Chapter 4
The Role of Polyphenols in Menopause

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Key Points

- Menopause gives rise to an increase in the rate of the ageing process, thus causing premature ageing.
- Oxidative stress occurs with menopause-related loss of oestrogens, this being responsible for premature ageing and much their of its associated physiological deterioration.
- Polyphenols are a group of pigments widely distributed in plants and are responsible for colouring. Besides, they play a protective role due to their antioxidant activity.
- Antioxidants, concretely polyphenols, can decrease the oxidative stress situation during menopause.
- Diets rich in polyphenols, especially flavonoids such as soy food and tea, can decrease the physiological consequences and symptoms of menopause, improving the state of health.
- Diets and supplements containing flavonoids such as isoflavones (phytoestrogens) could be an alternative to the pharmacological treatments frequently prescribed for menopausal and postmenopausal women.
- Since polyphenols improve immune system function, which is a marker of health, biological age and a predictor of longevity, the ingestion of these antioxidants could aid in slowing down the ageing process during menopause.

Keywords Polyphenols • Ageing • Menopause • Oxidative stress • Antioxidants • Immunosenescence

Abbreviations

ER	Estrogen receptor
CAT	Catalase
GPx	Glutathione peroxidase
GSH	Reduced glutathione

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GSSG	Oxidized glutathione
HRT	Hormonal replacement therapy
Mn-SOD	Mn-Superoxide dismutase
ROS	Reactive oxygen species
TNFα	Tumor necrosis factor alpha

Introduction

The role of polyphenols in menopause can be understood in the context of the ageing process and its characteristics. Ageing may be defined as a progressive and general impairment of the functions of an organism that leads to a lower ability to adaptively react to changes and preserve homeostasis. This difficulty in preserving the homeostasis is the basis of the increase of age-related morbidity and mortality. Thus, although with ageing all the physiological systems are affected, the regulatory systems, namely, nervous, endocrine and immune systems, are those in which the age-related deleterious effects are most clearly shown [1, 2]. Moreover, these systems are intimately linked, the communication between these regulatory systems being mediated by cytokines, hormones and neurotransmitters through the presence of their receptors on the cells of the three systems. Because of this, it is currently recognised that there is a "neuro-endocrine-immune" system, which allows the preservation of homeostasis and therefore of health [3]. This system also suffers an age-related deterioration [2, 4]. In addition, the above mentioned age-related impairment of physiological functions is linked to a chronic oxidative and inflammatory stress (a progressive imbalance between endogenous antioxidant/anti-inflammatory and oxidant/pro-inflammatory compounds, with higher levels of the latter) affecting all cells and especially those of the regulatory systems [2, 5]. Moreover, we have proposed the theory of oxidation-inflammation in ageing, in which the deterioration of the immune system with ageing, which is termed immunosenescence, can be involved in the "oxi-inflamm-ageing" situation of the organism and thus modify its rate of ageing [2, 6, 7].

Ageing is also a very heterogeneous process and thus there are different rates of age-related physiological changes in each system or tissue of the organism and in the diverse members of a population of the same chronological age. This fact justified the introduction of the concept of "biological age", which determines the rate of ageing experienced by each individual and therefore its life expectancy, having a better predictive value for longevity than chronological age [2]. Thus, the biological age is related to the mean longevity, which can be defined as the mean of the time that the members of a population that have been born on the same date live. Subjects of a population with a higher rate of ageing show an older biological age and a shorter lifespan. Although currently it is impossible to increase the maximum longevity (the maximum time that a subject belonging to a determined species can live), which is fixed in each species, the mean lifespan of individual organisms shows marked variability and can be increased by determined environmental factors. These allow the maintenance of good health and the approach to the maximum lifespan in good condition, this being in humans presently about 75–85 years in developed countries. In order to determine the "biological age" the parameters that change with age and show the tendency to a premature death should be analysed [8]. Since a positive relation has been shown between the good function of immune cells and longevity [9, 10], we have proposed several immune function parameters as adequate markers of "biological age" and therefore as predictors of longevity [2]. Moreover, the redox situation and inflammatory state of the immune cells are related to their functional capacity and to the lifespan of a subject. Subjects with a higher oxidative and inflammatory state in their immune cells show a worse function of these cells and die before their counterparts [2]. In addition, a confirmation of the central role of the immune system in oxi-inflamm-ageing is that several lifestyle strategies such as the administration of adequate amounts of antioxidants in the diet and physical and mental activity, improve the functions of immune cells, decreasing their oxidative and inflammatory stress, and consequently increasing the longevity of individuals [7].

If the ageing process has as its base an oxidative stress situation, an imbalance with higher amounts of oxidants and lower amounts of antioxidants [2, 11], it is logical that the incorporation of antioxidant compounds would recuperate the balance of oxidants/antioxidants needed for an appropriate cell function [1, 2, 7]. In fact, antioxidants are compounds that protect cells against the damaging effects of reactive oxygen species (ROS). These oxidant molecules, although necessary for many cell functions, can cause, if they are present in excess, damage to proteins, lipids and DNA [2, 11]. The antioxidant compounds and antioxidant enzymes are mainly responsible for the neutralisation of this excess of ROS avoiding their noxious effects on cells [1, 2, 7, 12].

In the context of the above, menopause, which is a depletion of a finite ovarian follicle supply [13] and therefore resultins in a complete failure of the ovary to produce hormones such as oestrogens, represents a situation of premature ageing. In fact, the cessation of the ovarian function at the time of menopause and the resulting hormonal changes are associated with many physiopathological reactions that are somehow related to those typically attributed to ageing, making women more prone to experience disease and disability [12]. Furthermore, many of the menopausal symptoms are linked to oestrogen loss and to high levels of oxidative stress [12]. Since oestrogens are antioxidant compounds and they also increase the expression of antioxidant defences of the organism [14], their loss in menopause could be the principal reason for the oxidative stress situation that accelerates the ageing process (Fig. 4.1).

Menopause marks the start of a new phase in the life of women. Although during the last decades of the twentieth century human life expectancy in developed countries has increased, the age at which women encounter their major age related hormonal change, that is, menopause, has remained essentially constant at about 50 years. Therefore, women spend nearly a third of their lives in an oestrogen-deficient state [12]. Due to this, research on menopause and especially on possible treatments to decrease its physiological consequences and symptoms, is very useful. Many of these studies have to be carried out in experimental animals such as mice and rats. Since rodents become anovulatory at a mature age (10–12 months old) but maintain a basal gonadal steroid secretion, in contrast to what happens in women [15], ovariectomy in these animals becomes the best tool to mimic human ovarian hormone loss, this being a "model of menopause".

Oestrogen Replacement Therapies and Plant-Derived Oestrogens

Since oestrogens have a regulatory role in many organs, the rapid decline in their circulating levels associated with menopause has many implications in a wide range of non-reproductive functions. They play a major role in the onset of menopausal hot flushes, bone loss, vaginal epithelium atrophy, acceleration of arteriosclerosis, skin ageing, immune dysfunctions, altered subcutaneous fat distribution, etc. [12]. Moreover, the psycho-emotional symptoms associated with menopause overlap depressive symptoms and include disturbed sleep, concentration, anxiety, irritability, frustration, mood lability, depression and fatigue.

Until recently, it had been generally accepted that the most effective treatment of menopausal symptoms was hormonal replacement therapy (HRT) with female sex hormones. Therefore, the fight against menopausal effects has been traditionally approached with HRT using exogenous oestrogens, whose administration causes rapid alleviation of menopausal symptoms and reduces the risk of heart disease and osteoporosis. Nevertheless, most women are still reluctant to use HRT mainly due to the possible increased risk of breast and endometrial cancer, vaginal haemorrhage, cardiovascular diseases, etc. [12]. Therefore, in view of these concerns about the safety of HTR, there has been a recent growing demand for alternative treatments that are able to protect against climacteric symptoms and minimise

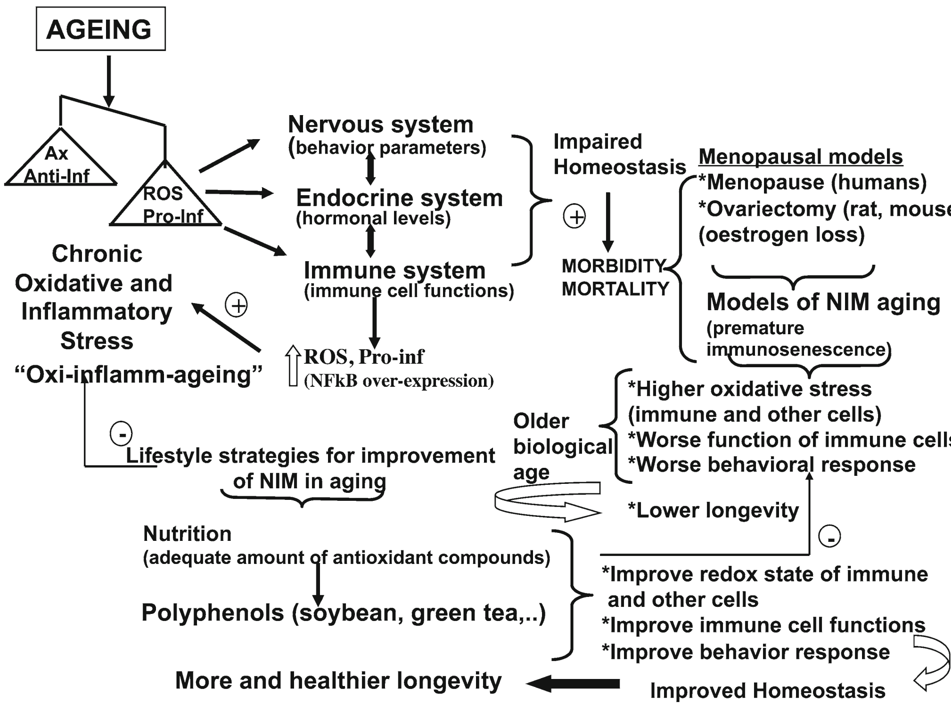

Fig. 4.1 Role of polyphenols in the ageing process. Ageing is a chronic oxidative stress condition affecting all cells, especially those of the regulatory systems, i.e. the nervous, endocrine and immune system and the communication among them. This explains the impaired homeostasis and the increased morbidity and mortality found in old age. In addition, we have proposed an "oxi-inflamm-ageing" situation in which the immune system is involved. Thus, this system, in its communication with the other homeostatic systems, can modulate the ageing process of the organism, concretely the rate of ageing. Menopause in humans and ovariectomy in rodents, as a consequence of oestrogen loss are useful models for the study of ageing of neuroimmunomodulation (NIM) since these subjects show high oxidative stress in the immune and other cells, impaired immune cell functions and behavioural responses. Thus, they show an older biological age and therefore more physiological deteriorations. An adequate nutrition, with ingestion of appropriate amounts of antioxidant compounds, such as plant-derived polyphenols, could be a good strategy of lifestyle to improve the immune functions, the redox state and the behavioural responses. Thus, these kind of diets could retard the ageing process, improving homeostasis and possibly increasing the longevity of the individuals. *Ax* antioxidant compounds, *Anti-inf* anti-inflammatory compounds, *ROS* reactive oxygen species, *Pro-Inf* pro-inflammatory compounds

at the same time the undesirable side-effects mentioned above. In this context, plant-derived oestrogens such as phytoestrogens, which are also antioxidants, seems to be a feasible alternative to the pharmacological treatments usually prescribed for menopausal and postmenopausal women [14].

Polyphenolic Antioxidants: Soybean and Green Tea Flavonoids

Polyphenols are a group of substances widely distributed in the plant kingdom. They are pigments and thus responsible for the colouring of plants, in which they play a protective role. They have many physiological actions, the best known being their antioxidant activity. Although their role in human health has been widely suggested this subject is very complex and needs much more research [16]. The functional activities of polyphenols are determined by their chemical structure. In this respect, they are characterised

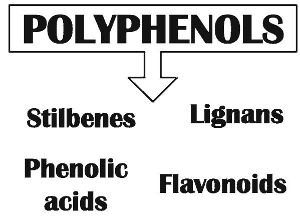

Fig. 4.2 Classification of the four main types of polyphenols

Table 4.1 The most important polyphenol compounds present in different foods

Group of polyphenols	Polyphenol	Food
Stilbenoids	Resveratrol	Grape skins and seeds, wine, nuts, peanuts
	Pterostilbene	Grapes; blueberries
Lignans		Seeds (sesame, sunflower, …); fruits (berries)
		whole grains (rye, oats, …); bran (wheat, oats, …)
Phenolic acids	Gallic acid	Tea; mango; strawberry; rhubarb
	Vanillin	Vanilla beans; cloves
	Curcumin	Mustard; curry
Flavonoids		
Anthocyanins	Pelargonidin	Raspberry; strawberry
	Cyanidin	Red apple; pear; cherry; plum; cocoa
Flavonols	Quercetin	Onions; tea; wine; apples; beans; cranberries
	Rutin	Citrus fruits; apricot; tomato; parsley; tea
Flavanols	Catechins	Tea; grapes; apple; cocoa; lentils
Flavanones	Naringenin	Citrus fruits
Isoflavones	Daidzein	Soy; peanuts; legumes
	Genistein	Soy; peanuts; legumes

by the presence of one or more phenol groups per molecule. Currently more than 8,000 polyphenols are known, but few plants containing an abundance of these compounds are common sources of food in the human diet [17]. These include the skin of red grapes, several fruits, vegetables, cereal grains, nuts and beverages such as tea, fruit juice, wine, coffee and chocolate [18]. Polyphenols have been classified into 16 groups according to their chemical structure, the most important being: stilbenes, lignans, phenolic acids and flavonoids (Fig. 4.2). The main stilbene is resveratrol, found primarily in grape skin, blackberry and peanuts. "Lignans" is a general term for a large family of compounds, whose main dietary source is linseed, but they are present also in whole-wheat flour, vegetables, fruits, coffee and tea. In the group of phenolic acids there are many polyphenols, which are derived from benzoic acid or cinnamic acid, the main sources of these compounds being cereals, vegetables, aromatic herbs, prunes and coffee. The group of flavonoids, which can be classified in several subgroups of compounds such as anthocyanins, flavonols, flavanols, flavanones and isoflavones, amongst others, are essential components of diet (Table 4.1). They have many biological properties, which contribute to gene and metabolism regulation as well as the scavenging of free radicals and thus they modulate cell cycle, proliferation and the redox state of cells. These compounds show antioxidant, anti-inflammatory, antithrombotic, antiviral, anticancerogenic and antiallergic properties as well as modulating immune system response [18]. Nowadays, many researchers focus on flavonoids, which appear to have played a major role in the successful medical treatments of ancient times, and their use has persevered up to now.

Isoflavones, one of the groups of flavonoids, are considered widespread in the plant kingdom, and they have been classically defined as phytoestrogens, for being compounds that exert oestrogenic effects. These isoflavones share structural features with oestrogens, and therefore they are able to evoke biological responses (Fig. 4.3). The presence of the phenolic ring enables isoflavones to bind

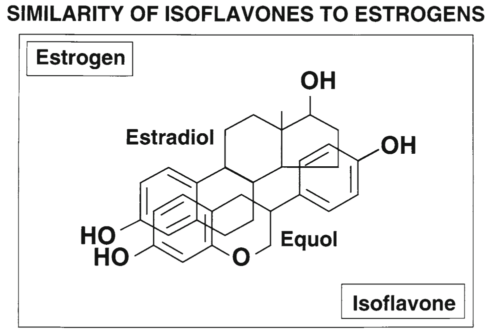

Fig. 4.3 Similarity of isoflavones to oestrogens. Chemical structures of equol (a type of isoflavone) and estradiol (an oestrogen)

both types of oestrogen receptors: ERα and ERβ. Unlike endogenous oestrogen, however, isoflavones bind with a much higher affinity to ERβ, which suggests that they may be more accurately defined as selective oestrogen receptor modulators capable of both pro-oestrogenic and anti-oestrogenic effects. However, they are much weaker than human oestrogens, with 10^2 to 10^5 times less activity [19].

Soy bean flavonoids: Isoflavones are mainly found in "*Leguminosae*" and are especially abundant in soybean (*Glycine max*.). Soybeans and their proteins have long been staples in the diets of the people of China and Japan, but their incorporation into the Western diet is minimal [20]. The number of foods sold in the West that have ingredients derived from soybeans has been increasing. Many of these have soybean oil, soy protein, or other ingredients serving functional roles in the food. Therefore, with increasing interest among consumers in dietary choices that help to improve health and reduce risk of disease, products in which soy is featured are quite readily available [20]. They have been found to have a wide range of hormonal and non-hormonal activities that provide plausible mechanisms for the potential health benefits of diets rich in these compounds. Among the soy food isoflavones, the best known and widely available are genistein, daidzein and glycitein [19].

Tea flavonoids: The most significant components of the tea plant are also polyphenols. The history of tea began over 5,000 years ago in ancient China. Currently, tea is the most popular beverage consumed by two-third of the world's population, well ahead of coffee, beer, wine and carbonated soft drinks [21]. Green, black and oolong tea are all derived from the *Camellia sinensis* plant, and the differences between these three varieties of tea lie in the differences in the manufacturing process. While green tea does not undergo fermentation, black tea is completely fermented, and oolong tea contains a mixture of both fermented and non-fermented leaves [21]. Green tea is favoured in Japan and China, and it has been considered a medicine and a healthy beverage since ancient times. Initial research on the benefits of green tea was carried out in these countries because of local customs, and traditional Chinese medicine has recommended this plant for headaches, body aches and pains, digestion, depression, detoxification, as an energizer and, in general, to prolong life. Although tea has been consumed for centuries, it has only recently been studied extensively as a health-promoting beverage that may act to prevent a number of chronic diseases and cancers [21–23].

Green tea leaves contain three main components, which act upon human health: xanthic bases (caffeine and theophylline), essential oils and, especially, polyphenolic compounds. The main green tea polyphenols are catechins, which constitute approximately 30 % of the dry leaf weight of the *Camellia sinensis* plant. Catechins contain a benzopyran skeleton with a phenyl group substituted at the 2-position and a hydroxyl (or ester) function at the 3-position. They consist of (−)-epicatechin, (−)-epicatechin-3-gallate, (−)-epigallocatechin and (−)-epigallocatechin-3-gallate [22, 23]. Its polyphenol content has made green tea attract a great deal of attention, as these compounds are strong antioxidants and present important biological properties, including chemopreventive efficacy, the induction of apoptotic cell death and cell cycle arrest in tumour cells, the reduction of plasma cholesterol levels, and, subsequently, the prevention of cardiovascular diseases and cancer [21, 22, 24].

Role of Polyphenolic Antioxidants in Menopause Effects

Organic polyphenols found in plants are the most abundant antioxidants in our diet. Many effects of flavonoids, which will be mentioned, are due to their antioxidant properties. They show the ability to scavenge ROS and they can neutralise free radicals since they are one-electron donors. Thus, they are capable of protecting unsaturated fatty acids in membranes against oxidation by ROS [19, 25]. Moreover, soybean isoflavones share with oestradiol the ability to up-regulate the expression of antioxidant defence genes such as glutathione peroxidase (GPx) and Mn-superoxide dismutase (Mn-SOD) [26]. In addition, tea catechins also display in the organism a crucial role as radical and oxidant scavengers, protecting the human body from oxidative stress [21, 22, 24]. Catechins are hypothesised to contribute, along with antioxidant vitamins (e.g. vitamins C and E) and enzymes (e.g. superoxide dismutase (SOD) and catalase), to the local antioxidant defence system [27].

Cardiovascular Diseases

The incidence of cardiovascular diseases rapidly increases in women after menopause thus resulting in an increased risk of heart disease [28]. Therefore, it could be suggested that endogenous oestrogens in premenopausal women provide protection against cardiovascular disease. Soybean isoflavones have been described as preventing atherosclerosis and reducing risk markers of cardiovascular disease [19, 25, 29]. Certain types of green tea cathechins may have the same preventive role when administered to postmenopausal women, as some studies suggest that their consumption is inversely related to the risk of coronary heart disease [21, 22, 27].

Regarding the most commonly described vasomotor symptoms during the menopausal transition, which are mainly hot flushes and night sweats, some authors have described soy phytoestrogens as good candidates for decreasing these symptoms [30], while others have found no effects [31].

Bone Health and Osteoporosis

Osteoporosis is a worldwide problem that affects mostly women, and it is clear that hormonal changes after menopause increase the rate of bone resorption, leading to greater risk of suffering this disease [28]. In this respect, it has already been described that soybean isoflavones improve bone mineral density in postmenopausal women, thus preventing such oestrogen-related bone loss [29]. Green tea consumption has also been associated with increased bone mineral density, one positive effect being the proliferation and improved activity of bone cells [27]. In fact, tea consumption has been described as protecting against the risk of hip fractures in people over 50 and as increasing bone mineral density in menopausal women. The same results have been obtained in ovariectomized rats, where bone mineral density increased after green tea polyphenol supplementation [22, 32].

Cancer Incidence

Disregulated proliferation appears to be a hallmark of increased susceptibility to neoplasia. Cancer prevention is generally associated with inhibition, reversion or retardation of cellular hyper-proliferation. Since advanced metastasised cancers are mostly incurable, an effort to control the process of carcinogenesis through chemoprevention has become an important, feasible strategy for cancer treatment. It is generally agreed that dietary flavonoids behave as general cell growth inhibitors. They have been demonstrated to inhibit proliferation in many kinds of cultured human cancer cell lines, and this mainly occurs through anti-aromatase, anti-proliferative and anti-angiogenic mechanisms [19, 29].

Numerous studies have also demonstrated that green tea and tea polyphenols possess a chemopreventive potential. Many of these effects are mediated by catechins, and this has been demonstrated in many different animal models of lung, skin, breast, oesophagus, prostate, rectal and liver cancers [21]. The results from all the above experiments indicate that tea offers a broad inhibitory role in the initiation, promotion and progression of carcinogenesis. However, the molecular mechanisms for these inhibitory actions are not fully understood. Possibly, these are most likely related to the antioxidant effects of the tea polyphenols, which protect DNA from damage and/or methylation, inhibit proteasome activity in tumour cells, induct apoptosis and inhibit tumour promotion-related events as well as angiogenesis.

Body Weight Control

Obesity has increased at an alarming rate in recent years and is now a worldwide health problem. Adipose tissue distribution is regulated by female sex hormones, so metabolic changes due to menopause lead to increased obesity in postmenopausal women [28]. In this respect, the effects of long-term feeding with tea catechins have been widely studied, suggesting a potential role of green tea in body weight control. Thus, green tea extracts may display thermogenic properties and promote fat oxidation, reducing or preventing body weight gain, together with visceral and liver fat accumulation [22, 27]. Furthermore, epidemiological observations and laboratory studies have shown that green tea has an effect on glucose tolerance and insulin sensitivity, increasing the activity of this hormone through an enhanced glucose uptake of adipocytes [27].

Cognition and Psycho-Emotional Symptoms

Oestrogens have been associated with cognitive and emotional processing since their receptors are present on neurons (on both dendrites and presynaptic terminals) and glial cells. These hormones have been reported to have beneficial effects on the nervous system, and it has been described that they can promote cognitive function when administered after the menopausal transition [33]. In addition, research using isoflavone supplementation in postmenopausal women, yields controversial results, with some studies suggesting that soybean isoflavones displayed a favourable effect on cognitive function, particularly verbal memory [34], whilst others describe no improvements or appreciable effects [35]. There are also reports that indicate that tea can improve neurologic and psychologic functions. Tea catechins possess divalent metal chelating, antioxidant and anti-inflammatory activities, penetrating the brain barrier and protecting against neuronal death in a wide array of cellular and animal models of neurological diseases [22]. Other components of tea, such as theanine, act as neurotransmitters in the brain and decrease blood pressure in animal models of hypertension. Moreover, this compound modulates brain serotonin and dopamine levels, thus improving memory, learning ability and affecting emotions [22]. Among age-associated pathologies and neurodegenerative diseases, green tea has been shown to afford significant protection against Parkinson's disease, Alzheimer's disease and ischemic damage [36].

Immune Function

The available data show that female sex hormones stimulate immune function, this being responsible of the usually better immune response of females than males in the mammalian species [2, 37–39]. As mentioned above, a great deal of research has shown that the ageing process is associated with a general impairment of immune function, commonly known as "immunosenescence", which has as its basis an oxidative stress situation [2, 6, 7]. Thus, we can understand how the oestrogen loss associated with menopause or ovariectomy accelerates immunosenescence in women and experimental animals, respectively. The consequences include impaired cellular and humoral immune responses and an altered oxidant/antioxidant balance, resulting in a pro-oxidative state [37–41]. Monocyte and macrophage functions such as the chemotaxis, phagocytosis and microbicidal capacities result dramatically altered as a consequence of ovariectomy (in experimental animals) or either premature ovarian failure (in women) [40, 42]. Lymphocytes are important effector cells whose activation is essential for the immune response, and among their key functions we can cite the chemotaxis and proliferative capacities and the NK activity, all three being severely impaired after menopause/ovariectomy [37–40, 43, 44]. In addition, it has been postulated that the oestrogen loss associated with the menopausal transition is directly linked to the higher levels of pro-inflammatory cytokines found in postmenopausal women [44]. Moreover, a marked overproduction of pro-inflammatory cytokines leads to immunosuppression [2]. In postmenopausal women and ovariectomised animals an increase in the oxidative imbalance has also been observed. In fact, these subjects show increased levels of oxidant such as oxidised glutathione (GSSG) and decreased levels of antioxidant such as reduced glutathione (GSH), which is the most abundant endogenous antioxidant, and constituting one of the first lines of defence against oxidation. As a consequence of this oxidative stress situation an increase in the oxidation damage to lipids, proteins and nucleic acids occurs [39, 41, 43]. Based on all the above, we suggested that menopause/ovariectomy is a situation of premature immunosenescence, and since ovariectomised animals also show senescence behavioural responses [40], they are prematurely ageing [39, 40] (Table 4.2).

In this respect, the administration of antioxidants, and concretely soybean isoflavones, to postmenopausal women and ovariectomised animals improves macrophage and lymphocyte functions such as those mentioned above (chemotaxis, phagocytosis, T-cell proliferation, NK activity, etc.) [38, 41, 43, 45, 46]. Moreover, in ovariectomised animals it has been recently described that the oral administration of a combined treatment of soybean isoflavones with green tea results in a stimulating effect of macrophage and lymphocyte activities [47] (Table 4.2). As previously mentioned, the structure of isoflavones resembles the steroid hormone 17β-oestradiol, being able to bind to the oestrogen receptors and acting though the same intracellular signalling pathways [19]. This could be the mechanism through which isoflavones exert their stimulatory effects on the immune cells, in a similar manner to oestrogens, due to the presence of their receptors in certain immune cells including T cells, monocytes and macrophages, natural killer cells and dendritic cells [48].

Green tea polyphenols (mainly catechins) have also been reported to play an immunomodulatory role in the organism. They inhibit endothelial exocytosis by limiting leucocyte adherence to the endothelial cells of the vessel walls increasing the synthesis of NO [49]. Regarding this, catechins present in green tea have been described as decreasing inflammation in a variety of animal models, including endotoxemia, asthma, autoimmune encephalitis and cystitis. They even limit infiltration of leucocytes into the skin of humans exposed to UV light. Regarding the molecular mechanisms that are responsible for such effects, it seems that they inhibit the activation of transcription factors (as NF-kB and AP-1) through the partial inhibition of the mitogen-activated MAP-Kinase (MAPK) cascade. This leads to a decrease in the expression of inflammatory gene products including lipoxygenase, cyclooxygenase, nitric oxide synthase and TNF-alpha. Catechins also induce apoptosis of several immune cells, which is another possible mechanism of its anti-inflammatory effects [49].

Table 4.2 Changes in function and oxidative-inflammatory stress parameters in immune cells from old and ovariectomised female experimental animals (mice and rats) versus adults and sham animals, as well as effects of a diet supplemented with antioxidants in old and ovariectomised animals

	Old animals	Ovariectomized animals	Antioxidant supplementation
Immune functions			
Mobility (chemotaxis) of macrophages	Decrease	Decrease	Increase
Phagocytosis capacity of macrophages	Decrease	Decrease	Increase
Digestion capacity (intracellular ROS)	Decrease	Decrease	Increase
Mobility (chemotaxis) of lymphocytes	Decrease	Decrease	Increase
Lymphoproliferative response to mitogens	Decrease	Decrease	Increase
Natural Killer (NK) activity	Decrease	Decrease	Increase
IL-2 release	Decrease	Decrease	Increase
Oxidant and pro-inflammatory compounds			
Extra-cellular superoxide anion	Increase	Increase	Decrease
Oxidised glutathione (GSSG)	Increase	Increase	Decrease
Oxidised/reduced glutathione (GSSG/GSH)	Increase	Increase	Decrease
Pro-inflammatory cytokines (TNFα; IL-6)	Increase	Increase	Decrease
Antioxidant and anti-inflammatory defences			
Reduced glutathione (GSH) levels	Decrease	Decrease	Increase
Superoxide dismutase (SOD) activity	Decrease	Decrease	Increase
Catalase (CAT) activity	Decrease	Decrease	Increase
Glutathione peroxidase (GPx)	Decrease	Decrease	Increase
Glutathione reductase (Gr)	Decrease	Decrease	Increase
Anti-inflammatory cytokines (IL-10)	Decrease	Decrease	Increase
Oxidative damage			
Malondialdehyde (MDA) (lipid peroxidation)	Increase	Increase	Decrease

In addition, it is of great relevance to notice that nutritional treatments with plant-derived polyphenols restore the oxidative balance with a decrease in the GSSG levels [41] and improve the redox status by trapping ROS and protecting against oxidative damage to lipid membranes, proteins and nucleic acids [22].

We have recently proposed an involvement of the immune system in the ageing process of the organism, concretely in the rate of ageing [2, 6, 7]. Thus, a worse immune function such as that accelerates occurs in a menopause/ovariectomy situation accelerates the ageing process. Nevertheless, the treatment with antioxidant polyphenols can be a good strategy to restore and even improve the rate of ageing.

Longevity

Longevity studies have been carried out on the Japanese population, which consumes green tea and soybean on a daily basis, and the results have shown a significant decrease in cancer as well as age-related conditions causing death. This has been found to be associated with the increased consumption of these products, especially in people over 79 years of age [22]. These results indicate that daily consumption of green tea in sufficient amounts would help to prolong life by avoiding premature death, particularly that caused by cancer [22].

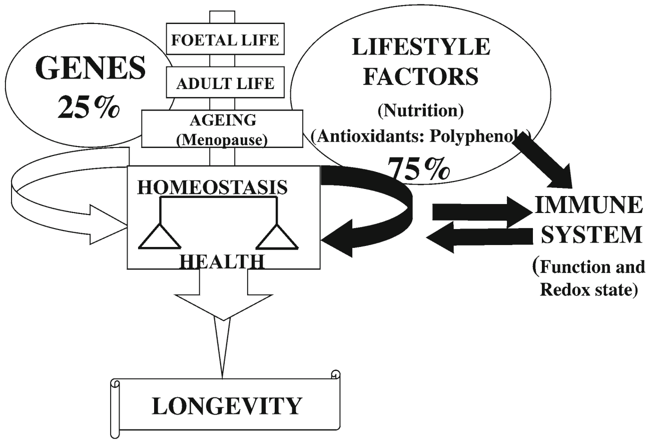

Fig. 4.4 How diet with appropriate amount of antioxidants, such as polyphenols, improves the ageing process and enabling a long and healthy mean longevity to be reached? The base of a functional longevity is the health maintenance, and this depends on preservation of homeostasis (the balance at all physiological levels). This health preservation depends approximately in a proportion of 25 % of the genes, but in a 75 % of the style of life and environmental factors. One of these factors of lifestyle is the nutrition and concretely the antioxidant compounds that we can take through diet. With ageing it is more difficult to maintain the homeostasis as consequence of deterioration of the regulatory systems. This loss of homeostasis is established at different rate in each subject, and this rate is the result of individual epigenetic mechanisms acting on genes from foetal life throughout the life of the subject. With the loss of oestrogens (menopause) females can accelerate the ageing process. Since the functions and redox states of the immune system are good markers of health and predictors of longevity, we have proposed their study in order to determine each particular rate of ageing and its response to changes in the style of life and environmental factors. Moreover, a younger immune system can be obtained with the ingestion of appropriate amounts of antioxidants and since the immune system is involved in the rate of ageing, this strategy of lifestyle can help achieve healthy longevity

Conclusions

Since it has been demonstrated that the immune system is an excellent marker of health, rate of ageing and predictor of longevity [2, 50], the impairment of this system in subjects with menopause/ovariectomy-related oestrogen loss shows with their accelerated ageing. In addition, the base of a functional longevity is health maintenance and this depends on the genes (approximately in a proportion of 25 %) and on the style of life and environmental factors (in a 75 %). The administration to aged subjects of adequate amounts of antioxidants in the diet improves several functions of immune cells, decreasing their oxidative stress, and consequently increasing the longevity of individuals [2, 6, 7] (Fig. 4.4). Thus, the replacement therapies in postmenopausal women with plant-derived polyphenols such as the ones present in soybean or green tea, constitute a promising tool to be applied. Despite all the results on these antioxidants described in the present chapter, more interventional trials are still required to reach definitive conclusions with respect their efficacy and safety in menopause transition. The next challenges to be faced will be to investigate on several physiological systems, especially the homeostatic systems, the effects of a wider number of possible diet-polyphenols, a wider range of doses as well as of the best design of administration, in order to optimise the beneficial effects of these compounds on health and longevity.

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