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Themed Section: Principles of Pharmacological Research of Nutraceuticals

EDITORIAL

Principles of pharmacological research of nutraceuticals

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LINKED ARTICLES

This article is part of a themed section on Principles of Pharmacological Research of Nutraceuticals. To view the other articles in this section visit http://onlinelibrary.wiley.com/doi/10.1111/bph.v174.11/issuetoc

Abbreviations

BCAAs, branched-chain amino acids; PEA, palmitoylethanolamide; RCTs, randomized controlled trials; TCM, traditional Chinese medicine

Tables of Links

TARGETS	
GPCRs[a]	**Enzymes**[c]
CB_1 receptors	Hydroxy-3-methyl-glutaryl-CoA reductase
CB_2 receptors	**Transporters**[d]
Nuclear hormone receptors[b]	P-glycoprotein
Pregnane X receptors	

LIGANDS	
Cholesterol	Hyperforin
Curcumin	Lovastatin
Epigallocatechin-3-gallate	PEA, N-palmitoylethanolamine
Genistein	

These Tables list key protein targets and ligands in this article which are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Southan *et al.*, 2016), and are permanently archived in the Concise Guide to PHARMACOLOGY 2015/16 ([a,b,c,d]Alexander *et al.*, 2015a,b,c,d).

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Introduction

The term 'nutraceutical', a hybrid term introduced in 1989 to designate the link between 'nutrition' and 'pharmaceutical agents', has actually no universally accepted definition (Aronson, 2017, Table 1). The broad canopy of 'nutraceutical' covers a wide range of different, naturally occurring, products, which are advocated to influence human health positively and so a variety of functional foods, fortified foods and dietary supplements have found their place here (Palthur *et al.*, 2010; Schmitt and Ferro, 2013; Drake *et al.*, 2017).

Nutraceuticals contribute to high rates of polypharmacy, particularly among multi-morbid older people (Brown, 2016; Pitkala *et al.*, 2016). If we only consider dietary supplements, it has been reported that American adults, with the exclusion of pregnant women, have used one or more dietary supplements at least once during the preceding month (Dickinson and MacKay, 2014; Borchers *et al.*, 2016). The main reasons for taking them are to enhance overall health and wellness, to fill dietary nutrient gaps, to stimulate immune health and to boost energy, bone and heart health (Brown, 2016). It has been estimated that herbal dietary supplements account for approximately 20–25% of dietary supplements sales in the USA (Borchers *et al.*, 2016; Brown, 2016), with the top best-sellers shown in Table 2 (Smith *et al.*, 2016).

Because of this widespread use, it is incumbent on the scientific community to have access to rigorous and reliable information of the experimental and clinical pharmacology of such products. Therefore, based on a number of informative reviews published in this themed issue, this article aims to provide an overview on the pharmacological basis of nutraceutical action, including efficacy and safety, with a special focus on herbal dietary supplements.

Pharmacologically active ingredients in dietary supplements

Herbal dietary supplements contain herbal extracts, that is, complex mixtures of phytochemicals of which the pharmacologically active compound(s), named active ingredient(s) or active principle(s), often constitute only a small part (Samuelsson, 1999). Minor constituents of the herbal extract may, in an additive or synergistic way, enhance the pharmacological action of the main active ingredient(s). Synergistic interactions have been advocated to explain the efficacy of apparently low doses of active constituents in herbal extracts (Williamson, 2001). The chief herbal, pharmacologically active, ingredients include carbohydrates, lipids, polyphenols, terpenes, steroids/ols and alkaloids (Samuelsson, 1999; Capasso *et al.*, 2003). Below, we report a brief overview on the pharmacology of some plant active ingredients. More comprehensive information regarding the pharmacological effects, the mode of action and the clinical pharmacology can be found in the accompanying review articles published in this themed issue (Bifari and Nisoli, 2017; Cicero *et al.*, 2017; Currò *et al.*, 2017; Goszcz *et al.*, 2017; Kunnumakkara *et al.*, 2017; Milani *et al.*, 2017; Peluso and Serafini, 2017; Petrosino and Di Marzo, 2017; Smeriglio *et al.*, 2017; Rietjens *et al.*, 2017).

Polyphenols

Polyphenols, being omnipresent in all plant parts, represent a prominent portion of the human diet, contained within fruits, vegetables and beverages (Bravo, 1998; Manach *et al.*, 2004; D'archivio *et al.*, 2007). Consumption of diets rich in polyphenols, such as the Mediterranean diet, is believed to be a nutritional strategy to improve or to prevent chronic diseases such as metabolic syndrome and cancer (Amiot *et al.*, 2016; Di Daniele *et al.*, 2017). The main classes of pharmacologically relevant polyphenols include coumarins, chromones, xanthones, stilbenes and flavonoids (Table 3). Flavonoids are most extensively widespread among the plant polyphenolic compounds and include the subclasses of flavones, flavonols, flavanols, isoflavones, flavanones, anthocyanidins and proanthocyanidins (Table 4).

Green tea and black tea are rich sources of plant polyphenols, the most abundant being epigallocatechin-3-gallate and theaflavins. In this issue of the BJP, Peluso and Serafini cover recent findings on the antioxidant activity of tea polyphenols as well as more specific pharmacological mechanisms such as enzymatic inhibition and interaction with transporters. Indeed, catechins and theaflavins have been shown to inhibit a number of enzymes involved in lipid and glucose metabolism, including maltase, glucosidase, amylase, lipases as well as the enzyme involved in cholesterol synthesis, that is, hydroxyl-3-methyl-glutaryl-CoA reductase (Peluso and Serafini, 2017). Although caution is needed in extrapolating to clinical situations from *in vitro* experimental studies, and despite the need for further research, the authors conclude that the regular consumption of tea can modulate antioxidant capacity of body fluids and could improve glucose and lipid metabolism (Peluso and Serafini, 2017). The authors' conclusion is supported by a recent systematic review and meta-analysis of observational studies, which revealed the association of tea consumption and decreased probability of developing the metabolic syndrome (Marventano *et al.*, 2016). Nevertheless, further high-quality clinical research is needed in this evolving area of nutritional pharmacology. Polyphenols in green tea and grapes are further considered by Santini and Novellino (2017) in the context of hypercholestrolaemia. The authors conclude that while positive effects may be suggested from *in vitro* and rodent studies, these do not extrapolate well to clinical evidence, with much higher doses being required, accompanied by safety concerns. Polyphenolic extracts from *Annurca* apples however have been endorsed by the FDA as safe and have potential to lower cholesterol. The authors provide an interesting example of how the beneficial properties of extracts can be significantly influenced by the species, with marked differences between closely related plants, in this case varieties of apples (Santini and Novellino, 2017).

The difficulties in interpreting the antioxidant effects of polyphenols are further explored by Goszcz *et al.* (2017) in the context of cardiovascular disease. Doubts exist as to whether the cardioprotective effects of these agents can be solely ascribed by the antioxidant properties demonstrated *in vitro* (Goszcz *et al.*, 2017). This is because of the rapid degradation and poor absorption of the original chemical species *in vivo*. Indeed, in contrast, potential pro-oxidant

Table 1

Some definitions in the nutraceutical field

Definiendum	Definition	Comment
Active ingredient (active principle)	A phytochemical contained in herbal drug (or extract) mostly responsible of its pharmacological activity.	Historical examples include the alkaloids morphine (from poppy opium) and atropine (from *Atropa belladonna* leaves). In cases where it is not possible to identify the active ingredients, the whole herbal medicine may be considered as one active ingredient.[a]
Dietary supplement	A substance added to the diet, often taken as a pharmaceutical formulation, to treat or prevent a deficiency.[b]	Dietary supplements include vitamins, amino acids, proteins, minerals, fibre and plant extracts. The arbitrary inclusion in the dietary supplement category of herbal medicinal products has been criticized.[c] Authentic supplements to the diet (i.e. vitamins, minerals), have nutritional value. Herbal extracts may contain pharmacologically active ingredients and should be regulated as medicines[c]
Herbal drug	Part of the plant (e.g. roots, stems, leaves, bark, fruits and exudates) used for pharmaceutical/nutraceutical purpose.	Crude drugs may be obtained from wild or cultivated plants. Quality specifications for crude drugs are given in Pharmacopoeias.[d] They constitute the starting material for preparation of herbal preparations, such as herbal extracts.
Herbal extract	Preparation of herbal drugs which contains all the constituents which are soluble in the solvent used in making the extract.[d]	Extracts are very complicated mixture of phytochemicals of which the pharmacologically active compound(s), named active principle(s) or active ingredient(s), often constitutes only a small part.[d] To ensure a reliable dosage, the content of key pharmacologically active constituent(s) should be determined or a HPLC fingerprint provided (extract standardization).
Herbal medicine	Herbal medicines include herbs, herbal materials, herbal preparations and finished herbal products that contain as active ingredients parts of plants, or other plant materials, or combinations.[a]	Medicines containing plant-derived pure compounds are not considered to be herbal medicines
Fortified food	Foodstuffs to which compounds of therapeutic or preventive efficacy have been added.[b]	Examples include bread with added folic acid to prevent neural tube defects, salt with added iodide to prevent hypothyroidism, milk derivatives containing phytosterols to decrease blood cholesterol levels.[b]
Functional food	No satisfactory definition.[b]	Health Canada has defined a functional food as one that 'is similar in appearance to, or may be, a conventional food that is consumed as part of a usual diet, and is demonstrated to have physiological benefits and/or reduce the risk of chronic disease beyond basic nutritional functions'.[b]
Nutraceutical	No satisfactory definition.[b]	The original definition of the term was 'a food (or part of a food) that provides medical or health benefits, including the prevention and/or treatment of a disease'. A recent analysis of the literature revealed the existence of 25 definitions, with the majority of them relating nutraceuticals to food, food components, or nutrients providing health benefits behind their nutritional value.[e]

[a]World Health Organization (WHO): http://www.who.int/medicines/areas/traditional/definitions/en/
[b]Aronson (2017)
[c]Marcus (2016)
[d]Samuelsson (1999)
[e]Palthur *et al.* (2010)

actions of breakdown products have been postulated. The authors present a broad overview of diverse direct cellular mechanisms, occurring at realistic concentrations and which may be invoked following diffusion of the polyphenol or its metabolite into the cell (Goszcz *et al.*, 2017). Interactions with pathways of inflammation, platelet aggregation and also modulation of oestrogen signalling through genomic and non-genomic mechanisms are discussed, leading to the

Table 2

Key information on the 25 best-selling herbal dietary supplements in the US mainstream multi-outlet channel in 2015

Rank	Common/ Latin Name	Retail sales [a]	% Changes 2014	Part of the plant generally used	Key constituent(s)	Condition frequently treated	Clinical efficacy[b] (Authors conclusions, reference)
1	Horehound[c] *Marrubium vulgare*	114,9	8.5	Leaves and flowering tops	Diterpenes (e.g. marrubiin; flavonoids)	Catarrh associated with cooling; Dyspepsia symptoms such as swelling or flatulence	No systematic review/meta-analyses available
2	Cranberry *Vaccinium macrocarpon*	65,7	16.0	Fruits	Proanthocyanidins	Urinary tract infection (prevention)	'Given the large number of dropouts/withdrawals from studies (mainly attributed to the acceptability of consuming cranberry products particularly juice, over long periods), and the evidence that the benefit for preventing UTI is small, cranberry juice cannot currently be recommended for the prevention of UTIs' (Jepson *et al.*, 2012)
3	*Echinacea Echinacea* spp	60.1	7.4	Roots, aerial parts	Alkylamides, polysaccharides, caffeic acid derivatives	Common cold (immunostimulant)	'Echinacea products have not here been shown to provide benefits for treating colds, although, it is possible there is a weak benefit from some Echinacea products: the results of individual prophylaxis trials consistently show positive (if non-significant) trends, although potential effects are of questionable clinical relevance' (Karsch Völk *et al.*, 2014)
4	Garcinia *Garcinia cambogia*	54.8	−23.3	Pericarp of the fruit	Hydroxycitric acid	Weight loss	'Garcinia extracts can cause short-term weight loss. The magnitude of the effect is small, and the clinical relevance is uncertain' (Onakpoya *et al.*, 2011a)
5	Green tea *Camellia sinensis*	48.9	−23.4	Leaves	Caffeine, polyphenols (e.g. epigallocatechin and epigallocatechin-3-gallate)	Prevention of cardiovascular diseases and cancer; weight loss	*Cardiovascular* 'The limited evidence suggests that tea has favourable effects on cardiovascular risk factors, but due to the small number of trials contributing to each analysis the

continues

Table 2 (Continued)

Rank	Common/ Latin Name	Retail sales [a]	% Changes 2014	Part of the plant generally used	Key constituent(s)	Condition frequently treated	Clinical efficacy[b] (Authors conclusions, reference)
							results should be treated with some caution' (Hartley *et al.*, 2013). *Cancer* 'There is insufficient and conflicting evidence to give any firm recommendations regarding green tea consumption for cancer prevention (Boehm *et al.*, 2009)'. *Weight loss* 'Green tea preparations appear to induce a small, statistically non-significant weight loss in overweight or obese adults' (Jurgens, 2012)
6	Black cohosh *Cimicifuga racemosa*	42.9	−5.1	Rhizome	Triterpenes (e.g. actein, cimicifugoside, 27-deoxyactein)	Menopausal symptoms	'There is currently insufficient evidence to support the use of black cohosh for menopausal symptoms' (Leach and Moore, 2012).
7	Flax seed/oil *Linum usitatissimum*	36.3	−1.4	Seeds	α-Linolenic acid, lignans, fibre,	Improvement of cardiovascular health	'The present meta-analysis suggests that consumption of flaxseed may lower blood pressure slightly. The beneficial potential of flaxseed to reduce blood pressure (especially diastolic blood pressure) may be greater when it is consumed as a whole seed and for a duration of >12 wk' (Khalesi *et al.*, 2015).
8	Ginger *Zingiber officinale*	25.6	21.8	Rhizome	Gingerols	Prevention of nausea and vomiting	'For mild symptoms of nausea and emesis of pregnancy, ginger…..is associated with greater benefit than placebo' (McParlin *et al.*, 2016).
9	Valerian *Valeriana officinalis*	25.3	4.0	Roots	Iridoids, valepotriates, sesquiterpenes	Insomnia	'There is insufficient evidence to support the use of herbal medicine [including valerian] for insomnia' (Leach and Page, 2015)
10	Bioflavonoid complex	24.6	24.4	[d]	Hesperidin, rutin, naringin, quercitin and others.	To support optimal health	[e]
11	Green coffee[f] *Coffea Arabica*	23.4	40.7	Seeds	Caffeine, chlorogenic acids, diterpenes, lipids	Weight loss	'the results …..are promising, but the studies are all of poor methodological quality' (Onakpoya *et al.*, 2011b)
12	Yohimbe	21.8	9.1	Bark			

continues

Table 2 (Continued)

Rank	Common/ Latin Name	Retail sales [a]	% Changes 2014	Part of the plant generally used	Key constituent(s)	Condition frequently treated	Clinical efficacy[b] (Authors conclusions, reference)
	Pausinystalia johimbe				Indole alkaloids (e.g. yohimbine)	body weight reduction, erectile dysfunction	No recent systematic review/meta-analyses published
13	Ivy Hedera helix	18.6	129.4	Leaf	Sterols, saponins, flavonoids, alkaloids	Respiratory diseases	'Although all studies report that ivy extracts are effective to reduce symptoms of upper respiratory tract infections, there is no convincing evidence due to serious methodological flaws and lack of placebo controls' (Holzinger and Chenot, 2011)
14	Aloe vera (Aloe gel) *Aloe vera*	17.1	1.5	Mucilaginous tissue from the leaves	Polysaccharides, aloins	Dermatological conditions	*Phlebitis* 'There is no strong evidence for preventing or treating infusion phlebitis with external application of Aloe vera.' (Zheng *et al*., 2014) *Acute and chronic wounds* 'There is currently an absence of high quality clinical trial evidence to support the use of Aloe vera topical agents or Aloe vera dressings as treatments for acute and chronic wounds' (Dat *et al*., 2012). *Psoriasis* 'Results on the effectiveness of Aloe vera are contradictory; our analysis reveals the presence of methodological gaps preventing to reach final conclusions' (Miroddi *et al*., 2015)
15	Saw palmetto *Serenoa repens*	16.8	−6.4	Fruits	Fatty acids, sterols	Benign prostatic hyperplasia	'*Serenoa repens*, at double and triple doses, did not improve urinary flow measures or prostate size in men with lower urinary tract symptoms consistent with benign prostatic hyperplasia' (Tacklind *et al*., 2012)
16	Milk thistle *Silybum marianum*	16.8	2.6	Fruits	A mixture of flavonolignans called silymarin	Liver diseases	'The clinical evidence of therapeutic effect of silymarin in toxic liver diseases is scarce... It is reasonable to employ silymarin as a supportive element in the therapy of *Amanita phalloides* poisoning but also (alcoholic and grade Child 'A') liver cirrhosis' (Saller *et al*., 2008).
17	Garlic *Allium sativum*	16.5	8.4	Bulb	Alliin, diallyl disulphide, ajoens	Hypercholesterolemia, Hypertension	*Hypercholesterolemia* 'Garlic reduces total cholesterol to a modest extent,without appreciable LDL lowering or HDL elevation' (Reinhart *et al*., 2009).

continues

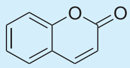
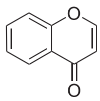
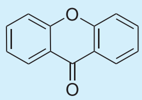
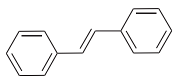
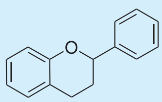
Table 2 (Continued)

Rank	Common/ Latin Name	Retail sales [a]	% Changes 2014	Part of the plant generally used	Key constituent(s)	Condition frequently treated	Clinical efficacy[b] (Authors conclusions, reference)
							Hypertension: 'Although evidence from this review suggests that garlic preparations may lower blood pressure in hypertensive individuals, the evidence is not strong' (Rohner *et al.*, 2015).
18	Plant sterols	16.2	46.5	NA	NA	Hypercholesterolemia, hypertriglyceridemia	'Results show that phytosterols exert a modest triclycerides-lowering effect which is dependent on baseline concentrations' (Demonty *et al.*, 2013).
19	Turmeric *Curcuma longa*	15.7	117.7	Rhizome	Curcuminoids	Inflammatory/autoimmune diseases Dermatological conditions	*Arthritis* 'These RCTs provide scientific evidence that supports the efficacy of turmeric extract in the treatment of arthritis. However, the total number of RCTs included in the analysis, the total sample size, and the methodological quality of the primary studies were not sufficient to draw definitive conclusions' (Daily *et al.*, 2016) *Dermatological conditions (acne, alopecia, atopic dermatitis, facial photoaging, oral lichen planus, pruritus, psoriasis, radiodermatitis, and vitiligo:* 'There is early evidence that turmeric/curcumin products and supplements, both oral and topical, may provide therapeutic benefits for skin health. However, currently published studies are limited' (Vaughn *et al.*, 2016)
20	Cinnamon *Cinnamomum* spp	14.6	2.2	Bark	Volatile oil, the main component is cinnamaldehyde	Loss of appetite, dyspepsia, diabetes	No recent systematic reviews/meta-analyses available

[a]Million US dollars in rounded figures (Sales are from Smith *et al.*, 2016);
[b]based on systematic reviews/meta-analyses of clinical data;
[c]herb coded as a primary substance in throat lozenges that may contain other herbs;
[d]Bioflavonoids are extracted from *Citrus* fruits;
[e]Citrus flavonoids are mainly promoted as antioxidants to promote and support optimal health. Many systematic reviews are available related to flavonoid intake and a number of conditions such as oxidative stress, immune functions, cancer prevention and decline of cognitive functions
[f]from not-roasted coffee beans;
NA = not applicable.

Table 3

Examples of pharmacologically relevant classes of polyphenols

Class	Basic structure	Occurrence	Comment
Coumarins		*Melilotus officinalis* (sweet clover), *Aesculus hippocastanum* (horse chestnut). Also widespread in the *Apiaceae* botanical family	This group include coumarins, furanocoumarins and psoralenes. A number of coumarins are reported to exert anticoagulant effects. Coagulation is impaired in cattle eating mouldy sweet clover, resulting in fatal haemorrhage (sweet clover disease). This discovery led to the introduction in therapy of dicoumarol as anticoagulant drug. Warfarin is chemically related to dicoumarol. Psoralens are used in photochemotherapy
Chromones		Ubiquitous in plants	Khellin, found in the fruit of *Amni visnaga* is a chromone formerly used as antispasmodic. Efforts to find better drugs led to the chemical development of sodium cromoglycate
Xanthones		Many higher plants, fungi, ferns, lichens and bacteria	Xanthones are present in the pericarp of the fruit of the tropical evergreen tree purple mangosteen (*Garcinia mangostana*), a nutraceutical promoted for metabolic syndrome
Stilbenes		Present in low quantities in the human diet. Present in limited and heterogeneous group of plant families such as *Vitaceae* and *Leguminosae*	Resveratrol, found in the skin of grapes, is the most studied among the stilbenes. It has been suggested that oral supplementation with resveratrol exerts cardioprotective effects, but a recent meta-analysis of available RCTs does not suggest any benefit of resveratrol supplementation on cardiovascular risk factors[a]
Flavonoids		Widespread in ferns and higher plants	Flavonoids contribute to the yellow colours of flowers and fruits where they are present as glycosides dissolved in the cell sap. More than 2000 flavonoids have been isolated so far and form part of human diet. The most common classes are flavanols, flavones, flavonols, flavanones, anthocyanidines, proanthocyanidins and isoflavonoids (Table 4)

General information, including chemistry and occurrence, has been extracted from Cui and Duke (2015); Samuelsson (1999); Manach *et al.* (2004); Sirerol *et al.* (2016);
[a]Sahebkar *et al.* (2015).

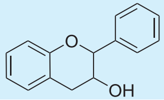
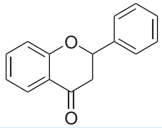
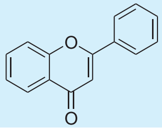
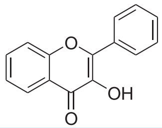
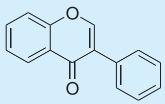
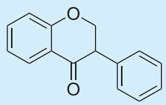
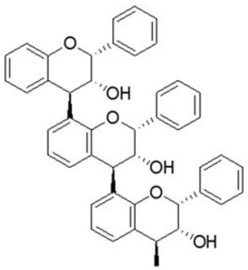
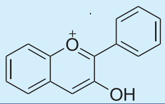
conclusion that the dogma of polyphenols acting mainly as antioxidants needs to be critically re-assessed

Anthocyanins. Anthocyanins (Greek *anthos*, flower and *kyáneos*, blue) are water-soluble flavonoids responsible for the varied red-orange to blue-violet colour of fruits and flowers. The basic structural unit of anthocyanins, which are mainly found in nature as glycosides (anthocyanidins), is the flavylium ion (2-phenylchromenylium) (Table 4). The main alimentary sources of anthocyanins include berries (blueberries, bilberries and strawberries), wine, grapes and red/purple vegetables (Wallace and Giusti, 2015; Vlachojannis *et al.*, 2015; Smeriglio *et al.*, 2016; Eghbaliferiz and Iranshahi, 2016). In this issue of the BJP, Lin *et al.* (2017) summarise the latest findings on the anti-cancer activities of anthocyanins. Mechanisms believed to be relevant for their anti-tumour action include antioxidant and anti-inflammatory effects, inhibition of cell growth, induction of cell cycle arrest, stimulation of apoptosis (or autophagy) and anti-invasion and anti-metastatic actions (Lin *et al.*, 2017). Clinically, there are conflicting results concerning the possible intake of anthocyanins and cancer prevention in humans (Lin *et al.*, 2017). It is noteworthy that an Italian observational study reported that moderate wine consumption exerted protective effects on radiotherapy-induced skin toxicity in breast cancer patients (Morganti *et al.*, 2009). Consequently, an intervention trial aimed at evaluating the possible protective effects of anthocyanin-containing dietary supplements on the inflammatory response to radiation and the resulting skin toxicity has been designed (Cerletti *et al.*, 2017).

Proanthocyanidins. Proanthocyanidins, also called catechin tannins or condensed tannins, are the most abundant plant-derived polyphenols widely available in fruits, vegetables, nuts, seeds, flowers and bark. Proanthocyanidins are oligomers or polymers, with flavanols being the building blocks (Table 4). As highlighted in this themed issue (Smeriglio *et al.*, 2017), in addition to well-established free radical scavenging and antioxidant properties, proanthocyanidins exert potentially relevant antimicrobial, anti-tumour, anti-inflammatory and cardioprotective actions. The potential beneficial pharmacological actions of proanthocyanidins have been attributed to their conjugated

Table 4

Examples of pharmacologically relevant classes of flavonoids

Class	Basic structure	Typical rich food source	Example	Comment
Flavanols[a]		Soy flour, red wine, green tea, grape, wine, cocoa, apricot, beans	Catechin, epicatechin	The intake of flavanol-rich foods (such as Cocoa flavonols) has been evaluated in relation to cardiovascular health[b]
Flavanones		Citrus fruits (Tomás-Barberán and Clifford, 2000)	Hesperetin, Naringenin	Flavanones and flavanones-rich botanical extracts have been a subject of great interest for scientific research for as a possible emerging treatment for diabetes and its complications and cardiovascular protection[c]
Flavones		Green leafy spices, for example, Parsley	Apigenin, Luteolin	Flavones can contribute to plant tissue colour, if they occur in high concentrations or are complexed with metal ions. Flavones participate in taste.
Flavonols		Nearly ubiquitous in foods, for example, quercetin. Main sources include yellow onion, curly kale and leek.	Kaempferol, Myricetin Quercetin	The most abundant flavonoid assumed with the diet is the flavonol quercetin
Isoflavonoids	 	Soybeans, soy foods and legumes	Daidzein, Genistein	Isoflavonoids are a distinct class of flavonoids with estrogenic activity. They are found almost exclusively in legumes, particularly soybeans. Isoflavonoid-containing preparations are promoted for alleviating menopausal symptoms
Proanthocyanidins		The foods with the highest levels of total proanthocyanidins are, in decreasing order, ground cinnamon, sorghum (sumac bran), dry grape seed, unsweetened baking chocolate, raw pinto beans, sorghum (high-tannin whole grain), choke berries, red kidney beans, hazelnuts and pecan nuts[d]	Pycnogenol proanthocyanidin A-2 (in hawthorn berry)	Also named condensed tannins, represents the most abundant plant-derived polyphenols. Proanthocyanidins are responsible for the astringent taste of fruits. Potential areas of medical interest include the prevention of cardiovascular and metabolic disorders.
Anthocyanidins		Red, purple and blue Berries (e.g. blackberry, strawberry, blueberry), aubergine, red wine	Cyanidin, Delphinidin, peonidin	Anthocyanins produce the blue and red coloration of berry fruits, cherries and plums, eggplant, red cabbage and radishes. Fruit anthocyanins content usually increases as the fruit matures

General information, including chemistry and occurrence, has been extracted from Peterson and Dwyer (1998); Samuelsson (1999); Beecher (2003); Manach *et al.* (2004); D'Archivio *et al.* (2007); Cui and Duke (2015);

[a]Flavanols may exist both as monomer (catechins) and polymer (proanthocyanidins) form;

[b]Lin *et al.* (2016); Vlachojannis *et al.* (2016);

[c]Chanet *et al.* (2012);

[d]Dixon *et al.*, 2005; Gu *et al.*, 2004.

metabolites derived from gut microbiota (Bladé *et al.*, 2016). A number of epidemiological studies have tried to correlate proanthocyanidin consumption with beneficial cardiovascular and metabolic effects (Bladé *et al.*, 2016; Nassiri-Asl and Hosseinzadeh, 2016; Akaberi and Hosseinzadeh, 2016). However, further studies are needed to firmly establish the potential benefits of increased proanthocyanidin intake to human health.

Phytoestrogens. Phytoestrogens represent a diverse group of naturally occurring polyphenols with structural similarity to 17β-oestradiol, the primary female sex hormone. Main dietary phytoestrogens include isoflavones (e.g. genistein), prenylated flavonoids (e.g. 8-prenylnaringenin), coumestans (e.g. coumestrol) and lignans (e.g. enterolactone). Dietary sources of phytoestrogens are nuts and oilseeds, soy products, cereals, breads and legumes (particularly soybeans) (Thompson *et al.*, 2006). In this issue of the BJP, a wide overview of the potential health effects of dietary phytoestrogens with a specific focus on cardiovascular diseases, obesity and metabolic syndrome, menopausal health and cancer prevention, is provided by Rietjens *et al.*, (2017).

Phytosterols

Phytosterols are plant-derived, non-nutritive steroid compounds structurally similar to cholesterol (Gylling and Simonen, 2015; Ogbe *et al.*, 2015). A Western-type diet contains about 200–500 mg cholesterol and up to 500 mg of phytosterols (Köhler *et al.*, 2017). 'Functional foods' supplemented with phytosterols are widely promoted as dietary modifiers of serum lipids as they impair the intestinal absorption of cholesterol by competing with it for absorption into micelles in the gastrointestinal tract (Hunter and Hegele, 2017). In this issue of the BJP, Köhler *et al.* (2017) summarize, on the basis of animal and human studies, the current evidence about phytosterol-containing functional foods and atherosclerosis. Starting from the premise that it is a misconception to accept as true that any treatment leading to a reduction in LDL cholesterol levels also leads to reduction of atherosclerosis, the authors conclude that 'clear evidence that functional foods supplemented with phytosterols are safe and effective in the prevention of cardiovascular diseases is as yet unavailable and individual studies show that they may even be harmful' (Köhler *et al.*, 2017).

Overall, current evidence seems to cautiously support the recommendation of phytosterols as LDL cholesterol-lowering agents (Gylling *et al.*, 2014; Hunter and Hegele, 2017), but, because most trials have been of short duration, no data are available to date on cardiovascular endpoints (Silbernagel *et al.*, 2015; Hunter and Hegele, 2017). Phytosterol supplements should be avoided in patients with sitosterolaemia, in which the excretion of dietary sterols is impaired (Hunter and Hegele, 2017).

Carotenoids

Carotenoids are lipid-soluble pigments widespread in the vegetable kingdom and are found in high concentrations in marine organisms such as algae and microorganisms. Chemically, they are isoprenoids and are classified into carotenes (e.g. β-carotene and lycopene) and xanthophylls (e.g. lutein, fucoxanthin and zeaxanthin). Beside provitamin A activity, carotenoids are potentially important as antioxidants and in disease prevention (Namitha and Negi, 2010). In this themed issue of the BJP, Milani *et al.* (2017) review the biochemical and pharmacological properties of the main carotenoids, their proposed mode of action and the clinical areas of interest including cancer prevention. A number of carotenoids have been shown to inhibit tumour cell growth, possibly *via* inhibition of angiogenesis, stimulation of apoptosis and scavenging free radicals (Milani *et al.*, 2017). Recent systematic review/meta-analyses of epidemiological studies have shown that (i) there is an inverse correlation between blood carotenoid levels and lung cancer risk (Abar *et al.*, 2016); (ii) there is an inverse relationship between α-carotene intake and risk of non-Hodgkin lymphoma (Chen *et al.*, 2016); (iii) higher lycopene consumption or circulating concentration is associated with a lower risk of prostate cancer (Chen *et al.*, 2015); and (iv) ingestion of tomatoes rich in carotenoids may have a small effect on the prevention of prostate cancer (Chen *et al.*, 2013). Overall, the potential of carotenoids in cancer prevention seems promising, although further and more rigorous studies are needed to confirm these associations.

Curcumin is one of the best studied carotenoids. It is a yellow hydrophobic polyphenol extracted from the rhizomes of *Curcuma longa* (turmeric), a perennial herbaceous plant of the ginger family (*Zingiberaceae*), which has been used for years in Ayurvedic medicine to treat a number of diseases such as dyspepsia, infections and liver diseases (Deguchi, 2015; Sreedhar *et al.*, 2016; Mazzanti and Di Giacomo, 2016). In this issue of the BJP, the clinical potential of curcumin for treating a number of diseases including metabolic diseases such as diabetes and inflammatory diseases has been reviewed (Kunnumakkara *et al.*, 2017). Recent systematic reviews and meta-analyses have provided promising, albeit preliminary, evidence of efficacy to treat joint arthritis (Daily *et al.*, 2016), skin disease (Vaughn *et al.*, 2016), depressive disorders (Al-Karawi *et al.*, 2016), inflammatory bowel disease (Langhorst *et al.*, 2015) and as an analgesic (Sahebkar and Henrotin, 2016). However, the quality of the primary study, the total sample size, the lack of long-term efficacy and other methodological caveats make it impossible to draw definitive conclusions. More rigorous and larger studies are needed to fully exploit the potential of curcumin for clinical application.

Palmitoylethanolamide

Palmitoylethanolamide (PEA) is a naturally occurring fatty acid amide isolated for the first time about 60 years ago, when it was believed to be the active anti-inflammatory ingredient of lipid fractions from egg yolk, peanut oil and soybean lecithin (Skaper *et al.*, 2015). Subsequently, it has been identified in a number of food sources, including human breast milk, common beans, garden peas, tomatoes, corn and peanuts. PEA is marketed as a food component for special medical purposes for a number of indications including pain and inflammation. In this issue of the BJP, Petrosino and Di Marzo (2017) have reviewed the pharmacology of PEA, with particular emphasis on neurodegenerative disorders, pain perception and inflammatory diseases. New PEA formulations (e.g. with small particle size) and their effect in combination with other plant-derived ingredients such as flavonoid luteolin and stilbenes are also highlighted (Petrosino and Di Marzo, 2017).

Amino acids and peptides

Branched-chain amino acids (BCAAs)

BCAAs are essential amino acids with aliphatic side-chains, such as isoleucine, leucine and valine. They are extensively utilized in protein synthesis, but their fate is dependent on the metabolic state of the organism, and they can be routed towards oxidation in a catabolic state, as shown by Bifari and Nisoli (2017) in their review in this BJP issue. There is increasing evidence that they can act as nutrient sensors, particularly leucine (Wolfson *et al.*, 2016), and changes in levels of BCAAs can modulate the levels of insulin, glucagon and adipokines. Against this background, supplementation has been proposed as being beneficial in catabolic states, to promote protein synthesis (Shimomura *et al.*, 2006) and also to regulate metabolic homeostasis. The authors review the evidence concerning the efficacy and safety of BCAA supplementation, addressing appropriate dosing and safety margins in human trials to date. They conclude that supplementation may be of benefit in catabolic states to normalize protein and amino acid homeostasis, but the value of supplementation in conditions such as obesity where BCAAs can modulate both catabolism and anabolism is less well supported. Bifari and Nisoli (2017) provide a thorough overview of clinical and preclinical data, including epidemiological data to support their conclusions.

Bioactive peptides

Bioactive peptides are specific protein fragments derived through enzymic hydrolysis of food proteins. Bioactive peptides are inactive within the sequence of the parent protein molecule. However, they can be released after gastrointestinal digestion, fermentation and hydrolysis by proteolytic enzymes (Udenigwe and Aluko, 2012; Bhat *et al.*, 2015). These peptides originate from foodstuffs containing milk, dairy products, eggs (Park and Nam, 2015), soybean, oat, wheat (Maestri *et al.*, 2016), fish and algae (Ruiz-Ruiz *et al.*, 2017) foodstuffs. A number of bioactive peptides derived from food sources have been incorporated in fortified foods or dietary supplements and are commercially promoted to reduce the risk of chronic diseases such as hypertension, hypercholesterolemia and obesity (Hayes and Tiwari, 2015).

In this BJP themed issue, Cicero *et al.* (2017) have reviewed the experimental and clinical data and the potential role of bioactive peptides in the prevention of chronic diseases, with a special focus on the cardiovascular system and on cancer prevention. The review of the literature revealed that, in spite of the promising experimental pharmacological studies, clinical evidence is at an early stage (Cicero *et al.*, 2017). Preliminary evidence in humans is related mainly to cardiovascular effects. A systematic review of the literature reported that there was limited but consistent evidence that consumption of fermented-milk products containing bioactive peptides improved arterial stiffness (Pase *et al.*, 2011). A subsequent review published in the *British Journal of Clinical Pharmacology* concluded that that 'while many studies have described promising health promoting effects of milk-derived peptides in cardiovascular disease, further studies and, in particular, more *in vivo* research with a focus on toxicity, will be required before their application' (Marcone *et al.*, 2017).

Drugs in specific conditions

Anti-ageing compounds. Ageing represents the greatest risk factor for nearly every major cause of morbidity and mortality (Fontana *et al.*, 2010). Despite this, in the past, research has focused on individual life-threatening age-related disorders rather than on the complex molecular pathways leading to ageing (Fontana *et al.*, 2010; Fontana and Partridge, 2015). In more recent years, robust preclinical evidence has demonstrated that life extension is, in most cases, accompanied by delayed or reduced morbidity, from cardiovascular disease, neurodegeneration and cancers among others (Fontana *et al.*, 2010; Colman *et al.*, 2014; Vaiserman and Marotta, 2016). The organisms most often used to detect age-related effects of genetic, pharmacological and/or dietary interventions are the nematode *Caenorhabditis elegans* (lifespan of ~2 weeks), the fruit fly, *Drosophila melanogaster* (lives for 2 months) and the mouse *Mus musculus* (lives for ~2 years).

A number of nutraceuticals have shown promising efficacy as anti-ageing agents (Longo *et al.*, 2015, Vaiserman and Marotta, 2016). In this issue, Shen *et al.* (2017) have reviewed the plant ingredients and nutraceuticals from traditional Chinese medicine (TCM), which have been reported to have anti-ageing effects in the past two decades. The main pharmacological mechanisms discussed include regulation of telomere and telomerase, sirtuins, nutrient and energy sensing pathways, including the TOT-S6K pathway, and free radical scavenging effects. While the experimental results on TCM nutraceuticals are of potential interest, it should be highlighted that clinical research is at a very early stage and efficacy and/or safety data of many TCM ingredients are mostly based on poor-quality research (Shen *et al.*, 2017). Therefore, any extrapolation to clinical applications must be made with caution.

Functional and inflammatory bowel disorders. Nutraceutical treatment for intestinal disorders involves the use of fibre, herbal medicinal products, probiotics, prebiotics and synbiotics (Ford *et al.*, 2014; Holtmann and Talley, 2015; Langhorst *et al.*, 2015; Somani *et al.*, 2015; Leiby and Vazirani, 2016). Probiotics are live microorganisms that may confer a health benefit to the host. The mode of action of probiotics includes strengthening of barrier function, changing immune responses and modulation of neurotransmitter release (Sanchez *et al.*, 2017). Prebiotics are fermented ingredients that can change the composition/activity of the gut microbiota, thus conferring health benefits to the host (Valcheva and Dieleman, 2016). Prebiotics are carbohydrate compounds, primarily oligosaccharides, resistant to digestion, which reach the colon where they are fermented by the gut microflora (Slavin, 2013).

Combinations of pro- and prebiotics presumed to have synergistic effects are called synbiotics. Curro *et al.* (2017) focused on recent advances in the understanding of the pharmacological mechanisms of these dietary supplements for the possible treatment of functional and inflammatory bowel disorders, with special reference to irritable bowel syndrome and inflammatory bowel disease. This review is complemented by a further original article demonstrating, in mouse models, the use of butyrate in a derivative form to deliver an unpalatable agent to the inflamed colon (Simeoli *et al.*, 2017). Varied formulation strategies have been exploited to enhance delivery of nutraceuticals in a number of settings including nano-particles.

Hypercholesterolemia. Many nutraceuticals have been evaluated for potential lipid-lowering properties. Those with the most promising evidence of efficacy include soy protein, green tea, plant sterols, probiotic yoghurt, marine-derived ω-3 fatty acids and red yeast rice (Hunter and Hegele, 2017). Lowering of cholesterol and triglycerides is an area where a number of nutraceuticals have received endorsement by the FDA or European Food Safety Authority. This is discussed in detail by Santini and Novellino (2017). This field provides an example of where the benefits derived from a foodstuff are actually brought about by an active ingredient, which is also marketed as a drug. Lovastatin is the active ingredient of red yeast rice, known to inhibit hydroxymethylglutaryl-CoA reductase and hence limit cholesterol synthesis. However, in contrast to the purified drug, red yeast rice may also contain toxins, exposure to which has been limited by the European Commission in 2014.

Clinical efficacy

As it is the case for prescribed medicines, the evidence obtained from high-quality randomized controlled trials (RCTs) represents the gold standard for assessing nutraceutical clinical efficacy (Visioli, 2012). In recent years, a number of systematic reviews and meta-analyses have provided researchers and healthcare professionals with updated conclusions (Izzo *et al.*, 2016). Unfortunately, although the reporting quality of primary studies has improved over the last several decades, the methodological quality is often still rated as unsatisfactory making it difficult to draw definitive conclusions (Pferschy-Wenzig and Bauer, 2015). Frequent shortcomings include inadequate sample size, short trial duration and dose variability among the trials. Furthermore, a specific issue related to herbal dietary supplements is the failure in reporting detailed information on the product itself, such as the part of the plant used, the Latin name of the plant, extraction solvent/type of extraction and phytochemical characterization of the herbal extract (standardization) (Izzo *et al.*, 2016; Sut *et al.*, 2016). This information represents a pivotal requirement for alignment within systematic reviews (Pferschy-Wenzig and Bauer, 2015; Izzo *et al.*, 2016). Combining clinical data from different preparations – even if derived from the same plant – would be like comparing apples and pears (Pferschy-Wenzig and Bauer, 2015).

The clinical evidence has to be evaluated according to each individual nutraceutical and *a priori* generalisations such as 'nutraceuticals work' or 'nutraceuticals are no more than placebo' cannot be scientifically accepted. The 'weight of evidence' and the 'direction of evidence' should be carefully monitored (Ernst *et al.*, 2008). The 'weight of evidence' is based on a combination of three largely independent factors, that is, the level of evidence (the highest level being systematic review/meta-analyses), the methodological quality of the trials and the sample size (i.e. the number of studies and patients). The 'direction of evidence' refers to the collective positive or negative outcome of the studies (e.g. positive, uncertain or negative results) (Ernst *et al.*, 2008). The clinical significance of the results (i.e. the robustness of the effect) should be taken also into account and indeed considered in relation to the effect size of conventional medicines. In relation to the clinical efficacy, herbal dietary supplements can be tentatively and cautiously categorized into six groups.

The *first group*, which represents a minority, comprises herbal dietary supplements whose evidence of clinical efficacy has been revealed by systematic reviews and meta-analyses published by the Cochrane library and/or by authoritative medical Journals (i.e. 'weight of evidence': satisfactory; 'direction of evidence': toward positive effects). Examples include horse chestnut (*Aesculus hippocastanum*) for chronic venous insufficiency (Pittler and Ernst, 2012) or ginger (*Zingiber officinale*) for mild symptoms of nausea in pregnant women (McParlin *et al.*, 2016). Conversely, the *second group* of herbal dietary supplements includes products, which have been (and are) extensively used for specific conditions, but robust clinical evidence does not support their use (i.e. 'weight of evidence': satisfactory; 'direction of evidence': toward negative effects). This is the case of *Echinacea* (*Echinacea* spp) for the common cold (Karsch-Volk *et al.*, 2014) or valerian (*Valeriana officinalis*) for insomnia (Leach and Page, 2015). The *third group* includes remedies, which have shown a small effect but of uncertain clinical significance [e.g. garcinia (*Garcinia cambogia*) and green tea (*Camellia sinensis*), both promoted for weight reduction (Onakpoya *et al.*, 2011a; Jurgens *et al.*, 2012)]. The *fourth group* is formed by herbal supplements, which have provided contradictory results [e.g. aloe vera (*Aloe vera*) for psoriasis (Miroddi *et al.*, 2015)]. The *fifth group* includes a large number of herbal dietary supplements, which have shown encouraging clinical data, but the overall effect is far from being compelling, and more rigorous studies are needed to fully support their use [e.g. Agnus castus (*Vitex agnus castus*) for premenstrual syndrome (van Die *et al.*, 2013), garlic (*Allium sativum*) as an antihypertensive (Rohner *et al.*, 2015); see Izzo *et al.*, 2016 for further examples). The *last group*, which includes the vast majority (Marcus, 2016), is formed by herbal dietary supplements that have been not evaluated in RCTs. Examples include yohimbe (*Pausinystalia johimbe*) for erectile dysfunction or horehound (*Marrubium vulgare* for respiratory diseases), just to mention two of the best-seller herbal dietary supplements, listed in Table 2.

In conclusion, generalisation about the efficacy of herbal remedies cannot be made, and judgements must be expressed on a case-by-case basis. In most instances, claims of effectiveness rely on poor-quality trials and definitive conclusions cannot be drawn. It is noteworthy that the vast majority of herbal dietary supplements, including some best-selling products, have not been evaluated in RCTs.

Adverse events and drug interactions

Many lay people believe that nutraceuticals are harmless because they are natural. The concept that "natural" means "safe" is obviously misleading, if we just consider that most potent poisons or toxins are naturally occurring molecules. A classical example is the death of the Greek philosopher Socrates, who was given a liquid preparation of hemlock plant (*Conium maculatum*), after being sentenced to death for corruption of young men and impiety. The hemlock plant contains a group of toxic piperidine alkaloids, of which the representative members include coniine (LD_{50} in the mouse: 7–12.1 $mg{\cdot}kg^{-1}$; Lee *et al.*, 2008] and the more toxic γ-coniceine (Reynolds, 2005).

The safety of herbal dietary supplements has become a relevant issue for healthcare regulatory authorities, based on the serious events reported in the literature (Shaw *et al.*, 2012). For example, although the incidence is difficult to estimate, green tea (*Thea sinensis*) extracts, ginseng (*Panax ginseng*), black cohosh (*Cimicifuga racemosa*) and Chinese herbs have been associated with drug-induced liver injury (Navarro *et al.*, 2017). Despite this alarming premise, recent careful analyses of the literature have shown that adverse events due to herbal dietary supplements are relatively infrequent (Di Lorenzo *et al.*, 2015; Lee *et al.*, 2016; Lude *et al.*, 2016), if assessed for causality. A systematic review published in the *British Journal of Clinical Pharmacology* concluded that there are numerous published reports of adverse events relating to the use of herbal dietary supplements, but after critical assessment of the causality, the number is strongly reduced (Di Lorenzo *et al.*, 2015). The top herbal supplements most commonly involved in adverse drug reactions are soybean (*Glycine max,* 19.3%, mainly allergic reactions), liquorice (*Glycyrrhiza glabra,* 12.2%, with hypokalaemia and hypertension being the most frequent adverse events), green tea (*Camellia sinensis*, 8.7%, mainly acute hepatitis) and gingko (*Ginkgo biloba,* 8.5%, adverse reactions usually associated with coagulation difficulties) (Di Lorenzo *et al.*, 2015).

Another relevant safety issue related to the use of dietary supplements is the possibility of drug interactions with prescribed drugs (Izzo and Ernst, 2009; Izzo, 2012; Posadzki *et al.*, 2013; Mouly *et al.*, 2016). As with interactions between synthetic drugs, dietary supplements-prescribed drug interactions can have both a pharmacokinetic and pharmacodynamic basis (Izzo *et al.*, 2002; Chen *et al.*, 2012; Sprouse and Van Breemen, 2016; Choi *et al.*, 2016). A systematic review of the literature identified 882 dietary supplements–drug interactions, with St. John's Wort, ginkgo, magnesium, calcium and iron having the greatest number of documented cases (Tsai *et al.,* 2012). Warfarin, insulin, aspirin, digoxin and ticlopidine were the most common conventional medicines involved in dietary supplement–drug interactions. Probably the best documented interaction is the decreased blood cyclosporin concentration (associated in some cases to rejection episodes) observed in patients who have also taken St John's wort (*Hypericum perforatum*) (Colombo *et al.*, 2014; Izzo *et al.*, 2016). St John's Wort contains hyperforin, which, *via* activation of the pregnane X receptors (Moore *et al.*, 2000), inhibits cytochrome P450 enzymes and P-glycoprotein, both involved in cyclosporine absorption, metabolism and elimination (Zhou *et al.*, 2004; Kober *et al.*, 2008).

In conclusion, although herbal dietary supplements are generally safer than prescribed drugs, the possibility of adverse effects should be considered and the risk–benefit ratio has to be carefully assessed individually, for each nutraceutical.

Adulteration with synthetic drugs

Concerns related to the use of dietary supplements may derive not only from intrinsic pharmacological/toxicological properties but also by the inadequate control of quality. Safety issues include misidentification of the plant, contamination (presence of microorganisms, pesticides, radioactivity and heavy metals) and adulteration (Yau *et al.*, 2015). Adulteration is believed to be the most significant safety concern posed by dietary supplements (Brown, 2016). Deliberate adulteration of dietary supplements with undeclared prescription and over-the-counter drugs, in order to obtain and/or intensify a therapeutic claim, is relatively common and can have a negative impact on consumer safety (Yau *et al.*, 2015; Khazan *et al.*, 2014; Skalicka-Wozniak *et al.*, 2016). The USA FDA reported 572 cases of adulteration from 2007 to 2014, mainly in products claimed to enhance sexual performance (238 entries) and for weight loss (228 entries). Synthetic drugs used as dopants included PDE5 inhibitors, sibutramine, fenfluramine and rimonabant (Da Justa Neves and Caldas, 2015). Similar figures have been reported by the European Union Rapid Alert System for Food and Feed (Da Justa Neves and Caldas, 2015). Adulterated dietary supplements have been associated with serious adverse effects on humans such as stroke, acute liver injury, kidney failure, pulmonary emboli and heart palpitations (Da Justa Neves and Caldas, 2015), and deaths have been reported. PDE5 inhibitors, sibutramine and fenfluramine, found in dietary supplements have led people to be hospitalized (Calahan *et al.*, 2016). Finally, undeclared synthetic drugs may cause adverse effects not only by themselves but also *via* interaction with other prescribed (synthetic) drugs in consumers unaware of their presence (Calahan *et al.*, 2016).

Mammalian receptors as target of plant- and food-derived compounds

Plant-derived ingredients represent an important tool for the discovery and characterization of receptor types as well as for their deorphanization. Historical examples of plant compounds known to bind mammalian receptors selectively include the alkaloids nicotine (from *Nicotiana tabacum*) and morphine (from the opium poppy, *Papaver somniferum*). In this issue of the BJP, Jürg Gertsch provides an evolutionary perspective on the connection between dietary components and the endocannabinoid system (i.e. cannabinoid receptors, endocannabinoids and enzyme involved in the biosynthesis and degradation of endocannabinoids). Dietary phytochemicals that may modulate the activity of the endocannabinoid system include the CB_2 agonists β-caryophyllene (widespread in edible plants and spices) and 3,3′- diindolmethane (contained in *Brassicaceae* vegetables), the CB_1 antagonist falcarinol (fatty alcohol found in carrots, parsley and celery), the endocannabinoid re-uptake/ enzymatic degradation inhibitors guineensine (from black pepper) and β-amyrin (a pentacyclic triterpene widespread in vegetables, including in the cuticular wax of tomato, eggplant and white cabbage) (Naumoska and Vovk, 2015; Gertsch, 2017). Although the *in vivo* experimental evidence is limited to few such compounds (e.g. β-caryophyllene, guineensine), it is possible that activation of CB_2 receptors by phytonutraceuticals may provide a dietary mechanism to counteract inflammation and, conversely, CB_1 blockade may have favourable effects on the metabolic syndrome (Gertsch, 2017).

Miscellaneous

The 15 review articles, which characterize the topic and represent the core of this themed issue, are complemented by two research papers that further stress the importance of nutraceutical research. Specifically, Simeoli *et al.* (2017) have explored the use of different formulations releasing butyrate in colitis, and Maione *et al.* (2017) have evaluated diterpenoid components (carnesol and carnosic acid) from *Salvia officinalis* extracts for their anti-nociceptive properties, mediated *via* eicosanoid pathways.

Conclusions

All information summarized in this Editorial and in the accompanying articles published in this Themed Issue have elucidated the common problems and future challenges related to the experimental and clinical pharmacology of nutraceuticals. In view of the enormous commercial success of such products, it is imperative to have reliable information on the experimental (mode of action) and clinical (efficacy and safety) pharmacology, with research conducted with the same care and rigour as in any other medical area. Currently, the evidence of efficacy of herbal dietary supplements is mixed. Given the suboptimal quality of many trials, further rigorous research is needed to determine the real beneficial effect of many nutraceuticals. Also, vigilance by healthcare professionals is needed in relation to safety, including drug interaction and deliberate adulteration with synthetic drugs. Specific and crucial issues related to herbal nutraceuticals include plant misidentification, lack of standardization of the extracts, failure to report the extract type and solvent used and confusion among the part of the plant used. Lastly, due to lack of rigorous regulation, the need for the manufacturer of the nutraceutical to prove efficacy, safety and quality of a marketed product is less strongly enforced than in the pharmaceutical sector. Therefore, many available products might be ineffective (Izzo *et al.*, 2016; Hunter and Hegele, 2017). Hopefully, this collection of articles and the present Editorial will strengthen our knowledge of the nutraceutical world and stimulate more rigorous research in this expanding area of pharmacology.

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Conflict of interest

The authors declare no conflicts of interest.

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