Chapter

Soybean Seed Compounds as Natural Health Protectors

Gabriel Giezi Boldrini, Glenda Daniela Martin Molinero, María Verónica Pérez Chaca, Nidia Noemí Gómez and Silvina Mónica Alvarez

Abstract

Glycine max (L) Merrill, better known as soy or soybean, is a legume of asian origin considered an excellent biotype, given the fact that it contains almost everything the human being needs for the diet. Its cultivation worldwide is one of the most important, and soy itself and its derivatives are highly on demand. The health effects of soy derived foods have been investigated for more than 25 years, and some of them remain controversial. On the other hand, we wondered if soy could be used to ameliorate the toxic effects of heavy metals. Therefore, in this chapter we review general characteristics of soy as well as its nutritional potential, and we compiled the newest information about the health effects of soy. In order to test our hypothesis, we developed a model of animals exposed to cadmium, and we gave them a soy based diet, comparing it with a casein-based diet as control. This allowed us to collect information about its effect on the respiratory and nervous system. Among the results of this review, we show that it reduces the cholesterol level and obesity while also having antidiabetic effects. We enumerate the benefits of soy-based diets on the respiratory system, such as protection against lung cancer and radiotherapy, better lung function in asthma patients and protection against cadmium intoxication. In the cardiovascular system it reduces the risk of coronary heart disease, improves blood pressure, glycemic control, and inflammation while it reduces not all but some of the alterations induced by cadmium exposure on the aorta and heart. It apparently promotes neurogenesis, improves cognitive functions, and reduces the oxidative stress and apoptosis induced by cadmium exposure in the cerebellum. Taken all together, this information let us conclude that soy consumption would exhibit numerous benefits for human health, although future studies should try to elucidate the best outcome considering variables such as gender, age, treatment duration and dosage of soy products consumption in the diet.

Keywords: Soybean, cadmium, oxidative stress, anti inflammatory

1. Introduction

Soybean has been consumed in many countries since before recorded history. The health effects of soy derived foods have been investigated for more than 25 years. Actually, more than 2000 soy related articles are published annually. Most of the research is conducted because there is evidence that soy has beneficial effects on health, specially preventing chronic diseases.

In our laboratory, we specialize in the effect of heavy metals intoxication on different organs and given the fact that soy is known for its antioxidant properties, we wanted to study if the addition of soy in the diets of exposed animals would ameliorate the deleterious effects of a heavy metal.

In this chapter, we begin providing some background information about soy characteristics and nutritional information; but the main intent of this review is to provide a compilation of the current understanding of the health effects of soybean derived foods mainly on the lipid profile and on different systems such as the respiratory system, the cardiovascular system and the central nervous system. We made a search compiling the most relevant works in the field and added our most outstanding results regarding the possible uses of soy to counteract some environmental intoxications.

2. *G. max* (L) Merrill "soy": general characteristics

The scientific name for soybeans is *G. max (L.) Merrill.* It is of Asian origin, native to north and central China [1]. It belongs to the *Fabaceae* family and the subfamily *Faboideae.* Depending on the country, it is popularly known by different names: soya (Portugal, France and England), soia (Italy) and sojabohne (Germany) [2]. It is an annual, herbaceous, shrubby species and its vegetative cycle ranges from three to seven months, depending on environmental conditions [3]. The optimal circumstances for its growth are the subtropical regions due to their permanently humid weather [4]. Morphologically, it is an erect and branched plant, reaching 80 to 100 cm in height. Almost all varieties show pubescence on the stems, leaves and pods. The basal leaves are unifoliate, oval, with a short half-life; from the second pair of leaves their folial development is alternate, trifoliate with oval or lanceolate leaflets, narrow or wide, depending on the variety, green in vegetative state and at maturity they turn yellow-brown.

After the vegetative growth period, the duration of which depends on the cultivar, latitude and environmental conditions (length of day and temperature) in addition to cultural practices, the soybean plant enters the reproductive phase. The flower is perfect (hermaphrodite), with axillary budding, developing a grouping of 2 to 35 flowers, which can be white or purple [5]. Palmer et al. [6] and Takahashi et al. [5] established that the color of soybean flowers is controlled mainly by six genes (W1, W2, W3, W4, Wm and Wp). Under the W1 genotype, the combination with W3W4 results in deep purple flowers, W3w4 has pale purple flowers or with purple coloration at the base of the petal, w3W4 produces purple flowers and w3w4 has almost white flowers [7].

The seed develops in pods 4 to 6 cm long; each pod has between 2 to 3 seeds. The seed has a shape that varies from round to subtly oval and can present different colors depending on the variety; they can be essentially yellow, black or green. The root system is pivotal and can reach a depth of 15–30 cm; it is capable of nodulation in symbiosis with bacteria of the genus *Rhizobium* [8].

Nutritionally, soy is an excellent biotype; since it contains almost everything the human being needs for his diet. It has between 38 and 40% protein, 18% fat due to its polyunsaturated nature, 15% carbohydrates and 15% fiber. It supplies most of the amino acids needed for protein synthesis, predominantly Lysine [9]. It is the only protein of vegetable origin with an amino acid score of 100%, when compared to proteins of animal origin, although it is limited in the amino acid methionine, so it is important that it is combined with a cereal (rice, quinoa, oats) or with animal proteins to be able to form complete proteins [10, 11]. It has a high concentration of potassium and is a good source of magnesium, phosphorus, iron, calcium, manganese and phosphates. It also provides vitamins such as vitamins E and B6 [9, 12].

Soy contains isoflavones, which are mainly found in roots and seeds [13]. The concentration ranges between 1.2 and 4.2 mg/g dry weight, depending on the characteristics of the soil in which it is grown, the climate, and the plant maturation at the time of harvesting the seeds [14]. Like other phenolic compounds, soy isoflavones are mainly found as glycosylated conjugates (> 80%), which are absorbed in the intestine and have low estrogenic activity [15]; only after hydrolysis do they acquire their maximum bioavailability and biological activity [16].

2.1 Soybean cultivation characteristics

The cultivation of soy (*G. max*) worldwide is one of the most important due to its profitability and high demand for the product and its derivatives [17]. To improve soybean crop yields, a set of variables such as genetic aspects, nutrient availability, as well as other factors (crop rotation) must be analyzed, with the aim of achieving sustainability in production.

Pérez [18] assures that in order for this variety to obtain adequate growth and yield, it needs a significant amount of available nutrients so that it is able to yield good grain production. The nutrient requirements per ton of harvested soybean grain exceeds that one needed by other field crops such as corn or wheat.

Among the macronutrients and micronutrients necessary for its development are: phosphorus (P), potassium (K), calcium (Ca), magnesium (Mg), zinc (Zn), sulfur (S), boron (B), copper (Cu) and organic matter (OM) [17]. According to Ortiz [19], soy contains high concentrations of nitrogen (N) in the grains and in the plant. Biological nitrogen fixation (BNF) increases as the crop develops, in this way the root nodules transfer between 30 and 50% of the fixed N to the vegetative stages, 80–90% between flowering and the formation of the fruit, reaching the maximum contribution during the filling of the grains [20].

2.2 Industrial use of soy

Soy is industrially used for the production of oil for both human and animal consumption. From the processed grain, 20% crude oil and 75% soy flour are obtained. Most of the soy flour is used as raw material for animals. Small percentages of protein are processed for human consumption in the form of soy milk, soy flour (SF), soy protein concentrate (SPC), tofu, and many retail food products [21].

Soy is also used for the production of industrial chemicals such as biodiesel, bio-composites, candles, ink, and wood. It is also used to produce synthetic wood floors and interior plywood. Soy products and other materials obtained from natural resources can be used as ingredients for the production of adhesives for wood due to their ability to bond with different materials [21]. Biodegradable soy-based adhesives are considerably less polluting for the environment than petrochemical adhesives [22].

Soybean residual biomass (a low-cost residue resulting from oil extraction) was functionalized with an industrial sulfur-based chelating agent, which is a precipitation agent used in industrial wastewater treatment. This biomass combination and chelating agent is used for removing heavy metals from aqueous solution, such as Pb (II), Ni (II) and Cu (II) [23].

Various derived by-products from the soy processing industry are used for the manufacture of food, cosmetics and cleaning products. Also, soy is one of the most widely used crops for the production of biodiesel [24].

Soy production represents a very important fraction of the PBI of the entire Southern Common Market (Mercosur) agribusiness, with great economic importance for these countries. Practically, the Mercosur countries make up 42% of the total soy planted in the world, compared to 33% planted in the US, satisfying together the growing world demand [25].

3. Soybean and health

Different studies have been conducted to determine which components of soy exert bioactive effects. Soy components include protein, lipids, fiber and phytochemicals including isoflavones. The three main isoflavones found in soybeans are genistein, daidzein and glycitein. Furthermore, genistein has been suggested to act as an inhibitor of oxidative stress, angiogenesis, and metastasis [26].

3.1 Anti-cancer soy property

It has been suggested that many of the health effects of soy may be related to estrogen receptors (ER), mediated by soy-associated phytoestrogens [27]. Epidemiologic studies have shown that isoflavones may exert their anticancer effects through an estrogen receptor (ER) signaling pathway in breast, endometrial, and ovarian cancers. In addition, some results from lung cancer studies link the decrease of lung cancer with soy intake. The mechanisms and active compounds in soybeans that may be responsible for this relationship will need to be elucidated in the future [28]. A research conducted in 2014 with separated women according to menopause status explored the association between breast cancer and soy isoflavone consumption and it concluded that soy isoflavone intake could reduce the risk of breast cancer for both pre- and post-menopausal women in Asian countries [29].

In men with benign prostatic hyperplasia (BPH), finasteride treatment induced epidermal growth factor receptor (EGFR) nuclear translocation, but, when finasteride was combined with soy isoflavones, EGFR remained on the cell membrane. Since nuclear EGFR is a predictor of poor outcome in prostate cancer, addition of ERβ agonists should be considered as a treatment that might offer some benefit to patients [30].

Other studies have demonstrated that high intake of total soybean and non-fermented soybean products could reduce the risk of gastric cancer, but fermented soybean products could increase that risk, indicating that the beneficial effect of soy-based food might be related to the non-fermented products [31]. Hua et al. [32] indicated that the isoflavone intake decreased the ovarian cancer risk by 33%, demonstrating that the intake of dietary isoflavones played a protective role against ovarian cancer. He et al. [33] showed that a daily diet rich in isoflavones might potentially decrease colorectal cancer incidence. In this sense, Yu et al. [34] results revealed that soy isoflavone consumption reduced the risk of developing colorectal cancer by 23%. Moreover, a higher intake of soy isoflavones was associated with a lower risk of mortality from lung, gastric, and colorectal cancers. Nachvak et al. [35] reported that an increase of 10 mg/day of soy isoflavones consumption was associated with a 7% lower risk of cancer mortality.

3.2 Soy enhances lipid profiles

The potential health effects of soybean in humans and animals remain controversial. One of the strongest health claims involves protection against coronary disease, based upon reductions in plasma cholesterol and triglycerides, and protection against atherosclerosis. However, the physiological mechanism by which soy may improve blood lipid profiles has been subject of numerous investigations. Additional health benefits involve antidiabetic effects, reduced weight gain, and improved body composition. Obesity clinically leads to nonalcoholic fatty liver disease (NAFLD), type 2-diabetes, and coronary heart disease. NAFLD is a potential risk factor for the development of both type 2-diabetes and metabolic syndrome. This illness is defined by excessive hepatic triglyceride (TG) content in the absence of excessive alcohol consumption. Moreover, NAFLD is the most common cause of chronic liver disease worldwide and it is a precursor of the more advanced liver disease nonalcoholic steatohepatitis (NASH). NAFLD is a condition that may progress to cirrhosis in up to 25% of the patients [36]. To date, the growing global disease burden of NAFLD has not been remedied by pharmaceutical treatment but soy derived foods in the diet have been proposed as a therapeutic tool for patients with NAFLD [37].

The amount of liver fat appears to be related to the amount of fat incorporated in the diet. Therefore, the excess of TG in the diet can favor fatty liver formation. Sources of hepatic TG were detected directly in NAFLD patients, as follows: a) TGs that come from non-esterified fatty acids, which flow into the liver through lipolysis of adipose tissue; b) TG in smaller amounts derived from *de novo* lipogenesis and dietary fat. Research shows that bioactive compounds in soy can prevent and treat NAFLD. Soy modulates lipid metabolism and regulates the expression of related transcription factors [36].

Hepatic lipid metabolism is partially controlled by transcription factors: sterol regulatory element binding proteins (SREBPs) and peroxisome proliferator-activated receptors (PPARs) [38]. Soybean intake decreases the expression of SREBP-1c and increases the expression of SREBP-2. SREBP-1c is a transcription factor that stimulates the expression of genes related to *de novo* lipogenesis. Insulin induces the expression of an inactive SREBP-1c precursor and likewise promotes its activation [37].

SREBP-1c stimulates the transcription of fatty acid biosynthesis genes such as acetyl-CoA carboxylase (ACC) and fatty acid synthase (FAS). In contrast, PPARα regulates genes involved in hepatic fatty acid oxidation. For example, carnitine palmitoyltransferase-1 (CPT-1) is an enzyme that regulates fatty acid β-oxidation [37, 38]. In conclusion, SREBP is associated with the regulation of hepatic lipogenesis and reduction of cholesterol synthesis [39].

Interactions between soy components are believed to improve fatty acid oxidation in the liver by increasing the expression of peroxisome proliferator activated receptor α (PPARα) regulated genes, thus decreasing lipid accumulation in the liver [38]. Another nuclear receptor involved in lipid metabolism is peroxisome proliferator-activated receptor (PPAR)γ2, whose expression is greatly increased in response to a high fat (HF) diet, especially a diet high in saturated and unsaturated fatty acids [36].

Japanese diet includes a high consumption of soy/isoflavones, fish/n-3 polyunsaturated fatty acids (PUFAs), salt/salted foods, and green tea, and a low consumption of red meat and saturated fat. Regarding this, inverse associations between soy/isoflavones or fish/n-3 PUFAs and diabetes have been found [36]. Several groups studied the effects of β-conglycinin, a soy protein, on the prevention and improvement of NAFLD. Soybean is a popular ingredient in Japan, used in foods such as tofu, miso, and natto. Ikaga et al. [36] found that in Japan the intake of soybeans and related foods was 58.6 g/day, and their protein intake was 5.1 g, while 30% of the soy protein was β-conglycinin.

In humans, supplementation with β-conglycinin is able to reduce and/or prevent intra-abdominal obesity; it is also necessary to emphasize that this protein is considered in numerous investigations as an allergen, although this information is controversial [40]. Small peptides released from β-conglycinin digestion may directly or indirectly affect lipid metabolism in adipose tissue and liver. In addition, digestion-released peptides were shown to activate low-density lipoprotein receptors and inhibit FAS biological activity. Therefore, β-conglycinin may be a promising dietary protein for NAFLD and intra-abdominal obesity amelioration. These results suggest that soy β-conglycinin could be a potentially useful dietary protein source for the prevention of hypertriglyceridemia, hyperinsulinemia, and hyperglycemia [36, 41].

Most studies on diet-induced obesity have always focused on the role of saturated fats, from animal fats, but there is enough evidence to suggest that polyunsaturated fatty acids (PUFAs), from vegetable fats also contribute to obesity [42–44]. On the other hand, there is strong evidence relating the cardiovascular health with soybean oil. Replacing high saturated FAs (SFAs) fats and oils or *trans*-FAs (TFAs) oils with either high–oleic acid soybean oil (H-OSBO) or oils high in n–6 PUFAs would have favorable effects on plasma lipid risk factors. Soybean oil (SBO) is the dominant edible oil in the marketplace and is a primary contributor of PUFAs in the US diet. (H-OSBO) is trait-enhanced oil high in oleic acid with superior functional properties, including high heat and oxidative stability for use in food manufacturing as an alternative to partially hydrogenated vegetable oils [45].

3.3 Soy and the respiratory system

It is known that nutrition is very important in lung health and defense [46–48]. Protection against lung cancer and the radioprotective effect of soy isoflavones are well described in the bibliography [49, 50]. Soy isoflavones seem to increase chemotherapy induced cell death in different types of lung cancer [51, 52]. They also improve survival of non-carcinogenic cells after chemo- or radiotherapy. Its mechanisms might be related to the inhibition of the infiltration and activation of macrophages and neutrophils [53–55].

Asthma is a chronic disease affecting a great number of people in the world and airway remodeling is one of the main pathological hallmarks of uncontrolled asthma. Remodeling is attributed to treatment failure with conventional medications and poor asthma control. Plasminogen activator inhibitor-1 (PAI-1) is associated with asthma severity due to its role in airway remodeling. Patients with asthma have demonstrated that consumption of soy isoflavones results in better lung function. Genistein induces reduction of PAI-1 generation from airway epithelial cells and may be part of the therapeutic mechanism [56]. Also, soy isoflavones recovered Th1/Th2 lymphocytes balance in bronchoalveolar lavage, inhibited eosinophil infiltration, collagen deposition and airway mucus production in murine models of allergic asthma [57, 58].

Hirayama *et al.* [59] provided evidence of a possible protective effect of the traditional japanese diet against tobacco carcinogen, showing significant reductions in the prevalence of COPD and breathlessness due to isoflavones. Additionally, Zhang *et al.* [60] reported that L-Lysine, an essential amino acid abundant in soy, was effective against sepsis-induced acute lung injury in a lipopolysaccharide induced murine model. Moreover, soy lecithins can be used for artificial pulmonary surfactant synthesis that are prepared at lower costs and they are useful for the treatment of respiratory distress, inflammatory pulmonary diseases, and dyspnea caused by asthma, among others [61].

It is known that the respiratory system is highly susceptible to environmental contamination. Airways are the access door to a number of chemical compounds, microorganisms or viruses that can injure lungs [62–66]. Cadmium is a heavy metal associated with lung damage or pulmonary cancer [67, 68] and the sources of cadmium contamination are related to industry applications, color pigments, fossil fuel combustion, Ni-Cd batteries, and the use of phosphate fertilizers [69]. The absorption of Cd takes place mainly through the respiratory tract and to a smaller extent via the gastro-intestinal tract. Cadmium induces oxidative stress and generates ROS, activates apoptosis, alters gene expression, inhibits respiratory chain complexes, and alters the inner mitochondrial permeability. Although inhalation is the most common source of intoxication, we recently demonstrated that ingested cadmium leads to pulmonary oxidative stress, cell death and fibrosis in rat lungs.

We developed a model of animals exposed to cadmium, and we gave them a soy based diet, comparing it with a casein-based diet as control. We showed that zinc and selenium levels in lungs were modified when cadmium intoxicated rats were fed with a soy-based diet. Zinc availability has an important role in lung redox-status maintenance [70]. The higher levels of Zn we found in the soy-fed Cd intoxicated animals suggests there is a protective effect exerted by the diet in cadmium intoxicated lungs. Selenium is an essential micronutrient associated with antioxidant defense, protection against cancers, and physiological functions in the nervous system [71]; it also is a cofactor of selenoproteins, such as glutathione peroxidases [72]. We observed a depletion of this element in animals fed with casein after 60 days of cadmium-induced pulmonary oxidative stress, however; Se concentration was maintained in soy-fed rats.

The enzymatic antioxidant system is composed by a group of proteins responsible for maintaining the redox state. Superoxide dismutase 2 (SOD-2) is in charge of transforming superoxide anions into hydrogen peroxide and oxygen, as McCord and Fridovich [73] well described. It is known that the expression of antioxidant enzymes is mediated by antioxidant response elements (ARE) [74]. SOD has been identified as Nrf2-regulated antioxidant enzyme [75, 76]. Our studies demonstrated that mRNA levels of Nrf-2 and SOD-2 increased only in soy fed Cd exposed animals, revealing an improvement in the antioxidant system when soy was included in the diet. Soy also reduces oxidative stress caused by other sources [77, 78]. It has been reported that flavonoids scavenge free radicals, chelate redox-active metal ions and increase metallothionein expression [79–81].

LDH activity measured in bronchoalveolar lavages is also an indicator of cell damage [82, 83]; we found a strong increase of its activity in casein-fed Cd exposed animals, which decreased in the soy-fed group. mRNA ratio of BAX (a pro-apoptotic protein) and Bcl-2 (anti-apoptotic) showed similar results to LDH activity. These data are in accordance with other studies that report that apoptosis is one of the main mechanisms involved in cell death induced by cadmium in the lungs [84–86]. Taking into account these data, we assume that a soy based diet exerts a protective effect against cadmium induced cell death in the lungs.

Pulmonary fibrosis is a common response to multiple pathologies [87–89]. Fibrosis is also related to aging [90], lung infection processes [91], and chemical intoxications [92–94]. Our study also showed that Cd caused advanced pulmonary fibrosis, capillary fragility, and numerous fused alveoli when casein was the protein source in the diet (**Figure 1A**). However, the animals that were fed with a soy diet showed less severe injuries in the lungs (**Figure 1B**).

3.4 Soy and the cardiovascular system

It is known that cardiovascular diseases (CVD) are the leading cause of death worldwide, which is affecting millions of people in both developing and developed countries. The association between CVD risk and dietary consumption has been investigated and Yan et al. [95] summarized several studies made in the last few years, showing that soy foods were associated with a reduced risk of CVD (including coronary heart disease [CHD] and stroke). Furthermore, the American Heart Association published a statement saying that daily consumption of ≥25 g of soy protein with its associated phytochemicals intact can improve lipid profiles in hypercholesterolemic humans and that soy protein without the isoflavones appears to be less effective [96].

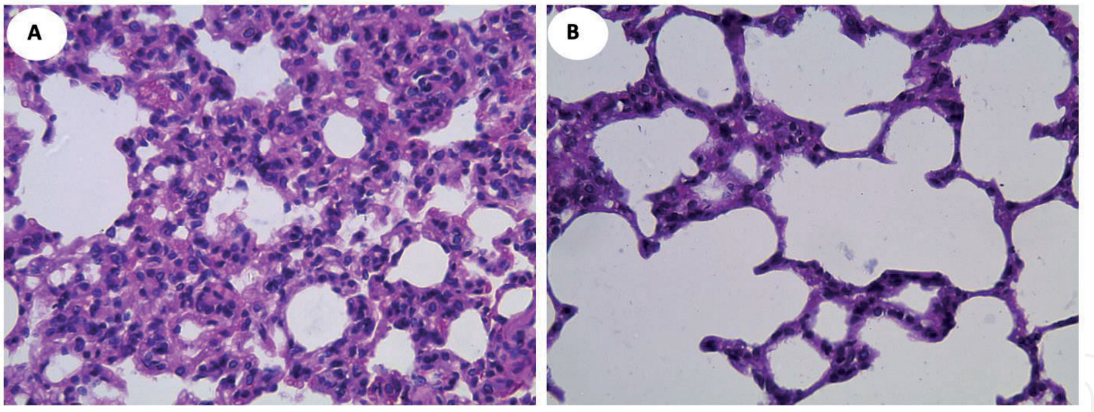

Figure 1.
Micrographs of lung parenchyma sections stained with H&E (40x). Casein-fed (A) and soy-fed (B) rat lungs exposed to 15 ppm Cd in drinking water for 60 days. (A) Presented numerous non-functional spaces, advanced pulmonary fibrosis, capillary fragility and fused alveoli. (B) Showed no evidence of capillary fragility and the number of fused alveoli was lesser; there also was evidence of pulmonary fibrosis but it was not homogeneous and the non-functional spaces were in the periphery of the lobes.

More recently, 3 prospective cohorts studies in the US showed that higher intake of isoflavones and tofu was associated with a moderately lower risk of developing CHD, and in women the favorable association of tofu were more pronounced in young women or postmenopausal women without hormone use [97]. All these results are consistent with what we mentioned above, about soy being able to decrease LDL-cholesterol levels. Besides, Ramdath et al. [98] reviewed the effects of soy on blood pressure, glucose levels, inflammatory markers, and obesity. They concluded that isoflavones and their metabolites may improve blood pressure, glycemic control, and inflammation.

On the other hand, epidemiological studies have shown that exposure to heavy metals is associated with high prevalence and incidence of cardiovascular diseases; therefore, Ferramola et al. [99] studied the effect of soy based-diets on animals exposed to cadmium in the myocardium. They found that those animals fed a soy-based diet while exposed to Cd had increased activity of CAT and SOD, suggesting an increased antioxidant response in the heart but it failed to protect the heart from Cd-induced histological alterations.

Working in the same model, Perez Diaz et al. [100] found that soy administered as a dietary protein source can modulate the pro-inflammatory and pro-apoptotic effects of a subchronic intoxication with Cd in rat's aortas. This was done by decreasing the expression of ICAM-1, which would result in a reduced leukocyte accumulation into the vasculature wall and by increasing the Bax/bcl-2 ratio respectively.

3.5 Soy and the central nervous system

It is known that soybean isoflavones influence neuronal proliferation *in vitro* and *in vivo* [101]. Besides, it has been reported that the *in vivo* administration of soybean protein hydrolysate increased the expression of brain derived neurotrophic factor (BDNF) in the cerebral cortex and the number of neurons in hippocampus and cerebral cortex, suggesting that it might promote neurogenesis [102]. Also, soy isoflavones, such as genistein, daidzein, and its metabolite, S-equol, have been informed to be an effective supplement to promote astrocyte migration in developing and/or injured adult brains, accelerating glial cell migration *via* GPER-mediated signal transduction pathway [103].

As we stated before, soy isoflavones are referred to as phytoestrogens because they bind to the estrogen receptor (ER) and as such, they affect estrogen mediated processes [104]. Soy isoflavones can exert both agonistic and antagonistic estrogenic effects [105], and have inhibitory effects on tyrosine kinase, topoisomerase and angiogenesis [106]. There are several studies that mentioned that soy isoflavones can improve cognitive function in both humans and rats [107, 108] and the SOPHIA study [109] observed the effects of soy isoflavone supplementation (110 mg/day) on cognitive function of postmenopausal women. A good performance was observed in this treatment. Duffy et al. [110] showed that postmenopausal women who received a daily treatment with 60 mg soy isoflavones along 12 weeks showed significantly better results in memorizing images and in sustained attention and planning tasks. Furthermore, isoflavone treatment showed no effect on menopausal symptoms. However, another study in healthy postmenopausal women aged 60 to 75 years showed no significant changes in cognitive function after 1 year of treatment [111]. Contradictory results have also been found in men. Some researchers have found that soy isoflavones appear to be detrimental to cognitive function in men [112], showing that middle-aged men with high tofu consumption had lower brain weight and greater cognitive decline compared to those who consumed less tofu. However, other studies demonstrated that supplementation with soy isoflavones improves cognitive function in men [108]. The treatment was carried out in young men, and consisted of the consumption of high doses of soy (100 mg of soy isoflavones/day), showing significant improvements in short- and long-term memory, as well as mental flexibility. Regardless, clinical trials indicate that soy isoflavones may improve cognitive function not only in postmenopausal women and young adults, but also in young adult men.

On the other hand, cognitive function was also evaluated in male rats and surprisingly the results were the same as in humans. Lund et al. demonstrated that the performance of a visual spatial memory test on male rats fed a soy isoflavone diet was less satisfactory than that executed on rats fed an isoflavone-free diet [113]. Other research showed that male rats that consumed soy isoflavones for life showed poorer performance in the radial arm maze test than male rats that switched to the isoflavone-free diet at 80 days of age and continued the same diet up to 120 days of age. However, another study reported that 10-month-old male rats fed 0.3 g/kg of isoflavone for 16 weeks had a significantly higher performance than male rats fed the isoflavone-free diet in the spatial water maze test [114]. The discrepancy between the two studies can be attributed to the difference in the age of the rats, dietary regimes, and maze tests.

Among the multiple mechanisms that soy has, it is also known to act at the tyrosine kinase level. Phosphorylation of this protein is a regulatory mechanism involved in numerous responses in the brain, including neuroregeneration [115], synaptic plasticity [116] and neuronal damage [117]. Protein tyrosine kinases are highly expressed in the brain and are reported to be involved in the induction of long-term potentiation (LTP) in the hippocampus [118], which is crucial for learning and memory. Genistein is known to inhibit tyrosine kinase [119], which is generally considered to be detrimental to a neuron. However, these effects appear to occur only when the level of genistein in a cell is high [120]. In a model of calcium ATPase inhibitor-induced apoptosis, low concentrations of genistein prevented apoptosis, however high concentrations reversed all phenotypes. High concentrations of genistein were also shown to induce apoptosis in primary cortical neurons [121], blocked tyrosine kinase activity, and contributed to H2O2-induced apoptosis in SH-SY5Y human neuroblastoma cells [122]. It can be postulated that LTP suppression by genistein is dose dependent, similar to its effects on neuroprotection.

On the other hand, Deol et al. [123] found that soy diets would produce significant dysregulation of gene expression in the hypothalamus of male mice, the most notable of which is the gene encoding Oxytocin (Oxt). These results demonstrated that different fatty diets can have differential effects on hypothalamic gene expression and increase the possibility that a rich soy diet could contribute both to increasing rates of metabolic disease as well as affecting neurological functions.

Also, just as we did with lungs, we analyzed the effect of a soy-based diet after chronic cadmium intoxication. Cadmium has been shown to have negative effects on the central nervous system, it has been observed that it is capable of crossing the blood–brain barrier (BBB), increasing its permeability in rats [124] allowing it to accumulate in the brain of developing and adult rats, thus affecting the integrity of the vascular endothelium, producing cellular dysfunction and cerebral edema [125–127]. These could induce cognitive dysfunctions [128, 129], leading to neurological alterations like olfactory dysfunctions, peripheral neuropathy, decreased ability to concentrate and neurodegenerative diseases [130, 131]. Moreover, it is known that oxidative stress is a factor involved in neurodegenerative disorders in adults, such as strokes, traumas and seizures [132], where the CNS is susceptible to free radicals damage [133].

In cerebellum, the motor coordination center, also involved in cognitive processing and sensory discrimination, the effects of Cd in experimental animals include cerebellar bleeding, cerebellar edema and hyperactivity [134, 135]. Our investigation revealed an increase in Cd concentrations in the cerebellum of the rats after 60 days of treatment while the animals fed a soy diet did not have high levels of the heavy metal. Soybean has an apparent defensive effect against Cd accumulation. Besides, some studies showed that a chronic ingestion of diet enriched in casein induced substantial BBB disruption in the cortex region resulting in non-specific blood-to-brain extravasation of plasma-derived proteins, while a diet enriched in soy protein showed no significant effects on BBB permeability [136]. Besides, it has been shown that certain amino acids found in protein-rich diets, specifically methionine, are associated with elevated plasma homocysteine levels [137, 138]. Tyagi et al. demonstrated that hyperhomocysteinemia induces structural and functional alterations of BBB by promoting oxidative stress and neuroinflammation in mouse models of cognitive dysfunction [139, 140].

Regarding the effect on the antioxidant defense system in cerebellum, we found a reduction of catalase activity in the intoxicated animals fed with soy, probably due to the isoflavones content, just like Halder [141] described in his study, where that an isoflavone like quercetin, helped to reduce Cd levels in brain tissue and modulated the antioxidant system of the cell by affecting expression of antioxidant enzymes at the transcription level. Furthermore, these animals showed increased expression of SOD-2, suggesting a protective, antioxidant effect of this protein source, as it was previously shown by Liu et al. [142].

It is known that the adult human brain contains about 20% of the body's total cholesterol [143], making cholesterol the main constituent of this tissue. Unlike cholesterol in other organs, in the brain it is primarily derived by *de novo* synthesis. The intact blood brain barrier (BBB) avoids the uptake of lipoproteins from the circulation [144]. Regarding the content of total cholesterol, it was significantly increased in both Cd exposed groups when compared to the respective controls, as well as the expression of HMGCoAR, the limiting enzyme in cholesterol synthesis. Additionally, we found an increase in total triglycerides (TG) and total phospholipids (PL) in the animals fed with casein, with no changes under a soy diet. The increased TG value was due to an increased expression of GPAT2, an enzyme that catalyzes the initial step in glycolipid biosynthesis. Similar results were found by Modi et al. [145] in the brain. Any of these modifications were found in the animals fed with soy, suggesting again a somewhat protective role of this diet.

Cd has been recognized as an inducer of apoptosis in a diversity of tissues including the brain [29]. In casein-fed cadmium intoxicated animals the Bax/Bcl-2 ratio increased. The replacement of casein for soy as dietary protein reduced this Bax increase but also increased Bcl-2 expression, changing the ratio. These data suggest that a soy diet inhibited Cd-induced apoptosis by increasing Bcl-2 expression, which may play an inducible cytoprotective role against Cd toxicity [146]. In this regard, it has been reported that a long-term intervention with genistein can lead to a decrease in apoptosis in hippocampal neurons of ovariectomized rats, upregulate the expression of Bcl-2, and downregulate the expression of Bax, playing genistein an anti-apoptotic and neuroprotective role [147]. This was also consistent with the structural changes observed, like a reduction in the number in the granular cells in the casein group and also with the morphometric results that indicated that Cd intoxication produced striking variations in the thickness of the granular layer in the casein group as reported by Mahmoud [148]. In the soy groups no significant differences were noticed, consistent with Farahmand who find that the antioxidant effect of *Salvia rhytidia* extract had an influence on the prevention of ischemia reperfusion injury of rat cerebellum and can reduce the ischemia injury confirmed by increase of the thickness of granular layer and size of Purkinje cells [149].

4. Conclusions

Soy (*G. max*) is a food of rich nutritional content, in which composition has proteins, oligosaccharides, dietary fiber, phytochemicals (especially isoflavones) and minerals.

Soy is used for the production of oil, flour, milk, protein concentrate and tofu, among others; products that can be used for both human and animal consumption. In addition, soybeans are used for the production of industrial chemicals such as biodiesel, in the treatment of industrial wastewater and in the manufacture of cosmetics and cleaning products.

In this chapter we summarized the benefits of adding soy to the daily diet. Its consumption exhibits numerous benefits for human health. It can reduce the risk of a variety of health problems, such as different cancers, cardiovascular diseases, stroke and it also acts as an anti-neuroinflammatory. What is more, it can ameliorate the toxic effect of cadmium intoxication in several organs.

Soy isoflavone may bind to some hormone receptors, such as estrogen receptors (ER). Therefore, the intake of phytoestrogens was found to be beneficial in breast, ovarian, endometrial and colorectal cancer and also in lung cancer. However, more research is needed to understand its effects, mechanisms and dosages. Several studies demonstrated that the intake of total soybean could also reduce the risk of gastric cancer. The consumption of soy protein and fiber reduces the risk of CVD and is associated with glycemic control. Soy is a high-quality protein that could be an alternative strategy to palliate pulmonary damage in several pathologies and to prevent the damage due to heavy metals intoxication.

Therefore, the use of soy in functional food is very interesting, but future studies should try to elucidate the best outcome considering variables such as genetic load, gender, age, treatment duration and the dosage of soy products consumption in the diet.

Conflict of interest

The authors report no conflicts of interest.

Author details

Gabriel Giezi Boldrini[1,2], Glenda Daniela Martin Molinero[1,2], María Verónica Pérez Chaca[3], Nidia Noemí Gómez[1,2,3] and Silvina Mónica Alvarez[1,2]*

1 Laboratory of Nutrition, Environment and Cell Metabolism, Faculty of Chemistry, Biochemistry and Pharmacy, National University of San Luis, Argentina

2 IMIBIO-SL CONICET, San Luis, Argentina

3 Laboratory of Morphophysiology, Faculty of Chemistry, Biochemistry and Pharmacy, National University of San Luis, Argentina

*Address all correspondence to: silvina.alvarez@gmail.com

References

[1] Gimenez AM. La soja, su evolución en Argentina [Internet]. 2018. Available from: https://www.monografias.com/trabajos82/soja-su-evolucion-argentina/soja-su-evolucion-argentina.shtml. [Accessed: 2021-05-01]

[2] Ridner E. Soja, propiedades nutricionales y su impacto en la salud. Sociedad Argentina de Nutrición, Buenos Aires. Grupo Q S.A. 2006; p 96.

[3] Singh G. The Soybean: Botany, Production and Uses; CABI. 2010; 1-494. DOI: 10.1079/9781845936440.0000

[4] Cortez JCO. Los rendimientos de cultivos y la agricultura en el estado plurinacional de Bolivia. Universidad Mayor de San Andrés. Revista de la Carrera de Ingeniería Agronómica, Apthapi. 2017;2(2):36-46.

[5] Takahashi R, Matsumura H, Oyoo ME, Khan NA. Genetic and Linkage Analysis of Purple–blue Flower in Soybean. Journal of Heredity. 2008;99(6):593-597. DOI:10.1093/jhered/esn041.

[6] Palmer RG, Pfeiffer TW, Buss GR, Kilen TC. Soybeans: improvement, production and uses Qualitative genetics. In: Boerma HR, Specht JE. 2004;editors. 3rd ed. 16: 137-233. https://DOI:.org/10.2134/agronmonogr16.3ed.c5.

[7] Mederos-Ramírez A, Ortiz-Pérez R. Analysis of the genotype environment interaction in the of soybean crop (Glycine max (L) Merrill). Cultivos Tropicales. 2021;42:1-10.

[8] Menjivar Menjivar A, Rivera Escobar SB, Vásquez Jovel KV. Evaluación fenológica y morfo-agronómica de ocho genotipos de soya (*Glycine max* L.) en la Estación Experimental y de Prácticas, Facultad de Ciencias Agronómicas, Universidad de El Salvador, San Luis Talpa, La Paz. [thesis], Universidad de El Salvador. 2017.

[9] Caicedo IM, Mejía-Gonzales A, Beltrán-Castro F. Industrialización del cultivo de soya. Revista Observatorio de la Economía Latinoamericana. 2019; ISSN: 1696-8352.

[10] Lope C, Ochoa X, Aguilera N. Soya. La oleaginosa de mayor importancia a nivel mundial [Internet]. 2018. Available from: http://www.oiapes.sagarhpa.sonora.gob.mx› paq-tec› paq-soya. [Accessed: 2021-04-27]

[11] Martín-Salinas C, López-Sobaler AM. Beneficios de la soja en la salud. Nutrición Hospitalaria. 2017;34:36-40. DOI:10.20960/nh.1569.

[12] Tosquy V, Alciva V, López R. Densidad de siembra en dos variedades de soya de temporal en Veracruz, México. Agronomía Mesoamericana. 2017;21: 63-72.

[13] Aguiar CL, Baptista AS, Alencar SM, Haddad R, Eberlin MN. Analysis of isoflavonoids from leguminous plant extracts by RPHPLC/DAD and electrospray ionization mass spectrometry. International Journal of Food Sciences and Nutrition 2007;58:116-124.

[14] Zhang J, Ge Y, Han F, Li B, Yan S, Sun J, Wang L. Isoflavone content of soybean cultivars from maturity group 0 to VI grown in northern and southern China. Journal of the American Oil Chemists' Society 2014;91:1019-1028.

[15] Nielsen ILF, Williamson G. Review of the factors affecting bioavailability of soy isoflavones in humans. Nutrition and Cancer 2007;57:1-10.

[16] de Cremoux P, This P, Leclercq G, Jacquot, Y. Controversies concerning the

use of phytoestrogens in menopause management: Bioavailability and metabolism. Maturitas 2010;65:334-339.

[17] Gerster G, Bacigaluppo S. Cómo alcanzar altos rendimientos en soja. Para mejorar la producción. INTA. 2009;vol. 42. ISSN: 2591-5088.

[18] Pérez B. Requerimientos nutricionales del cultivo de soya. IPNI. 2013;15(2),10-17.

[19] Ortiz, C. Calidad del grano de soya y su efecto en productos y subproductos industriales. Revista Soya noticias 2018;35(9):5-10.

[20] Hernández AJ, Guerra R, Tobía C, Villalobos E. Evaluación del potencial forrajero de diez cultivares de soya (*Glycine max* (L) Merr) en Venezuela. Agronomía Costarricense. 2013;37(2) (0377-9424):45-53. DOI: 10.15517/rac.v37i2.12761.

[21] Vnučec D, Kutnar A, Goršek A. Soy-based adhesives for wood-bonding – a review. Journal of Adhesion Science and Technology. 2016; 31:8, 910-931. DOI:10.1080/01694243.2016.1237278

[22] McDevitt JE, Grigsby W. Life Cycle Assessment of Bio- and Petro-Chemical Adhesives Used in Fiberboard Production. Journal of Polymers and the Environment. 2014; 22(4): 537-544. doi:10.1007/s10924-014-0677-4

[23] Bulgariu L,Bulgariu D. Functionalized soy waste biomass - A novel environmental-friendly biosorbent for the removal of heavy metals from aqueous solution. Journal of Cleaner Production. 2018;197(1): 875-885. DOI:10.1016/j.jclepro.2018.06.261

[24] Silva DR, Roa A, Quevedo RL, Quilodran BT. Production of biodiesel from soybean frying oil using native strains of Thraustochytrids. Chilean J. Agric. Anim. Sci. 2015;31(1): 29-41.

[25] Melgar R, Vitti G, de Melo Benites V. Fertilizando para altos rendimientos. Soja en Latinoamérica Instituto. 2011; 20. DOI: 10.3235/978-3-9523243-7-0.

[26] Mezei O, Banz WJ, Steger RW, Peluso MR, Winters TA, Shay N. Soy isoflavones exert antidiabetic and hypolipidemic effects through the PPAR pathways in obese Zucker rats and murine RAW 264.7 cells. J Nutr. 2003;133(5):1238-1243. DOI: 10.1093/jn/133.5.1238.

[27] Ronis MJ, Chen Y, Badeaux J, Badger TM. Dietary soy protein isolate attenuates metabolic syndrome in rats via effects on PPAR, LXR, and SREBP signaling. J Nutr. 2009;139(8):1431-1438. DOI: 10.3945/jn.109.107029.

[28] Yang WS, Va P, Wong MY, Zhang HL, Xiang YB. Soy intake is associated with lower lung cancer risk: results from a meta-analysis of epidemiologic studies. Am J Clin Nutr. 2011;94(6): 1575-1583. DOI: 10.3945/ajcn.111.020966.

[29] Chen M, Rao Y, Zheng Y, Wei S, Li Y, Guo T, Yin P. Association between soy isoflavone intake and breast cancer risk for pre- and post-menopausal women: a meta-analysis of epidemiological studies. PLoS One. 2014;9(2):e89288. DOI: 10.1371/journal.pone.0089288.

[30] Wu WF, Wang L, Spetsieris N, Boukovala M, Efstathiou E, Brössner C, Warner M, Gustafsson JA. Estrogen receptor β and treatment with a phytoestrogen are associated with inhibition of nuclear translocation of EGFR in the prostate. Proc Natl Acad Sci USA. 2021;118(13):e2011269118. DOI: 10.1073/pnas.2011269118

[31] Wang Y, Guo J, Yu F, Tian Y, Wu Y, Cui L, Liu LE. The association between soy-based food and soy isoflavone intake and the risk of gastric cancer: a systematic review and meta-analysis.

J Sci Food Agric. 2021 doi: 10.1002/jsfa.11334

[32] Hua X, Yu L, You R, Yang Y, Liao J, Chen D. Association among Dietary Flavonoids, Flavonoid Subclasses and Ovarian Cancer Risk: A Meta-Analysis. PLoS ONE. 2016;11:e0151134. DOI: 10.1371/journal.pone.0151134

[33] He X, Sun LM. Dietary intake of flavonoid subclasses and risk of colorectal cancer: Evidence from population studies. Oncotarget. 2016;7:26617-26627. doi: 10.18632/oncotarget.8562.

[34] Yu Y, Jing X, Li H, Zhao X, Wang D. Soy isoflavone consumption and colorectal cancer risk: A systematic review and meta-analysis. Sci. Rep. 2016;6:25939. doi: 10.1038/srep25939.

[35] Nachvak SM, Moradi S, Anjom-Shoae J, Rahmani J, Nasiri M, Maleki V, Sadeghi O. Soy, Soy Isoflavones, and Protein Intake in Relation to Mortality from All Causes, Cancers, and Cardiovascular Diseases: A Systematic Review and Dose-Response Meta-Analysis of Prospective Cohort Studies. J. Acad. Nutr. Diet. 2019;119:1483-1500. DOI: 10.1016/j.jand.2019.04.011

[36] Ikaga R, Li D, Yamazaki T. Dietary β-conglycinin prevents acute ethanol-induced fatty liver in mice. Biochem Biophys Res Commun. 2017;493(1):542-547. DOI: 10.1016/j.bbrc.2017.08.155.

[37] Seidemann L, Krüger A, Kegel-Hübner V, Seehofer D, Damm G. Influence of Genistein on Hepatic Lipid Metabolism in an In Vitro Model of Hepatic Steatosis. Molecules. 2021;26(4):1156. DOI: 10.3390/molecules26041156.

[38] Razzeto GS, Lucero López VR, Marra CA, Scardapane LA, Escudero NL, Gimenez MS. Soybean flour improves fatty acid profile and decreases hepatic triglyceride deposition in rats fed with normocaloric and hypercaloric diet. Food and Nutrition Sciences. 2015;6:1245-1257.

[39] Oliveira LP, de Jesús RP, Freire TO, Oliveira CP, Castro Lyra A, Lyra LG. Possible molecular mechanisms soy-mediated in preventing and treating nonalcoholic fatty liver disease. Nutr Hosp. 2012;27(4):991-998. DOI: 10.3305/nh.2012.27.4.5833. PMID: 23165534

[40] Wang T, Qin GX, Sun ZW, Zhao Y. Advances of research on glycinin and β-conglycinin: a review of two major soybean allergenic proteins. Crit Rev Food Sci Nutr. 2014;54(7): 850-862. DOI: 10.1080/10408398.2011.613534.

[41] Kohno M, Hirotsuka M, Kito M, Matsuzawa Y. Decreases in serum triacylglycerol and visceral fat mediated by dietary soybean beta-conglycinin. J Atheroscler Thromb. 2006;13(5): 247-255. DOI: 10.5551/jat.13.247.

[42] Costa, CAS;Carlos, AS;Santos, A;Monteiro, AM;Moura, EG;Nascimento-Saba, CC. Abdominal adiposity, insulin and bone quality in young male rats fed a high-fat diet containing soybean or canola oil. Clinics 2011;66(10),1811-1816. DOI: 10.1590/S1807-59322011001000022

[43] Deol P, Evans JR, Dhahbi J. Soybean oil is more obesogenic and diabetogenic than coconut oil and fructose in mouse: potential role for the liver. PloS One. 2015;10(7): e0132672. DOI: 10.1371/journal.pone.0132672. eCollection 2015.

[44] Deol P, Fahrmann J, Yang J. Omega-6 and omega-3 oxylipins are implicated in soybean oil-induced obesity in mice. Sci Rep. 2017;7(1):12488. DOI:10.1038/s41598-017-12624-9

[45] Huth PJ, Fulgoni VL 3rd, Larson BT. A systematic review of high-oleic

vegetable oil substitutions for other fats and oils on cardiovascular disease risk factors: implications for novel high-oleic soybean oils. Adv Nutr. 2015;6(6): 674-693. DOI: 10.3945/an.115.008979.

[46] Isaak M, Ulu A, Osunde A, Nordgren TM, Hanson C. Nutritional Factors in Occupational Lung Disease. Curr Allergy Asthma Rep. 2021;21(4):24. DOI: 10.1007/s11882-021-01003-0

[47] Damayanthi HDWT, Prabani KIP. Nutritional determinants and COVID-19 outcomes of older patients with COVID-19: A systematic review. Arch Gerontol Geriatr. 2021;95:104411. DOI: 10.1016/j.archger.2021.104411

[48] Nigro E, Perrotta F, Scialò F, D'Agnano V, Mallardo M, Bianco A, Daniele A. Food, Nutrition, Physical Activity and Microbiota: Which Impact on Lung Cancer? Int J Environ Res Public Health. 2021;18(5):2399. DOI: 10.3390/ijerph18052399

[49] Abernathy LM, Fountain MD, Joiner MC, Hillman GG. Innate Immune Pathways Associated with Lung Radioprotection by Soy Isoflavones. Front Oncol. 2017;7:7. DOI: 10.3389/fonc.2017.00007

[50] Yu Y, Xing Y, Zhang Q, Zhang Q, Huang S, Li X, Gao C. Soy isoflavone genistein inhibits has-circ-0031250/miR-873-5p/FOXM1 axis to suppress non-small-cell lung cancer progression. IUBMB Life. 2021;73(1):92-107. DOI: 10.1002/iub.2404

[51] Liu D, Yan L, Wang L, Tai W, Wang W, Yang C. Genistein enhances the effect of cisplatin on the inhibition of non-small cell lung cancer A549 cell growth in vitro and in vivo. Oncol Lett. 2014;8(6):2806-2810. DOI: 10.3892/ol.2014.2597

[52] Singh-Gupta V, Joiner MC, Runyan L, Yunker CK, Sarkar FH, Miller S, Gadgeel SM, Konski AA, Hillman GG. Soy isoflavones augment radiation effect by inhibiting APE1/Ref-1 DNA repair activity in non-small cell lung cancer. J Thorac Oncol. 2011;6(4):688-698. DOI: 10.1097/JTO.0b013e31821034ae

[53] Abernathy LM, Fountain MD, Rothstein SE, David JM, Yunker CK, Rakowski J, Lonardo F, Joiner MC, Hillman GG. Soy Isoflavones Promote Radioprotection of Normal Lung Tissue by Inhibition of Radiation-Induced Activation of Macrophages and Neutrophils. J Thorac Oncol. 2015;10(12):1703-12. DOI: 10.1097/JTO.0000000000000677

[54] Hillman GG, Singh-Gupta V, Lonardo F, Hoogstra DJ, Abernathy LM, Yunker CK, Rothstein SE, Rakowski J, Sarkar FH, Gadgeel S, Konski AA, Joiner MC. Radioprotection of lung tissue by soy isoflavones. J Thorac Oncol. 2013;8(11):1356-1364. DOI: 10.1097/JTO.0b013e3182a4713e

[55] Fountain MD, McLellan LA, Smith NL, Loughery BF, Rakowski JT, Tse HY, Hillman GG. Isoflavone-mediated radioprotection involves regulation of early endothelial cell death and inflammatory signaling in Radiation-Induced lung injury. Int J Radiat Biol. 2020;96(2):245-256. DOI: 10.1080/09553002.2020.1683642

[56] Bime C, Wei CY, Holbrook J, Smith LJ, Wise RA. Association of dietary soy genistein intake with lung function and asthma control: a post-hoc analysis of patients enrolled in a prospective multicentre clinical trial. Prim Care Respir J. 2012;21(4):398-404. DOI: 10.4104/pcrj.2012.00073

[57] Bao ZS, Hong L, Guan Y, Dong XW, Zheng HS, Tan GL, Xie QM. Inhibition of airway inflammation, hyperresponsiveness and remodeling by soy isoflavone in a murine model of allergic asthma. Int Immunopharmacol.

2011;11(8):899-906. DOI: 10.1016/j.intimp.2011.02.001

[58] Cho SH, Jo A, Casale T, Jeong SJ, Hong SJ, Cho JK, Holbrook JT, Kumar R, Smith LJ. Soy isoflavones reduce asthma exacerbation in asthmatic patients with high PAI-1-producing genotypes. J Allergy Clin Immunol. 2019;144(1): 109-117.e4. DOI: 10.1016/j.jaci.2019.01.020.

[59] Hirayama F, Lee AH, Binns CW, Hiramatsu N, Mori M, Nishimura K. Dietary intake of isoflavones and polyunsaturated fatty acids associated with lung function, breathlessness and the prevalence of chronic obstructive pulmonary disease: possible protective effect of traditional Japanese diet. Mol Nutr Food Res. 2010;54(7):909-917. DOI: 10.1002/mnfr.200900316

[60] Zhang Y, Yu W, Han D, Meng J, Wang H, Cao G. L-lysine ameliorates sepsis-induced acute lung injury in a lipopolysaccharide-induced mouse model. Biomed Pharmacother. 2019;118:109307. DOI: 10.1016/j.biopha.2019.109307

[61] Yukitake K, Nakamura Y, Kawahara M, Nakahara H, Shibata O, Lee S. Development of low cost pulmonary surfactants composed of a mixture of lipids or lipids-peptides using higher aliphatic alcohol or soy lecithin. Colloids Surf B Biointerfaces. 2008;66(2):281-286. DOI: 10.1016/j.colsurfb.2008.07.007

[62] Flood-Garibay JA, Méndez-Rojas MÁ, Pérez-Cortés EJ. Sistema inmune respiratorio y consecuencias de contaminación aérea por materia particulada [Respiratory immune system and consequences due to particulate matter in air pollution]. Rev Med Inst Mex Seguro Soc. 2019 May 2;57(3):170-180.

[63] Harker JA, Lloyd CM. Overlapping and distinct features of viral and allergen immunity in the human lung. Immunity. 2021;54(4):617-631. DOI: 10.1016/j.immuni.2021.03.010

[64] Ather B, Mirza TM, Edemekong PF. Airborne Precautions. StatPearls [Internet]. 2021. Available from: https://www.ncbi.nlm.nih.gov/books/NBK531468. Accessed: [2021-05-03]

[65] Torres A, Cilloniz C, Niederman MS, Menéndez R, Chalmers JD, Wunderink RG, Van der Poll T. Pneumonia. Nat Rev Dis Primers. 2021; 7:25. DOI: 10.1038/s41572-021-00259-0

[66] Bracken-Clarke D, Kapoor D, Baird AM, Buchanan PJ, Gately K, Cuffe S, Finn SP. Vaping and lung cancer - A review of current data and recommendations. Lung Cancer. 2021;153:11-20. DOI: 10.1016/j.lungcan.2020.12.030

[67] Luevano J, Damodaran C. A review of molecular events of cadmium-induced carcinogenesis. J Environ Pathol Toxicol Oncol. 2014;33(3):183-194. DOI: 10.1615/jenvironpatholtoxicoloncol.2014011075

[68] Ganguly K, Levänen B, Palmberg L, Åkesson A, Lindén A. Cadmium in tobacco smokers: a neglected link to lung disease? Eur Respir Rev. 2018;27(147):170122. DOI: 10.1183/16000617.0122-2017

[69] Genchi G, Carocci A, Lauria G, Sinicropi MS, Catalano A. Nickel: Human Health and Environmental Toxicology. Int J Environ Res Public Health. 2020;17(3):679. DOI:10.3390/ijerph17030679

[70] Gomez NN, Fernandez MR, Zirulnik F, Gil E, Scardapane L, Ojeda MS, Gimenez MS. Chronic zinc deficiency induces an antioxidant adaptive response in rat lung. Exp Lung Res. 2003;29(7):485-502. DOI: 10.1080/01902140303776

[71] Burk RF. Selenium, an Antioxidant Nutrient. Nutrition in Clinical Care. 2002;5:75-79. DOI: 10.1046/j.1523-5408.2002.00006.x

[72] Labunskyy VM, Hatfield DL, Gladyshev VN. Selenoproteins: molecular pathways and physiological roles. Physiol Rev. 2014;94(3):739-777. DOI: 10.1152/physrev.00039.2013

[73] McCord JM, Fridovich I. Superoxide dismutase. An enzymic function for erythrocuprein (hemocuprein). J Biol Chem. 1969;244(22):6049-6055.

[74] Jaiswal AK. Nrf2 signaling in coordinated activation of antioxidant gene expression. Free Radic Biol Med. 2004;36(10):1199-1207. DOI: 10.1016/j.freeradbiomed.2004.02.074

[75] Hu R, Xu C, Shen G, Jain MR, Khor TO, Gopalkrishnan A, Lin W, Reddy B, Chan JY, Kong AN. Identification of Nrf2-regulated genes induced by chemopreventive isothiocyanate PEITC by oligonucleotide microarray. Life Sci. 2006;79(20):1944-1955. doi: 10.1016/j.lfs.2006.06.01

[76] Leonard MO, Kieran NE, Howell K, Burne MJ, Varadarajan R, Dhakshinamoorthy S, Porter AG, O'Farrelly C, Rabb H, Taylor CT. Reoxygenation-specific activation of the antioxidant transcription factor Nrf2 mediates cytoprotective gene expression in ischemia-reperfusion injury. FASEB J. 2006 Dec;20(14):2624-2626. doi: 10.1096/fj.06-5097fje.

[77] Aoki H, Otaka Y, Igarashi K, Takenaka A. Soy protein reduces paraquat-induced oxidative stress in rats. J Nutr. 2002;132(8):2258-2262. DOI: 10.1093/jn/132.8.2258

[78] Rancan L, Puig A, Balibrea JM, Paredes SD, García C, Jiménez L, Fernández-Tresguerres JA, Vara E. Protective effects of 17-β-oestradiol and phytoestrogen on age-induced oxidative stress and inhibition of surfactant synthesis in rat type II pneumocytes. Int J Food Sci Nutr. 2021;72(1):26-36. DOI: 10.1080/09637486.2020.1757044

[79] Sichel G, Corsaro C, Scalia M, Di Bilio AJ, Bonomo RP. In vitro scavenger activity of some flavonoids and melanins against O2-(.). Free Radic Biol Med. 1991;11(1):1-8. DOI: 10.1016/0891-5849(91)90181-2

[80] Morel I, Lescoat G, Cogrel P, Sergent O, Pasdeloup N, Brissot P, Cillard P, Cillard J. Antioxidant and iron-chelating activities of the flavonoids catechin, quercetin and diosmetin on iron-loaded rat hepatocyte cultures. Biochem Pharmacol. 1993;45(1):13-19. DOI: 10.1016/0006-2952(93)90371-3

[81] Kameoka S, Leavitt P, Chang C, Kuo SM. Expression of antioxidant proteins in human intestinal Caco-2 cells treated with dietary flavonoids. Cancer Lett. 1999;146(2):161-167. DOI: 10.1016/s0304-3835(99)00253-0

[82] Drent M, Cobben N, Henderson R, Jacobs J, Wouters E, van Dieijen-Visser M. BAL fluid LDH activity and LDH isoenzyme pattern in lipoid pneumonia caused by an intravenous injection of lamp oil. Eur Respir J. 1996;9:2416-2418. DOI: 10.1183/09031936.96.09112416

[83] Li XY, Gilmour PS, Donaldson K, MacNee W. Free radical activity and pro-inflammatory effects of particulate air pollution (PM10) in vivo and in vitro. Thorax. 1996;51(12):1216-1222. DOI:10.1136/thx.51.12.1216

[84] Kwon K, Jang J, Kwon S, Cho C, Oh H, Kim S. Cadmium induced acute lung injury and TUNEL expression of apoptosis in respiratory cells. Journal of Korean Medical Science. 2003;18: 655-662. DOI: 10.3346/JKMS.2003.18.5.655

[85] Kiran Kumar KM, Naveen Kumar M, Patil RH, Nagesh R, Hegde SM, Kavya K, Babu RL, Ramesh GT, Sharma SC. Cadmium induces oxidative stress and apoptosis in lung epithelial cells. Toxicol Mech Methods. 2016;26(9):658-666. DOI: 10.1080/15376516.2016.1223240

[86] Xu YM, Wu DD, Zheng W, Yu FY, Yang F, Yao Y, Zhou Y, Ching YP, Lau AT. Proteome profiling of cadmium-induced apoptosis by antibody array analyses in human bronchial epithelial cells. Oncotarget. 2016;7(5):6146-58. DOI: 10.18632/oncotarget.6738

[87] Richeldi L, Collard HR, Jones MG. Idiopathic pulmonary fibrosis. Lancet. 2017;389(10082):1941-1952. DOI: 10.1016/S0140-6736(17)30866-8

[88] Meyer KC. Pulmonary fibrosis, part I: epidemiology, pathogenesis, and diagnosis. Expert Rev Respir Med. 2017;11(5):343-359. DOI: 10.1080/17476348.2017.1312346

[89] Klimova B, Kuca K, Novotny M, Maresova P. Cystic fibrosis revisited - A review study. Med Chem. 2017;13:102-109. DOI: 10.2174/157340641266616 0608113235

[90] Gulati S, Thannickal VJ. The Aging Lung and Idiopathic Pulmonary Fibrosis. Am J Med Sci. 2019;357(5):384-389. DOI: 10.1016/j.amjms.2019.02.008

[91] O'Hare M, Amarnani D, Whitmore HAB, An M, Marino C, Ramos L, Delgado-Tirado S, Hu X, Chmielewska N, Chandrahas A, Fitzek A, Heinrich F, Steurer S, Ondruschka B, Glatzel M, Krasemann S, Sepulveda-Falla D, Lagares D, Pedron J, Bushweller JH, Liu P, Arboleda-Velasquez JF, Kim LA. Targeting RUNX1 prevents pulmonary fibrosis and reduces expression of SARS-CoV-2 host mediators. Am J Pathol. 2021;S0002-9440(21)00161-9. DOI: 10.1016/j.ajpath.2021.04.006

[92] Della Latta V, Cecchettini A, Del Ry S, Morales MA. Bleomycin in the setting of lung fibrosis induction: From biological mechanisms to counteractions. Pharmacol Res. 2015;97:122-130. DOI: 10.1016/j.phrs.2015.04.012

[93] Hu X, Fernandes J, Jones DP, Go YM. Cadmium stimulates myofibroblast differentiation and mouse lung fibrosis. Toxicology. 2017;383:50-56. DOI: 10.1016/j.tox.2017.03.018

[94] Liu T, De Los Santos FG, Phan SH. The Bleomycin Model of Pulmonary Fibrosis. Methods Mol Biol. 2017;1627:27-42. DOI: 10.1007/978-1-4939-7113-8_2

[95] Yan Z, Zhang X, Li C, Jiao S, Dong W. Association between consumption of soy and risk of cardiovascular disease: a meta-analysis of observational studies. Eur J Prev Cardiol 2017, 24(7): 735-747. DOI: 10.1177/2047487316686441. Epub 2017 Jan 9.

[96] Erdman TW Jr. Soy protein and cardiovascular disease. A statement for healthcare professionals from the nutricion committee of the AHA. Circulation 2000;102: 2555-2559. DOI:.org/10.1161/01.CIR.102.20.2555

[97] Ma L, Liu G, Ding M, Zong G, Hu FB, Willett WC, Rimm EB, Manson JE, Sun Q. Isoflavone intake and the risk of coronary heart disease in US men and women. Results from 3 prospective cohort studies. Circulation 2020;141:1127-1137 DOI:.org/10.1161/CIRCULATIONAHA.119.041306

[98] Ramdath DD, Padhi EM, Sarfaraz S, Renwick S, Duncan AM. Beyond the cholesterol-lowering effect of soy protein: a review of the effects of dietary soy and its constituents on risk factors for cardiovascular disease. Nutrients. 2017;9(4):324. DOI: 10.3390/nu9040324.

[99] Ferramola ML, Perez Diaz MFF, Honoré SM, Sánchez SS, Antón RI, Anzulovich AC, Giménez MS. Cadmium-induced oxidative stress and histological damage in the myocardium. Effect of a soy-based diet. Toxicol Appl Pharmacol. 2012;265(3): 380-389. DOI: 10.1016/j.taap.2012.09.009.

[100] Perez Diaz MFF, Plateo Pignatari MG, Filippa VP, Mohamed FH, Marchevsky EJ, Gimenez MS, Ramirez DC. J Trace Elem Med Biol 2019;52: 239-246 DOI: 10.1016/j.jtemb.2019.01.007.

[101] Essawy AE, Abdou HM, Ibrahim HM, Bouthahab NM. Soybean isoflavone ameliorates cognitive impairment, neuroinflammation, and amyloid β accumulation in a rat model of Alzheimer's disease. Environ Sci Pollut Res Int. 2019;26(25):26060-26070. DOI: 10.1007/s11356-019-05862-z.

[102] Shimizu A, Mitani T, Tanaka S, Fujii H, Maebuchi M, Amiya Y, Tanaka M, Matsui T, Nakamura S, Katayama S. Soybean-Derived Glycine-Arginine Dipeptide Administration Promotes Neurotrophic Factor Expression in the Mouse Brain. J Agric Food Chem. 2018;66(30):7935-7941. DOI: 10.1021/acs.jafc.8b01581

[103] Ariyani W, Miyazaki W, Amano I, Hanamura K, Shirao T, Koibuchi N. Soy Isoflavones Accelerate Glial Cell Migration via GPER-Mediated Signal Transduction Pathway. Front Endocrinol. 2020;11:554941. DOI: 10.3389/fendo.2020.554941

[104] Molteni A, Brizio-Molteni L, Persky V. In vitro hormonal effects of soybean isoflavones. J Nutr. 1995;125(3 Suppl):751S-756S. DOI: 10.1093/jn/125.3_Suppl.751S.

[105] Miksicek RJ. Estrogenic flavonoids: structural requirements for biological activity. Proc Soc Exp Biol Med. 1995;208(1):44-50. DOI: 10.3181/00379727-208-43830.

[106] Adlercreutz H, Mazur W. Phyto-oestrogens and Western diseases. Ann Med. 1997 Apr;29(2):95-120. DOI: 10.3109/07853899709113696.

[107] Pan Y, Anthony M, Watson S, Clarkson TB. Soy phytoestrogens improve radial arm maze performance in ovariectomized retired breeder rats and do not attenuate benefits of 17h-estradiol treatment. Menopause. 2000;7:230 – 5. DOI: 10.1097/00042192-200007040-00004.

[108] File SE, Jarrett N, Fluck E, Duffy R, Casey K, Wiseman H. Eating soya improves human memory. Psychopharmacology. 2001;157:430 – 6. DOI: 10.1007/s002130100845.

[109] Kritz-Silverstein D, Von Muhlen D, Barrett-Connor E, Bressel MA. Isoflavones and cognitive function in older women: the SOy and Postmenopausal Health In Aging (SOPHIA) Study. Menopause. 2003;10:196 – 202.

[110] Duffy R, Wiseman H, File SE. Improved cognitive function in postmenopausal women after 12 weeks of consumption of a soya extract containing isoflavones. Pharmacol Biochem Behav. 2003;75:721 – 9. DOI: 10.1016/s0091-3057(03)00116-3.

[111] Kreijkamp-Kaspers S, Kok L, Grobbee DE, de Haan EH, Aleman A, Lampe JW. Effect of soy protein containing isoflavones on cognitive function, bone mineral density, and plasma lipids in postmenopausal women: a randomized controlled trial. JAMA. 2004;292:65 – 74. DOI: 10.1001/jama.292.1.65.

[112] White LR, Petrovitch H, Ross GW, Masaki K, Hardman J, Nelson J, et al. Brain aging and midlife tofu consumption. J Am Coll Nutr.

2000;19:242 – 55. DOI: 10.1080/07315724.2000.10718923.

[113] Lund TD, West TW, Tian LY, Bu LH, Simmons DL, Setchell KD. Visual spatial memory is enhanced in female rats (but inhibited in males) by dietary soy phytoestrogens. BMC Neurosci 2001;2:20. DOI: 10.1186/1471-2202-2-20.

[114] Lee YB, Lee HJ, Won MH, Hwang IK, Kang TC, Lee JY. Soy isoflavones improve spatial delayed matching-to-place performance and reduce cholinergic neuron loss in elderly male rats. J Nutr. 2004;134:1827 – 31. DOI:10.1093/jn/134.7.1827

[115] Bregman BS, Coumans JV, Dai HN, Kuhn PL, Lynskey J, McAtee M, Sandhu F. Transplants and neurotrophic factors increase regeneration and recovery of function after spinal cord injury. Prog Brain Res. 2002;137:257-273. doi: 10.1016/s0079-6123(02)37020-1

[116] Gurd JW. Protein tyrosine phosphorylation: implications for synaptic function. Neurochem Int. 1997;31:635 – 49. DOI:10.1016/S0197-0186(97)00022-3

[117] Phillis JW, Song D, O'Regan MH. Inhibition of tyrosine phosphorylation attenuates amino acid neurotransmitter release from the ischemic/reperfused rat cerebral cortex. Neurosci Lett. 1996;207: 151-154. DOI: 10.1016/0304-3940(96)12521-0.

[118] O'Dell TJ, Kandel ER, Grant SG. Long-term potentiation in the hippocampus is blocked by tyrosine kinase inhibitors. Nature. 1991;353:558 – 60. DOI: 10.1038/353558a0.

[119] Akiyama T, Ishida J, Nakagawa S, Ogawara H, Watanabe S, Itoh N. Genistein, a specific inhibitor of tyrosine-specific protein kinases. J Biol Chem. 1987;262:5592 – 5595.

[120] Linford NJ, Dorsa DM. 17h-Estradiol and the phytoestrogen genistein attenuate neuronal apoptosis induced by the endoplasmic reticulum calcium-ATPase inhibitor thapsigargin. Steroids 2002;67: 1029 – 1040. DOI: 10.1016/s0039-128x (02)00062-4.

[121] Linford NJ, Yang Y, Cook DG, Dorsa DM. Neuronal apoptosis resulting from high doses of the isoflavone genistein: role for calcium and p42/44 mitogen-activated protein kinase. J Pharmacol Exp Ther. 2001; 299:67 – 75.

[122] Bang OY, Hong HS, Kim DH, Kim H, Boo JH, Huh K, Mook-Jung I. Neuroprotective effect of genistein against beta amyloid-induced neurotoxicity. Neurobiol Dis. 2004;16: 21 – 8. DOI: 10.1016/j.nbd.2003.12.017

[123] Deol P, Kozlova E, Valdez M, Ho C, Yang EW, Richardson H, Gonzalez G, Truong E, Reid J, Valdez J, Deans JR, Martinez-Lomeli J, Evans JR, Jiang T, Sladek FM, Curras-Collazo MC. Dysregulation of Hypothalamic Gene Expression and the Oxytocinergic System by Soybean Oil Diets in Male Mice. Endocrinology. 2020;161(2):bqz044. DOI: 10.1210/endocr/bqz044.

[124] Antonio MT, Corredor L, Leret ML. Study of the activity of several brain enzymes like markers of the neurotoxicity induced by perinatal exposure to lead and/or cadmium. Toxicology Letters. 2003;143(3):331-340. DOI: 10.1016/s0378-4274(03)00194-2.

[125] Gabbiani G, Baic D, Déziel C. Toxicity of cadmium for the central nervous system. Exp Neurol. 1967;18(2):154-160. DOI: 10.1016/0014-4886(67)90037-4.

[126] Shukla A, Shukla GS, Srimal RC. Cadmium-induced alterations in blood-brain barrier permeability and its possible correlation with decreased

microvessel antioxidant potential in rat. Hum Exp Toxicol. 1996;15(5):400-405. DOI: 10.1177/096032719601500507.

[127] Mendez-Armenta M, Rios C. Cadmium neurotoxicity. Environmental Toxicology and Pharmacology. 2007;23(3):350-358. DOI: 10.1016/j.etap.2006.11.009

[128] Yokel, RA. Blood-brain barrier flux of aluminum, manganese, iron and other metals suspected to contribute to metal-induced neurodegeneration. Journal of Alzheimer's Disease. 2006;10(2-3), 223-253. DOI: 10.3233/jad-2006-102-309.

[129] Karri V, Schumacher M, Kumar V. Heavy metals (Pb, Cd, As and MeHg) as risk factors for cognitive dysfunction: a general review of metal mixture mechanism in brain. Environ Toxicol Pharm. 2016;48:203-213. DOI: 10.1016/j.etap.2016.09.016

[130] Monroe RK, Halvorsen SW. Cadmium blocks receptor-mediated Jak/STAT signaling in neurons by oxidative stress. Free Radic Biol Med. 2006;41(3):493-502. DOI: 10.1016/j.freeradbiomed.2006.04.023.

[131] Unsal C, Kanter M, Aktas C, Erboga M. Role of quercetin in cadmium-induced oxidative stress, neuronal damage, and apoptosis in rats. Toxicol Ind Health. 2015;31(12):1106-1115. DOI: 10.1177/0748233713486960

[132] Coyle JT, Puttfarcken P. Oxidative stress, glutamate, and neurodegenerative disorders. Science. 1993;262(5134):689-695. DOI: 10.1126/science.7901908.

[133] Cadet JL. Free radical mechanisms in the central nervous system: an overview. Int J Neurosci. 1988;40(1-2):13-18. DOI: 10.3109/00207458808985722.

[134] Abdalla FH, Schmatz R, Cardoso AM, Carvalho FB, Baldissarelli J, de Oliveira JS, Rosa MM, Gonçalves Nunes MA, Rubin MA, da Cruz IB, Barbisan F, Dressler VL, Pereira LB, Schetinger MR, Morsch VM, Gonçalves JF, Mazzanti CM. Quercetin protects the impairment of memory and anxiogenic-like behavior in rats exposed to cadmium: Possible involvement of the acetylcholinesterase and Na(+),K(+)-ATPase activities. Physiol Behav. 2014;135:152-167. DOI: 10.1016/j.physbeh.2014.06.008.

[135] Ferreira-Vieira TH, Guimaraes IM, Silva FR, Ribeiro FM. Alzheimer's disease: Targeting the Cholinergic System. Curr Neuropharmacol. 2016;14(1):101-115. DOI: 10.2174/1570159x13666150716165726

[136] Snelson M, Mamo JCL, Lam V, Giles C, Takechi R. Differential Effects of High-Protein Diets Derived from Soy and Casein on Blood-Brain Barrier Integrity in Wild-type Mice. Front Nutr. 2017;4:35. DOI:10.3389/fnut.2017.00035

[137] Ditscheid B, Funfstuck R, Busch M, Schubert R, Gerth J, Jahreis G. Effect of l-methionine supplementation on plasma homocysteine and other free amino acids: a placebo-controlled double-blind cross-over study. Eur J Clin Nutr. 2005;59:768-775. DOI: 10.1038/sj.ejcn.1602138

[138] Jakubowski H. Pathophysiological consequences of homocysteine excess. J Nutr. 2006;136:1741S–1749S. DOI: 10.1093/jn/136.6.1741S.

[139] Tyagi N, Kumar M, Pushpakumar SB, Lominadze D, Moshal KS, Sen U. Homocysteine attenuates blood brain barrier function by inducing oxidative stress and the junctional proteins. FASEB J. 2008 22:734.737. DOI: 10.3389/fnut.2018.00067

[140] Kalani A, Kamat PK, Givvimani S, Brown K, Metreveli N, Tyagi SC, et al. Nutri-epigenetics ameliorates

blood-brain barrier damage and neurodegeneration in hyperhomocysteinemia: role of folic acid. J Mol Neurosci. 2014;52:202-215. DOI: 10.1007/s12031-013-0122-5.

[141] Halder S, Kar R, Chakraborty S, Bhattacharya SK, Mediratta PK, Banerjee BD. Cadmium level in brain correlates with memory impairment in F1 and F2 generation mice: improvement with quercetin. Environ Sci Pollut Res Int. 2019;26(10):9632-9639. DOI: 10.1007/s11356-019-04283-2.

[142] Liu J, Chang SK, Wiesenborn D. Antioxidant properties of soybean isoflavone extract and tofu in vitro and in vivo. J Agric Food Chem. 2005;53(6):2333-2340. DOI: 10.1021/jf048552e

[143] Bjorkhem I, Meaney S, Fogelman AM. Brain cholesterol: Long secret life behind a barrier. Thromb Vasc Biol. 2004;24:806-815. DOI: 10.1161/01.ATV.0000120374.59826.1b.

[144] Pitas RE, Boyles JK, Lee SH, Hui D, Weisgraber KH. Lipoproteins and their receptors in the central nervous system. Characterization of the lipoproteins in cerebrospinal fluid and identification of apolipoprotein B,E (LDL) receptors in the brain. The Journal of Biological Chemistry. 1987;262(29):14352-14360.

[145] Modi HR, Katyare SS. Cadmium exposure-induced alterations in the lipid/phospholipids composition of rat brain microsomes and mitochondria. Neurosci Lett. 2009;464(2):108-112. DOI: 10.1016/j.neulet.2009.08.003.

[146] Kroemer G. The proto-oncogene Bcl-2 and its role in regulating. Nat Med. 1997;3(6):614-620. DOI: 10.1038/nm0697-614

[147] Peng Y, Jiang B, Wu H, Dai R, Tan L. Effects of genistein on neuronal apoptosis, and expression of Bcl-2 and Bax proteins in the hippocampus of ovariectomized rats. Neural Regen Res. 2012;7(36):2874-2881. DOI: 10.21203/rs.3.rs-258892/v1

[148] Mahmoud FY, El-Hakim AH, El Deen Amer AS, Fidal MW. Effect of exposure to cadmium on the hippocampus in adult albino rat and the possible role of L-carnitine. J Curr Med Res Pract. 2019;4:240-250. DOI: 10.4103/jcmrp.jcmrp_60_18

[149] Farahmand, M., Tadjali, M. Effect of Persian sage (Salvia Rhytidia) extract on histomorphometric changes of cerebellum following ischemia reperfusion injuries in rat. Comparative Clinical Pathology, 2014;24(5), 1129-1137. DOI: 10.1007/s00580-014-2046-z