyte membrane [226]. Schisandrin B, at 10 mmol/L, inhibited NADPH oxidation in mouse liver microsomes incubated with carbon tetrachloride [227,228] while at 110.0 μmol/L inhibited oxidation of erythrocyte membrane lipids induced by ferric chloride *in vitro* [225,229]. On the other hand, the inhibitory effects of schisandra extract on acne-related inflammation and UV-B-irradiated photo ageing revealed that it could dramatically alleviate the inflammatory responses in HDF cells, indicating its promising effects as a potent and efficient agent for acne therapy and photoaging prevention [230]. Also, the highly oxygenated triterpenoid schinchinenlactone D, isolated from roots of schisandra, demonstrated prominent anti-inflammatory properties [231]. Moreover, it was also demonstrated that plant-derived essential oil from schisandra pulps and seeds, rich in monoterpenes and sesquiterpenes, present modest antioxidant, antibacterial and cytotoxic activities [232]. On the other hand, it has been reported that PPAR-γ activation could be regulated by schisandrin B (SchB), a dibenzocyclooctadiene lignan isolated from *Schisandra chinensis,* which exerts anti-inflammatory action against LPS-stimulated BV2 microglial inflammation [233]. Moreover, SchB could inhibit TNF-α and IL-8 production in LPS-induced human umbilical vein endothelial cells and control LPS-stimulated VCAM-1 and ICAM-1 expression; SchB also inhibited NF-κB activation induced by LPS and improved Nrf2 and HO-1 expression in a concentration-dependent manner. Further, the inhibition of TNF-α and IL-8 production via SchB could block by transfection with Nrf2 siRNA [233]. On the other hand, it was reported that schinlignan D and (+)-schisandrol B from *Schisandra chinensis* fruits could suppress PCSK9 protein expressions, also exerting a critical role in LDL cholesterol metabolism, mainly acting as LDL receptor degradator [234]. In another study, selenizing schisandra polysaccharide (sSCP) demonstrated significant antioxidant activity in hepatocyte from chicken embryo [235]. The sSCP acted as a selenium-rich source of natural antioxidants that could dramatically give hepatocyte protection due to oxidative damage induced by hydrogen peroxide (H_2O_2). The protective effect might be

attributed to regulation of the expression of protein in mitochondrion dependence apoptotic and MAPKs signalling pathways. Also, kadsuphilactone B, a nortriterpenoid extracted from schisandra fruit, stimulates caspase-dependent apoptosis in human cancer cells via the modulation of Bcl-2 family protein and MAPK signalling [236]. In the same line, it has been demonstrated that lignans from petroleum ether fraction of schisandra fruits alleviate cognition disorders and attenuate brain oxidative damage stimulated by D-galactose in rats, suggesting their potential application in ageing-associated neurodegenerative diseases [237]. Schisandra extract has also shown to reduce non-alcoholic fatty liver by inhibiting ER stress in tunicamycin- or palmitate-treated HepG2 cells *in vitro*. Meanwhile, *Schisandra* inhibited alcoholic fatty liver accumulation in tunicamycin-injected mice or high-fat diet (HFD) in obese mice by inhibiting glucose-regulated C/EBP homologous protein (CHOP), X-box-binding protein-1 (XBP-1) and protein 78 (GRP78). In overall, *Schisandra* could be a potential protective agent against ER stress-induced human diseases [238].

Seaweeds

Seaweeds are rich sources of minerals (including sodium, calcium, potassium and phosphorus) and vitamins (such as A, B1, B2, B5, B9, B12, C, D and E vitamins) [239], also representing one of the primary sources of essential amino acids for health maintenance [240]. Moreover, there are more than 54 different trace elements in seaweeds, which are essential for human physiological haemostasis, and this content is significantly higher than what is present in terrestrial plants, including vegetables [240,241]. Seaweeds are traditionally used in Chinese medicine in the treatment of a wide variety of disorders, among them enlarged thyroid glands, liver diseases, cysts, swelling and phlegm. A study using 13C-NMR spectroscopy revealed that the primary antioxidant active compound present in acetone extract from *Hijikia fusiformis*, a common edible seaweed, is fucoxanthin [242]. In fact, fucoxanthin is the main marine carotenoid present in brown seaweeds that can protect against oxidative stress stimulated by UV-B radiation [243]. Moreover, two metabolites from fucoxanthin, namely fucoxanthinol and halocynthiaxanthin, have shown to exert numerous biological functions, among them antioxidant effects, acting both as free radical scavengers and singlet oxygen quenchers [244]. Also, fucoxanthin isolated from *Myagropsis myagroides*, widely known as brown algae, can suppress both iNOS and COX-2 mRNA expression, at the same time that decreases the release of TNF-α, IL-1β and IL-6, and even mRNA expression levels, in a dose-dependent manner. Besides, fucoxanthin could also inhibit oxidative stress stimulated by retinol deficiency, through regulation of Na^+Ka^+-ATPase, and CAT and glutathione-*S*-transferase enzymes activity, in rats both at the tissue and microsomal levels [245]. All these facts suggest that fucoxanthin could be a promising therapeutic remedy to apply in different kinds of inflammatory diseases [240,246]. Promissory antioxidant effects have also been stated by seven seaweeds from Madeira Archipelago, widely known as chlorophyte (*Ulva lactuca*), phaeophyte (*Zonaria tournefortii*) and rhodophytes (*Galaxaura rugosa, Asparagopsis taxiformis, Nemalion elminthoides, Grateloupia lanceola, and Chondrus crispus*) [247]. Moreover, *Porphyra tenera*, which are the most common edible red seaweeds in Asia, have shown to exhibit potent antioxidant activity, suggesting their potential use for cosmetic and food industries [248].

Grapes, Red Wine and Resveratrol

Resveratrol, notoriously present in grapes, red wine, peanuts, berries and other traditional medicines, [249] is a stilbene with presumptive anti-ageing properties [250,251]. The effect of this specific phytoalexin ameliorated cognitive impairment and neurodegeneration subsequent to senescence [252,253] and prevented further manifestations related to ageing [254,255]. In AD, experiments on mesenchymal stem cell transplantation using human umbilical cord-derived mesenchymal stem cells (hUC-MSCs) in a mouse model showed that the cotreatment with resveratrol enhanced the expression of the survival markers SIRT1, PCNA, p53, ac-p53, p21 and p16, promoting neurogenesis in hippocampal regions and inhibiting apoptosis [256]. The role of resveratrol in AD has been extensively reviewed [257–259]. This phenolic compound is also able to further prevent neurodegenerative diseases such as dementia [260] and PD [261]. In fact, wine stilbenes are formidable antioxidant molecules able to counteract metabolic disease and cardiovascular disorders [262–264]. To date, research has strong evidence to support the idea that a single dose of resveratrol can induce beneficial physiological responses and improve clinical outcomes from ageing-related pathologies [265]. Recently, it has been demonstrated that resveratrol alleviates ageing-associated metabolic phenotypes through the restriction of camp phosphodiesterases [266].

Concluding Remarks

Although the comprehension about the detailed ageing-related mechanism is still limited, several cellular and molecular pathways were already stated as being involved in this process. Up to the moment, cellular ageing can be stimulated through induction of tumour suppressor genes, telomere shortening and oncogenes, chronic inflammation, oxidative stress and ultraviolet irradiation. In fact, it has been documented that cells are undergoing ageing present increased levels of intracellular ROS, an over-expression of NF-κB transcription and hyperactivity of the inflammatory cytokines, such as TNF-α, IL-1β and IL-6. Therefore, chronic inflammatory process and oxidative stresses may be conceived as the most important risk factors underlying age-related diseases and ageing process. On the other hand, natural matrices have received growing attention while promising sources of biologically active components, among them antioxidant and anti-inflammatory molecules. Several investigations have been performed evaluating some plants, vegetables, fruits and even seaweeds,

widespread in nature, presenting all of them a rich chemical composition in terms of antioxidants sources, including vitamin A, C, E, carotenoids, phenolic compounds and other bioactive molecules that have a great ability to prevent free radical damage and to reduce the risk of chronic diseases. Many flavonoids and phenolic acids can prevent ageing-related damage, through their interaction with the signalling machinery and modulate cell survival. Interestingly, the most common molecular target of flavonoids and phenolic acids contained in the aforementioned plant extracts is the Keap1-Nrf2-ARE regulatory pathway. Inducers of the indirect antioxidant defence system, they are either Michael acceptors or can be metabolized to reactive electrophiles capable to alkyl cysteine thiols in Keap1 and/or can induce the formation of cytosolic ROS resulting in the release of Nrf2, followed by activation of transcription gene through the ARE, leading to the formation of cytoprotective proteins. For certain aspects, this is considered the most important mechanism for controlling oxidative stress in the human body, and not so much the direct antioxidant effect, which is the main mechanism of action that has been focused in this Mini Review. Besides, the major flavonoids, such as quercetin, luteolin, apigenin, which can be widely found in medicinal plants, also exert their activity through counteracting apoptosis in healthy cells and promote the same in cancer cells, inhibiting NF-κB and activating FOXO-3, AMPK/mTOR and sirtuin signalling (pro-survival and anti-ageing). All these actions culminate with the regulation of metabolism, energetic balance, immunity and senescence, also promoting autophagy rather than apoptosis. These bioactive molecules are better represented and bioavailable in plant-derived food products rather than nutraceuticals (diet supplementation), a direct reason to promote healthy dietary habits rather than supplementation panels. Anyway, and despite the existence of a huge deal of reports showing newly published evidence about anti-ageing plant extracts, further insights are needed to improve the knowledge and to incite the use of these natural compounds.

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