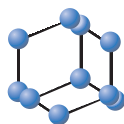
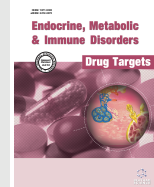


## REVIEW ARTICLE

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SCIENCE

## BPA and Nutraceuticals, Simultaneous Effects on Endocrine Functions

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**Abstract: Background:** Bisphenol A (BPA) is worldwide diffused as a monomer of epoxy resins and polycarbonate plastics and has recognized activity as Endocrine Disruptor (ED). It is capable to interfere or compete with endogenous hormones in many physiological activities thus having adverse outcomes on health. Diet highly affects health status and in addition to macronutrients, provides a large number of substances with recognized pro-health activity, and thus called nutraceuticals.

**Objective:** This mini-review aims at summarizing the possible opposite and simultaneous effects of BPA and nutraceuticals on endocrine functions. The possibility that diet may represent the first instrument to preserve health status against BPA damages has been discussed.

**Methods:** The screening of recent literature in the field has been carried out.

**Results:** The therapeutic and anti-oxidant properties of many nutraceuticals may reverse the adverse health effects of BPA.

**Conclusion:** *In vitro* and *in vivo* studies provided evidence that nutraceuticals can preserve the health. Thus, the use of nutraceuticals can be considered a support for clinical treatment. In conclusion, dietary remediation may represent a successful therapeutic approach to maintain and preserve health against BPA damage.

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## 1. INTRODUCTION

The main consequence of industrialization is the contamination of environment with chemical substances which get into living beings through different routes and impact health. Endocrine Disruptors (EDs) are natural and synthetic substances (*e.g.* chemicals, dioxins, drugs, pesticides, phytoestrogens, phthalates, plasticizers, polychlorinated biphenyls, *etc.*) with adverse health effects by means of interference or competition with endogenous hormones in many physiological activities. EDs may influence endocrine system at multiple levels, with main outcomes on male and female reproductive axis, reproductive functions and fertility rate, thyroid functions, growth and metabolism, immune response, behavior and developmental process (*e.g.* brain) [1, 2].

Bisphenol A (BPA, 2,2-bis (4-hydroxyphenyl) propane) has been used as plastic softener since the 1960s and is capable to interfere in steroid signaling. This ED is worldwide diffused as monomer of polycarbonate plastics and epoxy resins and has possible adverse effects on liver, lung,

thyroid, nervous, cardiovascular, immune and reproductive systems [2-8].

Diet highly affects health status. High caloric diet, added sugar consumption and fat rich diets are the main causes of illness such as metabolic disorders, cardiovascular and neurological diseases. Conversely, the consumption of fresh fruit and vegetables not only prevents obesity but also reduces the risk of many diseases. Thus, balanced diet is the main tool for health preservation and maintenance and for the prevention of diseases. In this respect, in addition to macronutrients, diet also provides a large number of substances with recognized healthy activity, and thus called nutraceuticals.

This mini-review aims at summarizing the possible opposite and simultaneous effects of BPA and nutraceuticals on endocrine functions. The possibility that diet may represent the first instrument to preserve health status against BPA damage has been discussed.

## 2. BPA: SOURCES, EXPOSURE ROUTE AND IMPACT ON HEALTH

## 2.1. Sources and Exposure

BPA is a ubiquitous industrial chemical used in the manufacture of polycarbonate plastics and epoxy resins, and thus commonly used for the production of food packaging,

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drinking and microwave containers, stretch films, thermal papers, flame retardants, sport equipments, metal cans coating *etc.* [2, 8]. BPA leaches from several consumer products into living being tissues, surface water, and soil [2, 9] (Fig. 1). Actually, it has assigned the third highest Toxicological Priority Index by the US Environmental Protection Agency (EPA) and US National Toxicology Program (NTP) [10, 11]. The detection of BPA in the urine of 93% of the USA population confirms the widespread exposure to BPA of human population [12].

At present many countries, including the USA, abandoned the use of BPA in products intended for infants like baby bottles and sippy cups. However, BPA is still used in other polycarbonate bottles and food containers, but also in the epoxy resins commonly used as inner coatings to protect metallic food cans from corrosion and rusting. Foods represent the primary source of BPA exposure. In fact, the exposure of food packaging/containers to high temperature as in microwave, dishwashing machine, boiling water and brushing but also pH changes or the contact of cans with oils, sodium chloride solutions or acid/basic foods all cause BPA leaching in foods, drinks and water [13-15].

After ingestion, BPA is rapidly metabolized into several inactive metabolites, such as BPA-glucuronide and BPA-sulfate; free BPA is excreted mainly in feces (56-82%) and its metabolites are found in urine. Bioaccumulation in adipose tissues has also been reported [16].

Apart from foods, additional exposure routes for humans are through respiration and skin absorption [15] (Fig. 1).

## 2.2. Impact on Health

BPA has estrogenic and anti-androgenic activities due to its ability to bind steroid receptors such as the nuclear Estro-

gen Receptor  $\alpha/\beta$  (ER $\alpha/\beta$ ), Androgen Receptor (AR) and the membrane estrogen receptor GPER30 [15]. In general, BPA outcomes on health strongly depends on doses, exposure route, duration and life stage [3, 5, 6]. The actual temporary Tolerable Daily Intake (t-TDI) of BPA is 4  $\mu\text{g}/\text{kgbw}/\text{day}$  and the daily human exposure is estimated to be less than 1  $\mu\text{g}/\text{kgbw}/\text{day}$ ; however, a review of recent relevant scientific evidence for BPA hazard assessment was carried out to reconsider the t-TDI [17, 18].

Specific time windows, such as early embryonic development, gestational stages BPA crosses placental barrier- [19, 20], neonatal period, childhood, peri-pubertal and pubertal period are actually considered most critical for BPA exposure due to the possible impact of BPA on developmental stages. Particular attention deserves also lactation phase. In fact, BPA may partition into fat, breast milk and human colostrum. Despite the reported levels are generally below the fixed limits, breast milk is considered a continuous low-level exposure to endocrine-active compounds for infants [21].

Impact on development, behavior, metabolic, reproductive, neurological, cardiovascular and immune functions have been reported [2-8, 22, 23]. However, literature concerning BPA outcomes on health is really large. Here we summarize the most recent evidence in endocrine and immune functions.

## 2.3. Metabolic Functions

BPA exposure raises the risk of overweight and obesity and many authors consider BPA an obesogenic substance [22]. BPA interferes in adipogenesis and impacts energy homeostasis promoting lipid and glucose dysregulation, inhibits the release of adiponectin, stimulates inflammatory adipokines (*i.e.* interleukin-6 and tumor necrosis factor),

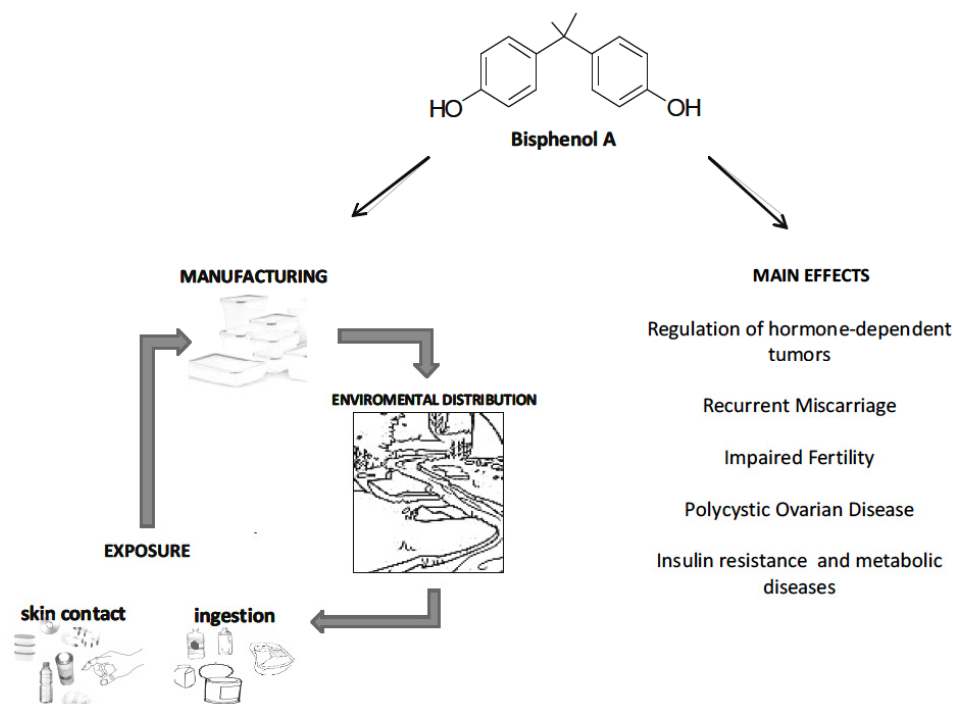


Fig. (1). Schematic representation of the main exposure routes to BPA and of the main effects on health.

alters insulin synthesis and/or release by pancreatic  $\beta$ -cells and insulin signaling within insulin-sensitive organs such as liver, muscle and adipose tissues. In the liver, it increases the storage of lipids, impairs mitochondrial function and induces oxidative stress, thus causing steatosis [24-27]. In addition, BPA strongly contributes to the pathophysiology of obesity. Centrally, BPA affects food intake and metabolism by means of direct activity on metabolic sensors produced in the arcuate nucleus [28, 29] such as the appetite (AgRP, NPY) and satiety (POMC) neuropeptides [30], with possible epigenetic mechanisms [29]. Furthermore, the bioaccumulation of BPA in adipose tissue [16] may lead to long-term effects.

As reviewed by Chevalier & Féniche in 2015, BPA exposure at pregnancy affects both mother and offspring. Mothers can gain an excess in body weight and develop insulin resistance and hyperinsulinemia. The offspring can develop obese phenotype with altered glucose homeostasis, increased weight and adipogenesis. In the adult, BPA can lead to glucose intolerance, insulin resistance and defects in insulin release [31].

#### 2.4. Inflammation and Cancer

CD4<sup>+</sup> T helper (Th) lymphocytes, B lymphocytes, macrophages, mast cells, Natural Killer (NK) cells and Dendritic Cells (DCs) are the main targets of BPA in the modulation of inflammation and immune response [23].

BPA is involved in the regulation of hormone-dependent tumors such as breast, ovarian, prostate cancer and others affecting cancer cell growth, survival, proliferation, migration, invasion, apoptosis and anticancer drug resistance through several signaling pathways [23]. Molecular mechanisms involving ER $\alpha$ / $\beta$ , AR, GPER30, Insulin-like Growth Factor-1 Receptor (IGF-1R) and Estrogen Related Receptor Gamma (ERR $\gamma$ ) have been recently summarized by Murata and Kang 2018 [23].

#### 2.5. Reproductive Functions

Reproductive functions strongly depend on endocrine, paracrine and autocrine communications along the hypothalamus-pituitary-gonadal factors, and in particular from sex steroids [32-34]. BPA affects the central and local control of reproduction, steroidogenesis, gametogenesis and gamete quality in both sexes as previously reported [2, 5, 7, 35-39].

In general, the main consequence of BPA exposure in the testis is the occurrence of oxidative stress and cell damage. Impairment of blood-testis barrier, apoptosis of Sertoli and germ cells, defective steroidogenesis, DNA breaking and reduced semen parameters (count, motility, viability) are the main outcomes on testis physiology and semen quality [40]. In rats exposed from gestational stage to BPA doses potentially considered safe for humans, impairment in both spermatogenesis and post-natal development of epididymis has been reported [41, 42], thus suggesting that BPA may affect the microenvironment in which spermatozoa maturation occurs.

Recently, the associations among urinary BPA concentrations, reproductive hormone and semen quality have been investigated in human revealing positive correlation with LH

(as marker Leydig cell capacity) and negative with sperm counts [40]. Sperm concentration and motility were significantly correlated to maternal serum BPA [43], confirming that oestrogenic environmental exposures during pregnancy may influence testicular function in the adult.

In females, BPA regulates the development of mammary gland, oocyte maturation, folliculogenesis and steroidogenesis [2, 7] and its exposure has been related to reduced oocyte quality, defective uterine receptivity and pathogenesis of polycystic syndrome, with conflicting results concerning the effects on premature puberty and endometriosis development [7]. By crossing the placenta, BPA affects embryo health and development and decreases birth weight centile [44]. A possible mechanism involving the rate of placental vascularisation has been suggested to explain the lower birth weight [45]. Lastly, the accumulation of BPA in placenta positively correlates with preeclampsia [46].

Upcoming evidence revealed BPA involvement in the definition of epigenetic signatures in embryo and gametes with possible trans-generational effects. During embryonic stages, BPA may interfere in epigenetic mechanisms as for imprinting, the process by which paternal or maternal copy of specific genes are selectively shut down. Later, during gametogenesis, it may affect the epigenetic signature of gametes (*i.e.* DNA methylation, chromatin remodeling, production of specific non-coding RNA) leading to poor gamete quality, impairment of early embryo development and possible pregnancy failure. In such a way, the effects of parental exposure fall on the next generations accordingly to a model of epigenetic transgenerational inheritance [2].

### 3. NUTRACEUTICALS: SOURCE AND IMPACT ON HEALTH

The term "nutraceutical" was coined from "nutrition" and "pharmaceutical" in 1989 by Stephen DeFelice, MD, founder and chairman of the Foundation for Innovation in Medicine (FIM). DeFelice defined nutraceutical as, "a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease" [47].

Nutraceuticals are pharmacologically active substances. They can be extracted from both vegetal and animal food, concentrated and administered in a suitable pharmaceutical form. Nutraceuticals have elements of both foods and medicinal products but do not completely satisfy the requirements of either regime. [48-50]. Contrarily to drugs, nutraceuticals are used with therapeutic value even in the absence of clinical trials that prove their efficacy; in addition, the natural origin of a nutraceutical does not necessarily correlate to safety and therapeutic efficacy.

Medicines can have mild to severe side effects. Nutraceuticals are often safer, presenting minimal undesirable effects compared to conventional drugs, in addition to having in many cases greater bioavailability. It is necessary to pay attention to the fact that nutraceuticals are not less complex than medicines and therefore it is advisable to reduce the risk of "do-it-yourself" [51, 52].

The basic information on several nutraceuticals has been summarized in Table 1.

**Table 1. Basic information on several nutraceuticals.**

Nutraceutical	Chemical Constituent	Food	Health Benefit
Allicin	Diallyl disulfide	Garlic ( <i>Allium sativum</i> ), onion	Antibacterial, antifungal, antithrombotic, hypotensive activities; anti-cancer, anti-parasitic, anti-inflammatory activities
Genistein, daidzein	Phytoestrogens (isoflavones)	Soybeans, legumes	Lowers LDL cholesterol, antioxidant activity, anti-cancer (prostate, breast, bowel) activities
Lycopene	Carotenoid (isoprenoid)	Tomatoes, pink grapefruit, guava papaya, watermelon	Anti-oxidant activity; protects against the formation of cancer mainly prostate, bladder, cervical, leukemia
Resveratrol	Polyphenolic compound	Dark grapes, raisins, peanuts, berries	Lowers total serum cholesterol increasing HDL; neuroprotective, anti-atherogenic, anti-thrombotic, anti-inflammatory, anti-oxidant, pro-angiogenic, vasorelaxing and anti-cancer effects
$\beta$ -Carotene	Carotenoid (isoprenoid)	Carrots, oranges, tangerines, corn, avocado, various fruits and vegetables	Anti-oxidant activity which neutralizes free radicals
Selenium	Mineral	Sardines, cod, sole, walnuts, peas	Anti-oxidant activity; anti-cancer activity; important constituent of balanced diet
Quercetin	Polyphenols (flavonol)	Vegetables, fruits, red wines, and blackberries.	Anti-oxidant, anti-inflammatory and neuroprotective properties
Catechin, epicatechin	Polyphenolic compounds (flavonoids)	Tea (extracted from <i>Camellia sinensis</i> ), citrus, apples, berries	Anti-oxidants anti-cancer properties; liver protection; apoptosis in human prostate cancer cells
Omega 3 Fatty acids (PUFA, Polyunsaturated fatty acids)	Fatty acids	Salmon, flax seed	Potent controller of the inflammatory processes; maintenance of brain functions; reduce cholesterol disposition; reduce the risk of coronary heart disease
Curcumin	Polyphenolic compound (diferuloylmethane)	Turmeric root	Anti-inflammatory; effective anti anti-clotting agent; anti-Parkinson, anti- HIV, anti-oxidant and anti-cancer activities
Retinol	Vitamin A	Beef liver, hen eggs, dairy products	Anti-oxidant activity; essential for growth and development in treatment of skin disorder
Lactobacilli, bifidobacteria	Probiotics/prebiotics	Yogurt, dairy applications	May improve gastrointestinal health and systemic immunity
Folic acid	Vitamin B	Hen eggs, goat liver, cereals, pulses and green leafy vegetables	Essential for the synthesis of DNA and proteins; important for tissues that undergo proliferation and differentiation processes

Some popular nutraceuticals include aloe-vera gels, echinacea, ephedra, folic acid, garlic, ginger, ginseng, glucosamine, green tea, cod liver oil, omega-3, calcium enriched orange juice, *etc.* Many nutraceuticals derive from vegetables. Plant extracts, as phytochemicals, containing secondary metabolites have served as anti-oxidants in phytotherapeutic medicines to protect against various diseases for centuries. Natural anti-oxidants exhibit a wide range of pharmacological activities and have been shown to have anti-cancer, anti-

inflammatory and anti-aging properties. Anti-oxidant activity is the fundamental property of phenolic medicinal plant compounds; it is important for their health protecting effects, including the anti-mutagenic, anti-carcinogenic, and anti-aging activity [53]. Phytochemicals (bioactive non-nutrient plant compounds) and their metabolic products may also inhibit pathogenic bacteria, while they stimulate the growth of beneficial bacteria, exerting prebiotic-like effects [54-56]. Interactions between functional food components, such as

prebiotics, probiotics, phytochemicals, and intestinal microbiota, have consequences on human health [54]. Phytochemicals have raised interest in human nutrition because of their potential effects as anti-oxidants, anti-estrogenic, anti-inflammatory, immunomodulatory, and anti-carcinogenic [54-58].

Polyphenols are phytochemicals with widespread distribution in foods of plant origin. Polyphenols possess a wide range of beneficial effects against atherosclerosis, brain dysfunction, stroke, Cardiovascular Diseases (CVD), and cancer [59-61]. These phytochemicals are structurally diverse, and include flavonoids, phenolic acids, stilbenes and lignans [62]. Flavones, mainly consisting of luteolin and apigenin glycosides, are less common than flavonols in fruit and vegetables; parsley and celery are the main edible sources of flavones. Flavanones, present in tomatoes and certain aromatic plants such as mint, are present in high concentrations only in citrus fruit. Isoflavones, flavonoids with structural similarities to estrogens, have the ability to bind to ERs, and thus are classified as phytoestrogens. They are found almost exclusively in leguminous plants. Flavanols occur as catechins (a monomer form) and proanthocyanidins (the polymer form) [63]. They are found in fruits, vegetables, cereal and legumes. Additionally, they are extracted from beverages produced from plant products such as tea, coffee, wine and cocoa.

Polyphenols found in grapes and grape derivatives, cocoa and tea are of interest in the prevention of Cardiovascular Disease (CVD) [64].

One of the most well-described mechanisms on neurovascular protection involves the ability of polyphenols to generate Nitric Oxide (NO), a potent vasodilator generated by endothelial cells, which can also regulate the expression of cardiovascular-related genes. Consequently, polyphenols prevent the progression of endothelial dysfunction, decreasing the development of atherosclerotic plaque, vascular thrombosis, and occlusion. In early stages of atherosclerosis development, polyphenols contribute to reducing LDL oxidation, improving antioxidant status, and decreasing the levels of inflammatory cytokines and adhesion molecules [61].

Several studies have indicated that grape polyphenols may influence plasma lipid concentrations. Consumption of grape juice has been associated with elevated HDL-Cholesterol [64, 65].

Resveratrol (3,5,4'-trihydroxy-trans-stilbene) is the most extensively studied grape-derived stilbene. Besides grapes, it is common to a variety of species including cranberries, blueberries, peanuts, and Japanese knotweed.

Quercetin has been suggested as a flavonoid and natural product for the treatment of Alzheimer's disease [66, 67]. Quercetin exhibits direct pro-apoptotic effects on tumor cells and thus can inhibit the progress of numerous human cancers. The anti-cancer effect of quercetin has been documented in numerous *in vitro* and *in vivo* studies that involved several cell lines and animal models. On the other hand, the high toxic effect of quercetin against cancer cells is accompanied with little or no side effects or harm to normal cells [68]. Quercetin and its derivatives lead to an enhancement in heart features, indicating the prospective for quercetin to be

used in the treatment of cardiac diseases. Several evidence-based studies suggest mechanisms to observe CVD such as aging effects, hypertension, angiotensin-converting enzyme activity and endothelial-dependent and independent functions. Different animal models including human are also used to elucidate the *in vivo* role of quercetin in CVD [69].

Berries contain a wide range of phytochemicals with nutraceutical properties, as anti-oxidants, anti-cancer, anti-neurodegenerative, anti-inflammatory. The chemopreventive agents in the berries include vitamins A, C, and E, folic acid, calcium, selenium,  $\beta$ -carotene,  $\alpha$ -carotene, lutein, polyphenols such as acid ellagic, ferulic acid, p-coumaric acid, anthocyanins, quercetin, and different phytosterols such as  $\beta$ -sitosterol, stigmasterol and kaempferol [70]. The ability of freeze-dried raspberries, blackberries and strawberries to inhibit the development of cancer has been studied in the laboratory [71, 72]. Berry extracts have been evaluated for their ability to inhibit line growth cancer cells (*i.e.* mouth, breast, colon, prostate); raspberry and strawberry showed the more significant pro-apoptotic effects, without any effect on normal cells. Blueberry-related cell signaling pathways include the decrease of Phosphatidylinositol 3-Kinase (PI3K)/Akt and of Nuclear Factor  $\kappa$ B (NF- $\kappa$ B), while the protein kinase C and the ERK kinase are not affected [71, 73].

Curcuminoids are polyphenolic compounds found as active ingredients in the dietary spice turmeric (*Curcuma longa*) and curcumin is the primary curcuminoid. Due to the several therapeutic properties, curcumin has been used in traditional medicine as a food additive and turmeric is used to treat many health conditions in India and other parts of Asia [74-76]. Many types of evidence support the multiple anti-tumor properties of curcumin, including the inhibition of proliferation, invasion, metastasis, angiogenesis and the induction of apoptosis, suggesting that curcumin has strong therapeutic potential in multiple tumors through regulation of tumor progression [77, 78]. At molecular levels, curcumin can regulate different signaling pathways linked to apoptosis and cell proliferation, such as the suppression of IGF2 and IGF2-mediated PI3K/AKT/mTOR signaling pathway [79, 80]. Furthermore, evidence accumulation indicates that curcumin plays an important role in cancer progression by altering specific miRNA expressions in different tumors [81-83].

Genistein (4',5,7-trihydroxyisoflavone) is an isoflavone found in high amounts in soy, but also in other legumes like peas, lentils, beans. This important compound has a large variety of biological activities, but it is best known for its ability to inhibit cancer progression. Increased tumor growth can arise from an increase in the rate of cell division (*i.e.*, proliferation) and/or a decrease in the rate of cell death (*i.e.*, apoptosis or programmed cell death). Genistein can affect both processes, through the modulation of key regulatory proteins such as Akt and NF- $\kappa$ B. [84-86]. A significant correlation between the serum/plasma level of genistein and the incidence of gender-based cancers in Asian, European and American populations suggests that genistein may reduce the risk of tumor formation. Genistein inhibits a tyrosine kinase (PTK), which is involved in the phosphorylation of residues in tyrosine of receptors membrane and inhibits the topoisomerase II, which participates to replication, transcription and DNA repair. At concentrations that are similar to those

achieved through dietary consumption, genistein can inhibit the pro-metastatic processes of cancer cell detachment, migration, and invasion through a variety of mechanisms, including the Transforming Growth Factor (TGF)- $\beta$  signaling pathway [87].

Tea, the most consumed beverage in the world next to water, is extracted from the plant *Camellia sinensis* and is processed in different ways in different parts of the world to give green, black, or oolong tea. There is a vast amount of scientific literature suggesting that (-)-Epigallocatechin-3-Gallate (EGCG) is responsible for the majority of the potential health benefits attributed to green tea consumption. Catechins are found in many types of fruit, like apples (peel on), apricots, cherries, peaches, blackberries, black grapes, strawberries, blueberries and raspberries [88- 90]. EGCG promotes apoptosis through the stabilization of p53, the regulation negative activity of NF-kB, activation of the caspase, the change in the Bax/Bcl-2 ratio, the chymotrypsin-like activity of the 20S proteasome (purified) and the 26S proteasome in tumor cell lysates. EGCG (as well as luteolin, quercetin, kaempferol, apigenin and taxifolin) selectively inhibits the activity of the fatty acid synthetase -the fundamental enzyme for the formation of the cell membranes that is super-expressed in many cancer lines- and causes apoptosis in cancerous cells, but not in non-tumor fibroblasts. EGCG possesses a potent antioxidant capacity and exhibits extensive pharmacological activities; it may be useful for reducing hepatotoxicity associated with oxidative stress by the activation of Nrf2 signaling pathway [91].

Vitamin E, selenium, vitamin D, green tea, soy, and lycopene are examples of nutraceuticals widely studied in human health [47]. Polyunsaturated Fatty Acids (PUFAs) (which include the omega-3 and omega-6 fatty acids) and phytochemicals also play an important role as healthy dietary bioactive compounds [30, 54, 56]. A balanced PUFA composition of food influences diverse aspects of immunity and metabolism [54]. Combined protein, leucine, vitamin D, and n-3PUFA supplements may convey added benefits and may represent an intervention strategy in the prevention of sarcopenia and functional decline [92].

Various studies in recent years have shown the beneficial effects of omega-3 Poly Unsaturated Fatty Acids (PUFAs) through diverse mechanisms including anti-inflammatory effects [30]. It has been hypothesized the potential of this class of compounds in neurodegenerative diseases, such as Parkinson's, Alzheimer's, Huntington's disease, and amyotrophic lateral sclerosis, therapy through specific action against the mammalian target of rapamycin (mTOR) signaling pathway [93].

Carotenoids and retinoids have several similar biological activities such as anti-oxidant, anti-cancer and pro-apoptotic properties. Supplementation with carotenoids can affect cell growth and modulate gene expression and immune responses. Epidemiological studies have shown a correlation between high carotenoid dietary intake and a reduced risk of breast, cervical, ovarian, colorectal cancers, and of cardiovascular and eye diseases. Cancer chemoprevention by dietary carotenoids involves several mechanisms, including the effects on the gap junctional intercellular communication, growth factor signaling, differentiation-related proteins, cell

cycle progression, retinoid-like receptors, nuclear receptors, anti-oxidant response element, AP-1 transcriptional complex, Wnt/ $\beta$ -catenin pathway and inflammatory cytokines. Moreover, carotenoids can stimulate the proliferation of B- and T-lymphocytes, the activity of macrophages and cytotoxic T-cells, effector T-cells function and the production of cytokines [94]. *In vitro* studies have shown lycopene ability to inhibit the proliferation of several types of cancer cells *via* cell-cycle arrest and induction of apoptosis. There is also a significant correlation between higher skin concentrations of lycopene and a decrease in skin roughness [95].

The mixture containing quercetin, curcumin, green tea, cruciferex, and resveratrol demonstrated significant inhibition of the growth of Fanconi anemia head and neck squamous cell carcinoma and dose-dependent inhibition of cell proliferation, Matrix Metalloproteinase (MMP)-2 and -9 secretions, cell migration and invasion [63].

Allicin is one of the major organosulfur compounds in garlic. It reduces both the synthesis (perhaps through inactivation of HMGCoA reductase) and the intestinal absorption of cholesterol [96] thus exhibiting lipid-lowering properties and 9 to 12% decrease of total cholesterol [97]. Different mechanisms have been proposed to explain the effects of cancer prevention by vegetables and sulfuric organ compounds extracted from *Allium* species. These include the inhibition of mutagenesis, the modulation of enzymes, the inhibition of DNA adduct formation, the detoxification of free radical and the effects on cell proliferation [96, 98]. Allicin is reported to be able to attenuate oxidative stress and has neuroprotective effects on rabbits' ischemia-reperfusion spinal cord injury and thus allicin could protect mice from ischemia-reperfusion brain injury through a series of mechanisms [99].

The expanding nutraceutical market indicates that end users are seeking minimally processed food with extra nutritional benefits and organoleptic value. This development, in terms, is propelling expansion in the nutraceutical market globally. The emerging nutraceutical industry seems destined to occupy the landscape in the new millennium. Its tremendous growth has implications for the food, pharmaceutical, health care, and agricultural industries.

#### 4. BPA AND NUTRACEUTICALS: SIMULTANEOUS HEALTH EFFECTS

As summarized in the previous paragraph, BPA exposure has adverse health effects like reproductive toxicity, abnormal inflammatory or immune response and developmental disorders of brain or nervous system through various cell signaling pathways [2-8, 22, 23]. BPA exposure can induce oxidative stress and tissue damage, impair mitochondrial activity, gamete quality/motility and serum concentrations of sex steroids and gonadotropins [39]. Thus, nutraceuticals, have been investigated for their preventive activities and possible role against EDs effects. Several *in vivo* studies confirmed that the anti-oxidant properties of nutraceuticals and their therapeutic actions may reverse the adverse health effects of BPA [100-104].

Prepubertal BPA exposure (250 $\mu$ g/kg/bw) induced cell proliferation in the mammary gland of adult rats with an

increased risk of cancer development; conversely, genistein exposure (250mg/kg AIN-76Adiet) at 21 post natal day positively correlated to mammary gland maturation. Interestingly, BPA/genistein combined exposure decreased cell proliferation in the adult counteracting BPA effects. Thus, BPA/genistein administration can influence mammary gland cancer susceptibility [102]. Several studies showed that increased green tea consumption inhibits breast cancer progression, probably due to its high content of catechins and flavonoid, recognized substances with anti-cancer, anti-inflammatory, and anti-bacterial properties (details in paragraph 3). Kuruto *et al.* demonstrated that the mechanism of action of tea catechins, can also prevent estrogenic cancer. Some catechins, like EGCG, may act as anti-endocrine disruptors due to their ability to suppress the ER $\alpha$ -mediated effects in BPA-treated HeLa cells [105].

*Bifidobacteria* are a genus of Gram-positive, very popular for their anti-microbial, anti-oxidative, anti-tumoral activity. Several *in vivo* studies showed that *Bifidobacteria* can act against BPA. This probiotic in fact, can suppress BPA entry into the blood and facilitate its excretion [106].

*In vitro* studies have suggested that curcumin administration to BPA treated liver hepatocellular cells (HepG2) counteracted the BPA-induced insulin resistance [22], thus reducing BPA-triggered damage. Lipid metabolism and body and organ weight can be influenced by EDs. As reported in paragraph 2, BPA interferes in adipogenesis [22]. The risk posed by prenatal BPA exposure to metabolic health has been evaluated in a multispecies study that combined human association and animal causal studies. BPA effects on Free Fatty Acids (FFAs) transport and balance, in parallel to nitrosative stress was evaluated revealing positive correlation [107].

Selenium (*Se*), present in selenoprotein P and Glutathione Peroxidase (GSH-Px), can be considered a membrane lipids protective agent against the oxidative stress induced by BPA exposure. Kaur *et al.* show that the co-administration of *Se* (0.5ppm/kg) and BPA (1mg/kg) decreased lipid peroxidation in BPA exposed mouse testis [108]. Lee *et al.* used 3T3-L1 adipocyte cell line, to evaluate the *in vitro* effects of BPA on oxidative stress and adipogenesis. They demonstrated that BPA increased the production of reactive oxygen species (ROS) and lipid accumulation, but these effects were inhibited by BPA/ $\beta$ -carotene combined treatment [109]. ROS are closely linked to liver pathology. Anthocyanins from Purple sweet potato (*Ipomoea batatas* L.) were found to have anti-oxidation, anti-mutation, and anti-diabetes activities. *In vivo* and *in vitro* studies explained the anti-oxidant activity of *Ipomoea batatas* (100-400mg/kg) and the anti-infertility efficacy of aqueous extract of *I. batatas* against BPA testicular toxicity [110, 111].

*Lespedeza cuneata* is a perennial legume from Asia used in traditional Chinese medicine for the treatment of asthma, protection of liver and kidney functions. Oral administration of ethanol extract of *L. cuneata* in BPA-exposed male mice restored testis weight, sperm count, motility, and testosterone levels; inhibited serum biomarkers and oxidative stress defences such as total cholesterol, triglycerides, HDL/LDL-cholesterol, glucose, FFAs, hs-CRP, angiotensinogen, angiotensin II, GOT, GPT, TBARS, GSH, CAT, and SOD1. *In vitro*, *L. cuneata* extract recovered cell viability in BPA-

treated TM4 Sertoli cells by attenuating Bax expression and activating caspase 3 and PARP [112].

Gametogenesis is highly sensitive to environmental insults and thus BPA exposure can influence fertility [4, 5, 7]. In addition to BPA, Doxorubicin (DOX) may affect the physiology of reproductive system and cause fertility damage. DOX, an anthracycline-group antibiotic, can cause apoptosis in the seminiferous epithelium and germ cell. Its effects can be counteracted by resveratrol (RES), a phytoestrogen found in grapes, mulberry, red wine and other fruits. *In vivo* studies demonstrated the potential protective role of RES against DOX-induced damage. Thus testicular dysfunction *in vivo* as oxidative damage was attenuated by co-administration of DOX (50 $\mu$ g/l) and RES (20 mg/kg) [113].

Lastly, increasing doses of *Cordyceps militaris* (200-400-800mg/kg/day), a medical fungus well known in Chinese medicine, to BPA treated rats (200 mg/Kg) amended the BPA toxic effects on rat testis and epididymis, thus restoring the normal testicular morphology of seminiferous tubules and sperm count and reducing the oxidative stress damage [100]. Similarly, lycopene can act as detoxifying agent against BPA testicular damages. Rats orally exposed to BPA (200mg/bw) decreased spermatogenic cells, sperm motility, testes and epididymis weight, as a consequence of increased oxidative stress in testes. Lycopene administration (10mg/bw) to BPA treated rats improved spermatogenic cells in the seminiferous tubules and preserved the normal testes architecture [114]. BPA-dependent histological damage and spermatogenesis alteration can be counteracted by quercetin which is a component of polyphenolic flavonoid class with antioxidant properties. BPA (50/mg/kg)/quercetin (50/mg/kg) co-administration amended the BPA toxic effects on rat testis and epididymis [103].

Another valid substance against BPA effects is ATRA, a natural metabolite of vitamin A, capable to inhibit the estrogenic activity of BPA. In rats subjected to subcutaneous co-administration of ATRA (5mg/kg) and BPA (100 mg/kg), ATRA can inhibit BPA action in uteri [115].

Lastly, melatonin (N-acetyl-methoxytryptamine) -the hormone produced by pineal gland- is widely used as a food supplement, dietetic product, and drug in many countries. Due to its anti-oxidant properties, it has potential as a nutraceutical agent [116]. Consistently, *in vivo* and *in vitro* studies revealed melatonin activity against BPA-induced oxidative toxicity in male and female reproductive tissues to preserve gamete quality and fertility [117-123], but also anti-proliferative action in BPA-treated porcine ovarian granulosa cells [124] and breast cancer cell lines [125, 126].

Upcoming data revealed that the epigenome is susceptible to environmental exposures especially during embryogenesis. Substances with estrogenic properties and functions, as BPA, can potentially influence and modify the epigenome determination [2]. Dolinoy *et al.* used Agouti mouse model to evaluate maternal BPA exposure effects on fetal epigenome. In pregnant females dietary exposed to BPA, CpG islands demethylation in the offspring and ectopic expression of *agouti* gene were observed [127]; as a consequence, offspring coat shift from brown (pseudoagouti) toward yellow and obesity and high cancer susceptibility were

observed. Such an effect can be counteracted by genistein co-administration during pregnancy [127, 128]. Thus, nutraceuticals may preserve the epigenetic signature.

## CONCLUSION

Recent literature revealed that the widespread use of BPA is of potential risk for environment and human health. Further researches are necessary to clearly evaluate the real risk assessment of BPA and to determinate the critical time windows, doses, and impact of its long-term exposure. In spite the development of BPA substitutes safe for health may contribute to solve the trouble, at present the main BPA substitutes [*i.e.* Bisphenol F (BPF) and Bisphenol S (BPS)] are not safe alternative [129]. Furthermore, the possibility that the simultaneous exposure to BPA and other EDs may have additive effects on health has been poorly investigated and deserve attention in the next future.

Thus, the main instrument to preserve health status against BPA is avoiding BPA bioaccumulation and/or repairing the BPA-dependent cell damage, for the most part, mediated by the oxidative stress resulting from the overproduction of free radicals. In this respect, *in vitro* and *in vivo* studies provided evidence that nutraceuticals can preserve the health against BPA damage and their use can be considered a support of clinical treatment. This does not mean that uncontrolled and self-made nutraceutical supplementation may substitute healthy diet, but proper dietary interventions may represent a successful therapeutic approach to maintain and preserve health against BPA damage.

## LIST OF ABBREVIATIONS

AR	=	Androgen Receptor
BPA	=	Bisphenol A
BPF	=	Bisphenol F
BPS	=	Bisphenol S
CVD	=	Cardiovascular Diseases
DCs	=	Dendritic Cells
DOX	=	Doxorubicin
EDs	=	Endocrine Disruptors
EGCG	=	(-)-Epigallocatechin-3-Gallate
EPA	=	US Environmental Protection Agency
Er $\alpha$	=	Estrogen Receptor $\alpha$
Er $\beta$	=	Estrogen Receptor $\beta$
ERR $\gamma$	=	Estrogen Related Receptor Gamma
FFAs	=	Free Fatty Acids
FIM	=	Foundation for Innovation in Medicine
GSH-Px	=	Glutathione Peroxidase
HepG2	=	Liver Hepatocellular Cells
IGF-1R	=	Insulin-Like Growth Factor-1 Receptor
MMP	=	Matrix Metalloproteinase
mTOR	=	Mammalian Target of Rapamycin
NF-K $\beta$	=	Nuclear Factor $\kappa$ B
NK	=	Natural Killer
NO	=	Nitric Oxide
NTP	=	US National Toxicology Program
PI3K	=	Phosphatidylinositol 3-Kinase
PUFAs	=	Poly Unsaturated Fatty Acids
RES	=	Resveratrol

ROS	=	Reactive Oxygen Species
TGF	=	Transforming Growth Factor
Th	=	T Helper
PTK	=	Tyrosine Kinase
t-TDI	=	Temporary Tolerable Daily Intake

## CONSENT FOR PUBLICATION

Not applicable.

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## CONFLICT OF INTEREST

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