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Possible Role of Nrf2 in Oxidative and Inflammatory Processes During Menopause

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Additional information is available at the end of the chapter

Abstract

The increase in life expectancy leads to the possibility of development chronic diseases, from special physiological conditions as occurs in the menopause, which is defined as the permanent cessation of ovulation, marked by the end of menstruation. It has been related to decreased ovarian function that occurs around an age of 45 years. This event involves the reduction in estrogen production and may contribute to the development of chronic-degenerative diseases. Many diseases developed during menopause have been associated with oxidative stress, such as osteoporosis, hot flushes, cognitive impairment, insulin resistance, dry skin, obesity, and cardiovascular events. The knowledge about the participation of Nrf2 in diseases that occur during menopause is very limited. Here, only diseases such as osteoporosis, cardiovascular diseases and dry skin, which are present during menopause and its later stages have been described. The Nrf2 pathway involves the participation of PI3K/Akt, MAPK, and eNOS, which act as mediators for cytoprotection and antioxidation. Compounds such as equol, fitoestrogens, alkyl cathecols, or curcumin could be offered as options to antioxidant treatment, added the fact that they are present in fruits and vegetables which are rich in vitamins, minerals and calcium, thus including all the required nutrients for an adequate nutrition.

Keywords: menopause, cardiovascular diseases, osteoporosis, obesity, inflammation, Nrf2

1. Introduction

Menopause is defined as the permanent cessation of menstruation by an year in a row, by decreasing the estrogen production, as a consequence of ovarian dysfunction. It occurs between 47 and 55 years of age and during the transition, women experience multiple symptoms [1].

Postmenopause is divided into two periods; an early stage, which includes the first five years after confirmation, and a later phase, which starts five years after the onset of menopause and lasts until the end of life; although the latter overlaps with aging. It is important to consider stage of menopause the woman is, because the metabolic disorders begin and are susceptible to be modified, also the biological functions change with age, environment and the co-morbidities.

The end of the reproductive phase and the onset of menopause brings several metabolic disorders, such as frequent vaginal infections, dyslipidemia, weight gain, visceral obesity, hyperinsulinemia, insulin resistance, osteoporosis, glucose impaired tolerance, mild cognitive impairment, alter coagulation, atherosclerosis, hardening of arteries, hypertension, dry skin and mucous (burning mouth syndrome); in addition, night sweats, and mood changes [2].

Several of the aforementioned disorders have been linked to oxidative stress and inflammation. In recent decades, it has been recognized that oxidative stress causes aging and several pathological conditions. In this regard, the menopause has both conditions, the susceptibility to the development diseases related to oxidative stress and aging.

Central adiposity has been linked to insulin resistance (measured using HOMA: homeostasis model assessment) and oxidative stress (oxidized low-density lipoprotein, urinary isopros-tanes [PGF2a], protein carbonyls, and DNA damage), coupled with the transient accumulation of iron in postmenopausal women, which provide ideal conditions for an inflammatory and oxidant state, which all together increases cardiovascular risk. So reducing centralized fat mass and maintaining a favorable lipid profile, antioxidant status and iron status may be important in protecting postmenopausal women from atherosclerotic disease [3].

Coronary artery disease, has a higher prevalence in obese postmenopausal women (with high levels of malondialdehyde and lower superoxide dismutase), but is less observed in younger women [4, 5].

Arterial stiffening worsens across the stages of the menopausal transition, which seems to be mediated, by oxidative stress, particularly during the late perimenopausal and postmenopausal periods. Through a model of rapid arterial dilating by infusion of ascorbic acid, it was found that the postmenopausal women have minor vasodilation and higher oxidative stress [6].

Considering the significance of oxidative stress in several diseases, the research studies have been focused at nuclear factor of transcription, Nrf2; which is considered as the most important regulator of the antioxidant response. Nrf2 modulates expression of many genes (related to antioxidant enzymes, inflammatory processes, tissue remodeling, carcinogenesis, and cognitive impairment). The participation of NrF2 in menopausal events has been studied in relationship to mainly, the vascular system, components of metabolic syndrome, osteoporosis, and skin.

Cardiovascular system: Nrf2 is an important component in antioxidant defenses in cardiovascular diseases, such as atherosclerosis, hypertension, and heart failure. Nrf2 is also involved in protection against oxidant stress during the processes of ischemia-reperfusion injury and aging. However, evidence suggests that Nrf2 activity can attenuate or stimulate cardiovascular disease processes.

Oxidative stress is an important factor to the development of endothelial dysfunction, and it has described that the polymorphisms 653A/G (rs35652124), −651G/A (rs6706649), and −617C/A (rs6721961) are located in the promoter region of the gene encoding NRF2 (NFE2L2) and can participate in forearm blood flow (FBF) and forearm vascular resistance (FVR) depending on the ethnic group. For instance, in African Americans −653G variant allele carriers had significantly lower FBF and higher FVR. In other hand, in White Americans, −617A variant allele carriers had significantly higher FVR. Polymorphisms within the NFE2L2 promoter were associated with impaired forearm vasodilator responses in an endothelial-independent manner, suggesting an important role of NRF2 in the regulation of vascular function in humans [7].

Aldosterone activates and increases Nrf2, this effect depends on the mineralocorticoid receptor and oxidative stress. In vivo, Nrf2 activation has beneficial effects on high blood pressure caused by aldosterone [8].

Skin: It has been observed that skin of women turns dry, during menopause, which is also exposed to the reactive oxygen species generated during cell metabolism or by accumulation of fat below skin. It is known that skin cells expresses the transcription factor Nrf2, before menopause, but its expression in postmenopausal stage is unclear [9].

Osteoporosis: This is frequent in postmenopausal women. Recently findings show that this is caused by redox imbalance, even the bone marrow presents higher levels of markers of oxidative stress. An association between elevated hydroperoxides serum levels and reduced bone density in postmenopausal women [10] has been reported.

This chapter presents evidence for the expression of NrF2 in alterations or diseases in menopause associated with oxidative stress.

2. Metabolic disorders during menopause

Menopause is the cessation of the ovarian cycle, so it terminate ovulation and the reproductive stage ends in women. This is because over the years, total ovogonias are reduced in the ovary and most become refractory to the action of the pituitary gonadotropins. As a result, the levels of estradiol are decreased; at the beginning of menopause, the menstruation become irregular and then disappears. The symptoms of menopause are different, depending on the age, culture, preexisting morbidities, diet, and ethnicity [11].

Hormone depletion can increase the vulnerability of tissues that are estrogen-sensitive to the development of diseases. The principle symptoms of menopause include vasomotor symptoms such as night sweats, urogenital atrophy, osteopenia, and osteoporosis, psychiatric

disorders, sexual dysfunction, dryness of skin and mucous, cardiovascular disease, cancer, and obesity [2]. Other symptoms are polyuria, fatigue, weakness, irritability, blurred vision, thirst, and increased appetite [12].

The most common metabolic disorders are dyslipidemia, glucose intolerance, insulin resistance, hyperinsulinemia, and type 2 diabetes [13].

The lipid metabolism disorder is characterized by high levels of low density lipoprotein (LDL) and low levels of high-density lipoprotein (HDL) [14]. This disorder makes the woman vulnerable to cardiovascular diseases (CVD) [15]. This is due to the fact that LDL is more susceptible to oxidation reaction, and thus are captured by the macrophage, which triggers an inflammatory process that favors the formation of the atheromatous plaque. Moreover, HDL has the opposite effect, but is diminished in menopause, and the protective effect is lost. Same situation is observed in induced menopause, after a bilateral oophorectomy [16].

Another altered parameter is the plasma glucose concentration. It has been reported that a high incidence of insulin resistance is a risk factor for developing diabetes. The other factors that cause type 2 diabetes are obesity, sedentary lifestyle, poor eating habits, smoking, and alcoholism [17].

After menopause, the incidence of obesity increases, even the body composition changes, from ginecoide type (accumulation in hips and thighs), passes to android type (deposit trunk). Although if the premenopausal women has android-type obesity, they have the same levels of triglycerides and insulin, and risk of metabolic syndrome [18].

The effect of polycystic ovary (PO) syndrome on menopause disorders is controversial. There are studies that support it as an additional cardiovascular risk even during premenopausal phase, because these patients develop early arterial disease, and have a higher prevalence of hypertension, dyslipidemia, incidence of myocardial infarction, thickness of the intima-media, arterial stiffness, and endothelial dysfunction [19]. This is aggravated if a woman has diabetes and dyslipidemia [20]. On the other hand, another study indicates that these patients had fewer climacteric symptoms than controls [21], further have insulin resistance attenuated. But, there were reports that did not find differences between postmenopausal patients with or without pre-polycystic ovary syndrome [22].

Adipocytes (fat cells) secrete leptin, adiponectin, resistin, and ghrelin; the interaction between them modulates the energy balance, appetite, insulin sensitivity, number and size of adipocytes, among other actions that result in the metabolism of fat tissue and the production itself. Additionally, the adipose tissue can synthesize androgens and estrogens, proinflammatory cytokines that may have effects on blood pressure, inflammation process, and lipoprotein metabolism [23].

It has been determined that postmenopausal women with metabolic syndrome have higher levels of serum testosterone levels and protein binding steroid hormones (SHBG)], leptin, resistin, insulin, and HOMA index and low levels of adiponectin. Additionally, the presence of higher level of interleukin-6 (IL-6), and lower level of urokinase plasminogen activator (uPA) were also documented [5]. A side effect of metabolic syndrome is the female sexual dysfunction, in both pre- and post-menopausal women [24].

3. Estrogens and Nrf2

Most disorders and diseases developed during menopause are related to hormonal depletion and the increase in oxidative stress, so that it is easy to assume that estrogens have antioxidant properties. 17β-estradiol is the more potent estrogen, which has been described as capable to inhibit the lipoperoxidation in brain homogenates in rat, induced by Fe^{3+}, due to its lipophilicity and polycyclic groups [25]. Also, this hormone induces the expression of superoxide dismutase, glutathione peroxidase and glutathione S-transferase in peripheral blood mononuclear cells in women who underwent total hysterectomy with bilateral salpingo-oophorectomy and treated with estrogens as HRT [26].

Estrogens have many biological effects, so it is interesting to study compounds of dietary origin with a similar effect. Recently, analysis of molecules similar to estrogens, which are present in vegetables, legumes or fruits, has gained importance due to its possible antioxidant properties as in the case of equol, which is a metabolite of genistein and daidzein, both present in broccoli. The equol has two isomers, the form S-(−)equol and R-(+)equol, of which the first is the most active, but only 30–50% of the population is capable to produce it. The isomer S-(−) can bind to estrogen receptor beta, inhibit MEK, activate eNOS and AMPK and act as antioxidant. It has been observed that this molecule releases nitric oxide, activates Nrf2 and as a consequence promotes the expression of antioxidant genes, before being mediated by the PI3K/Akt pathway, which has been implicated in protection against cytotoxicity, endothelial dysfunction mediated oxidative stress.

In HUVEC cells, S-(−) equol is capable to bind to the membrane estrogen receptor (GPR30) and to activate Nrf2and eNOS through Akt [27].

4. Proxidant conditions during menopause

Iron accumulation: The cessation of menses contributes to accumulation of iron in the body, resulting in elevated serum ferritin. In postmenopausal women, the consequences of this fact are controversial. For example, some studies have reported a direct relationship between iron and atherosclerosis, cerebrovascular risk, oxidation of low density lipoproteins, high cholesterol, inflammation, insulin resistance, and metabolic syndrome [28].

Changes of corporal composition: Greater waist circumference was associated with high oxLDL which is independent of BMI, suggesting that the same abdominal fat mass may induce oxidative stress, more than the general mass fat. Another study reported that the waist/hip ratio is directly associated with LDL-C and lipid oxidation, and inversely with HDL-C, and protein carbonyls or 8-OHdG, injury indicators [29, 30].

Studies carried out in pre and postmenopausal women, found that those who are obese have a higher concentration of malondialdehyde; but the concentration of superoxide dismutase enzyme was similar in all of cases [4].

5. Nrf2 and pathologies related to oxidative stress

5.1. Osteoporosis

Epidemiological studies show that the majority of postmenopausal women are affected by skeletal fragility caused by an excessive bone resorption [24]. Earlier, it was closely related to oxidative stress. It is due to reduction of estrogen plasma levels and its antioxidant action on bone [9, 31].

The estrogens activate Nrf2, which regulates the expression of antioxidant enzymes in bone marrow. As a consequence of this reduction, Nrf2 decreases and leads to the activation of the receptor activator of nuclear factor κB (RANKL), which promotes osteoclastogenesis [32, 33]. Moreover, the Nrf2 deficiency induces a reduction in the ratio cortical area/total area, higher trabecular spacing, osteoclast surface in ovariectomiced mice and Nrf−/− mice [34].

5.2. Cardiovascular diseases

In humans, it has been described, three single nucleotide polymorphisms within the promoter region of the gene encodes NRF2 (NFE2L2) (−653A/G, −651G/A, and −617C/A). The −617A variant allele has major risk to develop lung injury, mediated by oxidative stress. The NFE2L2 polymorphism has been associated to diseases with oxidative stress and inflammation, both mediated by drugs [35].

A study showed that Africans Americans carriers of −653G variant allele, have lower forearm blood flow and higher forearm vascular, resistant; in contrast with White Americans. With respect to −651G/A there were no differences between two populations. In White Americans, the −617 polymorphism carriers have lower forearm blood flow (FBF) and higher forearm vascular resistance (FVR) [6]. In clinical studies, it has been observed that African Americans have a higher prevalence of hypertension and the decreased endothelium compared to the white population. This predisposition to increased vascular resistance in African Americans leads to increased shear stress on endothelial cells, which activates NAD(P)H oxidase and mediates the formation of the oxygen species in the vascular system [36]. Accordingly, the NADPH oxidase equilibrium nitric/superoxide/peroxynitrite oxide in endothelial cells is shifted in favor of the reactive oxygen species in African Americans, which is associated with a deterioration of the vasodilator capacity [37].

The negative effects of pollution, promotes an oxidative state, which is associated with cardiopulmonary diseases. The solid matter alters lung, cardiovascular, nervous system functions, resulting in vascular inflammation, vascular dysfunction, and increased oxidative stress [38–41]. Nrf2 participates in resistance to hyperoxia-induced lung injury, it is also important in the response of epithelial cells particle exposure. The data suggest an alteration in the autonomic regulation of cardiac function during hyperoxia, which is modulated by Nrf2. Therefore, these changes may have important implications FVR for susceptibility to adverse cardiac response outcomes during oxidant exposure [42].

Oxidative stress is a component of the pathogenesis in many cardiovascular diseases, and atherosclerosis, hypertension, heart collapse, and ischemia/reperfusion injury. The sources of

reactive oxygen species (ROS) that lead to oxidative stress due to inefficiencies in the chain of mitochondrial electron transport, NADPH oxidase and xanthine oxidase everywhere, and the metal ions released during cell lysis [43–45].

Atherosclerosis is an inflammatory disease characterized by endothelial filtration and accumulation of oxidized lipoproteins of low density (LDL), physical damage to the endothelium (e.g., turbulent flow of blood, hypertension and/or smoking).

Susceptibility to atheroma formation is not uniform throughout the vascular system, which can be generated by shear stress generated by oscillatory flow, not unidirectional, and turbulent blood flow, which occurs, for example, at junctions or vessel branching points, which are the most susceptible. Conversely, atheromas are less likely to form in the vascular regions with unidirectional laminar blood flow. It is known, that shear-stress laminar flow into blood vessels stimulates the release of nitric (NO) oxide, but when the flow is oscillatory, the stenosis or branch vessels are developed. This reduces NO production and increases superoxide release, leading to oxidative stress and the progression of atherosclerosis. Laminar flow promotes activation of Nrf2, and the oscillatory blood flow suppresses activation of Nrf2, resulting in a favorable environment for atherogenesis [46].

It is increasingly evident that Nrf2 is important for long-term vascular integrity and endothelial functioning, for example, sustained release of NO and protection from apoptosis [47].

The levels of matrix metalloproteinase 9 (MMP9) are linked to plaque destabilization, which produces acute constriction of blood vessel flow and sudden cardiac or events. The atheroprotective effect of HO-1 may be associated with the partial deletion MMP9 to maintain or improve the stability of the plate, avoiding a coronary event or acute and potentially fatal brain [48, 49].

However, the effect of deficiency of Nrf2 on atheromatous plaque are controversial; for example, a study indicates that deficiency of ApoE and Nrf2 (*ApoE−/−Nrf2−/−*)in mice fed with fat diet had minor area of atheromatos plaque and lower softening arterial [50, 51].

Ischemia-reperfusion has been observed in processes such as thrombosis or vasospasm, leading to inflammatory and oxidizing conditions [52]. These conditions promote expression of the Nrf2 oxidant, as evidenced in cell culture cardiomyocytes rat after ischemia-reperfusion cycles, that increased mRNA and protein mRNA of Nrf2. If ischemia is lower, then Nrf2, can attenuate oxidative stress.

During an increase in blood pressure, the renin-angiotensin system increases the concentration of free radicals, also they contribute to this and NADPH oxidases, NOX 1 are known to activate Nrf2 [53].

It has been documented that the diseased myocardium increases oxidative stress, may increase susceptibility to arrhythmia by a direct toxic effect of increased necrosis and apoptosis. In a model overload it was found that the increased expression of Nrf2 decreased myocardial hypertrophy, cardiac fibroblasts and ROS production, the latter, most likely by modulating the activity of Nox4 [54]. Although the sharp increase in the Nrf2 content is cardioprotective, to

modulate the production of ROS, apparently chronic activation may have a contrary effect called "reductive stress", so more studies on their impact is required.

ERK's role is controversial, on the one hand it has been reported that oxidative stress index expression of ERK, and participates in Nrf2 signaling, but studies indicate that activation of ERK leads to apoptosis. Studies in rats and monkeys shown the reduction of the expression of several components of the signaling pathway Nrf2 [55–57].

5.3. Skin

Estrogens modulates several actions in skin, in example, they promotes the keratinocyte proliferation, the I and II collagen expression, and represents an antioxidant defense; but when menopause begins, the skin suffer many changes, principally, dryness, becomes thinner, decreased its elasticity, the collagen content is lower, and the vascularity is diminished [58]. Cells are exposed to physical, chemical, mechanical and thermal factors, which can develop oxidative stress, leading to changes in skin appearance, modifying cells and potential malignancies [8].

Nrf2 is expressed in all cell lines of the epidermis. It binds to promoter regions known as elements of antioxidant response (ARE) that transcribed genes of cytoprotective proteins and antioxidants like glutatión S-transferase (GST), quinone reductase NAD(P)H (NQO1), UDP-glucuronosyltransferases (UGT), epoxide hydrolase (EPHX), c glutamylcysteine ligase (GCL), heme oxygenase-1 (HO-1), glutathione reductase the (GR), thioredoxin reductase (TrxR), catalase (CAT) and superoxide dismutase (SOD). Nrf2 also promotes gene transcription nonenzymatic antioxidant proteins as thioredoxin and ferritin [59].

It has been reported that low levels of ROS cause an increase in Nrf2 expression but high levels, do not modify it, this leads to irreversible cell injury and apoptosis induction. An intermediate level of ROS maintains control of the balance between survival and apoptosis by activating transcription factor-NFjB [60].

The epidermis (outer skin layer) consists mainly of keratinocytes and melanocytes, Langerhans cells and Merkel cells. Nrf2 has two effects, firstly, promotes regeneration and expression of antioxidant enzymes [61], and secondly, it can perpetuate the survival of damaged cells by ROS generated during aerobic metabolism, and the respiratory burst of the immune cell system, increasing the resistance to apoptosis of cells in culture under UV ray [62]. Nrf2 can be activated by the sulforane (obtained from broccoli and Brussels sprouts) [8].
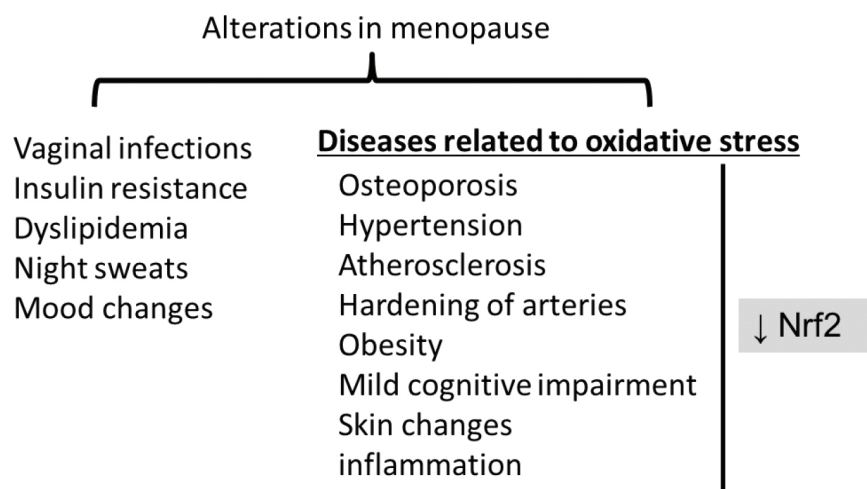
In melanocytes, the H_2O_2 is generated by tyrosinase enzyme and later is metabolized by catalase. The Nrf2 activity protects melanocytes against the effects of ROS. This effect is associated with a higher level of melanotropine (a-MSH), this unbalanced signal redox state arrives from the cytoplasm and begins the synthesis of molecules Nrf2 [63, 64].

The synthesis of Nrf2 is constant in melanocytes and alterations in this process, can reduce the resistance of cells to stress, both physical and chemical, leading to cell death or carcinogenesis [65, 66]. The Nrf2 level may be affected by hormones like estrogens. Curcumin is an extract from turmeric root, which acts as antifibrotic in systemic scleroderma, by reducing ROS that

causes suppression of the fibrotic process in scleroderma [67, 68]. In contrast, it reduces Nrf2 activity also by antioxidants thiol and thioredoxin, since the thiol group can prevent oxidation of Keap1, which favors the maintenance of Nrf2 in theKeap1 complex [69].

5.4. Immunological disorders

The adipose tissue is an important endocrine gland, it produces proinflammatory cytokines. In menopause, several inflammatory conditions, such as preexist diseases and oxidative stress, have been described, but possibly the most important factor is the centralized fat mass. In a study that considered healthy postmenopausal women of different ethnicity higher levels of proinflammatory markers, such as reactive C-reactive protein, interleukin-1β, and tumor necrosis factorα, are reported. This fact is very important, because, it marked a proinflammatory state associated only with the postmenopause [70].
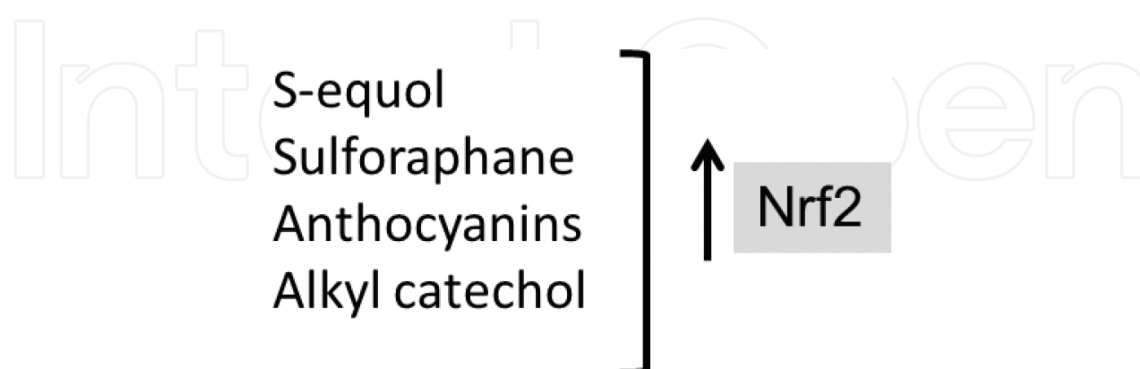

Figure 1. Alterations and diseases observed in menopause. Several diseases present in the menopause, are related to low levels.

The Nrf2 pathway plays a role in degenerative and immune disorders, such as atherosclerosis, inflammatory bowel disease (IBD), diabetes, rheumatoid arthritis, HIV/acquired immunodeficiency (HIV/AIDS) syndrome, neurological disorders, sepsis, cancer, Alzheimer's disease and many others [71]. Although the exact mechanism is unknown, studies in macrophages, indicate that genes Nrf2 inhibits pro-inflammatory cytokines [72], so this mechanism must be deregulated in this stage of life. Many studies on menopause are presented, but there some of them has been related to oxidative stress, which are characterized by a decreased level of Nrf2 (**Figure 1**).

6. Diet and Nrf2

Changes in body composition of women may have different causes, for example, mood swings can lead to eating disorders. Although, special diets are recommended for this stage; investi-

gations are providing substantial information based on its recommendation in relation to the activation of Nrf2 that can induce phytochemicals present in different foods, especially of plant origin. Among these compounds are curcumin, sulforaphane, anthocyanins and alkyl catechol. Lactobacilli are important too, as they contain phenolic acid decarboxylase enzyme, alkyl catechol (**Figure 2**) [73–75].

Figure 2. Modulators of Nrf2. Levels of Nrf2 can increase by compounds present in vegetables such as curcumin and broccoli.

7. Conclusions

Menopause is caused by the changes in the production of estrogens, hormones that modulate several functions in organs and tissues, but when its blood levels are diminished, different disorders are developed, such as, cardiovascular events, osteoporosis, dyslipidemia, changes in corporal composition, among others. All of them have been directly related to oxidative stress. The major regulator of this state is Nrf2, which is activated by estrogens, phytoestrogens, and alkyl catechol. In conclusion, the oxidative stress observed during menopause and its stages, can be modulated by activators of Nrf2, and vegetables and fruits have compounds with similar effect.

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