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Botanical ingredients: Intakes, regulations, risks and attitudes

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Abstract:

Botanical ingredients have been used for centuries in food and in medicines, typically to support and maintain physiological functions and as remedies for many ailments. Today, botanical ingredients are still ingested as part of food supplements or herbal medicines (HM). Industry reports suggest growing global sales of and revenue from HM and food supplements containing botanicals, hereafter called botanical food supplements (BFS). In the context of this suggested growing popularity, this article will introduce both BFS and HM and then explore the available data on BFS intakes and consumer attitudes to their use. It will describe the EU regulatory framework within which BFS sit and mention research suggesting possible interactions between botanical ingredients, herbal medicines and traditional medicines. It is intended as a brief overview rather than a comprehensive review of the area.

Key words:

Food supplements, botanicals, herbal medicines, dietary intake, risk, regulations.

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Botanical food supplements – intake, regulations, risks and attitudes.

Botanical ingredients and herbs have been used for centuries for the support and maintenance of physiological functions and for the treatment of a variety of illnesses and ailments. In the UK, 25% of the population are reported to use some form of complementary and alternative medicine, including botanical food supplements (BFS) and herbal medicines (HM) (Ritchie, 2007; Egan *et al.*, 2011). Recent market research has suggested that the UK market for all food supplements will reach £465 million by 2024, representing the fourth largest market share globally behind Italy, Russia and Germany (Mintel, 2020). Against this backdrop of suggested consumer desire and market demand, this article will provide a brief introduction to key considerations for products containing botanical ingredients (both BFS and HM). It is intended to provide a brief overview of these issues, rather than an exhaustive review on the subject area.

Classifying herbal substances: Botanical Food Supplements and Herbal Medicine

Under EU law, there are two relevant definitions for HM; that of medicinal products and that specialised for HM. The definition of a medicinal product is laid out in Article 1 of Directive 2001/83/EC as:

- (a) *Any substance or combination of substances presented as having properties for treating or preventing disease in human beings; [Limb 1]*
- (b) *Any substance or combination of substances which may be used in or administered to human beings either with a view to restoring, correcting or modifying physiological functions by exerting a pharmacological, immunological or metabolic action, or to making a medical diagnosis. [Limb 2]*

Separately, herbal medicinal products (HMPs) are defined in Directive 2001/83/EC as;

“Any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations..” (2001/83/EC)

Thus, herbal medicinal products must meet the requirements laid out in the definition for a medicinal product, and also contain an active ingredient of a herbal substance (the unprocessed form of the herb) or a herbal preparation (the processed form of the herb).

In contrast, for food supplements containing botanical ingredients, in the EU (and in the UK), such products fall under the general description of a “*food supplement*” and so are defined as;

“foodstuffs the purpose of which is to supplement the normal diet and which are concentrated sources of nutrients or other substances with a nutritional or physiological effect, alone or in combination, marketed in dose form, namely forms such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquids, drop dispensing bottles, and other similar forms of liquids and powders designed to be taken in measured small unit quantities.” (2002/46/EC).

More recently, as part of an EU amendment regarding levels of contaminants in foods, *botanical preparations* have been defined as;

“preparations obtained from botanicals (e.g. whole, plant parts, fragmented or cut plants) by various processes (e.g. pressing, squeezing, extraction, fractionation, distillation, concentration, drying up and fermentation). This definition includes comminuted or powdered plants, plant parts, algae, fungi, lichen, tinctures, extracts, essential oils (other than the vegetable oils referred to in point 6.1.1), expressed juices and processed exudates.” (2015/1933/EU).

However, some botanical or herbal ingredients can be used in BFS or HM, and the responsibility for their classification falls at a national level in EU Member States. Thus, the same plant substance can be classified as a ‘food’ in one Member State and as a ‘medicine’ in another (European Commission, 2020). This absence of harmonisation regarding classification is not only applicable to BFS and HM, it is across all sectors and enables a more flexible approach to classification to be undertaken across EU Member States. In the UK, the Medicines and Healthcare products Regulatory Agency (MHRA) has a statutory role in determining whether a product containing such a botanical ingredient is categorised as having a medicinal purpose in accordance with EU and national law, with similar national

regulatory bodies across Europe. Some determinants of whether such a product is a 'food' or a 'medicine' include the purpose of the herb's inclusion, presentation and what is the dominant purpose or function of the product (e.g. a medicinal or food use). Previous case law can also influence decision making with each product determined on a 'case by case basis' (MHRA, 2020).

In summary, a herbal product may be considered a medicinal product if it meets the requirements set out in Limb 1 of the definition and makes medicinal claims (e.g. to specifically treat or prevent a disease). Case law will then inform how Limb 2 is interpreted. This is typically assessed on a case by case basis. A BFS, which makes no medicinal claims and is not medicinal by composition, is not classified as a medicinal product. Food law prohibits medicinal claim on foods, including food supplements (Article 2 of Regulation 178/2002/EC). However, it may be possible for the same substance to be regarded as either a food or as a medicine.

Regulatory framework for Botanical Food Supplements and Herbal Medicines

Different regulatory frameworks exist for BFS and HM. Focusing on BFS, in addition to the aforementioned Directive 2002/46/EC (which provides detailed legislation pertinent to food supplements as a type of 'food' under food law), BFS are subject to all other relevant food legislation. Hence, they must comply with the following, which are intended as illustrative rather than an exhaustive list:

- Food safety (Regulation (EC) 178/2002)
- Food hygiene and HACCP (Regulation (EC) 852/2004)
- Food information to consumers (Regulation (EU) 1169/2011)
- Nutrition and health claims (Regulation (EC) 1924/2006)
- Maximum levels for residues and contaminants Regulation (EC) No 1881/2006 ?
- Approval of novel foods/ingredients (Regulation (EU) 2015/2283).

Other considerations may also apply at a national level, e.g. some EU countries require notification that a food supplement is being placed on the market (e.g. Ireland), whereas other countries do not (e.g. the UK).

HM are subject to a different regulatory framework. Certain exemption apply, but in the majority of cases, herbal medicines must be authorised before being placed on the market in the EU through demonstration of safety, quality and efficacy of the product at hand. Also, if a product meets the criteria for 'traditional use' it can be registered as a 'Traditional Herbal Medicinal Product' (THMP) where tradition of use is accepted as a basis for substantiating the safety and efficacy of the product (European Commission, 2020). However, this is restricted to minor conditions where medical supervision is not required and it follows that not all products which fall within the definition for HM can be classified as a THMP. In turn, these would otherwise be subject to the usual provisions for assessment as a medicine. HM are regulated through the Directive 2001/83/EC. This Directive sets out requirements for registration of HM to ensure maximum consumer protection including: meeting standards of quality and safety and providing sufficient evidence of traditional use (2001/83/EC; Dickinson et al., 2019). Following the publication of this legislation, the Traditional Herbal Registration (THR) Scheme was set up by the UK MHRA which sets out standards for the safety and quality of herbal medicines and includes the provision of information to the customer on the safe use of the product (Dickinson et al., 2019., MHRA, 2019).

One consideration relates to the lack of harmonisation in EU law for ingredients within food supplements, other than vitamins and minerals. An agreed list of permitted forms of vitamins and minerals within food supplements exists across all EU Member States (2002/46/EC), although agreement on maximum limits for amounts present has not been reached. For the 'other substances' (laid out in the definition of food supplements) which can occur in food supplements, there is no agreement on either the forms or maximum amounts which may be present. As a result, ingredients such as botanicals, enzymes, amino acids and pro- and prebiotics are not fully harmonised under EU food law, despite constituting a share of the EU food supplement market (European Advisory Services, 2007).

In an attempt to provide some harmonisation, and a more stringent approach to regulating the use of botanical ingredients in food supplements, some EU Member States have adopted a 'list-based' approach. Belgium, France and Italy have created 'BELFRIT' which outlines a list of ~1,500 plants eligible for use in food supplements within these three Member States and

which hopes to emphasise the need for regulatory harmonisation through this form of implementation. Alternatively, Germany has developed a list of “plants and plant parts” within the ‘List of Substances of the Competent Federal Government and Federal State Authorities’, for use in food or food ingredients which can be used as a guidance tool, as it is not implemented in legislation (Federal Office of Consumer Protection and Food Safety (BVL) 2014). Within this list, there are three ‘sub-lists’; List A: Substances not recommended for use in foods; List B: Substances for which restricted use in foods is recommended and List C: Substances which cannot yet be completely assessed due to lack of sufficient data, which are set out to align with Annex 3 of Regulation EC No. 1925/2006 (BVL, 2014; 1925/2006/EC). At present, no other Member States have made comparable attempts to help harmonise botanical food supplements in Europe. However, a list-based approach of ‘approved botanicals’ cannot be considered the most effective method of harmonisation as each EU Member State can come to their own determination on classification of products. The UK is an example of a country where no such approach has been adopted and where products are assessed on a product by product basis, in line with case law. Additionally, no confirmed clear plan of how this issue will be treated following the withdrawal from the EU has been published.

There is some disquiet regarding the lack of harmonisation across Europe. The European Consumer Organisation (BEUC) has suggested that the current EU legislation fails to guarantee that only safe food supplements reach the market (BEUC, 2016). Further, BEUC has suggested that labelling of BFS should not be limited to a plant’s name and should include the and should include the amounts of active compounds, where applicable and their amount, as well as potential effects when taken with other medications or substances (BEUC, 2016). The possibility may exist that the apparent lack of legislative stringency combined with an ever-growing market may put consumers at risk of gaining easy access to unsafe and misleading products online.

Nutrition and Health Claims for Botanical Food Supplements

The classification of botanicals as BFS or HM can be understood more clearly through the processes for assessing medicinal and health claims for both types of products. As mentioned, the MHRA determines whether a botanical/plant product is medicinal according to

the presentation, purpose, use and composition of the product at hand. For example, if a product is claiming to 'maintain', 'help maintain' or 'support' health, this may not be a medicinal claim and therefore be approved under food law as the MHRA are not responsible for food products (MHRA, 2020). However, if a product claims to 'relieve symptoms', 'treat' or to 'cure', then these claims are medicinal, and the product must be approved and dealt with as a HM (MHRA, 2020).

If classed as a BFS, under Regulation (EC) 1924/2006, clear descriptions exist for nutrition and/or health claims which are permitted on foods and food supplements. Simplistically, a health claim implies that the consumption of the product making the claim carries a specific health benefit, whereas a nutrition claim is a claim which implies that a food has beneficial nutritional properties due to the presence, absence, increased or reduced levels of a particular nutrient or other substance. As part of a multi-step process, before any such claim can be used on a product, the European Food Safety Authority (EFSA) is responsible for verifying the scientific substantiation of the claim, providing an independent scientific opinion which acts as a basis for the European Commission and Member States to decide whether to authorise the claim or not (EFSA, 2012). Aligned with this, an EU Register of Nutrition and Health Claims (NHCR) provides a record of all claims submitted, authorised or unauthorised (1924/2006/EC).

Since conception of this approach, EFSA has evaluated claims applications for botanicals but, as of 2010, none of the applications had been given an outright positive assessment and some had been classed as part substantiated (Geurts, 2018). In contrast to medicinal claims of THR products, BFS health claims cannot use 'tradition of use' as a basis for substantiation under EU law, despite comprising many of the same plant ingredients. The European Commission has since put all health claims for BFS 'on-hold' pending further evaluation for numerous reasons. Firstly, it became clear that the EFSA process for assessing the claims would lead to most of them being rejected as many of the health claims made by botanical products were based on tradition of use of the substance and not scientific evidence demonstrated by randomised control trials (RCT) (Gulati et al., 2014). Secondly, the decision to put claims 'on-hold' allowed for a review of the assessment methods used and to examine whether any amendments to the Nutrition and Health Claims Regulation (EC) 1924/2006 are

needed (432/2012/EU; Geurts, 2018). A simple search of the NHCR reveals the extent of botanical health claims which are only part-substantiated for use in food supplements and are therefore 'on-hold', pending further scientific evaluation before being considered for inclusion on the list of permitted health claims (1924/2006/EC; Gulati et al., 2014). In the interim, 'on hold' botanical claims are often used once they comply with the general principles of the Nutrition and Health Claims Regulation (EC) 1924/2006, the claims are scientifically substantiated, they follow the national provisions of the member state where used and do not mislead or suggest medicinal properties.

At UK level the Department of Health and Social Care sets out policy lead food law which is implemented by Trading Standards and Environmental Health. These stipulate that health claims cannot be made on any products unless they are authorised and included on the EU register of permitted health claims (NHCR). However, in the case of health botanical claims that have been submitted to the EFSA and are currently 'on-hold', the ASA may assess this claim subject to the advertiser submitting robust evidence (Advertising Standards Authority, 2015). Thus, botanical health claims which have been submitted at EU level may still be considered by the ASA for sale in the UK. Suggestions have been made by the Department of Health and Social Care on how the UK government will deal with nutrition and health claims post Brexit; the draft document was based on the event of a no-deal Brexit. However, the document which was published in 2019 and since withdrawn, has now been made a UK statutory instrument. [A statutory instrument is "a form of legislation which allows the provisions of an Act of Parliament to be subsequently brought into force or altered without Parliament having to pass a new Act" (House of Common, 2008)]. This document suggests the adoption of all authorised and rejected EU nutrition and health claims, which would be included in a 'United Kingdom Nutrition and Health Claims Register (Department of Health and Social Care, 2019). The claims must continue to comply with the regulations set out by Regulation (EC) 1924/2006 as amended (Department of Health and Social Care, 2019). Furthermore, if the European Commission has not come to a decision on an application for any health claims (including all botanical claims which are currently on-hold and the 2,000 part substantiated claims), a new application must be submitted to the necessary UK authorities

for assessment in order to be authorised for use in the UK (Department of Health and Social Care, 2019).

Proposed plans for HM were also published and subsequently withdrawn by the MHRA, which again were based on the event of a no-deal Brexit. These plans outline that in the event of a no-deal Brexit, the MHRA would expand the list of countries from which it will accept traditional evidence for HM and accept the 15 years of traditional evidence from these countries as well as those from European Economic Area (EEA) countries, subject to such countries having a similar pharmacovigilance system as the UK. The MHRA may also publish products which have been granted a THR in the UK (MHRA, 2019).

However, as these proposed suggestions for both BFS and HM have since been withdrawn until an agreement is reached on post-BREXIT arrangements with the European Union, it cannot be said for certain what will be implemented after the Brexit transition period between January-December 2020.

Population dietary intakes of botanical food supplements

Current data on the intake of BFS and HM is relatively scarce and in some cases difficult to quantify. For BFS, output from national food consumption surveys and/or from research papers botanicals rarely provide standalone descriptions, with BFS mainly falling into a category called 'other'. This can result in inadequate, unclear data on the proportion of the population taking BFS and associated dosages consumed. As an example, such is the case with UK and Irish national food surveys, where overall supplement intakes are typically reported and BFS presumably fall into the 'other supplement' section. Using data from the UK National Dietary and Nutrition Survey (NDNS), approximately 23% of adults aged 19-64 years reported taking at least one food supplement of any kind during the course of their 4-day food diary, with this figure rising to 39% in those aged >65 years (NDNS, 2012). There is no mention of BFS. Comparatively, for Ireland, the National Adult Nutrition Survey (NANS) reported over a 4-day period that 28% of adults aged 19-64 years had taken at least one food supplement,

with this figure increasing to 37% in those aged >65 years (IUNA, 2011). NANS makes brief mention of a category called 'Other Oils e.g. evening primrose/starflower oil' consumed by 9% of the population and a category called 'Other' consumed by 5% of the NANS population which presumably contains some BFS. Collectively this suggests that relatively low proportions of the general population consume BFS, but dosage is unknown. However, it has also been suggested that data on supplement intake may be under-reported when using methods such as a 4-day food diary as supplement intake patterns can be infrequent, intermittent or seasonal and thus may not be captured to the fullest extent (NDNS, 2012).

Beyond national food surveys, there are some descriptions of BFS intake within the scientific literature. In an attempt to add new knowledge at an EU level, in 2011-2012 the PlantLIBRA scientific consortium assessed dietary intakes of BFS (described as plant food supplements' (PFS) within this project), across 6 European countries (UK, Finland, Germany, Italy, Romania and Spain). To complete this, the consortium adapted the EU definition of food supplements to create a specific definition for PFS:

"Foodstuffs the purpose of which is to supplement the normal diet and which are concentrated sources of botanical preparations that have nutritional or physiological effect, alone or in combination with vitamins, minerals and other substances which are not plant-based. PFS are marketed in dose form, such as capsules, pastilles, tablets, pills and other similar forms, sachets of powder, ampoules of liquids, drop dispensing bottles, and other similar forms of liquids and powders designed to be taken in measured small unit quantities." (Garcia-Alvarez et al., 2014)

In this study, a questionnaire examined self-reported dietary intake of PFS across six European countries, as well as looking at other aspects such as self-reported adverse effects associated with intake of PFS (PlantLIBRA, 2014). Of the 2,359 participants assessed, 18% reported using at least one PFS and these were more likely to be older (those aged >60 were more likely to use more than 1 botanical product), were well educated, non-smokers in good general health (Garcia-Alvarez et al., 2014).

The results of this wider PlantLIBRA study were further explored by a validation study of the PFS questionnaire, conducted in two European cities (Las Palmas de Gran Canaria, Spain and Milan, Italy). This validation study compared the results from the self-reported survey with short (30 day) and longer term (180 day) food diaries completed by 48 and 49 participants respectively. The validation indicated good agreement with the main questionnaire (Garcia-Alvarez *et al.*, 2014). The overall results indicated that approximately 19% of the screened population were using PFS, which is noteworthy considering published data from national surveys suggests that 23-28% of the population are taking a broad range of food supplements – with usage of BFS likely to fall well below this after the consideration of vitamin and mineral supplements (IUNA, 2011., NDNS, 2012). The PlantLIBRA study was the first European based study to publish quantified data on PFS/BFS intake on a large scale; a greater number of such studies across different countries are needed to obtain accurate estimates of intake.

Two recent pilot studies conducted in England aimed to obtain information on the use of herbal medicines and users' experiences and attitudes towards them. The first study involved n=157 participants aged 18 to >75 years, of which 82% were women and 44% were aged 45-64 years (Zahn *et al.*, 2019). It was found that around 50% of the participants used 'medicinal plants' frequently, with 26% using them daily, and 24% using them several times per week (Zahn *et al.*, 2019). However, there is no clear distinction made in this survey between HM and BFS as they are mostly referred to as 'medicinal plants', with some mention of their use as food supplements and health foods. Thus we assume that both HM and BFS are included in the analysis of this survey.

The second pilot study involved n=408 participants who completed an online survey investigating the public's perception of herbal medicine and general use of herbs for health (Lazarou & Heinrich, 2019). Recruitment was conducted both online (through social media groups) and in person at the Eden Project under the auspices of Pukka Herbs stall. Participants were aged between 16 to >65 years, with HM being particularly popular among those aged 36-55 years. Seventy three percent of those aged 36-55 years reported using HM within the last week, and only 5% of 36-55 year olds had never used HM (Lazarou & Heinrich, 2019).

Overall, there is a need for national surveys to provide more detail on the intake of BFS and HM separately, to better understand their use as the market continues to grow and to assess potential risks associated with their use. Notably, their lack of representation in national food consumption surveys could also indicate that intake of BFS in particular, is limited compared to the intake of vitamins and minerals. On the other hand, users of BFS may not equate their use as a food, in the context of the food consumption survey they are undertaking.

Are there potential adverse effects and interactions from consuming botanical ingredients?

As with any food supplement, potential problems can occur if the ingredients (plant substances) present in both BFS and HM are taken incorrectly. For example, exceeding the stated maximum daily dose of pills/capsules/tablets or taking them in conjunction with other supplements or medication. Hence, in the UK and indeed in other EU Member States, food supplements and HM clearly list posology and include information about interactions and safety precautions in Patient Information Leaflets. For BFS, statements that they should not be used as a substitute for a varied diet, as stipulated specifically by the UK Food Supplements Regulations (2003) are also included.

In addition to the points above, the NHS information website provides guidance and highlights potential issues for consumers who are thinking of using or who currently use HM. In particular, they provide specific guidance to people who take other medication regularly, population groups who should avoid taking them, the risks of taking HM before surgery, what to be aware of when purchasing HM in shops and online and how to report any side effects experienced (NHS, 2018). The NHS website suggests that side effects experienced from medicines and herbal remedies should be reported via the MHRA Yellow Card Scheme in England, the Department of Health in Northern Ireland, Health Facilities in Scotland (HFS) and the NHS Governance E-Manual in Wales Yellow Card Scheme (NHS, 2018). In contrast, for BFS, although they can share the same active ingredients as HM, there is currently no specific advice for caution to be taken with these products, beyond those pertaining to regular food supplements, or how to report adverse effects potentially experienced from their use.

At EU level, the European Medicines Agency (EMA) coordinates the EU pharmacovigilance system which aims to detect, assess, understand and prevent adverse effects or any other

medicine-related problem across EU Member States, including those involving HM (EMA, 2015). Full details of adverse events reported following intake of individual plants can be found through the EMA EudraVigilance database of adverse drug reactions reports (<http://www.adrreports.eu/en/search.html>). The overarching EU pharmacovigilance system operates through cooperation between the EU Member States, EMA and the European Commission. There is no comparable formal system for food supplements, including BFS.

The issue of polypharmacy has been apparent for many years in human medicine, especially among older adults. Polypharmacy describes the concurrent use of multiple medications and, although in most definitions this does not include food supplements, foods or botanical ingredients, it is reported that these may increase risk of adverse health effects due to potential interactions and therefore should be considered (Agbabiaka *et al.*, 2018). Polypharmacy in relation to the use of multiple conventional medicines has been robustly investigated with a well-known example being warfarin, which has been recognized to interact with ~120 drugs, botanicals and foods to cause either a decreased effectiveness or increased risk of bleeding (Mayo Clinic, 2020). Examples of botanicals which have been known to interact with warfarin include: ginkgo biloba, ginseng, garlic and St. John's Wort (Mayo Clinic, 2020).

Taking St. John's Wort (SJW) as an example, this plant has been classified as a herbal medicine in some countries and a food supplement in others (based on intended use and claims being made). SJW is recognised to cause adverse interactions with various drugs such as cyclosporins, some anti-retrovirals, oral contraceptives and anti-depressants (NCCIH, 2015; Hammerness *et al.*, 2003; Soleymani *et al.*, 2017). A systematic review from 2003 reported that in the case of oral contraceptives, adverse effects such as changes in menstrual flow, breakthrough bleeding and irregular bleeding were reported by long-time users of oral contraceptives within a week of commencing the use of SJW (Hammerness *et al.* 2003). More recently an expert opinion has suggested that the concomitant use of SJW with oral contraceptives was postulated as resulting in unintended pregnancies (Soleymani *et al.*, 2017). However, well-designed clinical studies evaluating herbal supplement-drug interactions in general are lacking (NCCIH, 2015).

A relatively recent UK cross sectional study investigated potential drug-herb and supplement-herb interactions and identified (based on published herb-drug and supplement-drug interactions) three combinations of BFS/HMs and conventional drugs suggested as a 'significant hazard', three combinations deemed 'potentially hazardous' and a further 21 combinations described as 'doubts about the outcome of concurrent use' (Agbabiaka *et al.*, 2018). These combinations are displayed in Table 1.

Table 1: Suggested drug-herb and drug-supplement interactions of 'significant' and 'potential hazard' as identified by Agbabiaka *et al.*, 2018

Significant hazard	Potential hazard
Algal calcium with Vitamin K ₂ and D ₃ + Levothyroxine ¹	Glucosamine + Metformin ⁴
Peppermint (<i>Mentha x piperita</i> L.) + Lansoprazole ²	Omega 3 fish oil + Bisoprolol ⁵
St. John's Wort (<i>Hypericum perforatum</i> L.) + Amlodipine ³	Ginkgo (<i>Ginkgo biloba</i> L.) + Rabeprazole ⁶

¹Levothyroxine = used to treat hyperthyroidism (NHS, 2018) <https://www.nhs.uk/medicines/levothyroxine/>

²Lansoprazole = reduces stomach acid levels (NHS, 2018) <https://www.nhs.uk/medicines/lansoprazole/>

³Amlodipine = used to treat hypertension (NHS, 2018) <https://www.nhs.uk/medicines/amlodipine/>

⁴Metformin = used to treat Type 2 Diabetes Mellitus (NHS, 2019) <https://www.nhs.uk/medicines/metformin/>

⁵Bisoprolol = used to treat hypertension (NHS, 2018) <https://www.nhs.uk/medicines/bisoprolol/>

⁶Rabeprazole = reduces stomach acid levels (NHS, 2018) <https://www.nhs.uk/medicines/rabeprazole/#:~:text=About%20rabeprazole,prevent%20and%20treat%20stomach%20ulcers.>

The study involved 155 participant questionnaires from a cohort recruited through two UK GP practices during 2016, where the inclusion criteria included taking at least one prescription drug, being able to consent but being free of dementia or terminal illness (Agbabiaka *et al.*, 2018). The study cohort was 51% female, 71% aged 65 – 74 years and 85% identified as 'white'. Within this study, 33.6% of respondents reported concurrently using prescription

medication, herbal medicinal products and dietary supplements, with sixteen of these respondents being suggested to be at risk of potential adverse drug interactions (Agbabiaka *et al.*, 2018). Based on these findings, the authors suggest that up to 1.3 million older adults in the UK are at risk of at least one potential herb–drug or supplement–drug interaction (Agbabiaka *et al.*, 2018). Whilst the study sample is small and proposed hazard based on published data rather than direct diagnosis, this study highlights a potential issue facing users of herbal medicine, dietary supplements and BFS. It also emphasizes the need for healthcare professionals to be actively recording usage of dietary supplements within patient records and including this in their considerations when prescribing medications (Agbabiaka *et al.*, 2018).

The aforementioned PlantLIBRA study also recorded self-reported adverse effects following BFS consumption (described as PFS in this study). In this study, 3.5% of PFS users (approximately 83 people out of 2,359) across the six participating EU countries reported adverse effects, with this figure rising to 5 -6% in Finland, Germany and Spain (Restani *et al.*, 2016). The tables below outline the PFS most frequently associated with self-reported adverse effects and those adverse effects most commonly self-identified by the PlantLIBRA study (Restani *et al.*, 2016).

Table 2: PFS with the highest number of reported adverse effects from the PlantLIBRA study (Restani *et al.*, 2016)

PFS/botanical used:	Percentage of self-reported cases of adverse effects
Garden valerian (<i>Valeriana officinalis</i> L.)	9.2
Tea (<i>Camellia sinensis</i>)	8.0
Ginkgo (<i>Ginkgo biloba</i> L.)	6.9
Guarana (<i>Paullinia cupana</i>)	6.9

Table 3: Most commonly reported adverse effects and examples of PFS which exhibited these effects as reported in the PlantLIBRA study (Restani *et al.*, 2016).

Most commonly affected physiological systems:	Most reported symptoms:	Examples of types of PFS used which caused symptoms:
Gastrointestinal	Nausea, diarrhoea	Tea (<i>Camellia sinensis</i>), Guarana (<i>Paullinia cupana</i>), Maca (<i>Lepidium meyenii</i> Walp)
Nervous system	Insomnia, dizziness, migraine	Tea (<i>Camellia sinensis</i>), Ginkgo (<i>Ginkgo biloba</i> L.), Garden valerian (<i>Valeriana officinalis</i> L.) Guarana (<i>Paullinia cupana</i>)
Cardiovascular system	Tachycardia	Guarana (<i>Paullinia cupana</i>), Panax Ginseng (<i>Panax ginseng</i> C.A.Mey)

Similar proportions are recorded in previous research, such as from the US Health and Diet Survey (2002). This study was a national survey and involved 2,743 noninstitutionalized English-speaking adults aged 18 years or older (Timbo *et al.*, 2003). This study revealed that of the 73% of participants reported taking dietary supplement in the previous year, and 4% of these reported experiencing adverse effects (Timbo *et al.*, 2006). Collectively, although these proportions are relatively small, it still indicates that there are potential adverse effects associated with PFS use. It has been suggested that a lack of information on food supplement packaging, with regards to its consumption with other medications, may perhaps

lead consumers to believe that there are not any risks associated (BEUC, 2016). As with all supplements and medications, it should not be assumed that there are no associated risks – even with products which are marketed as being ‘natural’ (Mayo Clinic, 2017).

Consumer attitudes towards BFS in a growing market

Consumer attitudes towards food supplements in general are typically positive which may be attributed to their perceived health benefits. For BFS, positive attributes may also arise from the marketing of botanicals as ‘natural’, having a long history of use or being ‘of plant origin’ (BEUC, 2016). For HM, positive attributes may include a perception that they are ‘natural’ and have ‘fewer side effects’ and may be viewed alongside a changing relationship with conventional medicines (Lazarou & Heinrich, 2019).

The UK Food Standards Agency conducted a two-phase study on consumer attitudes and behaviours towards all food supplements in 2017-2018. The first phase involved desk-based research and a consumer survey with 2,081 participants. The second phase used focus groups and in-depth interviews to gain more knowledge and perspective on the consumers’ attitudes towards food supplements (FSA, 2018). The participants regularly reported their reasons for taking food supplements to be: ‘for a general health or as an energy ‘boost’; to have ‘control over their own health or the health of others i.e. children’; for ‘added immunity from illnesses’; and, in some cases, due to a ‘specific event or time in their life’ or due to an ‘existing medical condition or deficiency’ (FSA, 2018). When asked about the perceived efficacy of food supplements, views ranged from strong belief to cynicism. There was also a strong view overall that most supplements are ‘harmless’, with the exception of various weight loss supplements and products aimed at sports enthusiasts (FSA, 2018). There was little concern in relation to mixing different food supplements or consuming them alongside prescription medication, and most respondents reported that they would not think of mentioning their supplement use to their doctor (FSA, 2018). Eighty eight percent of respondents reported that they followed the dosage recommendations, while others reported ‘over-dosing’ for the purpose of added immunity when they felt ill or felt symptoms of conditions worsening (FSA, 2018). Furthermore, some reported noticing a real change in symptoms

when they didn't take them compared to when they did, while others couldn't tell if they made a difference at all (FSA, 2018).

In their pilot study, Zahn and colleagues found that 80% of 157 UK participants used medicinal plants (both HM and BFS) for multiple health benefits including health protection, disease prevention and treatment (Zahn et al., 2019). Ninety five percent of participants believed in the medicinal power of plants and 51% felt that herbal products were safe (Zahn et al., 2019). Furthermore, 55% of participants felt they experienced fewer side effects when compared with pharmaceutical medicines and only 24% of participants informed their doctor that they were taking medicinal plants (HM or BFS). Furthermore, almost one third of participants used both herbal and conventional prescribed medication, with the majority of them (51%) not disclosing this information to medical practitioners (Zahn et al., 2019). This was found to be very similar to results from the National Omnibus survey (Great Britain) published in 2004 involving 1,794 respondents, which found that 52% of those who reported use of complementary and alternative medicine (including HM) did not disclose this information with their general practitioner (Thomas and Coleman, 2004). This may highlight a potential communication issue between patients and medical practitioners and could be a causal factor in adverse events that occur due to the concurrent use of HM and BFS with prescribed medication.

Interestingly, the previously mentioned UK study (Lazarou & Heinrich, 2019) that recruited participants through social media and the Eden project (a visitor attraction, educational charity and social enterprise which houses plants from across the world inside two biomes. <http://www.edenproject.com>), hinted at differences in attitudes by gender. The authors found through semi-structured interviews with male participants ages 22-59 years, that men can feel ridiculed in certain circles when discussing the potential benefits of HM, as it could be perceived as "sissy stuff" (Lazarou & Heinrich, 2019). This was further substantiated by a single male interview in which he stated that "women are more likely to fall for herbal medicines and most men would prefer to use scientifically proven pharmaceuticals". This was somewhat reflected in the results of an associated online survey where 63% of men

believed HM to be effective for minor health conditions compared to 82% of women (Lazarou & Heinrich, 2019).

Overall, there is considerable consumer trust in BFS (and indeed food supplements in general) and HM. This is despite suggestions by some consumer groups that supplements, including BFS being sold on the EU market, may be 'unsafe' and 'misleading' due to a lack of regulatory stringency of the marketing, labelling, categorisation and distribution (BEUC, 2016). HM and BFS are easily accessible on the market today from supermarkets, pharmacies and health food stores which may lead consumers to believe they are safe to take without considering possible side effects or interactions which may occur. This ease of access paired with an apparent reluctance to share information about their intake of HM or BFS with medical practitioners suggests that increased efforts may be needed to open up communication and education between medical practitioners and patients regarding their use of food supplements and complementary and alternative medicine to ensure best practice when taking prescribed medications alongside these products. Further research is needed to gauge specific consumer behavior and attitudes towards BFS as a separate entity from other food supplements and HM, to better understand reasons for taking them, perceived efficacy and benefits as well as perceived risks. There remains a need (as with all food and food supplements) to ensure all products sold are safe and of high quality.

Conclusion

Overall, it is evident that botanical ingredients will continue to be used as methods of treating illnesses or disease (HM) or for maintaining and supporting other physiological functions (BFS). Currently, there is a range of relevant regulatory frameworks relevant to HM and BFS at EU and national level. For BFS products, extra consideration is needed for botanical health claims which are still currently 'on-hold' at an EU level, but where the chief outcome is to 'help better informed consumers make better choices' (Directorate General for Health & Consumers, 2020). As yet, it remains unclear how this may be addressed in the UK after the Brexit transition period. It is also noted that detailed descriptions of BFS intake is lacking, either in bespoke or national food consumption surveys; there is a need for this to be

addressed to better understand the patterns and levels of usage in the UK and beyond. There is also scant data regarding intake of HM. The potential exists for adverse effects and interactions involving botanicals in supplements, HM and conventional medicines to occur. Despite this being the case, consumer attitudes towards BFS and HM are positive, with a general consensus among consumers that they come without risk of adverse effects and are 'natural'. Efforts are needed to enhance awareness and improve communication between consumers and health (medical) practitioners to reduce the likelihood of adverse events occurring.

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References:

Advertising Standards Authority (ASA) (2015) *Food: Health Claims*, Available at: <https://www.asa.org.uk/advice-online/food-health-claims.html> (Accessed: 14th May 2020).

Agbabiaka, T. B. et al. (2018) 'Prevalence of drug-herb and drug-supplement interactions in older adults: a cross-sectional survey', *Br J Gen Pract*, 68(675), pp. e711-e717.

BEUC The European Consumer Organisation (2016) *Food Supplements: Challenges & risks for consumers.*, Available at: https://www.beuc.eu/publications/beuc-x-2016-092_ipa_beuc_position_on_food_supplements.pdf (Accessed: 16th October 2019).

Commission Regulation (EU) 2015/1933 of 27 October 2015 amending Regulation (EC) No 1881/2006 as regards maximum levels for polycyclic aromatic hydrocarbons in cocoa fibre, banana chips, food supplements, dried herbs and dried spices [2015] OJ L282 p.11-13

Commission Regulation (EU) No 432/2012 of 16 May 2012 establishing a list of permitted health claims made on foods, other than those referring to the reduction of disease risk and to children's development and health [2012] OJ L136 p.1-40

Department of Health and Social Care (2019) *Guidance Bulletin [Withdrawn] The Nutrition (Amendment etc.) (EU Exit) Regulations 2019: Practical Changes for Industry*, GOV.UK: Department of Health and Social Care.

Dickinson, R. et al. (2019) 'What has been the impact of the Traditional Herbal Registration (THR) scheme in the UK on information provided with herbal products bought over the counter?', *BMC Complementary Medicine and Therapies*, 19(85), pp. 1-8.

Directorate General for Health & Consumers (2020) *Comments on EFSA's opinions and stakeholder concerns. Second Collective Answer*, Available at: https://ec.europa.eu/food/sites/food/files/safety/docs/labelling_nutrition-claims-health_claims-collective_answer_20052011_en.pdf (Accessed: 7th June 2020).

European Advisory Services (2007) *THE USE OF SUBSTANCES WITH NUTRITIONAL OR PHYSIOLOGICAL EFFECT OTHER THAN VITAMINS AND MINERALS IN FOOD SUPPLEMENTS*, Available at: https://ec.europa.eu/food/sites/food/files/safety/docs/labelling_nutrition-supplements-2007_a540169_study_other_substances_en.pdf (Accessed: 20th May 2020).

657

658 European Commission (2020) *Commission Staff Working Document Executive Summary of*
659 *the Evaluation of the Regulation (EC) No 1924/2006 on nutrition and health claims made on*
660 *foods with regard to nutrient profiles and health claims made on plants and their*
661 *preparations and of the general regulatory framework for their use in foods*, Available
662 at: [https://ec.europa.eu/food/sites/food/files/safety/docs/labelling_nutrition-](https://ec.europa.eu/food/sites/food/files/safety/docs/labelling_nutrition-claims_swd_2020-95_part-1.pdf)
663 [claims_swd_2020-95_part-1.pdf](https://ec.europa.eu/food/sites/food/files/safety/docs/labelling_nutrition-claims_swd_2020-95_part-1.pdf) (Accessed: 1st June 2020).

664

665 Federal Office of Consumer Protection and Food Safety (BVL) (2014) *List of Substances of*
666 *the Competent Federal Government and Federal State Authorities Category "Plants and*
667 *plant parts"*, Berlin: Springer.

668

669 Geurts, S. (2018) 'Health Claims and Botanicals: How to Proceed with European
670 Harmonisation?', *European Food and Feed Law Review*, 13(1), pp. 29-33.

671

672 Lazarou, R. and Heinrich, M. (2019) 'Herbal Medicine: Who Cares? The Changing Views on
673 Medicinal Plants and Their Roles in British Lifestyle', *Phytotherapy Research*, 33 2409-2420

674

675 Medicines and Health Products Regulatory Agency (MHRA) (2019) *Guidance on new*
676 *provisions for traditional herbal medicinal products and homoeopathic medicinal products in*
677 *a no-deal Brexit*, Available at: [https://www.gov.uk/guidance/guidance-on-new-provisions-for-](https://www.gov.uk/guidance/guidance-on-new-provisions-for-traditional-herbal-medicinal-products-and-homoeopathic-medicinal-products-in-a-no-deal-scenario)
678 [traditional-herbal-medicinal-products-and-homoeopathic-medicinal-products-in-a-no-deal-](https://www.gov.uk/guidance/guidance-on-new-provisions-for-traditional-herbal-medicinal-products-and-homoeopathic-medicinal-products-in-a-no-deal-scenario)
679 [scenario](https://www.gov.uk/guidance/guidance-on-new-provisions-for-traditional-herbal-medicinal-products-and-homoeopathic-medicinal-products-in-a-no-deal-scenario) (Accessed: 1st June 2020).

680

681 Medicines and Health products Regulatory Agency (MHRA) (2019) *Herbal medicines*
682 *granted a traditional herbal registration (THR)*, Available
683 at: [https://www.gov.uk/government/publications/herbal-medicines-granted-a-traditional-](https://www.gov.uk/government/publications/herbal-medicines-granted-a-traditional-herbal-registration-thr)
684 [herbal-registration-thr](https://www.gov.uk/government/publications/herbal-medicines-granted-a-traditional-herbal-registration-thr) (Accessed: 18th May 2020).

685

686 Medicines and Health products Regulatory Agency (MHRA) (2020) *A guide to what is a*
687 *medicinal product. MHRA Guidance Note 8*, Available
688 at: [https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/872742/GN8_FINAL_10_03_2020_combined.pdf)
689 [_data/file/872742/GN8_FINAL_10_03_2020_combined.pdf](https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/872742/GN8_FINAL_10_03_2020_combined.pdf) (Accessed: 23rd May 2020).

690

691 Mintel (2020) *Health Food Retailing - UK - March 2020 Market Segmentation*, University
692 College Dublin: Mintel Group Ltd..

693

694 National Center for Complementary and Integrative Health (NCCIH) (2015) *Herb-Drug*
695 *Interactions*, Available at: [https://www.nccih.nih.gov/health/providers/digest/herb-drug-](https://www.nccih.nih.gov/health/providers/digest/herb-drug-interactions)
696 [interactions](https://www.nccih.nih.gov/health/providers/digest/herb-drug-interactions) (Accessed: 3rd June 2020).

697

Department of Health and Social Care (2012) National Diet and Nutrition Survey. Headline results from Years 1, 2 and 3 (combined) of the Rolling Programme (2008/2009 – 2010/11), Department of Health and Social Care: Department of Health and Social Care.

Directive 2001/83/EC of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use [2001] OJ L311 p. 67

Directive 2002/46/EC of the European Parliament and of the Council of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements [2002] OJ L183 p. 51-57

Directive 2004/24/EC of the European Parliament and of the Council of 31 March 2004 amending, as regards traditional herbal medicinal products, Directive 2001/83/EC on the Community code relating to medicinal products for human use [2004] OJ L136/85.

Egan, B. et al. (2011) 'An overview of consumer attitudes and beliefs about plant food supplements', *Food Funct*, 2(12), pp. 747-52.

European Medicines Agency (2015) Pharmacovigilance, Available at: https://www.ema.europa.eu/en/documents/leaflet/pharmacovigilance_en.pdf (Accessed: 28th May 2020).

Food Standards Agency (2018) *Food Supplements Consumer Research*, <https://www.food.gov.uk/research/research-projects/food-supplements-consumer-research>: Food Standards Agency.

Garcia-Alvarez, A. et al. (2014) 'Usage of plant food supplements across six European countries: findings from the PlantLIBRA consumer survey', *PLoS One*, 9(3), pp. e92265.

Gulati, O. P., Berry Ottaway, P., & Coppens, P. (2014). Botanical Nutraceuticals, (Food Supplements, Fortified and Functional Foods) in the European Union with Main Focus on Nutrition And Health Claims Regulation. *In: Nutraceutical and Functional Food Regulations in the United States and Around the World (Bagchi, D. ed)*, Academic Press, London, pp 221–256.

Hammerness, P. et al. (2003) 'St John's wort: a systematic review of adverse effects and drug interactions for the consultation psychiatrist', *Psychosomatics*, 44(4), pp. 271-82.

House of Commons (2008) *Statutory Instruments House of Commons Information Office Factsheet*, Available at: <https://www.parliament.uk/documents/commons-information-office/I07.pdf> (Accessed: 16th February 2020).

Irish Universities Nutrition Alliance (2011) *National Adult Nutrition Survey*, Available at: <https://irp-cdn.multiscreensite.com/46a7ad27/files/uploaded/The%20National%20Adult%20Nutrition%20Survey%20Summary%20Report%20March%202011.pdf> (Accessed: 2nd December 2019).

Mayo Clinic (2017) *Herbal supplements: What to know before you buy*, Available at: <https://www.mayoclinic.org/healthy-lifestyle/nutrition-and-healthy-eating/in-depth/herbal-supplements/art-20046714> (Accessed: 30th November 2019).

Mayo Clinic (2020) *Warfarin side effects: watch for interactions*, Available at: <https://www.mayoclinic.org/diseases-conditions/deep-vein-thrombosis/in-depth/warfarin-side-effects/art-20047592> (Accessed: 15th May 2020).

NHS (2018) *Herbal medicines*, Available at: <https://www.nhs.uk/conditions/herbal-medicines/> (Accessed: 19th January 2020).

PlantLIBRA (2014) *About the project*, Available at: <https://www.eurofir.org/plantlibra/> (Accessed: 10th December 2019).

Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety [2002] OJ L31 p.1-24

Regulation (EC) No 1924/2006 of the European Parliament and of the Council of 20 December 2006 on nutrition and health claims made on foods [2006] OJ L404/9

Regulation (EC) No 1925/2006 of the European Parliament and of the Council of 20 December 2006 on the addition of vitamins and minerals and of certain other substances to foods [2006] OJ L404 p. 26-38

Regulation (EC) No 852/2004 of the European Parliament and of the Council of 29 April 2004 on the hygiene of foodstuffs [2004] OJ L139/1

Regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015 on novel foods, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001 [2015] OJ L 327 p.1-22

Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers, amending Regulations (EC) No 1924/2006 and (EC) No 1925/2006 of the European Parliament and of the Council, and repealing Commission Directive 87/250/EEC, Council Directive 90/496/EEC, Commission Directive 1999/10/EC, Directive 2000/13/EC of the European Parliament and of the Council, Commission Directives 2002/67/EC and 2008/5/EC and Commission Regulation (EC) No 608/2004 [2011] OJ L304 p. 18-63

Restani, P. et al. (2016) 'Adverse Effects of Plant Food Supplements Self-Reported by Consumers in the PlantLIBRA Survey Involving Six European Countries', *Plos One*, 11(2). e0150089.

Ritchie, M. R. (2007) 'Use of herbal supplements and nutritional supplements in the UK: what do we know about their pattern of usage?', *Proc Nutr Soc*, 66(4), pp. 479-82.

Soleymani, S. et al. (2017) 'Clinical risks of St John's Wort (*Hypericum perforatum*) coadministration ', *Expert Opinion on Drug Metabolism & Toxicology*, 13(10), pp. 1047-1062.

Thomas, K. and Coleman, P. (2004) 'Use of complementary or alternative medicine in a general population in Great Britain. Results from the National Omnibus survey', *Journal of Public Health*, 26(2), pp. 152-157.

Timbo, B.B. et al. (2006) 'Dietary Supplements in a National Survey: Prevalence of Use and Reports of Adverse Events', *Journal of the American Dietetic Association*, 106(12), pp. 1966-1974.

Zahn, R. et al. (2019) 'Use of herbal medicines: Pilot survey of UK users' views', *Complementary Therapies in Medicine*, 44, pp. 83-90.

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826

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828

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