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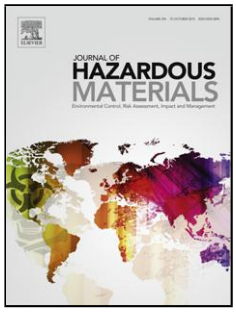

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Hazards of bisphenol A (BPA) exposure: A systematic review of plant toxicology studies

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Highlights:

- Exposure risks and emerging issues of BPA have become a global concern.
- This review provides a general view on the current knowledge of BPA phytotoxicity.
- Research advances in phytoremediation of BPA contamination have described.
- Suggested research directions on BPA phytotoxicity are put forward.

Abstract: The widespread use of bisphenol A (BPA) has led to its ubiquity in the natural environment. Thus, BPA is considered as a contaminant of emerging concern. Due to its widespread use, BPA has been detected in a range of soils and surface waters. This is of concern because BPA has been shown to elicit slight to moderate toxicity to plants. Based on current research and our own work, this paper reviews the toxic effects of BPA on plant growth and development, including effects at the macroscopic (e.g. seed germination, root, stem and leaf growth) and microscopic (photosynthesis, uptake of mineral nutrient, hormone secretion, antioxidant systems, and reproductive genetic behavior) levels. Furthermore, this paper will discuss effects of BPA exposure on metabolic reactions in exposed plant species, and explore the use of high-efficiency plants in BPA pollution control (e.g. phytoremediation). Finally, this paper proposes some ideas for the future of BPA phytotoxicity research.

Abbreviations：

BPA: bisphenol A; Chl: chlorophyll; ROS: reactive oxygen species; PS II: photosynthetic system II; P_n: net photosynthetic rate; IAA: indole-3-acetic acid; ABA: abscisic acid; ZT: zeatin; GA: gibberellic acid; ETH: ethylene; SOD: superoxide dismutase; CAT: catalase; MDA: malondialdehyde; AFs: actin filaments; CA: chromosomal aberration; MTs: microtubule arrays; ER: endoplasmic reticulum

Keywords: Bisphenol A; Toxicity; Plants; Growth and development; Physiological processes; Phytoremediation

Contents

1. Introduction

Bisphenol A [2,2-bis (4-hydroxyphenyl) propane, BPA; CAS No. 80-05-7] was first synthesized by Russian chemist Aleksandr P. Dianin in 1891. More recently, this chemical has become known for its estrogen-like endocrine disrupting properties (Vogel, 2009; Rubin, 2011; Kobroob et al., 2018). Since 1950s, BPA has been used primarily to produce polymer materials such as epoxy resins, polycarbonates and polysulfone resins (Staples et al., 1998). BPA-based polymer materials are widely used in making industrial products, such as thermal paper, food containers, flame retardants, building materials, electronic products, and medical equipment (Wang et al., 2016; Bjornsdotter et al., 2017; Geens et al., 2012a). Because of the widespread use of these products, BPA has become one of the world's most productive chemicals (Vandenberg et al., 2007). In 2012, the global BPA exceeded 4.6 million tons, with BPA produced in Asia accounting for nearly 53% of the total production, followed by Europe (25%) and North America (18%). The United States, China, South Korea, and Japan are the four largest BPA producers worldwide (Merchant Research & Consulting Ltd, 2013). Between 2013 and 2019, global BPA production was expected to grow at an annual rate of 4.6% (Wang et al., 2016). The mass production and frequent use of BPA has resulted in its sustained release and widespread distribution in the natural environment. Soil concentrations range from 2 to 14 μg/kg of soil dry weight in the United States, and BPA has been detected at concentrations up to 140 μg/kg and 48.68 μg/kg of soil dry weight in Europe and Korea, respectively (Kwak et al., 2017). BPA has been detected in surface water and river sediments all over the world. The highest concentrations of BPA were found in river water and river sediments in Taiwan, China (up to 3 μg/L and 10.5 μg/g, respectively) (Huang et al., 2012). Furthermore, Fu and Kawamura (2010) reported the widespread presence of BPA in the atmosphere in many cities around the world. In particular,

atmospheric BPA was detected at concentrations ranging from 200 - 17,400 pg/m^3 in Chennai, India. In addition, high BPA concentration (up to 17.2 mg/L) was detected in landfill leachate in Japan (Yamamoto et al., 2001) and in hazardous landfill leachate in Germany (4.2 - 25 mg/L) (Schwarzbauer et al., 2002). BPA concentrations in the effluent and sludge released from wastewater treatment plants ranged from 3 - 316 ng/L and 0.42 - 25,600 ng/g dry weight of sludge, respectively (Tran et al., 2015; Lee et al., 2015; Song et al., 2014; Yu et al., 2015). Moreover, with an increasing demand for BPA and BPA materials and the increasing disposal of BPA-containing products, the release and accumulation of BPA in the natural environment is likely to increase. Biological and toxicological experiments have confirmed that BPA can adversely impact both the environment and exposed organisms (Völkel, 2017). Therefore, it is necessary to investigate the risk that BPA may pose to contaminated ecosystems.

2. Bisphenol A is an environmental contaminant of emerging concern

BPA is considered to be an environmental contaminant of emerging concern due to its widespread presence in the environment and its endocrine disruption properties (Lunardi et al., 2016; Berhane et al., 2017). BPA can cause negative effects in the natural environment and organisms, which has attracted the attention of scientists and the public. Over the past two decades, many studies on BPA exposure have been carried out by international academia, especially studies related to human and animal health. Several published studies have reported the presence of BPA in human and animal blood, urine, adipose tissue, breast milk, placenta and amniotic fluid (Gerona et al., 2013; Chen et al., 2015; Geens et al., 2012b; Aris, 2014). Fish, amphibians, reptiles, and birds exposed to high concentrations of BPA (> 22.8 μg/L) displayed a change in sex ratio, and lower concentrations of BPA (1.75 - 5.00 μg/L) were shown to cause gonadal dysgenesis in vertebrate species (Guo et al.,

2017). BPA exposure was shown also to be associated with the development of diseases linked with reproduction and fertility, including various cancers (ovarian, breast, uterine, testicular, prostate, and liver) (Tharp et al., 2012; Fernández et al., 2010; Newbold et al., 2007; Prins et al., 2014; Nanjappa et al., 2012; Weinhouse et al., 2014). Epidemiological findings support the association between BPA exposure and increased incidence of cardiovascular disease, childhood obesity, and type II diabetes (Lang et al., 2009; Rochester, 2013; Rancière et al., 2015; Khalil et al., 2014). In addition, BPA exposure has been associated with brain sex differentiation and neurobehavioral disorders in children, leading to cognitive impairment and learning, and issues with memory faultiness (Rubin et al., 2006; Braun et al., 2017).

Because plants are primary producers in ecosystems, effects of contaminants on the survival and development of plants can affect directly or indirectly all consumers and decomposers, and that can then threaten the safety of entire ecosystem. BPA has been detected in landfill leachate, effluent and sludge released from sewage treatment plants, surface water, and air (Huang et al., 2012; Fu and Kawamura, 2010). When effluent is used to irrigate farmland (Dodgen et al., 2013), or sludge is used for soil remediation (Staples et al., 2010), or various plastic products are degraded, or landfill leachate leaks, the terrestrial and aquatic plants (such as algae) can be exposed to BPA. However, compared with amount of research that has been done on the effects of BPA on animals, there have been relatively few published studies focused on the effects of this chemical on plants. The impacts of BPA on plant growth and development are worthy of further exploration. Currently, this is the field of extensive research, with new discoveries constantly being presented. Hence, this paper aims to review research published by the international community (along with our own work) to describe the phytotoxic effects of BPA and underlying mechanisms behind BPA phytotoxicity. We aim to do

this to promote understanding of how BPA affects living organisms and provide a more comprehensive perspective for a BPA ecological risk assessment.

3. Methods for detecting bisphenol A in plants

Accurate determination of BPA content in plants is essential for quantification of the toxicological effects that this chemical can have on plant survival and metabolism. Radioisotope detection combined with high performance liquid chromatography (HPLC) was the first method used to study the fate of BPA in plants. Specifically, ^{14}C-labeled BPA was used with cell suspension cultures to determine BPA fate in heterotrophic plants (Schmidt and Schuphan, 2002; Nakajima et al., 2004). Liquid chromatography-tandem mass spectrometry (LC-MS/MS) was also used to analyze and identify BPA residues and its metabolites in cell suspension cultures or water samples (Watanabe et al., 2012). In recent years, capillary zone electrophoresis has also been widely used to determine BPA concentrations in water samples (Zhong et al., 2011; Wang et al., 2013). To determine the BPA content in plants, plant tissues are typically processed as follows: drying, grinding, methanol extraction, centrifugation, acetonitrile extraction, and then analysis of the extracts by HPLC (Nakajima et al., 2002; Ferrara et Al., 2006; Imai et al., 2007; Saiyood et al., 2010; Loffredo et al., 2010). Several studies have characterized BPA content in fruits, vegetables and plant oils using isotope dilution combined with gas chromatography-tandem mass spectrometry (GC-MS/MS; Lu et al., 2012, 2013, 2015; Chai et al., 2003; Wu et al., 2016; Wang et al., 2018). The recovery rates of the standard-added analyte tested by this method were all above 90%, the limits of detection (LOD) ranged from 0.01 - 0.20 μg/kg, and the limits of quantification (LOQ) ranged from 0.04 - 0.60 μg/kg. The results showed that this method would be suitable for determining trace concentrations of typical estrogen pollutants (such as BPA) in vegetables and fruits (Lu et al., 2012, 2013). Niu et al. (2012)

established a technique involving liquid chromatography-electrospray ionization-tandem mass spectrometry (LC-ESI-MS/MS) coupled with solid phase extraction for the determination of BPA in cereals (including rice, corn and wheat). The target compound was extracted by acetonitrile, purified by an on-line solid phase extraction column and analyzed by LC-MS/MS in negative ion mode. The method had a LOQ of 0.5 μg/kg for BPA in three cereals. In addition, the distribution of ^{14}C-labeled BPA in plant organs can be indirectly analyzed by measuring ^{14}C radioactivity in plant organs by a liquid scintillation counter (Dodgen et al., 2013).

4. Toxic effects of bisphenol A in plants

Previous studies have confirmed BPA can have a range of toxicities (from mildly toxic to moderately toxic – depending on outcome and species of interest), which can affect plant growth and development (Alexander et al., 1988; Staples et al., 1998). However, a number of studies have also shown that low doses of BPA (< 3 mg/L) can be beneficial to plant growth to a certain extent (Terouchi et al., 2004; Ali et al., 2016; Qiu et al., 2013; Pan et al., 2013; Nie et al., 2015a, 2015b; Li et al., 2018a). In the following sections, we review several plant metabolic and physiological processes that can be affected by BPA.

4.1 Uptake and biotransformation of bisphenol A

Previous studies have shown that hydrophobicity is an important factor in the diffusion and absorption of chemicals by plant species. Chemicals with octanol-water partition coefficients (log K_{ow}) between 1 and 3.5 have the greatest uptake potential by plants (Briggs et al., 2010; Dodgen et al., 2013). BPA is comparatively hydrophobic, with an estimated log K_{ow} between 2.20 and 3.82 (best estimate is log K_{ow} = 3.40) (Staples et al., 1998; Schmidt and Schuphan, 2002). Therefore, BPA exhibits moderate soil-sediment adsorption and bioaccumulation (Staples et al., 1998). BPA can be

rapidly biodegraded in natural waters, generally displaying a lifespan of less than 5 days, with an average half-life of 2 - 4 days (Staples et al., 1998; Kang et al., 2007). BPA bioaccumulation in aquatic organisms is generally low, but bioconcentration varies depending on organism of interest (Staples et al., 1998). Previous research has found that bioaccumulation is closely relatedly to BPA biodegradation (Kang et al., 2007). Schmidt and Schuphan (2002) first studied the absorption and metabolism of BPA in wheat, soybeans, thorn apples, and purple foxgloves using cell suspension cultures. By evaluating the distribution of ^{14}C-labeled BPA in these cell suspension cultures, they found that the cultured plant cells generally absorbed BPA relatively rapidly. In a study on BPA uptake with intact plants (using tobacco seedlings), Nakajima et al. (2002) found that plant roots were able to absorb BPA and transfer it to leaves. However, they found that compared to stems and leaves, the partitioning of BPA was highest to tobacco seedling roots. These researchers also found that BPA absorbed by roots of tobacco seedlings could be metabolized into various compounds (e.g. D-glucoside) through glycosylation, and these metabolites are also transferred to leaves. In another study, the edible plant, water convolvulus, was also found to effectively absorb BPA via roots and metabolize it through glycosylation. However, in contrast to previous findings, the metabolites were mostly retained in the roots, moderately retained in the stems, but not retained in the leaves (Noureddin et al., 2004). Ferrara et al. (2006) evaluated the toxicity of BPA to hydroponic tomatoes, broad beans, lettuce, and durum wheat and found that although all tested plants could absorb BPA by roots, their absorptive capacities were different. BPA residues were found mostly in roots of the tested plants. Tomatoes accumulated a large amount of BPA in roots, and also transferred BPA to their branches. BPA in roots and branches of tomato seedlings did not undergo complete biotransformation and detoxification. This information was consistent with the growth inhibition that

was observed in tomatoes. In contrast, with broad beans, BPA was not detected in their buds, and only low toxicity was detected. Dodgen et al. (2013) evaluated BPA uptake and accumulation in two leafy vegetables (lettuce and collards) irrigated with reclaimed water. They found that accumulation of BPA in leaves and stems of lettuce and collards did not differ significantly, but BPA accumulation in roots was significantly higher than that in other plant tissues. By calculating a translocation factor (the total BPA amount in stems, new leaves, and original leaves divided by the amount in roots), these researchers determined that BPA was poorly transferred from roots to upper parts following uptake. Lu et al. (2015) studied the absorption and distribution of BPA in two vegetable crops (lettuce and tomato) irrigated with reclaimed water using two different methods (subsurface root exposure and overhead foliar spraying). BPA was detected in different organs (roots, stems, leaves, and fruits) of both plants in either root or leaf BPA treatments, suggesting that BPA could be absorbed by crops by roots and leaves when they are irrigated with reclaimed water. Similarly to a study by Dodgen et al. (2013), Lu et al. (2015) found that BPA has limited movement in both plant species (lettuce and tomato). However, the exposure pathway was found to affect BPA distribution in both crops. For lettuce, with the root exposure irrigation method, BPA concentration was highest in roots, followed by leaves and then stems. In contrast, using the foliar exposure treatment, the highest BPA concentration was found in leaves, followed by roots and then stems. Similarly to lettuce, in tomato BPA accumulation under subsurface root exposure was highest in roots and lowest in stems (e.g. root > fruit > leaf > stem), whereas with overhead foliar exposure BPA accumulation was highest in leaves and lowest in stems (e.g. leaf > fruit > root > stem). In general, BPA tended to be distributed more evenly between roots and leaves in lettuce, regardless of the exposure pathways, and was a tendency of low distribution of BPA in tomatoes. Wang et al. (2018) studied the migration

of BPA in a reclaimed water-irrigated soil-winter wheat system. By measuring BPA concentration in different organs (roots, stems, leaves and kernels) of winter wheat, they found that BPA concentrations in organs did not increase with an increase in initial soil BPA concentration. In all five differential dosage treatments, the highest concentration of BPA was found in roots, and BPA was not detected at all in wheat grains. Consistently, BPA has displayed the highest bioconcentration factor in roots, followed by stems and leaves, and the lowest is kernels. By calculating the attenuation rate (defined as the ratio of the loss of pollutants with respect to the amount of pollutants initially added to the soil) of BPA in the soil-winter wheat system, they determined that the total amount of BPA in soil and winter wheat accounted for 2.35 - 4.95% of the initial amount. This indicated that a large amount of BPA was likely degraded or metabolized during wheat growth (Wang et al., 2018). The authors suggested that this may be due to the fact that the hydroxyl group of BPA can interact with binary ions or compounds (such as sulfates and glucuronic acid) in the soil and form conjugated estrogens, which could alter the mobility of BPA in soil-plant system (Shrestha et al., 2012; Goepper et al., 2015). The variable capacity of plant tissues to absorb different forms of pollutants can also lead to differential distributions of pollutants in tissues (Dong et al., 2015). Previous studies have reported that pollutants with a log K_{ow} of more than 5 are more likely to get adsorbed on plant root surfaces, thus displaying limited movement in plants (Ryan et al., 1988). As the log K_{ow} of BPA is 3.40, it likely has weak migration in plants, displaying a tendency to accumulate in plant roots that tend to have high fat content (Wang et al., 2018). Finally, it has also been found that BPA biodegradation in winter wheat may not just involve the plant metabolic pathways, but also require input from soil microbes (Wang et al., 2018).

As BPA is an organic compound, it is often changed after plant absorption. Previous studies

have reported that crude enzymes (such as polyphenol oxidase and potato crude enzyme preparations) extracted from vegetables and fruits can oxidize BPA to decrease or eliminate estrogen-like activity (Yoshida et al., 2002; Xuan et al., 2002; Schmidt and Schuphan, 2002; Kang and Knodo, 2006; Matsushima et al., 2015). Schmidt and Schuphan (2002) found that plant cells could rapidly produce BPA metabolites after absorbing BPA. They pointed out that BPA was metabolized in three main ways in plant tissues: glycosylation, formation of non-extractable/non-bound residues, and formation of highly polar polymeric products. Several other studies also reported that following uptake by plant cells, BPA may be metabolized into multiple compounds via selective hydroxylation, glucosylation or redox reactions (Hamada et al., 2002; Nakajima et al., 2002, 2004, 2007; Morohoshi et al., 2003; Noureddin et al., 2004; Knodo et al., 2006). Plant defense systems also play a role in BPA metabolism. For example, in *Arabidopsis thaliana* the detoxification genes such as glutathione transferase and UDP-glucosyltransferase were overexpressed strongly after BPA exposure. Furthermore, enzymes related to reactive oxygen species (ROS) signal transduction were activated by BPA exposure (Tian et al., 2014).

In summary, the schematic diagram of BPA uptake and biotransformation by plants is shown in Figure 1. The differences in the distribution of BPA and its metabolites in plants organs may be attributed to the differences in BPA absorption capacity, metabolic pathways and transport capacity among diverse plant species. However, the initial concentrations of exogenous BPA used, the exposure time of plants to BPA, and the different detection methods used may also be the reasons for differences observed in different studies. Plants have been shown to detoxify BPA through multiple metabolic pathways (Ferrara et al., 2006). However, if a detoxification pathway is saturated, excessive concentrations of BPA can lead to bioaccumulation and induce toxic effects (Kang et al.,

2007). The physicochemical characteristics of BPA may affect its existence in the environment (i.e. environmental fate), which should be taken into account when conducting BPA ecotoxicity assessment. Furthermore, as it can be metabolized both within plants and in the external environment, the risk of BPA derivatives and primary metabolites in the ecosystem should also be considered when evaluating the total risk of this compound. In addition, human health risks should be considered. BPA is preferentially distributed in plants roots, which may lead to an increase in potential human health risks via consumption of rhizomatous vegetables, such as radishes, carrots and onions. Finally, the discovery of various metabolic pathways of BPA in plants highlights new opportunities for BPA detoxification in the environment – i.e. plants could be used as 'biofilters' to absorb and detoxify BPA from environmental media.

4.2 Morphogenesis

Plant growth and development are important biological processes for species survival and reproduction. These processes are continuous and rely mainly on external resources present in the growth environment (Shanker et al., 2005). The presence of BPA in external environments can lead to changes in the plant growth and developmental patterns.

4.2.1 Seed germination

Seed germination is the process by which the radicle and germ break through seed coat and develop into a new individual. It is the starting point of plant life. Because seed germination is the first physiological process affected by BPA, the germination capacity of seeds in BPA-containing environments reflects their tolerance to BPA. Ferrara et al. (2006) previously reported that 10 and 50 mg/L BPA exposure had no significant effects on seed germination of hydroponic lettuce, tomato, durum wheat, and broad bean. Similarly, Dogan et al. (2010) showed that germination of chickpea

seeds was not affected by 10 and 50 mg/L BPA treatments, but was inhibited by exposure to 100 mg/L BPA. Similarly, *Arabidopsis thaliana* seed germination began to be inhibited at doses of BPA around 68.5 mg/L (Tian et al., 2014). Loffredo et al. (2010) observed that with eight herbaceous plants [five forage grasses: fescue, white clover, Siberian wheatgrass, couch grass, and perennial ryegrass; and three horticultural species: marrow plant, cucumber and radish] there were no effects on seed germination following exposure to BPA concentrations of 4.6 mg/L and 46.0 mg/L. Mung bean seeds sowed in soil were also relatively unaffected by BPA. Even at exposures exceeding 250 mg BPA/kg soil dry weight, seed germination was only slightly affected (Kim et al., 2018). The above results showed that different concentrations of BPA can have different effects on seed germination. In general, the higher BPA concentration, the greater inhibition of seed germination. This may be related to the inhibition of energy metabolism by BPA during seed germination, but there is currently no evidence. Furthermore, at the same concentrations, the germination rates of various species were different, indicating that there were differences in BPA tolerance among seeds of various plant species.

4.2.2 Plant root growth

Plants roots are the main organs directly exposed to BPA stress. Root growth changes caused by BPA stress are the most easily recognized adverse effects associated with BPA toxicity. Several studies have shown that BPA can have varying effects on plant root growth. Indeed, a low-dose BPA (< 3 mg/L) exposure has been shown to significantly promote root growth (including root length, root volume, root surface area, and fresh/dry weight) of soybeans and *Arabidopsis thaliana* in their early growth stages (Sun et al., 2013b; Pan et al., 2013; Nie et al., 2015a; Wang et al., 2015b; Ali et al., 2016; Li et al., 2017, 2018a). We speculate that low-dose BPA has a cytokinin-like effect, which

may induce root cell elongation and proliferation, thereby promoting root growth (Terouchi et al., 2004). In addition, a low-dose BPA exposure increased the levels of indole-3-acetic acid (IAA), zeatin (ZT) and gibberellin (GA) in roots, stimulating root cell elongation and division, thereby regulating development of primary and lateral roots (Wang et al., 2015b; Li et al., 2017, 2018a). It is expected that the changes in endogenous hormone content in roots under BPA exposure are involved in root growth and development. However, the molecular mechanisms of various endogenous hormones regulating root growth and development under BPA exposure remain unclear and need further investigation. A low-dose BPA exposure also enhanced mitochondrial energy production in root cells, key enzyme activities in root respiration, and uptake of mineral elements (Nie et al., 2015a, 2015b; Xiao et al., 2019). There was a significant positive correlation between increased mineral elements and root dry matter accumulation (Nie et al., 2015a). In hydroponic lettuce, tomatoes, broad beans, and durum wheat the root morphological changes were induced by exposure to either 10 or 50 mg/L of BPA for 21 days, with effects being particularly dramatic in the 50 mg/L BPA treatment (Ferrara et al., 2006). They found that a high-dose BPA exposure was associated with a decrease in root length, increased sparsity of lateral roots, and enhanced formation of gelatinous substances, together resulting in blackening and necrosis of local roots, and decreased fresh/dry weight. Similarly, exposure to 10 - 100 mg/L BPA inhibited root growth in many plant species, including chickpeas, peas, perennial ryegrass, Siberian wheatgrass, rice, and *Arabidopsis thaliana*. The higher the concentrations of BPA, the more obvious the inhibitory effects on roots growth. Thus, BPA was found to affect roots in a dose-dependent manner (Dogan et al., 2010; Loffredo et al., 2010; Adamakis et al., 2013; Pan et al., 2013; Tian et al., 2014; Ali et al., 2016). Recent studies showed that BPA-induced plant root tip cell death might be one of the causes of root growth inhibition (Xiao et

al., 2019). Furthermore, BPA may have a hormesis effect, with low concentrations of BPA promoting root growth, and higher concentrations inhibiting it. Finally, the sensitivities of diverse plant roots to BPA stress differ, indicating strong species-to-specific differences.

4.2.3 Aboveground organ growth

The effects of BPA on the growth of aboveground organs (measured as plant height, stem and leaf fresh/dry weight, and/or leaf area) have been reported in a number of prior studies. Similarly to root growth (i.e. hormesis), low concentration of BPA (1.5 mg/L) increased plant height, stem fresh/dry weight, leaf fresh/dry weight and leaf area of soybean (*G. max*), suggesting that low-dose BPA can also promote the growth of aboveground plant organs (Qiu et al., 2013; Jiao et al., 2017b; Li et al., 2018a). In contrast, treatments with BPA at concentrations of 10 mg/L and higher can result in decreased plant growth. This has been observed with soybeans, lettuce, tomatoes, broad beans, durum wheat, and mung beans. Increasing exposure time resulted in brown spots on mung beans, etiolated leaves in *Arabidopsis thaliana* and broad beans, and decreased numbers of leaves and exacerbated local necrosis in lettuce (Ferrara et al., 2006; Qiu et al., 2013; Jiao et al., 2017b; Li et al., 2018a; Kim et al., 2018). Similarly, although the 5 mg/L and 10 mg/L BPA treatments had no effects on leaf growth of mangrove plant *Bruguiera gymnorhiza*, when BPA concentrations increased to 20, 30, 45 and 60 mg/L, the leaves became yellow and necrotic (Saiyood et al., 2013). Therefore, these results also reflect the typical hormesis effect of BPA on the aboveground parts of plants. In addition, Pan et al. (2013) found that BPA affected leaf differentiation in *Arabidopsis thaliana* in a light-dependent manner. The above-mentioned mechanism of BPA affecting plant growth may be related to the changes in physiological and biochemical processes (Section 4.3 Physiology and biochemistry) such as photosynthesis, mineral element uptake, endogenous hormone secretion, and

content of ROS, and even reproductive and genetic regulation.

4.2.4 Algae growth

Algae are major primary producers of aquatic ecosystems, and represent the base of the aquatic food chain. Therefore, they play an important role in maintaining the stability, diversity and function of aquatic ecosystems. However, algae (phytoplankton) are relatively sensitive to chemicals (Xiang et al., 2018). In general, for environmental pollutants, algal toxicity is assessed via growth inhibition tests (Zhang et al., 2014). The widespread presence of BPA in water bodies has drawn some attention to the potential toxic effects this chemical can have on algae. The toxicological responses of various algal species to BPA have been reported previously. Exposure to 5 mg/L BPA for 8 days had no effects on the growth of eight species of freshwater microalgae (*Pseudokirchneriella subcapitata*, *Micractinium pusillum*, *Scenedesmus acutus*, *Coelastrum reticulatum*, *Carteria cerasiformis*, *Gonium pectoral*, *Scenedesmus quadricauda*, and *Cyanophora paradoxa*), but 10 mg/L BPA was found to inhibit growth of *P. subcapitata*, while having no effects on other species (Nakajima et al., 2007). When the marine microalga, *Cyclotella caspia*, was exposed to a range of BPA concentrations (4 - 12 mg/L), biomass and growth rate showed a significant concentration-dependent relationship with BPA (Li et al., 2008). The 96-h EC_{50} value (the effective concentration of BPA causing 50% algal growth inhibition after 96 hours of exposure) was calculated to be 7.96 ± 0.23 mg/L. Similar response to BPA were recorded in the marine microalga *Stephanodiscus hantzschii*, displaying the EC_{50} value of 8.65 ± 0.26 mg/L at 96 h (Li et al., 2009). Further investigation revealed that the growth inhibition in *C. caspia* and *S. hantzschii* was due to the inhibition of cell division, cell wall decomposition, and disintegration of chlorophyll molecules and whole chloroplasts, which affected the normal physiological processes in algae cells (Li et al., 2009). In addition, BPA accumulation in *S.*

hantzschii was found to vary with exposure time and initial BPA concentration (Li et al., 2009). Liu et al. (2010) investigated the growth responses of diatom *Navicula incerta* to BPA exposure in marine environments. Results showed that growth rate was negatively correlated with BPA concentrations (0 - 5 mg/L), but algal cell size was not affected by BPA exposure. The 96-h EC_{50} value for this marine diatom was 3.21 mg/L, indicating that this species was more sensitive to BPA exposure than freshwater microalgae. Based on the above results, Xiang et al. (2017) postulated that the use of a single species of algae was inadequate for assessing the effects of BPA on algae communities. In addition, these results were mainly derived using eukaryotes; hence, the comparative effects of BPA on the growth of prokaryotic (*Cylindrospermopsis raciborskii* (cyanobacteria)) and eukaryotic (*S. quadricauda* (green algae)) organisms were investigated. Researchers found significant differences in BPA tolerance between these two organisms. The 96-h EC_{50} values of BPA to *C. raciborskii* and *S. quadricauda* were 9.663 ± 0.047 mg/L and 13.233 ± 0.069 mg/L, respectively. Therefore, the studies show that the sensitivity to BPA exposure is highly dependent on the prokaryotic/eukaryotic nature of organisms and initial BPA concentration.

An in-depth understanding of the impact of BPA on aquatic organisms can provide useful information regarding the ecological risk assessment for this chemical. Numerous studies found that BPA can accumulate in algal cells (Li et al., 2009; Liu et al., 2010; Gattullo et al., 2012). Moreover, Guo et al. (2017) found that BPA derivatives absorbed and metabolized by algal cells were transferred from algae to rotifers. These facts illustrate the possibility of BPA accumulating throughout the aquatic food chain, which could have negative impacts on these aquatic ecosystems. On the other hand, the accumulation of BPA by algal cells could have positive consequences – providing a method for BPA bioremediation in contaminated water bodies.

4.3 Physiology and biochemistry

4.3.1 Mineral element absorption

BPA exposure has been reported to affect the absorption of mineral nutrients by plant species. Sun et al. (2013a, 2013b) reported that BPA exposure could inhibit ammonia assimilation in soybean seedling roots, resulting in insufficient soluble protein and amino acid content in roots. This was found to be associated with changes in root growth. Nie et al. (2015a, 2015b) reported that the absorption capacity of soybean roots and the activities of key respiratory enzymes (hexokinase, pyruvate kinase, phosphofructokinase, isocitrate dehydrogenase, and cytochrome C oxidase) were promoted under low concentration of BPA (1.5 mg/L), thereby enhancing uptake of mineral elements (P, Mg, K, Mn, Zn, and Mo) by roots. In addition, exposure to 1.5 mg/L BPA promoted mitochondrial energy production in root cells (Xiao et al., 2019), which may provide an energy basis for low-concentration BPA to promote root growth. At higher concentrations of BPA (> 3 mg/L), BPA inhibited the activity of key respiratory enzymes involved in root energy metabolism (Nie et al., 2015b; Xiao et al., 2019), and even destroyed the cell structural integrity (Xiao et al., 2019), resulting in a decrease in the capacity of roots to take up the above-mentioned mineral elements. It is concluded that the BPA-induced disturbance of the activity of key enzymes in the root cell respiration and the damage of cell structure may be underlying mechanisms of BPA affecting plant uptake of mineral elements.

4.3.2 Photosynthesis

Plant growth is highly dependent on photosynthesis. Therefore, if a plant photosynthetic system is destroyed or altered by exposure to environmental contaminants, plant growth is affected (Qiu et al., 2013; Jiao et al., 2017b; Kim et al., 2018). The effect of BPA on plant photosynthesis was first

described by Li et al. (2008, 2009), who found that BPA exposure can reduce chlorophyll a (Chl a) content in two different algal species (*C. caspia* and *S. hantzschii*). Cell morphology observations confirmed that BPA-induced ROS generation that damaged chloroplast membranes and led to functional changes, which was postulated to cause a decrease in Chl a content. Conversely, in a later study, Liu et al. (2010) reported that BPA had no significant effects on Chl a and total Chl c content in marine diatom (*N. incerta*). This difference in finding may be due to differential absorption and tolerance to BPA in different algal species. The study by Gattullo et al. (2012) found that BPA exposure damaged the photosynthetic apparatus of photosynthetic system II (PS II) in freshwater green algae (*Monoraphidium braunii*), decreasing both Chl a and net efficiency of the PS II. Recently, Xiang et al. (2017) investigated the effects of BPA on PS II of *C. raciborskii* and *S. quadricauda*, and found that BPA concentrations higher than 1 and 2 mg/L (respectively) could significantly decrease total Chl a concentrations. At higher concentrations (e.g. BPA = 10 mg/L), the Chl fluorescence parameters such as F_v/F_m (maximum potential quantum efficiency of PS II), $\Delta F/F_m$' (actual photochemical efficiency of PS II), and q*P* (photochemical quenching coefficient) were all significantly decreased in *C. raciborskii*, but not in *S. quadricauda*. Changes in α (initial slope of light response curve before light saturation) and rETR_{max} (maximal relative electron transfer rate) obtained from the fast photoresponse curves for the two algal species following BPA exposure were similar to what was seen with F_v/F_m, $\Delta F/F_m$' and q*P*. However, the non-photochemical quenching coefficient was much higher in *C. raciborskii* than that *S. quadricauda*. These results suggest that PS II may be an *in vivo* target for BPA. The differences in physiological responses of the two algae also indicate that the effect of BPA exposure on photosynthesis likely varies with algal species and contaminant concentrations. In view of the fact that most of the above studies were focused on

eukaryotes, Xiang et al. (2018) also investigated the effects of BPA on photosynthesis of the prokaryote, *Cylindrospermopsis raciborskii* (an invasive cyanobacterium). After exposure to BPA for 96 h, Chl a fluorescence was disturbed and photosynthesis was inhibited. High-throughput sequencing results showed that the expression of light-capture genes and photosynthesis-related response center complex genes (50 genes) were significantly down-regulated. In addition, a metabolic network analysis of *C. raciborskii* revealed that BPA affected many metabolic pathways involved in energy production and metabolism, including glycolysis, tricarboxylic acid cycle, and protein and fatty acid metabolism. It is speculated that interference with the electron transport on the PS II receptor side and the inhibition of cellular metabolites may be responsible for the toxicity of BPA to *C. raciborskii*.

Qiu et al. (2013) was one of the first to publish the effects of BPA on photosynthesis in higher plants. When soybean seedlings were treated with low concentration of BPA (1.5 mg/L), the net photosynthetic rate (P_n), Chl content and Chl fluorescence either increased or did not change. However, at higher concentrations of BPA (7.0, 12.0, 17.2 and 50.0 mg/L) there were significant decreases in the P_n, Chl content, F_v/F_m, Φ_{PSII} (actual photochemical yield), and *ETR*. Only F_0 (initial fluorescence) was found to increase. Correlation analysis showed that the changes in P_n of soybean seedlings exposed to BPA were associated with the changes in Chl content and the Chl fluorescence parameters (F_0, F_v/F_m, Φ_{PSII}, *ETR*). Jiao et al. (2015, 2017a) further studied how BPA can affect Chl content in soybean seedling leaves. By quantifying the concentrations of essential intermediates and the activities of key enzyme in Chl synthesis, they confirmed that BPA exposure could interfere with Chl synthesis, leading to decreases in Chl content in the leaves. Zhang et al (2015) evaluated the effects of BPA on Chl fluorescence in five plant species, including tomato, lettuce, soybean, corn,

and rice seedlings. They found that low-dose BPA (< 3.0 mg/L) increased the efficiency of PS II, whereas high-dose BPA (10.0 mg/L) impaired the PS II reaction center in a concentration-dependent manner. Indeed, the effects of BPA were most pronounced at the highest dose of BPA (17.2 mg/L). These results were consistent with the experimental results obtained by Qiu et al. (2013), but there were differences in a degree of influence BPA exposure had on the Chl fluorescence in each of the five plants. Jiao et al. (2017b) investigated the mechanism by which BPA could affect photosynthesis using soybean seedlings, focusing on the stomatal and non-stomatal factors. They found that low dose of BPA (1.5 mg/L) increased P_n by promoting the stomatal factors, whereas high doses of BPA (17.2 and 50.0 mg/L) decreased P_n by simultaneously inhibiting the stomatal and non-stomatal factors. Correspondingly, the increase in P_n under low concentration increased the relative growth rate of soybean aboveground organs, and accelerated seedling growth; the opposite effects were observed at high concentrations (Jiao et al., 2017b). Kim et al. (2018) also found that exposure to BPA (> 500 mg BPA/kg of soil dry weight) decreased stomatal size as well as Chl a and Chl b content in leaves, and interfered with Chl fluorescence; the reduction in stomatal pore size may result in decreased nutrient uptake, leading to an inadequate supply of the nutrients requires for Chl synthesis. These findings provide a hypothesis for further characterization of how BPA can affect plant photosynthesis. Li et al. (2018b) exposed cucumber leaves (not roots) to BPA to study the mechanisms by which BPA could affect the photosynthetic apparatus. This study confirmed that BPA could directly inhibit leaf photosynthesis. However, the authors posited that this photosynthetic inhibition was not the result of BPA-induced destruction of PS II. Instead, they found that BPA mainly inhibited carbon assimilation, leading to surplus electrons in the electron transfer chains, excessive excitation of the PS II reaction centers, and excessive production of ROS under high-light

conditions. Indeed, accumulation of ROS can inhibit the repair of photo-damaged PS II and exacerbate PS II photoinhibition under strong-light conditions. Furthermore, they did not observe significant differences in Chl content between the different treatments, thus concluding that the inactivation of photosynthetic machinery caused by BPA was not likely to be associated with the degradation of photosynthetic pigments. Tian et al. (2014) used microarray analysis to study the changes in gene expression in *Arabidopsis thaliana* in response to BPA stress, and found that exposure could elicit a down-regulation of mRNA involved in photosynthesis. In addition, they found that photosynthesis, Chl content, and expression of targeted chloroplast proteins were also reduced following exposure to BPA.

4.3.3 Hormone and signal transduction

It is well known that plant growth at the cellular level depends on cell division, expansion and differentiation. Indole-3-acetic acid (IAA), zeatin (ZT), gibberellin (GA), abscisic acid (ABA) and ethylene (ETH) are key endogenous hormones regulating the growth and development of plant cells. The changes in their contents are the internal factors affecting the growth of plant cells (Pozo et al., 2005). For example, IAA and ZT can promote cell division and elongation, regulate the development of primary and lateral roots and promote leaf growth; whereas high concentration of free auxin inhibits root growth (Pozo et al., 2005; Saini et al. 2013; Pan et al., 2013). ETH is involved in regulating root growth by affecting cell expansion, and increased ABA level inhibits primary root cell division and differentiation, and may also inhibit IAA and ZT synthesis (Popko et al., 2010; Swarup et al., 2007; Zhang et al, 2010; Li et al., 2014). In plant leaves, ETH and ABA indirectly affect leaf growth by regulating stomatal behavior (Mustilli et al., 2002; Tanaka et al., 2005). Under normal environmental conditions, the contents and proportions of these hormones are in relative

equilibrium. However, when external stresses occur, this homeostasis is disrupted by the individual action and crosstalk of hormones (Pozo et al., 2005; Wang et al., 2015b). Studies have revealed that BPA exposure could interfere with the secretion of endogenous hormones (IAA and ZT) and the ratio of growth-promoting hormones to stress hormones (ABA/IAA, ABA/GA, ABA/ZT, ETH/IAA, ETH/ZT) in roots, thereby affecting plant biological properties, manifested in the growth changes of roots and leaves. For example, exposure to low concentrations of BPA (0.8, 1.5 mg/L) increased IAA and ZT levels in roots, which promoted root growth, and increased IAA levels in leaves promoted leaf growth (Wang et al., 2015b; Li et al., 2017, 2018a). However, under high BPA (17.2 mg/L) exposure, both IAA and ZT contents in roots decreased, whereas ABA content increased; IAA content in leaves decreased, and ABA and ETH levels increased (Wang et al., 2015b; Li et al., 2017, 2018a). Overall, changes in these hormone levels under high BPA exposure resulted in inhibition of root and leaf growth. Recent studies have reported that genistein levels in mung bean can change after exposure to BPA (Kim et al., 2018). This finding is noteworthy because it means that plant can also display estrogenic changes after exposure to typical endocrine disruptors such as BPA. It is postulated that phytoestrogens are a plant defense mechanism that controls the reproduction of herbivores to protect plant populations (Hughes, 1988). Therefore, it is speculated that these changes in genistein levels may be a defense response of mung bean to external chemical stress (Kim et al., 2018). In another study, Terouchi et al. (2004) treated soybean callus with both BPA and ZT (an original cytokinin in plants). They found that both chemicals increased the fresh weight of soybean callus, but the effect of 0.1 mg/L BPA on the fresh weight of soybean callus was stronger than that of ZT. They also cultured callus from carrot roots in BPA-containing medium for 40 days, and found that low concentrations of BPA (0.1 mg/L) induced differentiation and germination, whereas high

concentration of BPA (10 mg/L) inhibited budding. These experimental results showed that low concentrations of BPA can promote plant growth and tissue differentiation by acting like cytokinin. Terouchi et al. (2010) found that in *Arabidopsis* response regulators (ARRs), mRNA transcription levels were affected by BPA exposure in a way that was similar to how cytokinin-induced ARRs participate in His-to-Asp phosphoric acid transfer signal transduction. This study was the first evidence that BPA could play a role in intracellular signal transduction. Furthermore, Frejd et al. (2016) found that BPA can disrupt the expression of hormone signaling transduction genes (e.g. the *Arabidopsis* auxin gene or ethylene synthesis/response transcription factors), and that this disruption could be one of the mechanisms underpinning BPA effects on plant flowering. Ali et al (2017) investigated the role of ethylene in BPA-induced oxidative stress in plant using wild-type, ethylene-insensitive *Arabidopsis* mutants (*ein2-1* and *etr1-3*) as test materials. They found that BPA induced an increase in ROS, lipid peroxidation and other oxidative stress markers, which indicated that BPA-mediated toxicity could involve an oxidative stress pathway. Overall, they found that the wild-type *Arabidopsis* was more affected by BPA than the *ein2-1* and *etr1-3* mutants. Antioxidant enzyme activity and antioxidant-related genes expression revealed that the antioxidant defense systems of the two mutants were activated more efficiently than that of the wild-type *Arabidopsis*, which suggested that ethylene perception and signaling might be involved in regulating BPA-induced oxidative stress responses in plants. Speranza et al. (2011) found that BPA induced substantial changes in the hormone environment in pollen tubes of kiwifruit, resulting in excessive production of 17 β-estradiol, progesterone and testosterone. They believed that the strong inhibitory effect of BPA on the emergence and elongation of kiwifruit pollen tubes observed was related at least partly to a dramatic imbalance of steroid hormones in pollen tube tissues.

4.3.4 Reactive oxygen and antioxidant system

Under normal circumstances, plants maintain a dynamic balance of ROS levels (using antioxidant systems). Under high stress scenarios, the balance is disturbed, allowing for ROS to accumulate, which can cause membrane lipid peroxidation in plant cells (Breusegem et al., 2001). In the process of plant evolution, a protective antioxidant system (including antioxidant protease system and antioxidant substances) was formed to handle this external ROS stress. The antioxidant system can effectively resist external stresses to a degree, but when the stress intensity exceeds the resistance threshold the damage occurs (Foreman et al., 2003; Czarnocka and Karpinski, 2018). The effects of BPA on the antioxidant system of plant species were first seen when research groups evaluated the toxicity of BPA to algae. Exposure of *C. caspia* (early growth stage) to BPA (4 - 6 mg/L) enhanced the activity of superoxide dismutase (SOD), which effectively eliminated ROS allowing the algal cells to maintain normal physiological functions and morphology. However, exposure to high concentrations of BPA (10 - 12 mg/L) and the prolonged exposure time led to excessive production and accumulation of ROS in algal cells, overwhelming the scavenging capacities of SOD and other components of the antioxidant system, and resulting in peroxidation damage in algal cells (Li et al., 2008). Furthermore, Liu et al. (2010) found that activities of SOD and glutathione transferase in a marine diatom (*N. incerta*) were positively correlated with BPA concentrations. Zhang et al. (2014) evaluated the acute and chronic toxicity of BPA in *Chlorella pyrenoidosa* and *Scenedesmus obliquus*, and found that at all BPA concentrations SOD and catalase (CAT) activities were elevated in both algae. In contrast, the antioxidant systems of different species have also been shown to respond differently to BPA exposure (Xiang et al., 2017). For example, SOD activity was more sensitive to BPA stress in *S. quadricauda* than *C. raciborskii*, whereas for CAT activity, *C. raciborskii* was found

to be the more sensitive algal species. This indicates that the two algal species likely exhibit different protection mechanisms against BPA stress. Indeed, *C. raciborskii* had the potential to prevent oxidative damage by increasing the antioxidant enzyme CAT activity, whereas *S. quadricauda* was protected by both CAT and SOD activities. Thus, and in accordance with previous findings, *S. quadricauda* was protected by increasing the antioxidant enzyme CAT activity, *S. quadricauda* is likely to be more tolerant to BPA stress. Increases in SOD and CAT activities in response to BPA stress suggest that there was as overproduction of superoxide anion ($O_2^{\cdot -}$). However, after a specific threshold concentration of BPA was exceeded, antioxidant compounds and enzymes were not sufficient to withstand abnormal increase in hydrogen peroxide (H_2O_2) and ROS levels, which was reflected in the significant increase in malondialdehyde (MDA) observed in algal cells at concentrations of 5, 10 and 20 mg/L of BPA, indicating that algal cells were undergoing peroxidative damage (Xiang et al., 2017).

Studies on the effects of BPA on the antioxidant systems of higher plant species have also been conducted. BPA was found to stimulate the production of ROS (e.g. H_2O_2) in root cells of chickpeas, suggesting that BPA induced an oxidative stress response in root cells, although the mechanism by which BPA triggered ROS production was unclear (Dogan et al., 2010). In addition, MDA content in chickpea roots was found to increase with increasing BPA concentrations, and the concentration of H_2O_2 was positively correlated with the MDA content. Peroxidation damage to roots caused by BPA exposure was confirmed via histochemical staining, which indicated that the plasma membrane integrity of root cells was damaged by oxidative stress induced by BPA exposure. In addition, BPA exposure was found to stimulate ROS production in these plants, resulting in a decrease in the protein content in roots, which was likely due to the use of antioxidant proteins (such as glutathione)

for scavenging excessive ROS (Dogan et al., 2010). Wang et al. (2015a) found that soybean seedling roots exposed to low concentration of BPA (1.5 mg/L) displayed mild membrane lipid peroxidation, but did not activate the antioxidant system; whereas higher concentrations of BPA (> 3.0 mg/L) induced ROS production, activated antioxidant system, and exacerbated membrane lipid peroxidation. Similarly, another study showed that the level of lipid peroxidation in rice seedlings increased in a dose-independent manner (along with the increase in BPA concentration), and that the H_2O_2 and hydroxyl radical (·OH) content corresponded to the pattern of lipid peroxidation (Ali et al., 2016). The adverse effects of BPA on rice seedlings were related to oxidative stress (Ali et al., 2016). However, as increased oxidative stress and lipid peroxidation might affect antioxidant enzyme activities, there could have been other attenuating factors. The activities of key antioxidant enzymes (SOD, CAT and ascorbate peroxidase) increased following exposure to low concentrations of BPA (2.3, 11.4 and 22.8 mg/L), which could be considered as a cellular defense mechanism against external stress. Yet, the increase in antioxidant enzymes activity in the seedlings treated with the highest concentration of BPA (45.7 mg/L) suggested that BPA exposure at this concentration might have overwhelmed the plant self-defense system, resulting in cell structural and functional damage (Ali et al., 2016). In contrast to previous studies, Zhang et al. (2018) found that when soybean root cells were exogenously exposed to 1.5 and 3.0 mg/L of BPA, ROS could demonstrate a degree of protection. Indeed, ROS were shown to participate in the degradation of BPA, decreasing the concentration of BPA in plants, and thereby reducing the damage caused by BPA exposure. This dose-response relationship and the discovery of the protective activity of ROS are important when trying to understand the complex mechanisms behind BPA phytoremediation and when trying to assess the risks of BPA in the environment.

4.3.5 Reproduction and heritability

Several studies have reported that BPA can affect the reproductive behavior of plants (Speranza et al., 2011; Chang et al., 2015; Jadhav et al., 2012). In an *in vitro* study with kiwifruit, Speranza et al. (2011) found that the emergence and elongation of pollen tubes were inhibited in a dose-dependent manner at a BPA concentration greater than 10 mg/L, and the pollen tubes were obviously distorted under BPA concentrations of 30 mg/L. Another study by Chang et al. (2015) also reported that BPA exposure had a dose-dependent inhibition effect on pollen tube germination and elongation in the gymnosperm *Picea meyeri*. Further investigation revealed that BPA dissipated calcium ion (Ca^{2+}) concentration gradient by acting on Ca^{2+} channels and disrupting the actin filaments (AFs) organization in the pollen tubes of *P. meyeri*. This resulted in abnormal actin-dependent vesicle trafficking and further affected the deposition of cell wall components. This was suggested as a toxic mechanism of BPA concerning the growth of pollen tube tips (Chang et al., 2015). In a broader context, the activity of BPA may pose a potential threat to the reproductive success of higher plants.

Jadhav et al. (2012) evaluated the genotoxic effect of BPA by examining chromosomal aberration (CA) in root meristem cells of onion. The results showed that 50 mg/L BPA can induce CA in onion root cells, and under 200 mg/L BPA exposure can disrupt the cell mitotic process (mitotic index, mitotic phase difference, micronuclear) and inhibit root growth. Furthermore, they found that this cell damage may be passed on to offspring. Adamakis et al. (2013) found that BPA exposure can inhibit mitosis and cause abnormal chromosome morphology in the root meristem cells of pea seedlings. They postulated that this might be attributed to the destruction of root tip cytoskeletal microtubule arrays (MTs) under BPA exposure, and that MTs may be the main subcellular target of BPA toxicity in plants. Furthermore, Adamakis et al. (2016) investigated the

effect of BPA on mitosis in root tip cells of the gymnosperm *Abies cephalonica*, and found that BPA can induce CA in root tip cells, resulting from mitotic microtubule disorders. This is consistent with the effects of BPA on MTs observed in the root tip meristem region of pea seedlings. Further studies have confirmed that BPA can indirectly affect endoplasmic reticulum (ER) in *A. cephalonica* cells by inducing damage to MTs. Using immunohistochemical analysis of ER in BPA-exposed cells, the morphological changes in ER were confirmed to be the result of pathological changes in MTs. In addition, BPA was shown to act as a destructive agent for cell MTs, inducing the formation of multipolar spindles, which might be related to the centrosomal properties of gymnosperms. As there is typically a dynamic interaction between MTs and AFs, the effects of BPA on the two basic components of the plant cytoskeleton are likely related. Therefore, Stavropoulou et al. (2018) investigated the effects of BPA on AFs in apical meristem cells and leaf cells of maize. The results showed that BPA could rapidly destroy actin in a concentration- and time-dependent manner. First the filaments were affected, followed by the subcortical bundles, which formed a rod-like and circular conformation. The observed difference in sensitivity between protodermal and cortical cells was likely due to a deeper position of the latter. The sensitivity of AFs to BPA depends on the integrity of MTs. As the concentrations of BPA used were much higher than what would likely be found in the environment, Adamakis et al. (2018) also investigated the effects of environmentally relevant BPA concentrations (0.03 -3 μg/L) on leaf elongation and cytoskeleton (MTs and AFs) in the seagrass *Cymodocea nodosa*. They found that the highest BPA concentration (3 μg/L) significantly affected leaf elongation at the beginning of the experiment, and cytoskeleton disturbance was observed even at lower concentrations. Indeed, MTs were initially disrupted at 0.1 μg/L (i.e., "lowest observed effect concentrations", LOECs), whereas AFs were destroyed at even lower concentrations

(around 0.03 μg/L). AFs thus appeared to be more sensitive to low BPA concentrations than MTs. Furthermore, there was also a correlation between leaf elongation damage and MTs defects. Therefore, in this particular species and at BPA concentrations ranging from 0.03 - 3 μg/L, AFs damage, MTs disruption, and leaf elongation impairment appear to be the sensitive biomarkers of BPA stress.

5. Bisphenol A plant tolerance and phytoremediation

Phytoremediation is considered to be an economical and green biotechnology, which is focused on the concept of eliminating pollutants from soil or water bodies via absorption, transfer and biotransformation/biodegradation by plants. Sufficient evidence has shown that BPA can be absorbed by algae and higher plants and metabolized to mildly toxic or non-toxic forms through hydroxylation, glycosylation or redox reactions (Yoshida et al., 2002; Xuan et al., 2002; Schmidt and Schuphan, 2002; Nakajima et al., 2002, 2004, 2007; Hamada et al., 2002; Kondo et al., 2006; Watanabe et al., 2012). This provides a possibility of using phytoremediation for BPA pollution in water and soil.

The existing studies have reported the use of freshwater green algae and marine microalgae to decontaminate simple water systems containing BPA, achieving positive results (Hirooka et al., 2003, 2005; Nakajima et al., 2007; Li et al., 2008; Gattullo et al., 2012; Ouada et al., 2018). Hirooka et al. (2003, 2005) reported that under photoautotrophic conditions, green algae *Chlorella fusca* had a strong capacity to scavenge BPA at concentrations ranging from 2.3 - 18.3 mg/L, and that scavenging was actually the result of cell biodegradation, not just simple accumulation in cells. Because the high BPA concentrations have been detected in the environment (e.g. up to 17.2 mg/L in landfill leachate) (see Introduction), *C. fusca* could be a useful organism to use in BPA removal (e.g. for landfill leachate, *C. fusca* could be incubated with wastewater in closed photobioreactors). Peng et al. (2006)

found that the photodegradation of BPA was enhanced in simulated lake water containing algae (*Chlorella vulgaris*), humic acid and ferric ions (Fe^{3+}). When humic acid was proportional to Fe^{3+} (4 mg/L humic acid, 20 mol/L Fe^{3+}), the photodegradation efficiency of BPA was the highest. Li et al. (2009) reported that the marine diatom *S. hantzschii* isolated from the tidal water of the Futian Mangrove Reserve in Shenzhen, China, had a high removal capacity for BPA in media containing low BPA concentrations. *S. hantzschii* showed strong resistance to BPA at low concentration (< 3.00 mg/L), and efficiently bioaccumulated and biodegraded this chemical contaminant. Indeed, after treatment for 16 days the diatom removed 88%, 99%, 92%, 61%, 48%, 28%, and 26% of BPA from media supplemented with 0.01, 0.10, 1.00, 3.00, 5.00, 7.00, and 9.00 mg/L BPA, respectively. Gattullo et al. (2012) studied the capacity of freshwater alga (*M. braunii*) to remove BPA from aquatic environments, and found that *M. braunii* both tolerated BPA at concentrations up to 4.0 mg/L and efficiently removed BPA after 4 days of growth. Thus, *M. braunii* appears to be a promising species for phytoremediation of BPA from aquatic environments. However, further detailed studies would be required to determine how to successfully cultivate algae that maintain a high BPA removal capacity outdoors. Ouada et al. (2018) recently isolated an extremophilic microalgae strain with high tolerance to BPA from an alkaline, wastewater and household sewage pond. This microalga, *Picocystis* (an alkaliphilic chlorophyta), was shown to be resistant to low concentrations of BPA (0 - 25 mg/L) (i.e. no inhibitory effects on the growth and photosynthesis during 5 days of exposure), and relatively resistant to higher BPA concentrations (50 and 75 mg/L) (i.e. growth inhibition rate did not exceed 43%). Furthermore, this microalga was found to efficiently remove BPA, displaying removal rates of 75% and 42%, respectively, at 25 mg/L and 75 mg/L BPA. The high tolerance and high removal capacity of *Picocystis* make it a promising species for BPA bioremediation.

Several higher plant species have also been reported to remove BPA effectively, including *Portulaca oleracea*, *Rumex crispus*, rice, water hyacinth, *Phragmites australis*, *Salvia* cultivars, *Dracaena sanderiana*, and several herbaceous species (Imai et al., 2007; Takahashi et al., 2005; Kang and Kondo, 2006; Toyama et al., 2009; Okuhata et al., 2010; Saiyood et al., 2010; Suyamud et al., 2018; Loffredo et al., 2010). Out of more than 100 different plant species studied, Imai et al. (2007) found that *P. oleracea* was the best at rapidly removing BPA from wastewater. Their results showed that for BPA concentration below 11.4 mg/L, there was almost 100% removal within 24 hours. Even at concentration of 114 mg/L, more than 95% of initial BPA was removed after 100 hours. Furthermore, they also found that removal of BPA by *P. oleracea* was not dependent on light conditions, and was not affected by temperature within the range of 15 - 30 °C. However, Okakuta et al. (2010) argued that although *P. oleracea* was a promising plant for removal of organic pollutants in warm areas, it is sensitive to low temperatures and thus not suitable for low-temperature regions. Instead, these researchers used cold-resistant *Salvia* plants to study their capacity to be used in BPA phytoremediation. The selected 25 cultivars of *Salvia* plants showed a high removal capacity for BPA, which might have been due to the abundant quantity of aromatic secondary metabolites (such as terpenoids and phenolics) contained in the root tips, and the lipophilic properties of plant roots (allowing them to take up and metabolize BPA well). Loffredo et al. (2010) studied the removal efficiency of BPA by eight herbaceous plants (five forage grasses and three horticultural species; see 4.2.1 section) in hydroponics during seed germination and growth stages. They found that BPA was absorbed and biotransformed during the germination and seedling growth stages, and that the tested forage grasses removed BPA more efficiently than the horticultural species. However, the optimal plant species, best suited for phytoremediation of BPA was not determined. In addition, they also

found that microbial decomposition promoted by root secretion also contributed to the removal of BPA. Saiyood et al. (2010) evaluated *D. sanderiana* and *Dracaena fragrans* (as representatives of tropical evergreen plants with fibrous roots) for their BPA tolerance and uptake capacity to determine if these plants represent good phytoremediators. *D. sanderiana* was found to exhibit higher tolerance and BPA removal than *D. fragrans*, and was found to tolerate up to 18.4 mg/L of BPA. *D. sanderiana* plants were found to secrete extracellular polysaccharide mucus in the non-sterile growth systems, possibly serving as a protective barrier against BPA toxicity. In addition, the study reported that bacteria adhering to the root surface played an important role in BPA biodegradation and enhanced BPA dissipation in hydroponics. Finally, they tried to use *D. sanderiana* to remove BPA from hazardous landfill leachate (BPA concentrations ranging from 7.8 to 15.5 mg/L). During the 20-day treatment, *D. sanderiana* plants survived without any signs of damage. These plants were found to tolerate BPA toxicity in the leachate and remove up to 60% of initial BPA (at 7.8 mg/L). Based on the above findings, Suyamud et al. (2018) screened two plant growth-promoting bacterial strains, *Bacillus thuringiensis* and *Pantoea dispersa* to use as inocula to *D. sanderiana*. Compared non-inoculated and *B. thuringiensis*-inoculated plants, the plants inoculated with *P. dispersa* showed a higher removal efficiency for BPA. This result was likely due to a higher population of the endophytic inoculant *P. dispersa* within plant tissues, which maintained the physiological levels of IAA required by the plant and decreased the level of intracellular ROS produced due to BPA exposure, decreasing BPA toxicity. This study also suggested that not all plant growth-promoting endophytic bacteria could improve BPA removal efficiency. Before using plant inoculation to enhance phytoremediation, the efficiencies of different bacterial inoculation and submersion times should be considered. Therefore, it is necessary to further identify and characterize the optimal plants

for decreasing or eliminating BPA pollution, and to explore the potential for applying microorganisms when using phytoremediation for BPA pollution.

6. Concluding remarks and future perspectives

In the paper, we reviewed the current knowledge about the effects of BPA on growth and physiological status of various plant species. A comprehensive description of BPA phytotoxicity, based on current research, is presented in Figure 2. However, with the current state of research, it is still difficult to gain a comprehensive understanding of the toxicological and ecological effects of BPA contamination. This can make it difficult for environmental managers to establish an accurate framework for assessing environmental risks of BPA and to develop protectionary practices to use against BPA pollution. Regarding plants and phytoremediation, future research should focus on the following four aspects:

1. To improve environmental monitoring and risk assessment, it is necessary to identify BPA-sensitive plant species in natural plant populations, and characterize sensitive biological traits and growth stages. Indeed, using this research, a macroscopic visual index system that can predict the occurrence of BPA pollution in time and be used to succinctly and quickly evaluate the risk of BPA pollution to plant populations should be established. Further identification of specific biomarkers associated with BPA stress and characterization of the dose-response relationships of various plant species and BPA would greatly supplement this macro-visual index and aid in risk assessment.

2. The effects of BPA on morphology and ultrastructure of plant cells should be studied. This could reveal BPA-induced changes in physiological and biochemical processes, and represent a microscopic basis that could explain macroscopic effects of BPA exposure in plants. Changes in

morphology and ultrastructure of plant cells may underpin a series of abnormal physiological activities in plants under external stress and may help elucidate mechanisms of BPA phytotoxicity at the cellular level.

3. Continue to carry out in-depth research on the effects of BPA on plant signal transduction. Plant signal transduction systems enable plants to perceive environmental stimuli and transmit signals to cells, inducing plant responses, regulating gene expression, and changing cell metabolism to adapt to the growing environment. When plants are subjected to BPA stress, they can produce large amounts of ROS (Wang et al., 2015a; Zhang et al., 2018; Ali et al., 2016, 2017). ROS, as a signal messenger, triggers stress responses in plant antioxidant systems (Czarnocka and Karpinski, 2018). Previous studies have reported that BPA can have a cytokinin-like function (Terouchi et al., 2004) and also that ethylene can participate in BPA-induced oxidative stress (Ali et al., 2017). So, it is important to determine what roles other plant hormones such as ABA, auxin, gibberellin, and salicylic acid play in BPA toxicity.

4. Determine how BPA exposure can affect cellular biochemical reactions. Many studies have reported that BPA can affect plant cell physiological and biochemical reactions. These biochemical reactions are essentially enzymatic reactions at room temperature. So, it is of high theoretical value to explore the mechanisms behind BPA-dependent regulation of enzyme activity in plant cell biochemical reactions, as well as the expression of genes controlling the synthesis of related enzymes. Unfortunately, there are few research reports on these aspects at present.

Studies on the mechanisms of BPA toxicity in plants have gradually expanded from those exploring the BPA influence on physiological and biochemical processes to those focusing on effects on cytological and molecular mechanisms. Only through a multi-faceted and multi-level systematic

research approach can we provide a solid theoretical basis for the scientific evaluation of the ecological risk of BPA. However, there are still some deficiencies in the current studies. Most studies on BPA pollution and its effects on terrestrial plants are carried out in hydroponic systems. Thus, they exclude the roles of soil and soil microbes. Therefore, results obtained in the current research need to be confirmed in the natural soil-plant systems. This will allow the inclusion of more reliable scientific information when establishing environmental regulations and performing risk assessments for BPA in terrestrial environments.

Conflict of interest

All authors declare no conflict of interest and approve the manuscript.

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Figure 1 Uptake, distribution and biotransformation of BPA by plant

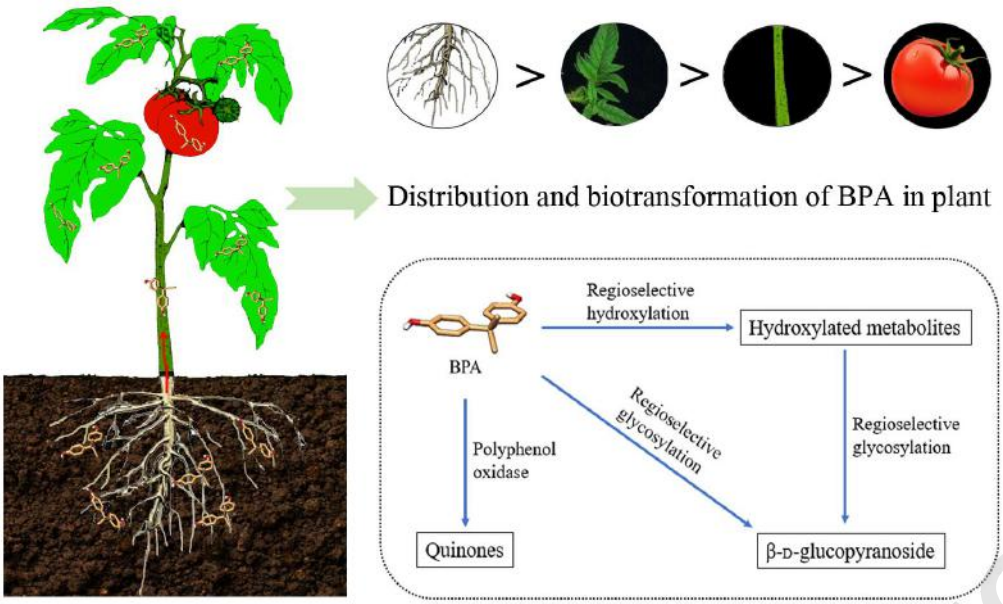

Figure 2 The inimical effects of BPA stress on plant