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Endocrine Disruptors, Nutraceuticals and their Simultaneous Effects in Hormone-Sensitive Tissues: A Review

Alzbeta Bujnakova Mlynarcikova* and Sona Scsukova

Laboratory of Molecular Endocrinology, Institute of Experimental Endocrinology, Biomedical Research Center, Slovak Academy of Sciences, Dubravska cesta 9, 845 05 Bratislava, Slovakia

Review Article

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***For Correspondence**

Alzbeta Bujnakova Mlynarcikova, Institute of Experimental Endocrinology, Biomedical Research Center, Slovak Academy of Sciences, Dubravska cesta 9, 845 05 Bratislava, Slovakia

E-mail: ueenamly@savba.sk

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ABSTRACT

The increase in hormone-sensitive types of cancers as well as in fertility problems has been linked to population burden with environmental endocrine disruptors (EDs). On the other hand, antioxidant or chemo preventive properties of various phytochemicals are known, resulting in an increased interest in intake of supplements containing various vitamins or herbal extracts. Thus, organism is exposed simultaneously to xenobiotics of various origins; however, until now there is only limited data and inconsistent results on the combined effects of EDs and nutraceuticals. The aim of this minireview is to provide a brief summary on the issue of EDs, nutraceuticals, and to discuss some of the data available on their simultaneous effects obtained through experimental research, with the focus on the effects on reproductive parameters and hormone-related types of cancer.

INTRODUCTION

Continuous global development of all areas of industry has resulted in the contamination of the environment with plethora of chemical substances, which through the different routes get into the human body. It is reasonable to suppose that such systematic exposure of the population to industrial xenobiotics may have adverse effects in terms of deterioration of various health indicators. On the other hand, diet rich in certain substances and micronutrients is considered a main tool for health maintenance and disease prevention; and for the purpose of supplementation with such substances, numerous so-called Nutraceutical preparations are promoted to and used by majority of general population, even without proof of their effects. The real-life situation then results in the simultaneous exposure of the organism to various xenobiotics. The aim of this paper is to provide an overview on the issue of endocrine disruptors, nutraceuticals, and to discuss some of the data on their concurrent effects obtained through experimental research with the focus on the effects on reproductive parameters and hormone-sensitive types of cancer.

Endocrine Disruptors

An increase in infertility and reproductive disorders in both sexes, and of several types of cancer, especially hormone-related, has been associated with a burden of population with substances referred to as endocrine disruptors (EDs) due to their ability to disrupt endocrine functions [1,2]. According to the definitions of the European Commission and the US Environmental Protection Agency, EDs are exogenous substances capable of interfering with the various aspects of endogenous hormones effects–synthesis, secretion, metabolism, action, and cause adverse health effects in the intact organism, or its progeny, secondary to changes in endocrine functions [3,4]. Agents acting as EDs are released from many areas of industrial use: plastics manufacturing, consumables, metallurgy, electrochemistry, flame retardants, pesticides. These substances have different chemical structures that may resemble the structure of endogenous estradiol. The molecules of EDs usually contain one or more aromatic rings, and are substituted by a various number of different hydrocarbon radicals or halogen atoms, which contribute to their lipophilic

nature. The most studied ED substances include the agents from the group of phenol derivatives (bisphenols, alkyl phenols), phthalate esters, polychlorinated biphenyls (PCBs), polybrominated diphenyl ethers (PBDE). Chemical structures of the several EDs are shown in **Figure 1** and illustrative information in **Table 1.**

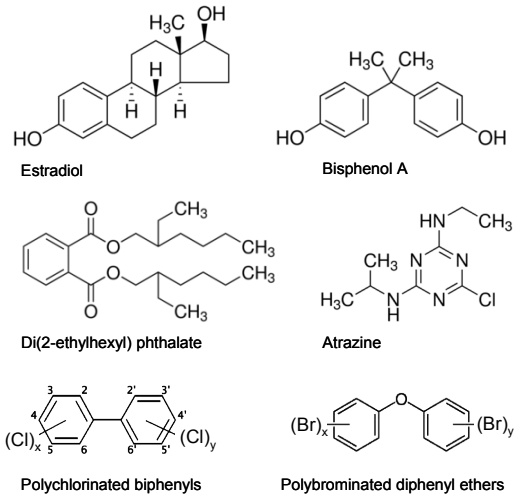

Figure 1. chemical structure of several endocrine disruptors, and comparison to the endogenous hormone 17β-estradiol.

Table 1. Examples of endocrine disruptors.

Substance	Sources and concentrations in human serum
Bisphenol A	Polycarbonate plastics, cans, thermal paper, dental sealing's (0.5-7.1 ng/mL) [20]
4-Nonylphenol	Ethoxylated detergents, plastic bottles for drinks (0.5-1 ng/g serum lipids) [81]
Mono-2-ethylhexyl phthalate	Major metabolite of di(2-ethylhexyl) phthalate; PVC plastics; covers for food, cosmetics, medicine products (0.6-1.15 µg/mL) [82]
Di-n-butyl phthalate	Personal care products, lacques, adhesives (0.67-2.02 µg/mL) [83]
Polychlorinated biphenyls, congener 153	Electrochemistry, pesticide additives (16.2-628 ng/g serum lipids) [10]
Polybrominated diphenyl ethers, congener 47	Flame retardant in various products (2.06 ± 1.80 ng/g serum lipids) [12]

Due to changes in temperature or pH, aging or damage of the plastics, EDs are released from those materials, e.g. covers, and contaminate the content (food, beverages, and cosmetics). EDs can enter the human body via several routes (ingestion, inhalation, dermal absorption), and ingestion is considered a major route of EDs intake. Bio monitoring studies show permanent intake of EDs by populations of all ages, including children [5,6]. The presence of EDs and their metabolites were detected in Nano molar ranges in various biological samples–human serum, urine, fat, breast tissue, amniotic fluid, umbilical cord blood, fluid of ovarian follicles [7-10]. These facts point to the need for intensive and detailed research of the EDs' effects, including studies in populations, organisms, organ systems, and specific cellular and molecular actions and targets.

At the level of reproductive parameters, negative effects of EDs have been found in both sexes. Increased concentrations of flame retardants PBDE in women are put into connection with decreased fecund ability and impaired implantation of embryos [11,12]. High levels of widely used substance biphenyl A (BPA) may correlate with the incidence of polycystic ovary syndrome and steroid metabolism disturbances in women [13]. The negative effect of BPA on steroid genesis was also confirmed in *in vitro* studies on ovarian cells [14]. The inhibitory effect on the maturation of oocytes caused by BPA may result in fertilization impairment [15]. Phthalate plasticizers known as female reproductive toxicants also modify steroid production by ovarian cells [14,16]. Serum concentrations of organ chlorine pesticides β-hexachlorcyclohexane and mirex were positively associated with endometriosis [17]. Even low doses of BPA caused the damage of animal testicular functions by increased oxidative stress and impaired glucose metabolism [18]; phthalates exhibited antiandrogenic properties and decreased testosterone levels in various animal models and possibly in males [19].

In last decades, a concern for the correlation between the levels and effects of EDs with an increased incidence of cancer has risen. Increased plasma concentrations of metabolites of BPA and di (2-ethylhexyl) phthalate (DEHP) were found in women with increased breast density, which represents a risk factor for breast cancer [20]. Analysis of PCBs concentrations showed significant association with the risk of prostate cancer [21]. Experimental studies have confirmed the proliferative effects of various EDs in hormone-sensitive cells of the breast and prostate [22,23], which are caused by several mechanisms, e.g. BPA can mimic

estrogen to interact with estrogen receptors, leading to stimulation of the expression of the components of the cell cycle [24], changes in cell proliferation, apoptosis, or migration. At the genetic level, BPA has been shown to be involved in multiple oncogenic signaling pathways, such as the MAPK and PI3K/AKT pathways [25]. In addition to cancers of the reproductive system, studies have documented the effect of EDs in promoting the growth and progression of tumors of other systems, such as gastrointestinal [26].

Primarily, the mechanism of action of EDs has been considered to be mediated by their binding and activation of nuclear steroid (estrogen or androgen) receptors due to virtual similarity of their chemical structures with those of endogenous steroids [27]. Subsequent research, however, have shown that the effects of EDs are mediated by many mechanisms independent of estrogen receptor (ER) and endogenous steroid mimicking, or by non-genomic mechanisms. For example, EDs can induce oxidative stress, which is associated with inhibition of the growth of normal tissue and tumor growth promotion [23], can affect the signaling of the receptors involved in the action and metabolism of xenobiotics (aryl hydrocarbon receptor) and other nuclear receptors involved in xenobiotic effects (peroxisome proliferator activated receptor, pregnane X receptor) [28,29], or can dysregulate expression of specific microRNAs [30]. Thus, the available evidence indicates that the effects of EDs cannot be simply predicted only as "hormone-like". In addition, the effects of EDs may also vary between the differently substituted compounds within a single chemical group with the same basic structure, for instance, different effects on the production of estradiol by granulosa cells were described for PCB congeners 126 and 153 [31]. Another factor that may affect the action of EDs is the degree of metabolization and the effect of the major metabolites of a particular substance in the body. For example, the metabolites of PBDE congener-47 was found to have different mechanisms in affecting ovarian steroid genesis than the parent compound [32]. The findings show that for understanding the exact mechanisms of EDs' action, it is necessary to examine individual substances in different functional model systems; nevertheless, the organism is exposed actually to a mixture of industrial environmental compounds depending on lifestyle habits, occupational exposure, etc.

NUTRACEUTICALS

On the other hand, in the last years, research worldwide has focused on the phenomenon of a lower incidence of some diseases including breast or prostate cancers [33,34] in the countries with a high intake of foods containing phytochemicals like soy is flavones or tea polyphenols [35,36]; or better general health believed to be achieved through dietary habits like Mediterranean diet [37]. A number of experiments indeed show that many bioactive substances may have chemo preventive activity caused by their antioxidant, Antiproliferative, anti-inflammatory effects [38,39]. Therefore, public interest in health maintenance or disease prevention by taking dietary supplements, or broadly termed "nutraceuticals"–various herbal extracts, vitamins, micronutrients, has increased significantly, even though the effectiveness of most of these products has not been documented clinically in humans, and their mechanisms of action are not defined in detail [40,41]. The use of dietary supplements is widespread; with reports indicating approximately 75% of individuals in developed countries use one or more dietary supplements [42]. Basic information on several nutraceuticals is given in **Table 2.**

Table 2. Basic information on several nutraceuticals.

Nutraceutical	Chemical synonyms	Sources of natural intake
Vitamins and their precursors		
Vitamin C	L-ascorbic acid	Fruits and vegetables in general
Vitamin D	1α,25-dihydroxycholecalciferol	Exposure of skin to UV rays; vitals, fish, milk and spreads fortification
Vitamin E	α-tocopherol	Oils, nuts, seeds; antioxidant in food processing
β-carotene		Certain kinds of fruits, vegetables, etc.
Phytochemicals		
Quercetin	3,3′,4′,5,6-pentahydroxyflavone	Main dietary flavonoid; apples, citruses, onion
Resveratrol	3,4′,5-trihydroxy-trans-stilbene	Grape skin, red wine
Genistein	4′,5,7-trihydroxyisoflavone	Soy beans and soy-derived products
Epigallocatechin gallate	(-)-epigallocatechine-gallate	Green tea
Curcumin	diferulloyl methane	Turmeric spice; used as food colorant
Indole-3-carbinol		Cruciferous vegetables

Biological endpoints and molecular mechanisms of nutraceuticals' actions depend on individual substances and include an extremely broad range of signaling pathways, receptors, biochemical events, target processes and molecules to be generalized. Regarding reproduction, several studies have suggested positive effects of vitamins C, E and β-carotene on male [43] and female fertility depending on age [44], or improvement in the condition in women with PCOS after they reached increased levels of vitamin D [45]. In the area of cancer chemoprevention, extensive research has been conducted, revealing several mechanisms through which certain natural substances may exert antitumor actions. Polyphenol compounds of green tea can modulate intracellular signaling pathways, and have antiangiogenic and proapoptotic effects, which may reduce the incidence of breast and other types of cancer [46]. Polyphenols/flavonoids quercetin, resveratrol, curcumin, genistein and apigenin have been shown to regulate the proteins involved in cell cycle control thus may inhibit cancer cell proliferation [37]. Phytochemical from cruciferous vegetables,

indole-3-carbinol suppressed responsiveness to estrogen and decreased the expression of ERα in hormone-dependent cells, including mammary and prostate cancer cells [47].

On the opposite, several other studies have shown that excessive intake of micronutrients from supplements does not have significant beneficial effects [48], or even may pose a health risk [49]. For example, dietary supplementation of antioxidants (Vitamins C, E, or D) did not improve reproduction parameters of sub fertile women [50]. The randomized trial "Selenium and Vitamin E Cancer Prevention Trial" (SELECT) demonstrated an increased incidence of prostate cancer in men taking Vitamin E supplements in the form of synthetic α-tocopherols [51]. Importantly, some phytochemicals have been reported to have negative effects what calls for the need to investigate their mechanism of action at the molecular level. Iso-flavones genistein and daidzein, ingested through soy-rich diet and used in many menopause symptoms-relieving preparations, are proven phytoestrogens and can act as endocrine disruptors [52]. Flavonoids quercetin and luteolin caused endocrine disrupting effects in the models of breast and endometrial cancer [40]. Excessive concentrations of epigallocatechin-3-O-gallate from green tea reduced the *in vitro* maturation and fertilization of oocytes [53] and induced embryo toxicity in mouse [54]. Some phytochemicals, particularly at high concentrations, may be involved in maintaining the progression of tumors, as it was reported for genistein in breast or ovarian cancer cells [55,56]. Briefly, a biphasic activity of phytoestrogens has been reported during cancer development in estrogen-sensitive tissues and the effects of phytoestrogens depend on the timing of exposure. Initially, phytoestrogens are able to slow down cell growth by activating ERβ, thereby generating an Antiproliferative expression signature. Due to the genetic instability of malignant cells, however, the expression of ERβ may be abrogated by gene deletion or promoter methylation. In such late-stage cancer cells, phytoestrogens can induce a transcriptional profile that promotes the proliferation of those clones that exhibit high amounts of ERα but little ERβ. Thus, the potentially beneficial effect of phytoestrogens should be reevaluated [57,58].

Simultaneous Effects of Endocrine Disruptors and Nutraceuticals

The available studies mostly investigate the actions of individual EDs or natural substances in the model systems. However, the organism in the context of its real environment is a subject of simultaneous actions of various xenobiotics of artificial or natural origins that enter the tissues and cells. So far, knowledge on the combined actions of EDs and nutraceuticals is limited to several available studies and provide scattered data on a few co-administered substances. It could be assumed that due to their "beneficial" (chemo protective, antioxidant) properties, the co-administration of nutraceuticals is able to reverse the adverse effects of EDs, what has been confirmed by several studies. Combinations of curcumin with iso-flavonoids genistein or equol, respectively, inhibited cell growth induced by DDT or industrial surfactant compounds nonylphenol and octylphenol in both ER-positive and ER-negative breast cancer cells [59]. Curcumin inhibited the proliferative effects of BPA on MCF-7 breast cancer cells and this action seems to be exerted through modulation of miR-19/p53 axis [30]. Growth of ovarian adenocarcinoma cells, induced by various EDs including BPA, nonylphenol or methoxychlor, was reversed by resveratrol via its ability to down regulate cell cycle progression [60].

As for reproduction, studies in male rats and obtained reproductive parameters have been mostly used for the research of EDs-Nutraceutical combinations. Simultaneous supplementation of α-tocopherols in PCB-exposed rats resulted in significant restoration of altered gonadal parameters, e.g. serum testosterone, estradiol, androgen and estrogen receptor expressions [59]. Quercetin amended the toxic effects of BPA on rat testis and epididymis by restoring normal spermatogenesis, testicular tissue damage, and hormonal levels suggesting that quercetin may be a potential therapeutic against BPA induced testicular toxicity [61,62]. Histopathological abnormalities and increased oxidative stress in DEHP-treated male rats were effectively normalized by pretreatment with quercetin [63]. Likewise, quercetin protected rat Leydig cells from toxicity induced by pesticide atrazine by restoring the expression of NF-κB, steroid genic activity and by preventing oxidative stress [64]. DEHP-induced testicular dysfunction in rats manifested as oxidative damage and declined serum testosterone levels were attenuated by pretreatment with resveratrol and curcumin, probably due to due to their intrinsic antioxidant properties along with enhancing testicular gene expression [65]. Epigallocatechin-3-O-gallate treatment markedly attenuated testes lesions, sperm deformity, and spermatogenic cell apoptosis in mice exposed to DEHP (66). Indole-3-carbinol attenuated the deleterious gestational effects of *in utero* BPA exposure on the prostate gland of male rat offspring's by increased apoptosis in prostate and decreased prostate histopathological disorders [47]. In female rats, α-tocopherols was beneficial in preventing BPA-induced oxidative damage in liver and ovarian tissues [66,67].

Nevertheless, not all results are consistent in terms of restraining the harmful effects of EDs by substances from the group of nutraceuticals. For example, a paradoxical increase in oxidative stress in the reproductive system of rats was observed after co-administration of L-ascorbic acid (Vitamin C) or resveratrol with BPA, octylphenol or nonylphenol. Histological examination showed that vitamin C co-administrated groups had increased atrophy, germinal cell debris in testes, and abnormal sperm percentages of in comparison to individual ED-treated groups [68]. Co-administration of Vitamin C also aggravated the oxidative kidney and liver damage in rats administered to BPA, octylphenol or nonylphenol [69]. DEHP and genistein given in combination induced long-term reproductive toxicity in male rats at doses not previously reported to produce any conspicuous long-term effects [70]. Low doses of phytoestrogens genistein and daidzein from soy formula together with BPA resulted in additive effects on transcriptional activation, and such co-exposure enhanced endogenous gene regulation and functional effects on proliferation in human breast cancer cells [52].

In order to study the simultaneous effects of EDs and nutraceuticals, *in vitro* and *in vivo* experiments are requisites

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for obtaining the complex picture of such effects. Nevertheless, there are several items to take into account when drawing conclusions on definite impact of the substances and their combinations on the studied (patho) physiological processes. The concentrations of EDs and/or nutraceuticals used in *in vitro* cultures or doses administered in *in vivo* studies are often excessively high in comparison to those detected in humans/wildlife animals. In such case, the potential toxicity of the compounds may account for some adverse effects, thus it is necessary to analyze their cytotoxicity using various *in vitro* and *in silico* methods [71]. Therefore, the use of environmentally relevant concentrations of the respective substances would be more rational. Moreover, in *in vivo* models, the administration route (perioral, intravenous) can highly affect the actual concentrations of the substances in the tissues, since their bioavailabity can be limited [72]. Further, some effects observed *in vivo* may be partially ascribed to the metabolites of the tested substances, and the amounts and actions of the metabolites may vary depending on various biological conditions. Importantly, for testing the EDs action, many studies use the rodent (mouse, rat) or other animal *in vivo* or *in vitro* models, which are convenient for practical and ethical reasons. However, due to possible interspecies differences in the metabolism of the particular substances [73], and/or in the particular processes, e.g. steroid genesis [74], it cannot be determined certainly to what extent the results would apply to humans.

Testing the actions of such a large scale of chemicals of interest against all the potential targets in biological models is an important but also difficult and time- and cost-consuming task; therefore, more rational approaches are urgently needed [75]. In this context, methods established in drug discovery, where the task is to identify bioactive compounds from multitude of substances, can be applied to ED's research. Computational methods, such as virtual screening, quantitative structure activity relationships (QSAR), and docking, are already a well-established tool in drug development and can also support ED's studies. To name a few examples, QSAR models of the estrogen and androgen receptor binding affinity of a large data set of heterogeneous chemicals have been built previously [75]. For nutraceuticals, 3D-QSAR and docking methods have been employed for evaluation of a series of flavonoid derivatives to determine the most appropriate comparative molecular field analysis prediction models for selective CYP inhibition and to block the carcinogenic activity mediated by CYP activation mechanisms [76].

As indicated, data obtained through *in vitro* and *in vivo* studies may be of practical importance to develop evolving dietary or pharmacological strategies against the adverse health effects of environmental chemicals. For these purposes, enhancement of delivery and beneficial effects of nutraceuticals may be desirable. Molecular encapsulation of chemical compounds with cyclodextrins, a form of oligosaccharides, has drawn much attention for its ability to improve drug pharmacokinetic and pharmacodynamics properties and to potentiate biological effects [77,78]. As an example, coencapsulation of resveratrol along with its cyclodextrin complex in liposomal formulations was shown to be a plausible option for the enhanced delivery of the hydrophobic chemotherapeutic agent in colon cancer cells [72]. Likewise, complexation of curcumin with cyclodextrin derivative positively influenced anticancer and antioxidant activity of curcumin in hepatic cancer cell culture [79].

Although a thorough analysis of combined actions of mixtures of EDs and nutraceuticals and their physiological effects needs to be undertaken, such simultaneous actions are little explored so far due to enormous number of possible combinations. The effects of several combinations of EDs and nutraceuticals are outlined in **Table 3.** The molecular mechanisms of concurrent interactions of these substances are far from elucidation, thus protective effects of nutraceuticals against the effects of EDs are not yet clearly confirmed.

Table 3. Overview of several simultaneous effects of endocrine disruptors and nutraceuticals.

Endocrine disruptor	Nutraceutical	Biological system	Effect of Nutraceutical	Ref.
		Positive (beneficial)		
DDT, nonylphenol, octylphenol	Curcumin, genistein, equol	MCF-7, T47D, MDA-MB-231 human breast cancer cells	Inhibition of cell growth induced by EDs	59
BPA	Curcumin	MCF-7 human breast cancer cells	Inhibition of proliferative effects of ED	30
BPA, nonylphenol, methoxychlor	Resveratrol	BG-1 human ovarian adenocarcinoma cells	Inhibition of growth promoting effects of EDs	60
PCBs	α-Tocopherol	Male Wistar rats	Restoration of gonadal parameters altered by EDs	61
BPA	Quercetin	Male Sprague Dawley rats	Restoration of gonadal parameters altered by ED	62
DEHP	Quercetin	Male Wistar rats	Normalization of histological abnormalities and oxidative stress caused by ED	63
Atrazine	Quercetin	Rat Leydig cells	Restoration of steroidogenic activity, prevention of oxidative stress caused by ED	64
DEHP	Resveratrol, curcumin	Male Wistar rats	Prevention of ED-induced testicular dysfunction	65
DEHP	Epigallocatechin gallate	Male mice	Attenuation of testes lesions and sperm deformities	66
BPA	Indole-3-carbinol	Male Sprague Dawley rats	Protection from gestational ED imprinting on the prostate	47
BPA	α-Tocopherol	Female Wistar rats	Prevention of ED-induced oxidative damage in liver and ovarian tissues	67

Negative (harmful)				
BPA	L-ascorbic acid, resveratrol	Male Wistar rats	Increase in oxidative stress in the reproductive system	68
BPA, nonylphenol, octylphenol	L-ascorbic acid	Male Wistar rats	Aggravation of oxidative kidney and liver damage	69
DEHP	Genistein	Neonatal male Sprague Dawley rats	Induction of long-term reproductive toxicity by lower doses	70
BPA	Genistein, daidzein (soy formula)	MCF-7 human breast cancer cells	Enhanced cell proliferation	52

CONCLUSIONS

The current knowledge in the field and the results of research studies underscore the need to assess the simultaneous administration of natural and industrial substances that may affect many target parameters at the cellular and molecular levels in an antagonistic/synergistic manner. Such a cumulative assessment of several biological parameters approximates the real situation [80-83]. Taking into account the continuous release and contamination of the environment and the food chain and subsequent exposure of the organisms to EDs on one hand, and the presence of nutraceuticals in food in the usual doses, and the availability of certain nutraceuticals as supplements for therapeutics and chemoprevention (often leading to pharmacological concentrations of the substances in the body) on the other hand, it is necessary to study and define the mutual modulation of the effects of these substances. Research in this area is highly needed due to requirements for the sanitation of the environmental burden of industrial EDs in the population.

A comprehensive assessment of interactions of EDs and nutraceuticals, clarification of the mechanisms of action on the various processes, and further determination of interference with endogenous hormones, which reflects the real situation of the organism, needs a lot of further research. These goals require the use of relevant model systems and complementary experimental methodological approaches in the areas of molecular biology, biochemistry, endocrinology, toxicology and pharmacology.

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