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EDITORIAL

A practical guide for transparent reporting of research on natural products in the *British Journal of Pharmacology*: Reproducibility of natural product research

1 | INTRODUCTION

Natural products continue to be an important source of medicines and drug templates. Indeed, it has been estimated that approximately a third of all Food and Drug Administration (FDA)-approved drugs over the past 20 years are based on natural products or their derivatives (Thomford et al., 2018). This is likely due to the vast chemical diversity of natural products, which increases the probability of finding structurally distinct 'lead compounds' for different targets and diseases (Gu et al., 2013). For instance, the Dictionary of Natural Products has thus far recorded ~200,000 plant secondary metabolites, including about 170,000 unique structures (Harvey, Edrada-Ebel, & Quinn, 2015). The diversity and growing opportunity is also reflected in the size of natural product libraries that have been created, such as Supernatural II (http://bioinf-applied.charite.de/supernatural_new/index.php?site=home), which has 325,508 different natural compounds (Banerjee et al., 2015), and the open access initiative (led by the US National Cancer Institute) with libraries of ~80,000 plants, ~20,000 marine samples and ~6,000 microbes. This latter initiative estimates that ~1,000,000 distinct fractions will be derived over the next 3–4 years (https://dtp.cancer.gov/organization/npb/npnpd_prefractionated_library.htm).

In addition to the well-established role in drug discovery, natural product pharmacology is relevant in the context of dietary supplements, which are part of the vast and nebulous nutraceutical market and includes vitamins, amino acids, proteins, minerals, fibres, plant extracts and natural compounds (Andrew & Izzo, 2017). Due to a lack of rigorous regulation in many countries, dietary supplements can be marketed without clinical evidence of efficacy and with uncertain composition (Andrew & Izzo, 2017). Despite this shortcoming, demand for dietary supplements continues to grow (Williamson, Liu, & Izzo, 2020). Herbal dietary supplement sales in the United States experienced record growth in 2018 and consumers spent $8.842 billion on herbal supplements across all market channels (Smith, Gillespie, Eckl, Knepper, & Reynolds, 2018). Furthermore, traditional medicine (such as Ayurveda, traditional Chinese medicine and Unani) not only continues to form an integral part of treatment within certain cultures but has also entered Western culture (Williamson et al., 2020).

Considering the above, it is not surprising that *BJP* receives many submissions that focus on the pharmacology of specific natural products. For the great majority of natural product papers published in *BJP*, the authors include final summative statements that propose a naturally occurring molecule for further clinical development or immediate use as a dietary supplement in the nutraceutical market. Many of these papers also identify novel drug targets, elucidate the mode of action, discover lead compounds and offer potential natural product repositioning (see Table 1 for a list of examples). All of these issues are highly relevant for *BJP* and offer novel pharmacological approaches to discovery science as well as potential therapies.

However, the acceptance rate of 'natural product' submissions in *BJP* is lower than for manuscripts dealing with other topics (approximately 11% vs. 22% acceptance rate in 2019—see Table 2). The editors of *BJP* consider natural product research as a fundamental field of pharmacology and seek to publish research in this area of the highest quality and with excellent reproducibility. In order to support authors in understanding the expectations for natural product research manuscripts, we (the senior editorial team) have written this editorial with the aims of

i providing clear advice to authors regarding the minimum standards required for publication in *BJP*, so as to maximize the possibility of acceptance of such articles submitted to the journal (and possibly elsewhere), and
ii helping *BJP* editors and reviewers in focusing on simple—but important—points that are often overlooked during the review process but essential to support transparency and reproducibility of pharmacological natural product research.

2 | *BJP* HAS A SPECIFIC PHARMACOLOGICAL FOCUS

BJP does not publish papers that are limited to identification of natural products. Isolation, purification, elucidation of structure and semi-synthesis of chemical compounds are considered only in a context in which both a robust, deep and detailed pharmacological analysis and mechanism(s) for biological activity attributed to the natural product are provided. As an example, in a *BJP* paper published by Yin et al. (2015), the authors provided evidence of the synthesis of a previously isolated metabolite from Danshen (*Salvia miltiorrhiza*), which was identified by using MS and proton and carbon NMR spectra. In addition, the authors provided a detailed pharmacological analysis,

TABLE 1 Examples of articles on natural products published in the *BJP*

Article type	Example in the *BJP*	Reference
Papers promoting a phytochemical for possible clinical investigation	Betulic acid, via FXR activation, attenuated markers of non-alcoholic fatty liver disease (NAFLD) in an animal model of hepatic steatosis. The authors conclude that 'Our data suggest that the effects of Betullic acid may be used to develop a novel therapy for the management of NAFLD'.	Gu et al., 2019
Papers promoting a phytochemical for immediate use in humans as a dietary supplement	β-Caryophyllene protects against experimental alcoholic steatohepatitis. The authors conclude that 'Our data suggest that the effects of Betullic acid may be used to develop a novel therapy for the management of NAFLD'	Varga et al., 2018
Papers investigating the effect of a phytochemical in the context of a diet	Resveratrol exists in high quantities in certain foods such as muscadine grape and red wine (Durazzo et al., 2019). A *BJP* paper found that resveratrol, incorporated into the diet, at a dose able to achieve relevant circulating resveratrol levels, protected against bone loss.	Zhao et al., 2018
Paper providing the pharmacological basis able to justify the use of a dietary supplement in humans	Palmitoylethanolamide (PEA) is a food supplement marketed to alleviate inflammatory bowel disease, even in the absence of clinical trials substantiating this claim. A *BJP* paper found that oral administration of PEA is therapeutic in a murine model of colitis. The authors believe that the results could justify the use of PEA for IBD in humans. This example is reminiscent of the ethnopharmacological approach, i.e., the study of natural medicines that have been traditionally used by ethnic groups. Ethnopharmacology uses the 'reverse pharmacology approach', which was applied in India to develop medicines from Ayurvedic medicines (Patwardhan & Mashelkar, 2009).	Borrelli et al., 2015
Papers depicting the mode of action of a commercially available dietary supplements	PEA is a food supplement with a well-stablished analgesic activity in animals. A *BJP* paper unveiled the molecular mechanism involved in PEA-induced analgesic effects by showing its ability to activate and desensitize TRPV1 in sensory neurons.	Ambrosino, Soldovieri, Russo, & Taglialatela, 2013
Papers depicting the mode of action of a major ingredient contained in a commercially available dietary supplement	Extract from *Petasites hybridus* (butterbur) are used for migraine prevention. A *BJP* paper showed that a isopetasin, a major ingredient of butterbur, activated TRPA1 channels, resulting in excitation of neuropeptide-containing nociceptors, followed by marked heterologous neuronal desensitization. The authors conclude that 'such attenuation in pain and neurogenic inflammation [by isopetasin] may account for the anti-migraine action of butterbur'.	Benemei et al., 2017
Papers repositioning old natural drugs	Digoxin inhibited endothelial focal adhesion kinase and angiogenesis induced by different growth factors. The authors conclude that 'These novel findings suggest a potential repositioning of digitoxin as a broad-spectrum anti-angiogenic drug for diseases where pathological angiogenesis is involved'.	Trenti et al., 2017
Papers related to naturally occurring drugs of abuse	A *BJP* paper investigated the involvement of the CRF2 receptor in social dysfunction and stress vulnerability induced by repeated administration of cocaine and withdrawal from cocaine. The authors conclude that 'These findings demonstrate a central role for the CRF2 receptor in social behaviour deficits and biomarkers of vulnerability induced by cocaine withdrawal'.	Morisot, Monier, Le Moine, Millan, & Contarino, 2018
Papers promoting a phytochemical as lead compound for the development of new medicines	Novel tetracyclic triterpenoid compounds, isolated from the mushroom *Poria cocos*, were demonstrated to be effective against experimental renal fibrosis. The authors conclude that 'Our results provide several potential leads for the development of novel compounds for effective treatment of chronic kidney disease'.	Wang et al., 2018
Papers in which a natural compound is used as a chemical probe to block or activate a specific target	Acid-sensing ion channels (ASICs) are voltage-insensitive cation widely expressed in central and peripheral nerves. Peptide toxins from animal venoms, such as mambalgins, target different ASIC subtypes. In a *BJP* paper, mambalgin-1, a specific inhibitor of ASIC1a- and ASIC1b-containing channels, was used as a chemical probe to reveal the role of such channels in mechanical allodynia in a rodent model of migraine.	Verkest et al., 2018
Papers comparing the effect of a natural compound with a related semi-synthetic compound	Dihydrodiosgenin, the parent aglycone of diosgenyl saponin, protected against pancreatic acinar cell against three clinically relevant models of experimental acute pancreatitis.	Shen et al., 2018

TABLE 1 (Continued)

Article type	Example in the *BJP*	Reference
Papers reporting the effect of a naturally occurring molecule on specific targets (e.g., receptors and enzymes)	The diterpene ester tonantzitlolone displayed nanomolar potency as an activator of transient receptor potential canonical (TRPC) 1/4/5 channels.	Rubaiy et al., 2018
Papers providing pharmacokinetic data	*Ginkgo biloba* extracts are widely promoted for conditions related to microcirculatory and memory deficits. A *BJP* paper delineated the pharmacokinetics of flavonols and terpene lactones (i.e., the main active ginkgo ingredients) after dosing standardized *G. biloba* leaf extracts to rats.	Chen et al., 2013
Papers promoting a natural compound for cosmetic use	Kazinol U is a prenylated flavan isolated from the Chinese and Japanese plant *Broussonetia kazinoki*. A *BJP* paper showed that kazinol U reduced melanogenesis. The authors conclude that 'These findings indicate that kazinol U might be therapeutically and cosmetically applied for several hyperpigmentation skin disorders and skin whitening'.	Lim et al. (2019)
Papers describing novel formulations for dietary supplement delivery	Curcumin is a widespread dietary supplement whose clinical use is limited by the poor oral bioavailability. A *BJP* paper provided evidence that biodegradable nanosystem encapsulation have the potential to better translate to humans.	Ganugula et al., 2017

TABLE 2 Acceptance rate of natural product papers in *BJP*

Year	Natural product submissions	No. of acceptances	% of acceptance	Total submissions	No. of acceptances	% of acceptance
2014	16	0	0	1,636	447	27
2015	7	0	0	1,091	301	28
2016	121	3	2.50	1,148	252	22
2017	212	25	12	1,558	391	25
2018	198	19	10	1,543	292	19
2019	162	19	12	1,487	340	23

Note: Submissions citing the keyword 'natural product' and their acceptance rate in *BJP* since 2014 in comparison with overall submission and acceptance. In 2016, *BJP* began an international initiative to increase awareness of the need for natural product research to adhere to the highest standards of pharmacological research. This initiative has coincided with a substantial increase in submissions to the journal and an increasing acceptance rate. Annual average total submissions ~1,550 manuscripts with acceptance rate for original papers of 23% for 2019.

which revealed that the natural compound prevented isoprenaline-induced cardiac fibrosis by inhibiting a NOX2/ROS/p38 pathway. Identification of the possible mechanism of action of the natural product is mandatory for publication in *BJP*.

3 | *BJP* WILL PUBLISH STUDIES OF MIXTURES OF COMPOUNDS (SUCH AS HERBAL EXTRACTS) ONLY WHEN ACCOMPANIED BY IDENTIFICATION (AND THE MODE OF ACTION) OF THE ACTIVE COMPONENT

BJP considers only papers that describe studies on purified active compounds; in such cases, the purity of the compound, as well as major impurities, must be reported. *BJP* does not consider papers on mixtures of compounds (such as herbal extracts) alone, unless these observations are accompanied by evidence identifying and demonstrating similar activity of a purified component(s) of that extract. In some cases, the activity of an extract or mixture may be due to additive or synergistic activities of multiple compounds. If this is the case, then this finding should be shown by combining purified constituents and demonstrating functional activity that replicates the mixture. Overall, it is important to define which, and how, compounds of the extract contribute to the pharmacological activity.

As an example in which evaluation of an extract was followed by a detailed pharmacological analysis of the main active ingredient, a *BJP* paper reported that multiple distinct Chinese herbal medicine extracts increased the expression of uncoupling protein 1 in isolated adipocytes (Nie et al., 2018). The authors found that extracts from the Chinese plant *Astragalus membranaceous* had the highest activity and then went on to isolate and purify the components of that extract (with data from HPLC identifying the constituents). The authors identified the isoflavone formononetin as the chemical component responsible for the functional activity. Subsequently, the authors elucidated the pharmacological profile and the mode of action of formononetin, using a number of pharmacological and molecular

approaches, clearly showing its binding to PPARγ and that it blunted weight gain and increased energy expenditure in obese mice.

However, there are some exceptions to the above tenet:

i *BJP* will *consider* studies on chemically characterized herbal extracts with applications that are potentially clinically interesting. For instance, Whalley et al. (2019) evaluated the effect of diverse *Cannabis* extracts, with different concentrations of Δ^9-tetrahydrocannabinol (euphoric and convulsant) and cannabidiol (non-euphoric and anticonvulsant), on experimental seizures in animals. The authors discovered that the controversy surrounding the reported proconvulsant effects of Δ^9-tetrahydrocannabinol was in part derived from species differences in cannabinoid signalling and that these differences should be considered when seeking to better understand this potentially serious side effect.

ii *BJP* will *consider* studies aimed at identifying the pharmacokinetic profile of single constituents after the administration of chemically characterized, clinically well-studied extracts. For example, Chen et al. (2013) delineated the pharmacokinetics of flavonols and terpene lactones after dosing rats with standardized *Ginkgo biloba* leaf extracts via systemic or oral administration.

4 | *BJP* REQUIRES FULL DISCLOSURE REGARDING EXTRACT AND NATURAL PRODUCT PREPARATION

Full details regarding the provenance and handling of extracts must be provided. That is, the part of the plant/marine entity or microbe used, the method of extraction, the yield of dried extract as a percentage weight of the starting fresh or dried material, and type and concentration of extraction solvent should be detailed. For all starting materials, the formal biological name should be given from which the extract is derived. The scientific name (including the family) should be used, as per the Integrated Taxonomic Information System website, and should be in the binomial format composed of the genus and species. There are instances where naming is not straightforward, in which case full explanations and justifications should be provided.

The source of the product (i.e., country and region, from the wild or in captivity) should be stated. For rare organisms and all plants, a logged sample/voucher specimen stored within an accessible database in a recognized institution must be provided to enable others to access the sample and conduct analyses (Culley, 2013). Samples held in personal and private stores that are not available to other scientists are not considered acceptable for publication in *BJP*.

To ensure reproducible pharmacological activity, the extract must be chemically characterized (e.g., by HPLC fingerprint and metabolomics) and the content of marker compound(s) must be measured with validated analytical methods. For extracted compounds, phytochemical characterization, purity (%) and methods used to determine compound identity and purity must be stated. Most compounds should be tested at high purity (95–99%). In some instances, this may be difficult to achieve and, if so, authors are required to provide a clear description of the other constituents and explain how these other components have been accounted for in the analyses. A figure that shows the structure of the extracted compound must be included in the manuscript. For commercially available compounds, the name of the supplier must be given. Overall, reproducibility of findings is facilitated by the full disclosure of source of plant/tissue (provenance) and extraction process. To enable the latter, *BJP* has no word count restriction on methods. All extracts used must be available to readers either via an open access facility or from the authors.

5 | *BJP* REQUIRES THAT THE EFFECTS OF THE VEHICLE EMPLOYED MUST BE TESTED AND REPORTED

Many compounds of natural origin are not easily soluble in water or saline, and hence, they may be dissolved in organic solvents, such as DMSO, ethanol, vegetable oils (sesame oil and corn oil) or ethanol. Unfortunately, many organic solvents, at relatively low concentrations, affect cell lines or isolated tissues in ways that affect outcomes of in vivo investigations. Cell-based assays are often intolerant to solvent concentrations of greater than 1% (Hughes, Rees, Kalindjian, & Philpott, 2011). For example, DMSO, which is probably the most frequently used organic vehicle, exerts a number of pharmacological actions including differentiation of malignant cells, antioxidant and antibacterial activity, vasodilatation and smooth muscle relaxation, and behavioural and in vivo cardiovascular effects (Castro, Hogan, Benson, Shehata, & Landauer, 1995; Jacob & Herschler, 1986; Parisi et al., 2010).

Therefore, we advise that assessment of the minimum concentration of vehicle required to enable solubilization is conducted and mandate that the effect of the vehicle on the responses under study is reported. Inadequate consideration of the effects of the vehicle can lead to incorrect judgement regarding responses to the intervention. A recent example of incomplete consideration of vehicle effects occurred in studies of cardiovascular therapeutics by marine lipids. A substantial literature has reported positive effects of marine lipids on circulating triglyceride levels; raised plasma triglycerides correlate with worse outcome in terms of cardiovascular events (Sarwar et al., 2007). Results for a large prospective study assessing the impact of icosapent ethyl in patients with increased triglyceride levels (REDUCE-IT) was recently published (Bhatt et al., 2019). The investigators suggested that icosapent ethyl reduced the cumulative incidence of cardiovascular events compared to the placebo (a mineral oil mimicking the colour and consistency of the fish oil), However, LDL cholesterol (LDL-C), whilst similar in both groups at baseline (75 mg·dl^{-1}), rose 2 mg·dl^{-1} in the active intervention group but rose 7 mg·dl^{-1} in the placebo (mineral oil) group. This level of LDL-C is known to be associated with an increase of events and thus raised the possibility that the icosapoent ethyl might be simply preventing the detrimental effects of another component of the fish oil.

There are also instances when, in order to reach high concentrations of the compound under investigation (e.g., to construct a full

concentration–response curve in agonist/antagonist studies), the vehicle can affect the response being studied. In such cases, concentration–response curves for both the vehicle and the compound under investigation must be compared and shown. As an example, in *BJP*, Thomas et al. (2007) reported that the plant-derived compound cannabidiol displayed high potency as an antagonist of CB_1 and CB_2 receptors. The [^{35}S]GTPγS binding assay was used to determine both the efficacy of cannabidiol and the ability of cannabidiol to antagonize cannabinoid receptor agonists at the mouse CB_1 and the human CB_2 receptor. In this assay, the concentration–response curve related to the vehicle (DMSO) was clearly shown in figures and enabled comparison with the curve related to the effect of cannabidiol in the vehicle.

6 | *BJP* REQUIRES THAT A POSITIVE CONTROL BE INCLUDED

A further issue in the study of natural products is the need for testing a positive control, that is, comparison of the natural compound under investigation with a well validated drug that is effective in the selected pharmacological model. Unfortunately, in many published papers, this requirement is ignored. Examples in *BJP* where such active controls were used are below:

i Dexamethasone (subcutaneous treatment) and budesonide (aerosol treatment) were used as active (often termed positive) controls in evaluating the effect of the sesquiterpene α-humulene in an experimental model of allergic inflammation in airways (Rogerio el., 2009).
ii Tirofiban (an antiplatelet glycoprotein IIb/IIIα antagonist) was used as an active control in investigating the protective effect of the anti-thrombotic agent anfibatide (a glycoprotein Ib antagonist derived from snake venom) in a murine model of brain ischaemia (Li et al., 2015).

The comparison should also consider the magnitude of the effect and its possible clinical relevance. There are cases in the literature in which, although a conventional statistical significance is reached, the size of the effect is of little, or no, interest in the context of the disease target. As highlighted in a previous *BJP* editorial, a '10% change may be relevant in some gene expression studies, whereas a 90% reduction in virus titre may be irrelevant in some viral infection studies' (Curtis et al., 2015).

7 | *BJP* REQUIRES THE CONCENTRATION USED IN VITRO TO BE APPROPRIATE FOR FURTHER PHARMACEUTICAL DEVELOPMENT

Commonly used pharmacological screening assays for new compounds, isolated from natural sources, are cell culture systems or isolated organs. A major advantage of in vitro studies is that it is possible to test a broad range of high drug concentrations that cannot be reached in vivo. Whilst we do not prohibit publication of assessment of only high concentrations of active compounds in in vitro studies, we discourage observations where few, or no, possibilities exist for in vivo application or where the concentrations are inappropriate for further pharmaceutical development and drug discovery (Heinrich et al., 2020). The natural product literature contains many examples in which high concentrations have been used to evoke a pharmacological effect that is then associated with claims for a therapeutic use (Butterweck & Nahrstedt, 2012; Gertsch, 2009). However, it has been argued that the molecular structures of natural compounds facilitate interaction with proteins and so, at high concentrations, are likely to produce unwanted effects (Gertsch, 2009). Indeed, testing compounds targeting specific proteins (e.g., receptors and enzymes) at concentrations that exceed by 10-fold the IC_{50} or K_i for the molecular target increases the possibility of introducing off-target actions (Liston & Davis, 2017; Smith & Houghton, 2013).

Unfortunately, there are no accepted limits on concentration beyond the cut-off concentrations commonly used in the pharmaceutical industry (EC_{50} < 10 μM) (Gertsch, 2009). Compound screening assays for hit discovery are typically run at 1- to 10-μM compound concentration (Hughes et al., 2011). A recent guide authored by editors of journals specialized in natural products research suggests that concentrations higher than 30–50 μM should not be used (Heinrich et al., 2020). For the evaluation of certain pharmacological activities, some suggestions are reported elsewhere. For example, antimicrobial activity is believed to be meaningful at concentrations below 25 μM (Cos, Vlietinck, Berghe, & Maes, 2006). For antiproliferative/cytotoxic studies, it is recommended that compounds have selectivity and are not 'anti-life' (Heinrich et al., 2020).

BJP has elected *not* to have a policy restricting concentration other than that the concentrations tested are achievable in vivo without causing unwanted biological effects (off or on target). In studies assessing antiproliferative effects in the context of development of treatments to limit carcinogenesis, a comparison between the compound effect on tumours versus healthy cells is recommended. If the aim of the study is to identify the constituent responsible for effects of particular dietary approaches, the effects of the compound must occur at concentrations commensurate with those achieved from dietary consumption.

In general, it may be wise to ask the following question: 'can the concentrations used in vitro be present in the blood and tissue/cellular target after the administration of a therapeutic dose of the compound under investigation'? The answer to this simple question requires knowledge of the pharmacokinetic profile of such a compound.

An interesting study that investigated the in vivo relevance of a concentration used in vitro was recently published in *BJP* (Yeo, Fenwick, Barnes, Lin, & Donnelly, 2017). The authors found that the dietary polyphenol isorhapontigenin inhibited IL-6 release from airway epithelial cells. On the basis of pharmacokinetic data obtained in rats in vivo, the authors postulated that the concentration used in vitro can be reached following oral dosing of isorhapontigenin and that at

least 30% inhibition of IL-6 release can be attained through a single oral dose of isorhapontigenin (Yeo et al., 2017).

It is important to note that the compound under investigation might be a pro-drug—or, more generally, may be metabolized in vivo before the absorption phase, and hence, the results obtained in vitro could be misleading. This is common for natural products since many plant compounds exist in nature as glycosides, which are generally deglycosylated by intestinal microbiota, making the non-sugar portion available for absorption.

8 | *BJP* REQUIRES THAT THE DOSE USED IN VIVO HAS TRANSLATIONAL RELEVANCE

Extrapolation of dose from animal experiments to the human situation can be difficult (Nair & Jacob, 2016). In addition to body weight, a number of variables should be considered, including body surface area, pharmacokinetic parameters (clearance and volume of distribution) and interspecies differences in the pharmacodynamics. A comprehensive analysis of the principles of interspecies dose extrapolation is beyond the scope of this editorial. However, we refer readers to a paper published several years ago in *BJP* (Sharma & McNeill, 2009).

Allometric scaling of drug doses from preclinical experiments has been frequently used to predict the dose for single dose studies for first-in-human trials. This empirical approach is based not only on body weight but also on the normalization of dose to body surface area ($mg \cdot m^{-2}$). Tables created from FDA guidelines, available elsewhere (Nair & Jacob, 2016; Sharma & McNeill, 2009), represent a tool for the conversion of doses between animals and humans. Unfortunately, interspecies dose conversion is rarely considered. By analysing papers on natural products published in *BJP* recent years, we have identified three common scenarios where dose extrapolation is required:

i to promote the compound under investigation as a candidate for clinical development or as a dietary supplement (extrapolation from animals to humans),
ii to investigate the mechanism of action of natural drugs or already marketed dietary supplements (extrapolation from humans to animals) and
iii to unravel the possible beneficial (or detrimental) effect of a natural compound in the context of a diet or an ingested food.

An example of a study in *BJP* in which the dose has been correctly extrapolated from humans to animals is that of Simeoli et al. (2017). The authors compared the effect of the dietary supplement butyrate (a postbiotic compound) with a more palatable butyrate-releasing derivative in a murine model of colitis. The daily dose (20 $mg \cdot kg^{-1}$) used in the mouse is convertible to a human equivalent dose (Nair & Jacob, 2016) of 113.4 mg, for an adult human subject weighing 70 kg, which is in the range of the common dose of butyrate used in humans.

Conversely, resveratrol is an example of a compound where dose ranges of activity in research studies do not match dietary approaches. In an article published in *Nature* some years ago, resveratrol improved survival of mice on a high-calorie diet (Baur et al., 2006), and this led to speculation that some of the benefits of red wine relate to such an effect. However, extrapolation of the dose used in animals in this study, using allometric scaling (Nair & Jacob, 2016), which considers body weight and surface area, leads to the conclusion that an average weight person would have to drink 55 bottles of wine per day.

In summary, dose ranges in animal experiments must be relevant from a preventive or therapeutic viewpoint and evidence supporting this must be provided. In general, multiple-dose testing is recommended (in the context of compliance with the 3Rs): Single doses are acceptable only in complex pharmacological models.

9 | *BJP* REQUIRES THAT THE ROUTE AND TIMING OF ADMINISTRATION ARE APPROPRIATE

The route of administration is a fundamental factor to consider in the design of experiments using animals. In traditional medical systems, most herbal remedies are administered orally: for example, in the form of infusions or decoctions (Abdul & Huang, 2015). Similarly, natural products that are available in the market are generally dispensed in pharmaceutical forms for oral use. Therefore, the oral route of administration is preferred in pharmacological translational experiments related to natural products, especially when the study aims

i to promote the compound under investigation as a dietary supplement,
ii to explain the possible beneficial effect of an ingredient found in the diet or
iii to validate the traditional use of a natural compound (ethnopharmacological studies).

Parenteral administration, such as s.c., i.p. or i.v., thus have little value in the context of the dietary supplements market and should be restricted to studies related to conventional drug discovery.

In addition to traditional oral/parenteral dosing methods, compounds under investigation can be incorporated into the diet. An example is a study, published in *BJP*, that assessed the impact of dietary supplementation for 2 months with the plant product quinic acid on glucose metabolism (Heikkilä et al., 2019). In order to determine how much compound needs to be mixed into the diet, it is essential to know key pieces of information, including the daily dose that the researcher aims to give to animals, the weight and usual daily food intake of the animal (Ricci, 2012). The inclusion of compounds into the diet has a precise significance when the study aims to unravel the relevance of a specific natural compound in the context of a diet.

The timing of drug administration (preventive vs. curative) is also important. Where the clinical setting means that treatments can only be delivered following disease establishment and diagnosis, the timing of administration of compounds under study should be

clinically relevant, unless the authors are evaluating a possible candidate for prevention. For settings in which the goal is to cure rather than prevent, compounds should be given after administration of the insult.

10 | *BJP* REQUIRES THAT THE POTENTIAL TOXICITY OF THE COMPOUND UNDER EVALUATION IS CONSIDERED

Many drugs fail in the clinic because they are not safe (Hughes et al., 2011). Thus, at the preclinical level, the determination of safety is as important as the proof of efficacy, both for initiation of a clinical trial and for promoting a natural compound as a food supplement. *BJP* is a pharmacological journal, and thus, we do not ask for in vivo toxicology, but, whenever possible, we encourage authors to provide information on the toxicity of the product under evaluation. For example, if a study is solely performed in vitro, some assessments of in vitro toxicity, such as cell viability or mitochondrial function, are advised. For in vivo studies, measures of potential toxicity could include assessment, for example, of liver, renal or cardiac function. For selected pharmacological activities, such as antiproliferative/cytotoxic activity, the authors should show that extracts or compounds have selectivity versus cancer cells and are not 'anti-life' drugs (Heinrich et al., 2020). Ideally, a comparison should be provided of the effect between cancer and healthy cells (if available), especially when the effect is observed at high concentrations.

Finally, authors are also encouraged to review the literature to verify if toxicological information has already been reported. For example, Romano et al. (2013) found that the plant cannabinoid cannabichromene ameliorated experimental colitis at a dose, which was more than 100-fold lower than the subacute LD_{50} dose reported in the literature.

11 | *BJP* GUIDELINES MUST BE ADHERED TO

Since 2015, the *BJP* has adopted a series of guidelines to support transparency and reproducibility. A major initiative has been the publication and implementation of guidelines related to design and analysis of experiments. The journal has published two editorials on this topic describing the requirements for submissions to the journal (Curtis et al., 2015; Curtis et al., 2018). Key issues highlighted in these guidelines include a need for blinding and randomization in design, ideally evidence of sample size determination and a requirement for minimum n values of 5 prior to subjecting datasets to

TABLE 3 Author checklist for manuscripts to be submitted to the *British Journal of Pharmacology*

	Questions	Comment/Advice
1	Is the mechanism of action of the natural product reported?	*BJP* seeks to advance understandings of the mechanisms of action of pharmacological compounds.
2	Does the study report the activity of a mixture of compounds (e.g., herbal extracts) or a pure compound?	*BJP* ordinarily does not publish papers on mixture of compounds unless the manuscript also demonstrates that any activity evidenced is reproduced by a purified component of that mixture. Purity must be evidenced and % stated.
3	What is the origin of the natural product?	Methods must disclose source, extraction and purification/synthesis process.
4	Has the effect of the vehicle on the response under study been reported?	Vehicle effects must be clearly reported, with mean ± SEM or SD, with appropriate statistical analysis and with $n \geq 5$.
5	Has a positive control been used?	The effect of the compound under investigation should be compared with a clinically effective drug. If the positive control has been not reported, include a valid scientific justification (e.g., there are no clinically effective drugs for the specific disease). Discuss the size of the effect in relation to the disease under evaluation.
6	Are the concentrations used in vitro appropriate for further pharmaceutical development?	Rationale for the selection of concentrations used must be provided. Include a valid scientific justification if high concentrations (e.g., ≥25 μM) are used. Pharmacokinetic data on plasma levels following systemic administration should be considered. Concentrations much higher than the IC_{50} or K_i reported for the compound under investigation must not be used.
7	Are the doses used in vivo relevant for translation?	The rationale for the selection of the doses used must be provided. If testing as a potential therapeutic, relevance to the clinical setting must be provided.
8	Is the dosing schedule appropriate?	The rational for the selection of the route, timing and frequency of administration should be provided.
9	Is the compound under investigation safe?	Evidence of safety should be provided, or if not available, discuss issues regarding potential toxicity.
10	Are experimental design and analysis, data presentation and sharing in line with *BJP* guidelines? Has sex been considered as a biological variable?	*BJP* guidelines must be adhered to, using editorials as a reference (Alexander et al., 2018; Curtis et al., 2018; Docherty et al., 2019; George et al., 2017; George et al., 2019). Checklists are available on *BJP* website.

comparative statistical analysis. For all studies involving animals, animal tissues or primary cultures, authors must address issues raised in the *BJP* editorial 'Implementing guidelines on reporting research using animals (ARRIVE etc.): New requirements for publication in *BJP*' (McGrath & Lilley, 2015). Authors are encouraged to read *BJP* editorials on data presentation and sharing (George et al., 2017; George et al., 2019) as well as on the goals and the practicalities of immunoblotting and immunohistochemistry (Alexander et al., 2018). Checklists covering these requirements are available on the *BJP* website (https://bpspubs.onlinelibrary.wiley.com/hub/journal/14765381/declaration_english).

Finally, *BJP* now requires sex to be considered as a variable for all experimental reporting (Docherty et al. 2018). *BJP* editors recommend that all experiments (in vitro, in vivo and ex vivo) should include both sexes, unless there is a specific justification not to do this.

12 | CONCLUSIONS

This editorial illustrates major requirements that authors should consider before submitting articles to *BJP* (see Table 3 for authors' checklist). It also highlights some common shortcomings in natural product pharmacological research, which could be prevented if experiments have appropriate planning and experimental design.

BJP is a leading journal in the pharmacological field, in which important new advances are published, and thus, novelty is a major determinant of acceptance for publication. Studies showing the effect of natural products, without a substantial investigation into the mode of action, are not considered. Articles limited to repetition of well-known data or that report similar pharmacological activities of similar chemical compounds are generally not suitable for *BJP*.

The editors of *BJP* recognize the wealth of opportunity for therapeutics that comes from the natural world and are keen to publish excellent natural product pharmacology that advances understanding of mechanisms of both physiological and pathological processes or that identifies potential new therapeutics.

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