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REVIEW ARTICLE

Naturally occurring bisphenol F in plants used in traditional medicine

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Abstract

Bisphenol F (BPF, 4-[(4-hydroxyphenyl)methyl]phenol) is a bisphenol that is structurally similar to bisphenol A (BPA). In response to consumer concern towards BPA, industry has started to substitute BPA for BPF and other bisphenol analogues in the production of epoxy resins and coatings for various applications. In 2016, it was reported that commercially sold mustard contained naturally occurring BPF. Here, the existing literature was reviewed to investigate whether other natural sources of BPF among edible plants exist, including their impact on human exposure to BPF. *Coeloglossum viride* var. *bracteatum* (rhizome), *Galeola faberi* (rhizome), *Gastrodia elata* (rhizome), *Xanthium strumarium* (seeds) and *Tropidia curculioides* (root) were found to contain naturally occurring BPF. Botanical extracts from these plants are used in traditional Chinese medicine. The highest values of BPF were recorded for *G. elata* and *T. curculioides.* Information on precise doses of the plant extracts used is scarce; however, for *G. elata*, also known as Tian Ma and available in powder form, a daily exposure of BPF from this source could theoretically amount up to 4.5 µg/kg body weight per day (based on a 70 kg body weight). Therefore, herbal products used in traditional Chinese medicine should be considered as a potential source contributing to the overall human exposure when assessing endocrine-active bisphenolic compounds.

Keywords Bisphenols · Endocrine disruptors · Edible plants · Traditional medicine

Abbreviations

BPF	Bisphenol F
BPA	Bisphenol A
4-HBA	4-Hydroxybenzyl alcohol
EFSA	European Food Safety Authority

Introduction

Bisphenol F (BPF, 4-[(4-hydroxyphenyl)methyl]phenol, CAS 620-92-8, EC number 210-658-2) is a bisphenol with the chemical formula $(HOC_6H_4)_2CH_2$). It is structurally similar to bisphenol A (BPA) (Fig. 1). In response to consumer concerns towards BPA, industry has started to substitute BPA for BPF and other bisphenol analogues in the production of epoxy resins and coatings for various applications, such as lacquers, varnishes, liners, adhesives, plastics, water pipes and dental sealants (OEHHA 2017). Concern has been raised about the use of BPA because of its estrogenic activity and, therefore, to potentially act as an endocrine-active chemical with effects on human health (Ben-Jonathan and Steinmetz 1998; vom Saal and Hughes 2005). This has prompted several countries such as France, Denmark and Canada to ban the use of BPA in some packaging for food intended for infants. The European Food Safety Authority (EFSA) has assessed the safety of BPA for use in food contact materials several times, most recently in 2015 (EFSA CEF Panel (EFSA Panel on Food Contact Materials Enzymes Flavourings and Processing Aids) 2015). A recent systematic review of both in vitro and in vivo studies has suggested that the potency in hormonal effect of BPF is in the same order of magnitude as that of BPA (Rochester and Bolden 2015). More recent studies have confirmed the similarities in the reported biological effects between BPF and BPA (Goldinger et al. 2015; Kim et al. 2017; Lee et al. 2017; Mesnage et al. 2017; Rosenfeld 2017). Zoller

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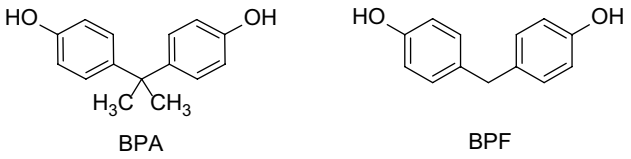

Fig. 1 Structures of bisphenol A and 4,4′-bisphenol F

et al. (2016) identified for BPF a LOAEL of 10 mg/kg body weight per day based on a subacute oral toxicity study in rats by (Higashihara et al. 2007). The critical effects were decreased body weight, decreased serum total cholesterol, glucose and albumin values as well as increased thyroxine levels in the serum of female rats. They derived a TDI of 11 µg/kg body weight per day (Zoller et al. 2016), which is in the same order of magnitude as the current t-TDI of BPA established by EFSA (EFSA CEF Panel (EFSA Panel on Food Contact Materials Enzymes Flavourings and Processing Aids) 2015) [see also Dietrich and Hengstler (2016)].

In 2016, it was reported that commercially sold mustard contained naturally occurring BPF up to a concentration of around 8 mg/kg (Zoller et al. 2016). The authors ruled out that the origin of the identified BPF was from contamination of the raw products, packaging or from epoxy resins or other sources where technical BPF is used. Furthermore, only mild mustard made of the seeds of *Sinapis alba* contained BPF. Of the potential isomers, only the 4,4′-BPF isomer (Fig. 1) was identified (Zoller et al. 2016). More recently, Reger and co-workers confirmed the presence of BPF in mustard with the highest concentrations found in medium hot mustard (up to around 11 mg/kg), and the lowest in hot mustard (Reger et al. 2017). The latter authors also reported that the levels of BPF in mustard increased with time of storage and confirmed that 4,4′-BPF was the nearly exclusive isomer detected.

The aim of this work was to review the existing literature to investigate whether other natural sources of BPF among edible plants exist, including their impact on human exposure to BPF. While no other plants used for food with naturally occurring BPF were identified, a number of botanical extracts used in traditional Chinese medicine are reported in the published literature to contain BPF.

Methods

A comprehensive literature search on Bisphenol F was conducted with the following search terms including synonyms from the Toxnet Hazardous Substances Data Bank (HSBD) as well as MeSH synonyms: 'bisphenol F' OR '4,4′-methylenediphenol' OR 'bis(4-hydroxyphenyl)methane' OR 'bis(*p*-hydroxyphenyl)methane' OR '4,4′-dihydroxydiphenylmethane' OR '4,4′-dihydroxydiphenyl-methane' OR '620-92-8' OR '4,4′-bisphenol F' OR '4,4′-methylenebis(phenol)' OR '*p*-hydroxydiphenylmethane'. The search fields included title, abstract and keywords, covered all years (search date: 28 May 2018) and was performed in Scopus. The search produced 367 results that were screened manually to extract publications reporting the presence of naturally occurring BPF in plants.

Zoller et al. (2016) proposed that 4-hydroxybenzyl alcohol (4-HBA) may be a possible intermediate in the formation of BPF during the processing of white mustard seeds. Therefore, an additional literature search was conducted with the following search terms including synonyms from the Toxnet Hazardous Substances Data Bank (HSBD) as well as MeSH synonyms: 'gastrodigenin OR 623-05-2 OR 4-HBA OR 4-hydroxymethyl phenol AND plant'. The search fields included title, abstract and keywords, covered all years (search date: 06 June 2018). The search yielded 520 articles that were screened manually to extract publications reporting the presence of 4-HBA in edible plants.

Results and discussion

Occurrence data for BPF

Out of the 367 publications retrieved, 13 report the detection of BPF in five different plant species (Table 1). These are *Coeloglossum viride* var. *bracteatum* (rhizome), *Galeola faberi* (rhizome), *Gastrodia elata* (rhizome), *Xanthium strumarium* (seeds) and *Tropidia curculioides* (root). These plants have been indicated as herbal medicine. Only *G. elata* was also found to be commercially available via Internet vendors as food supplement. *C. viride* var. *bracteatum* (rhizome) is a traditional Tibetan remedy for cough and asthma (Huang et al. 2002, 2004) and is often referred to as Wang La. *G. faberi* is a Chinese folk medicine for treating venomous snake bites (Li et al. 1993). *G. elata* is a traditional Chinese medicine, under the name of Tian Ma, for treating seizure, tetanus, headache, dizziness, numbness in limbs, and pain due to rheumatism (Chinese Pharmacopoeia Commission 2015; Noda et al. 1995). *X. strumarium* (synonym: *Xanthium sibiricum*, Siberian or common cocklebur) is a traditional Chinese medicine for treating common cold and headache (Lee et al. 2008).

Table 1 shows the levels of BPF that were detected in the plants (expressed per kg dried material), which were reported to range from 3.3 to 4.6 mg/kg for *C. viride* var. *bracteatum,* to be 7.2 mg/kg for *G. faberi*, to range from 0.2 to 69.5 mg/kg for *G. elata*, to be 38.0 mg/kg for *T. curculioides* and 0.1 mg/kg for *X. strumarium*. The highest values of BPF recorded for *G. elata* and *T. curculioides* exceeded the concentrations of BPF reported in mustard (Reger et al. 2017; Zoller et al. 2016).

Table 1 Occurrence of BPF in plants used in traditional medicine and the estimated BPF intake based on recommended doses

Plant	Family	Sample type	BPF content (mg/kg)	Recommended dose of herb (g/day)	Exposure to BPF based on recommended dose (µg/kg bw/day)	References
Coeloglossum viride var. *bracteatum* (rhizome)	Orchidaceae	Dried	3.3	9–15	0.4–0.7	Huang et al. (2002)
Coeloglossum viride var. *bracteatum* (rhizome)	Orchidaceae	Dried	4.6	9–15	0.6–1.0	Huang et al. (2004)
Galeola faberi (rhizome)	Orchidaceae	Dried	7.2	Not found	n/a	Li et al. (1993)
Gastrodia elata (rhizome)	Orchidaceae	Dried	50	2.0–4.5	1.4–3.2	Noda et al. (1995)
Gastrodia elata (rhizome)	Orchidaceae	Fresh	n/a	n/a	n/a	Hye et al. (1998)
Gastrodia elata (rhizome)	Orchidaceae	Dried	19.9	2.0–4.5	0.6–1.3	Lee et al. (2006)
Gastrodia elata (rhizome)	Orchidaceae	Dried	19.9	2.0–4.5	0.6–1.3	Jang et al. (2010)
Gastrodia elata (rhizome)	Orchidaceae	Dried	69.5	2.0–4.5	2.0–4.5	Duan et al. (2013)
Gastrodia elata (rhizome)	Orchidaceae	Dried	0.2	2.0–4.5	0.006–0.013	Wang et al. (2013)
Gastrodia elata (rhizome)	Orchidaceae	Dried	7.5	2.0–4.5	0.2–0.5	Jeon et al. (2016)
Gastrodia elata (rhizome)	Orchidaceae	Dried	n/a	2.0–4.5	n/a	Dai et al. (2017)
Tropidia curculioides (Root)	Orchidaceae	Dried	38.0	Not reported	n/a	Sarkar et al. (2018)
Xanthium strumarium (seeds)	Asteraceae	Fresh	0.1	3–10	0.004–0.014	Lee et al. (2008)

kg bw kg body weight, *n/a* not available

BPF was also reported to be present in canned braised bamboo shoots (0.623 mg/kg) (Liao and Kannan 2014); however, this finding could not be confirmed in samples of preserved bamboo shoots [concentrations of BPF of 0.05 mg/kg in acid-preserved bamboo shoots and below the limit of detection in bamboo shoots not preserved in acid or fresh (Zoller et al. 2016)].

Exposure scenarios for BPF

We attempted to determine potential intake levels from these sources based on their uses in traditional medicine. Information on precise doses for most of the plants identified here to contain BPF was difficult to find, partly because of the scarcity of information identifiable through commonly used research tools such as Scopus, PubMed or Web of Knowledge on the use of whole plant parts (as compared to the substantially larger body of publications available on individual active ingredients of the plants). More information was retrievable using search engines such as Google but their sources were generally non-verifiable or commercial sources. An additional complication is that in traditional medicine complex extracts of the plants of interest, often in collaboration with additional plants are generally used, which makes it difficult to determine exposure scenarios.

Among the plants identified here to contain BPF, *G. elata* is perhaps the best described. It is known as Tian Ma in traditional Chinese medicine. Also, because it has been reported that the *G. elata* tuber cannot be cooked for long time because of the volatility of its main active ingredient gastrodin, it is available in powder form [source (accessed 23/07/2018): http://www.shen-nong.com/eng/herbal/tianma.html]. Published doses for *G. elata* rhizome in dry form range from 1 to 1.5 g/person (Song et al. 2001; Teoh 2016) to be given two to three times per day (Friesen and Friesen 2012). This would equate to a total daily dosage of 2.0–4.5 g *G. elata* rhizome per person. A similar dose range of 1.0–1.5 g, administered two or three times per day is cited by the Gale Encyclopedia of Alternative Medicine [source (accessed 23/07/2018): http://www.encyclopedia.com/medicine/encyclopedias-almanacs-transcripts-and-maps/gastrodia] and by the Institute for Traditional Medicine and Preventive Health Care, Inc. (ITM) [source (accessed 23/07/2018): http://www.itmonline.org/arts/gastrod.htm]. Based on the above daily total dose of 2.0–4.5 g dried rhizome from *G. elata* per person per day and the highest BPF content of 69.5 mg/kg dried rhizome from *G. elata* found in the literature (Duan et al. 2013), a daily exposure to BPF from this source could amount up to 4.5 µg/kg body weight per day (based on a 70 kg body weight).

No published reference on recommended doses for *C. viride* (Wang La) was found but one website [source (accessed 24/07/2018): https://www.mdidea.com/products/proper/proper093.html] states '9–15 g, decoction, or powder, or dip into drink and taken, take as tea, cook with chicken, mutton, etc.' Using this figure as a daily dose and assuming complete extraction of BPF from the plant to provide 4.6 mg BPF per kg dried rhizome from *C. viride* (Wang La) (Huang et al. 2004), a daily exposure of BPF from this source could theoretically amount up to 1.0 µg/kg body weight per day (based on a 70 kg body weight). According to the Chinese Pharmacopeia

Table 2 Occurrence of 4-HBA in edible plants or plants used in traditional medicine

Plant	Family	Sample type	4-HBA content (mg/kg)	References
Anoectochilus formosanus	Orchidaceae	Fresh whole plant	10	Shih et al. (2005)
Argania spinosa (argan)	Sapotaceae	Seeds (oil and press cake)	Not reported	Rojas et al. (2005)
Arundina graminifolia	Orchidaceae	Rhizome (dried)	75	Liu et al. (2004)
Coeloglossum viride var. *bracteatum* (rhizome)	Orchidaceae	Rhizome (dried)	6	Huang et al. (2002)
Coeloglossum viride var. *bracteatum*	Orchidaceae	Rhizome (dried)	8.4	Huang et al. (2004)
Cucurbita pepo (zucchini)	Cucurbitaceae	Male flowers	Not reported	Itokawa et al. (1982)
Daucus carota (carrot)	Apiaceae	Flowers (dry)	177	Kobayashi et al. (2003)
Galeola faberi	Orchidaceae	Rhizome (dried)	3.6	Li et al. (1993)
Gastrodia elata	Orchidaceae	Rhizome (dried)	500	Noda et al. (1995)
Gastrodia elata	Orchidaceae	Rhizome (dried)	16.5	Ji et al. (2006)
Gastrodia elata	Orchidaceae	Rhizome (dried)	16.5	Jang et al. (2010)
Gastrodia elata	Orchidaceae	Rhizome (dried)	9.1	Duan et al. (2013)
Gastrodia elata	Orchidaceae	Rhizome (dried)	0.34	Wang et al. (2013)
Gastrodia elata	Orchidaceae	Rhizome (dried)	10.4	Jeon et al. (2016)
Gastrodia elata	Orchidaceae	Rhizome (dried)	Not reported	Wang et al. (2018)
Gastrodia elata	Orchidaceae	Rhizome (dried)	Not reported	Tang et al. (2018)
Ophiopogon japonicus	Ophiopogon	Rhizome	Not reported	Zhao et al. (2017)
Rhodiola imbricata	Crassulaceae	Root (dried coarse powder)	15	Choudhary et al. (2015)
Sinapis alba L.	Brassicaceae	Seeds	Not reported	Morra et al. (2018)
Vanilla planifolia	Orchidaceae	Pods freeze-dried and powdered	8.7 g/kg dry weight	Palama et al. (2009)
Vanilla pompona	Orchidaceae	Fruits freeze-dried and powdered	17.3–35.5 g/kg dry weight	Maruenda et al. (2013)

and the Modern Chinese Traditional Medicine Library, dried seeds of *X. strumarium* (*X. sibiricum*) can be used in a quantity of 3–10 g per portion prescribed, simmered into a broth. Likewise, assuming complete extraction of BPF from the seeds into the broth from 10 g fresh *X. strumarium* seeds to provide 0.1 mg BPF per kg seeds (Lee et al. 2008), a daily exposure of BPF from this source could theoretically amount up to 0.014 µg/kg body weight per day (based on a 70 kg body weight). No information on dosage was found for *G. faberi* and *T. curculioides*.

In 2015, EFSA set a temporary tolerable daily intake (t-TDI) of 4 µg/kg body weight per day for BPA (EFSA CEF Panel (EFSA Panel on Food Contact Materials Enzymes Flavourings and Processing Aids) 2015). The potency of BPF for endocrine activity has been reported to be within the same order of magnitude as that of BPA (Rochester and Bolden 2015). Zoller et al. (2016) derived a TDI of 11 µg/kg body weight per day (Zoller et al. 2016), which is in the same order of magnitude as the current t-TDI of BPA. Here, we compared the potential exposure to BPF from *G. elata* at the above recommended doses with the provisional TDI for BPA, and assuming that the levels of BPF detected in the dried rhizome are representative, the exposure to BPF could reach the t-TDI for BPA but not that derived by Zoller et al. (2016) for BPF [see also Dietrich and Hengstler (2016)].

Occurrence data for 4-HBA

The origin of the endogenous BPF in *C. viride* var. *bracteatum*, *G. faberi*, *G. elata*, *X. strumarium* and *T. curculioides* is not clear. Zoller et al. (2016) proposed that 4-HBA (gastrodigenin) may be a possible intermediate in the formation of BPF during the processing of white mustard seeds. Indeed, these authors found that BPF could be formed from 4-HBA in a condensation reaction under acidic conditions. Therefore, we conducted an additional search of the literature to investigate the presence of 4-HBA in edible plants, including those used in traditional Chinese medicine. Out of the 520 publications identified, 43 report the detection of 4-HBA in plants of which 13 are classified as edible or used in traditional Chinese medicine (Table 2). Both BPF and 4-HBA were detected in *C. viride* var. *bracteatum*, *G. faberi* and *G. elata.* While the harsh acidic conditions used by Zoller et al. (2016) to synthesise BPF from 4-HBA may not be found in the living plants, the conditions used to dry and store might favour the reaction. Alternatively, enzymatic formation of BPF cannot be ruled out. However, co-existence does

not demonstrate a chemical link between BPF and 4-HBA and the biochemical formation of BPF may have occurred through an alternative pathway.

Conclusions

In conclusion, a search for the presence of the endocrine-active substance BPF in edible plants has revealed its presence in plants used in traditional Chinese medicine and food supplements. Exposure to BPF from these sources is expected to be limited and, therefore, probably of low concern for human health for the general population. However, herbal products used in traditional Chinese medicine should be considered as a potential source contributing to the overall human exposure when assessing endocrine-active bisphenolic compounds.

Compliance with ethical standards

Conflicts of interest The authors declare that they have no conflict of interest.

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