Natural product pharmacology: the British Journal of Pharmacology perspective

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MINI-REVIEW

Natural product pharmacology: the British Journal of Pharmacology perspective

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Natural products (NPs) have long been used as a rich source of bioactive compounds for drug development. Recent technological advancements have revitalised natural products research as evidenced by increased publications in this field. In this editorial review, we highlight key points from the 2020 *British Journal of Pharmacology* (BJP) practical guide, which outlines standards for natural products research reports, and provide papers published in BJP between years 2020 to 2023 that demonstrate adherence to these guidelines. Looking ahead, we discuss the potential of chemical proteomics approaches to elucidate natural products mechanisms of action and identify therapeutic targets for future research. By fostering innovation, we aim to advance natural products research and contribute to the development of novel therapeutics that will have a significant impact on healthcare.

KEYWORDS
chemical proteomics, drug discovery, natural products

1 | INTRODUCTION

Natural products (NPs) provide an important source of bioactive compounds in drug discovery. Despite the significance of natural products, past research encountered numerous challenges, particularly regarding the isolation, identification and synthesis of these compounds, which prompted a decline of natural product-based drug discovery. In recent years, accelerated technological developments,

Abbreviations: ABPP, activity-based protein profiling; AhR, aryl hydrocarbon receptor; ASK1, apoptosis signal-regulating kinase 1; Btk, Bruton's tyrosine kinase; CMA, chaperone-mediated autophagy; DEX, dendritic cell-derived exosomes; GLI1, glioma-associated oncogene homolog 1; HCC, hepatocellular carcinoma; HDAC1, histone deacetylase 1; ITC, isothermal titration calorimetry; LA, licochalcone A; LAMP2A, lysosome-associated membrane protein 2A; LAP2α, lamina-associated polypeptide 2 alpha; MD2, myeloid differentiation factor 2; Nrf2, nuclear factor erythroid 2–related factor 2; NSCLC, non-small cell lung cancer; PPARγ, peroxisome proliferator-activated receptor gamma; Prx2, peroxiredoxin 2; SFK, Src family kinase; SIRT1, sirtuin 1; SNG, sanguinarine; SPR, surface plasmon resonance; SSBP1, single-strand DNA-binding protein 1; STAT3, signal transducer and activator of transcription 3; TLR4, toll-like receptor 4; TP, triptolide; Vav, Vav guanine nucleotide exchange factor.

For affiliations refer to page 7

exemplified by the advent of advanced analytical tools, multi-omics techniques, sophisticated synthesising strategies and refined microbial culturing practices have opened new avenues for overcoming the traditional hurdles faced in natural products research (Atanasov et al., 2021). These advancements have not only expanded the scope of pharmaceutical research but have also rekindled interest in natural products, as one of the most promising yet challenging areas of study.

Despite the rise of synthetic chemistry and molecular biotechniques, the discovery of natural products remains a crucial pathway for the development of novel pharmaceuticals. This is especially evident in the search for new antimicrobials, anticancer agents and anti-inflammatory compounds, in which complex molecules with potent biological activities are found but not easily replicated by synthetic analogues. The flowchart shown in Figure 1 provides herein an outline of the systematic approaches for natural product research, illustrating the critical steps from the initial sourcing of biological materials to the final steps of compound pharmacological testing which can serve as a guideline for preparing natural products (NP) research papers for the *British Journal of Pharmacology* (BJP).

Considering the aforementioned changes in natural product research and its implications for drug discovery, the aim of this editorial review is to summarise the previous practical guide for transparent reporting of research on natural products published in 2020 by the BJP (Izzo et al., 2020). This practical guidance and review will serve as a blueprint for researchers, by providing a set of standards for enhancing the quality, reproducibility and transparency of natural product research. As the field continues to evolve, it is imperative to evaluate and explain the latest scientific advancements of natural product papers published in BJP.

This practical guidance reviews recently published manuscripts in BJP after the 2020 practical guide was released, to assess technological and scientific advances in natural product research. We explore how these advances have shaped the strategies for natural product discovery and analysis, highlighting the significance of these compounds in the development of new therapeutics. In doing so, we emphasise the importance of robust and reproducible methodologies that can exploit the full potential of natural products in drug discovery.

This editorial review makes a connection between traditional approaches and modern technologies, providing guidelines for current and future investigations aimed at developing novel therapeutics based on natural products research. Consequently, we underscore the necessity of continuous innovation and adaptation in the methodologies employed, ensuring that the field attracts significant attention from researchers.

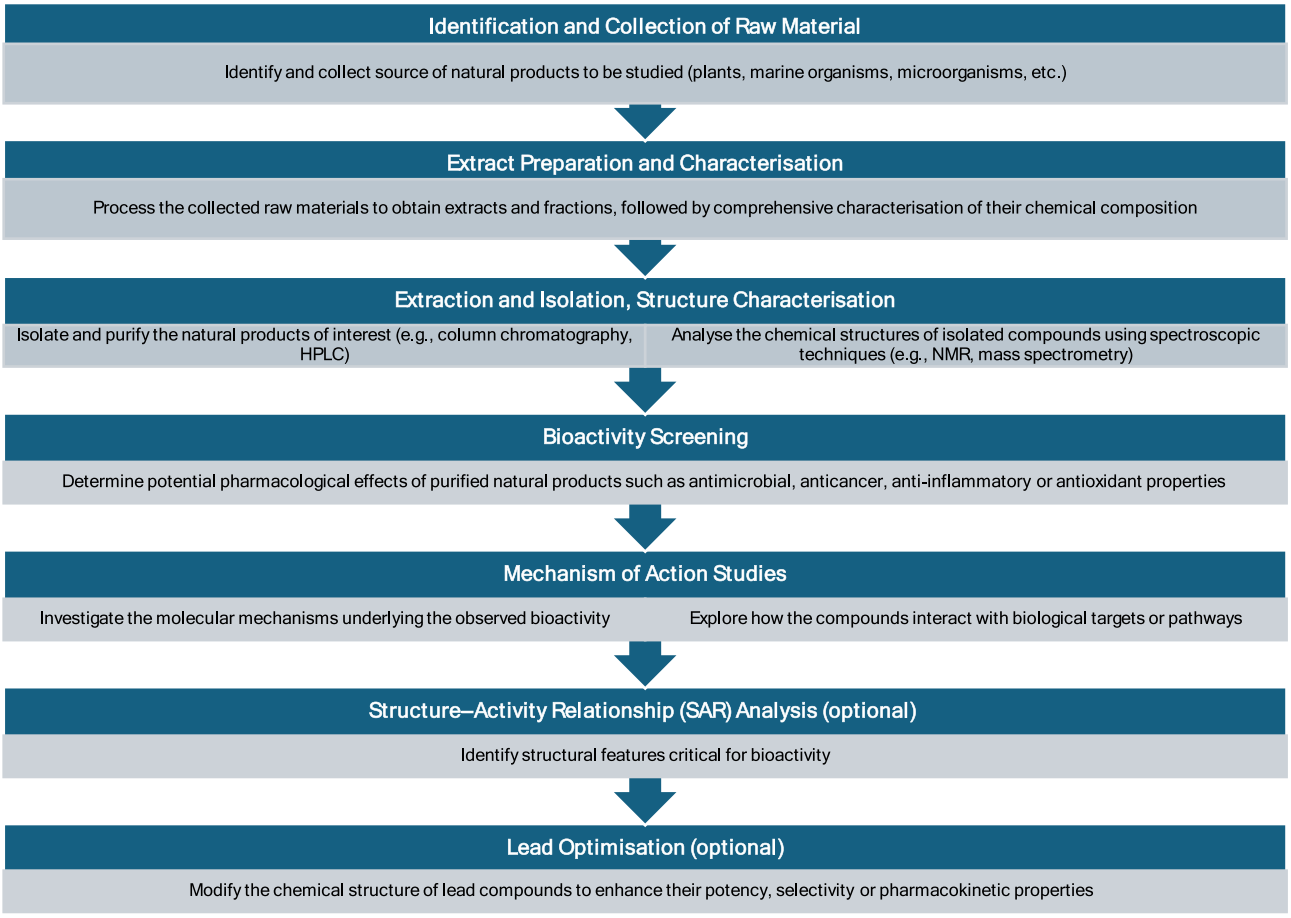

FIGURE 1 The flowchart for preparing natural product (NP) research papers for BJP.

2 | HIGHLIGHTS OF THE 2020 BJP PRACTICAL GUIDE

The 2020 BJP practical guide aimed at ensuring transparent reporting in natural product pharmacological research. The guide highlights the pivotal role that natural products play in drug discovery (Izzo et al., 2020). Table 1 summarises the most relevant points of the guide. The guide clarifies the need for well-defined standards and publication expectations for manuscripts related to natural product research, to ensure high quality and reproducibility. Regarding the current focus, the guidelines emphasise that the journal requires pharmacological analysis and elucidation of the mechanisms of action of natural products rather than studies solely reporting their chemical identification. Furthermore, the guidelines specify that BJP considers investigations into compound mixtures only if they provide a detailed identification and the mode of action of the active constituent(s), thus highlighting BJP commitment to scientific rigour and depth in natural product research. In the guideline, various categories of natural product papers that BJP publishes are described, ranging from those describing phytochemicals poised for clinical trials or immediate use as dietary supplements, to studies that explore the impact of phytochemicals within dietary contexts. The journal also considers studies that provide a pharmacological basis for the application of dietary supplements or that of repurposing traditional natural medications. This diversity in research themes reflects BJP comprehensive approach to natural product pharmacology, which is essential for closing the gap between traditional use and contemporary scientific validation.

TABLE 1 Key points of the BJP 2020 practical guide for transparent reporting of research on natural products.

Key points	Advice
Mechanisms of action	Report the mechanism of action. Aim for advancements in understanding pharmacological actions.
Compound type	Focus on pure compounds; if using mixtures, demonstrate activity with purified component(s).
Methodology details	Detail source, extraction, and synthesis/purification processes.
Vehicle effects	Report vehicle effects with number of experiments and appropriate statistical analysis.
Positive control	Compare the effect with a clinically effective drug.
Clinical relevance	Discuss the size of the effect and disease relevance.
Concentration usage	Justify selected concentrations. Avoid excessively high concentrations unless scientifically justified.
Dose relevance	Explain dose choice; ensure clinical relevance for therapeutic potentials.
Dosing schedule	Justify administration route, timing, and frequency.
Safety and toxicity	Provide safety evidence or discuss potential toxicity.

Besides highlighting the various research categories that are preferred by BJP, the 2020 BJP practical guide offers explicit advice on methodological rigour. For instance, it requires the comparison of concentration–response curves for both the vehicle and the investigated compound, and insists on the inclusion of a positive control. The significance of selecting and testing *in vitro* concentrations that are appropriate to pharmaceutical development and drug discovery is also highlighted. For *in vivo* studies, the 2020 BJP practical guide specifies that dosages should bear translational significance, with correct extrapolation between animals and humans, emphasising that the route and timing of administration should align with the natural products intended use. These guidelines aim to increase the translational relevance of research findings, thereby supporting the mission of BJP to advance transparency and reproducibility in natural product research.

3 | THE EDITORS CHOICE OF 4-YEAR PAPER

Since the publication of our practical guide in 2020, there have been significant improvements in the quality of manuscripts received by the BJP. This likely reflects the increased research standards within the field of natural product research. However, despite the enhanced quality of submissions, the acceptance rate for NP manuscripts over the last 4 years (2020–2023) is unchanged compared to previous years and continues to be lower than the average acceptance rate, as detailed in Table 2.

Table 3 shows exemplary papers from the 2020–2023 period that reflect the rigorous methodologies and innovative approaches adopted. These selected papers not only adhere to but also often surpass our strict expectations. They represent a significant contribution to the advancement of pharmacological research on natural products. Through these examples, we illustrate the impact of our

TABLE 2 Acceptance rate of natural product (NP) papers in BJP from 2020–2023.

Year	NP papers submitted	NP papers accepted	NP acceptance rate	Total papers submitted	Total papers accepted	Total acceptance rate
2020	178	19	11%	1793	335	19%
2021	122	15	12%	1511	228	15%
2022	141	18	13%	1325	180	14%
2023	150	10	7%	1374	240	17%

TABLE 3 Editors choice from 2020–2023.

Article type	Short summary	Reference
2020		
Investigating the anti-cancer properties of geniposide	Geniposide, derived from *Gardenia jasminoides*, was investigated for its effect on hepatocellular carcinoma (HCC). Geniposide was found to inhibit HCC proliferation, invasion, angiogenesis and lung metastasis. The study revealed that geniposide suppresses **VEGF** secretion independently of hypoxia inducible factor 1 subunit alpha (HIF-1α) by directly inhibiting the **TLR4**/myeloid differentiation primary response 88 (MyD88) pathway.	(C. Zhang et al., 2020)
Investigating dietary flavonoid supplementation in experimental chronic kidney disease	This study identified endogenous 1-aminopyrene (AP) as a novel mediator of progressive chronic kidney disease (CKD) via activation of the **aryl hydrocarbon receptor (AhR)**. Increased levels of aryl-containing metabolites during CKD progression were associated with AhR and its target genes. The research suggested AhR as a therapeutic target for CKD. Importantly, dietary flavonoid supplementation was found to ameliorate CKD and renal fibrosis by partially inhibiting AhR activity.	(Miao et al., 2020)
Investigating neuroprotective effects of astaxanthin in traumatic brain injury	The carotenoid astaxanthin reduced oxidative stress and apoptosis in neuronal cells after traumatic brain injury in mice, enhancing neurological function. Astaxanthin protective effects were mediated through the **sirtuin1 (SIRT1)**/**NRF2**/paired mesoderm homeobox protein 2 (Prx2)/**ASK1**/**p38** pathway.	(X. S. Zhang et al., 2021)
Investigating flavonoid interactions in immune regulation	The flavonoid **kaempferol** modulated T cell activation and showed therapeutic effects in atopic dermatitis. Kaempferol worked by binding to **multidrug resistance-associated protein 1 (MRP1/ABCC1)**), suppressing **JNK** phosphorylation and the NF-κB pathway, alleviating symptoms in an atopic dermatitis mouse model.	(Lee & Jeong, 2021)
2021		
Investigating a plant isoflavone in intrahepatic cholestasis	**Tectorigenin**, a plant isoflavone, inhibited hepatic macrophage activation and promoted bile transporter expression to alleviate intrahepatic cholestasis through **PPARγ (NR1C3)** activation. Tectorigenin enhanced bile salt export pump expression and demonstrated dependency on PPARγ for its hepatoprotective effects, positioning it as a potential for intrahepatic cholestasis therapy.	(Xiang et al., 2021)
Investigating trienomycin A against pancreatic cancer	Trienomycin A, a secondary metabolite produced by the actinomycete *Streptomyces cacaoi*, was identified as a potent **STAT3** pathway inhibitor. Trienomycin A inhibited the phosphorylation of STAT3, resulting in reduced colony formation, proliferation, migration and invasion of pancreatic cancer cells *in vitro*, along with significant inhibition of tumour growth *in vivo*, without apparent toxicity at effective doses.	(He et al., 2021)
Investigating Bletinib for neutrophilic inflammation and ALI treatment	Bletinib, derived from the Chinese plant *Bletilla striata*, inhibited **Src family kinase** phosphorylation reducing human neutrophil functions, such as degranulation, respiratory burst and neutrophil extracellular trap (NET) formation. Bletinib ameliorated neutrophilic inflammation and lung injury in acute lung injury models by targeting the SFK-**Btk**-Vav pathway, showing promise as an anti-inflammatory drug.	(Kao et al., 2021)
Investigating disruption of LAP2α/HDAC1 complex by a phytochemical in liver fibrosis	Physalin B, from the traditional Chinese medicinal plants of the *Physalis* species, attenuated liver fibrosis by interfering with the lamina-associated polypeptide (LAP)2α/**HDAC1** complex, enhancing glioma-associated oncogene homolog 1[zinc finger protein] (GLI1) acetylation and curtailing hepatic stellate cell activation. Through modulation of non-canonical Hedgehog signalling, physalin B effectively reduced histopathological injury and fibrotic marker expression in liver fibrosis models. This study demonstrates the potent antifibrotic activity of physalin B, offering a promising avenue for liver fibrosis therapy by targeting the GLI1 transcription factor and its regulatory mechanisms.	(X. Zhu et al., 2021)
2022		
Investigating a novel target delivery of triptolide for autoimmune disease therapy	The study presents an innovative targeted therapy approach using dendritic cell-derived exosomes (DEX) to encapsulate and deliver triptolide (TP, a diterpene trioxide obtained from the plant *Tripterygium wilfordii*) for treating ulcerative colitis and rheumatoid arthritis. Such targeted therapy	(Rao et al., 2023)

TABLE 3 (Continued)

Article type	Short summary	Reference
	reduced the systemic toxicity of TP in murine models, while effectively modulating the immune response, as demonstrated by the decreased inflammation and autoimmune damage. Through DEX-TP, the research highlighted a novel immunosuppressive strategy that specifically targets dendritic cells, paving the way for safer and more focused treatments of autoimmune diseases.	
Investigating the potential of allicin as a topical treatment for psoriasis	This study explores the efficacy of **allicin**, a bioactive compound from garlic, in mitigating psoriasis-like skin inflammation. Focusing on the interaction between **IL-17A** and keratinocytes, which is critical to the persistence of psoriatic inflammation, allicin was observed to interfer with this interaction. Pharmacodynamic assessments in mouse models, complemented by skin sensitization tests in guinea pigs, showed the ability of allicin to restore epidermal architecture was by suppressing keratinocyte hyperproliferation and minimising apoptosis. Mechanistic investigation revealed that allicin disrupted the IL-17A mediated signalling pathways within keratinocytes, disrupting the cycle of inflammation typical of psoriasis. Notably, topical application of allicin proved safe and suitable for prolonged use, signifying its potential as an effective treatment modality for psoriasis.	(L. Zhang et al., 2023)
Investigating anti-obesity compounds from *Garcinia cambogia*	The study highlights guttiferone J (GOJ), from *Garcinia cambogia*, as a potent anti-obesity compound. GOJ reduced lipid accumulation and promoted adipocyte browning via **SIRT3** activation. GOJ, along with other *Garcinia cambogia* ingredients (that are **garcinol** and 14-deoxygarcinol), was identified using bioactivity-based molecular networking. In obese mice, GOJ showed protective effects against adiposity, hyperlipidaemia and **insulin** resistance, suggesting its potential as a therapeutic agent for obesity and metabolic disorders.	(Feng et al., 2023)
Investigating a plant-derived glucocorticoid receptor modulator for reduced side effects	Caesaldekarin e (CA-e), from the *Caesalpinia* genus, was identified as a selective **glucocorticoid receptor (GR/NR3C1)** modulator, offering anti-inflammatory benefits with fewer side effects than dexamethasone. By inhibiting GC response element (GRE)-mediated transactivation and altering GR interactions with NF-κB, CA-e prevented GR dimer formation, suggesting a new pathway to reduce glucocorticoid therapy side effects. This study positions CA-e as a promising candidate for safer glucocorticoid treatments, potentially improving therapy for inflammatory conditions.	(Y. Wang et al., 2023)
2023		
Investigating lipopeptide targeting FPR1 in acute respiratory distress syndrome (ARDS) therapy	By targeting the **formyl peptide receptor 1 (FPR1)**, this study identified anteiso-C13-surfactin (IA-1), from the marine bacterium *Bacillus amyloliquefaciens*, as a potential therapy for neutrophil-dominant acute respiratory distress syndrome (ARDS). IA-1 demonstrated competitive inhibition of FPR1, reducing neutrophil activation and ameliorating pulmonary inflammation in a mouse model of ARDS. This approach highlights the therapeutic potential of IA-1 in mitigating the progression of ARDS through its anti-inflammatory effects on neutrophils, thus suggesting a novel treatment pathway for this critical condition.	(Yang et al., 2023)
Investigating a novel inhibitor of chaperone-mediated autophagy in NSCLC	This research discovers polyphyllin D (PPD), from the Chinese plant polyphylla, as a potent inhibitor targeting the **HSC70**-lysosome-associated membrane protein (LAMP) 2A interaction in chaperone-mediated autophagy (CMA) within non-small cell lung cancer (NSCLC) cells. PPD not only disrupted CMA but also induced cellular stress mechanisms, leading to tumour growth inhibition in NSCLC models. By preventing the regulatory compensation typically induced by CMA inhibition, PPD emerges as a promising NSCLC therapeutic agent, offering a new avenue for targeting autophagy pathways in cancer treatment.	(Dong et al., 2023)
Investigating the apoptotic effects of sanguinarine in osteosarcoma	This research investigates **sanguinarine (SNG/pseudochelerythrine)**, primarily found in plants such as *Sanguinaria canadensis*, *Chelidonium majus* and *Argemone mexicana*), highlighting its potent anticancer effects in osteosarcoma by modulating the STAT3/single-strand DNA-binding protein 1 (SSBP1) signalling pathway. The findings demonstrate SNG	(K. D. Wang et al., 2023)

(Continues)

TABLE 3 (Continued)

Article type	Short summary	Reference
	ability to up-regulate SSBP1 expression, disrupt mitochondrial function and to induce apoptosis through inhibiting the STAT3 and **PI3K/Akt/mTOR** signalling pathways. These results indicate that SNG is a promising therapeutic candidate for osteosarcoma, underscoring the previously unknown apoptotic potential of SSBP1 in osteosarcoma cells.	
Investigating licochalcone A as a novel MD2 inhibitor for ALI/ARDS therapy	This paper investigates the capacity of licochalcone A (LA, a chalcone-like compound isolated from liquorice) to inhibit **lipopolysaccharide (LPS)**-induced acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) through a novel mechanism of directly binding to **myeloid differentiation factor 2 (MD-2)**. By inhibiting the **toll-like receptor 4 (TLR4)** signalling pathway, licochalcone A has a potent anti-inflammatory effect *in vivo*, significantly reducing pulmonary inflammation and immunocyte infiltration. The study positions licochalcone A as a promising therapeutic agent for ALI/ARDS, offering a direct molecular target for intervention in inflammatory pulmonary diseases.	(W. Zhu et al., 2023)

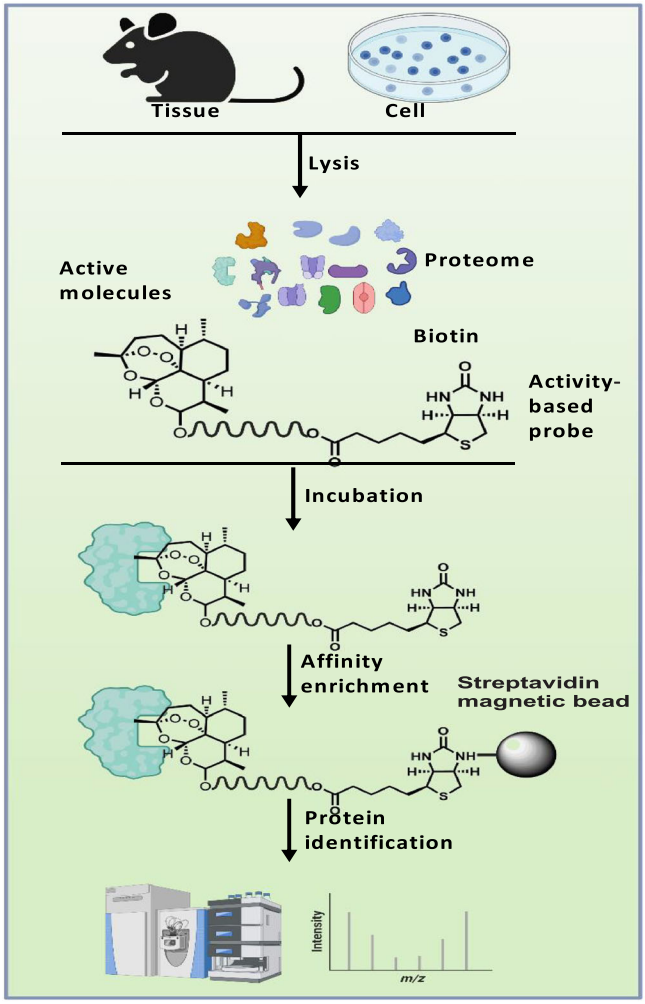

FIGURE 2 Activity-based probe profiling. Natural products (NPs) are functionalised with biotin labels to create activity-based probes, which are subsequently utilised for the specific capture of target proteins from cultured cell or tissue lysates. These target proteins are enriched through affinity-based purification using streptavidin magnetic beads and are subsequently identified via LC–MS analysis for further biological mechanism study.

comprehensive guidelines on research quality and reproducibility, while also acknowledging the ongoing challenges in achieving a higher acceptance rate for natural product studies.

4 | OUTLOOK

In future research, the potential of natural products in disease prevention and treatment will be exploited not only through their diversity and complexity but also based on how precisely their mechanisms of action can be understood. While traditional research methods have succeeded in identifying connections between natural products and disease prevention/treatment, they often overlook a broad target spectrum of natural products due to their structural characteristics. This raises the question of which targets have direct biological significance in the development of specific diseases. To address this issue, more systematic and refined research approaches need to be brought in. Chemical proteomic has emerged as a new method to comprehensively screen and identify the protein targets of active small molecules including natural products, involving two crucial steps in target identification: chemical probe design and synthesis, as well as target fishing and identification (Chen et al., 2020). Figure 2 illustrates one of the chemical proteomics methods workflows, that is, the activity-based protein profiling (ABPP). In the ABPP approach, probes are designed and synthesised from parent molecules based on structure–activity relationships to ensure that the probes retain the pharmacological activity of the original molecules. These probes are then incubated with cell lysates, or tissue homogenates which bind to target proteins, followed by the enrichment and identification of the protein targets using proteomics techniques. Subsequently, the target information can be validated through methods such as surface plasmon resonance (SPR), microscale thermophoresis (MST) and isothermal titration calorimetry (ITC). In the ABPP approach, biotin-labelled natural products can be employed as molecular probes to identify their direct binding targets through the principle of biotin and avidin interaction in cells. This method will not only identify target proteins directly interacting

with natural product molecules via avidin-bound magnetic beads but also allow for further refinement and narrowing down of key targets through biological function studies.

Overall, the steps in chemical proteomics approaches involve probe design and synthesis, incubation with target samples, enrichment of bound proteins, identification of protein targets, validation of target information and pharmacological effects. This strategy can reveal the direct relationship between natural products and key targets in specific diseases, laying a solid foundation for precision treatment. Moreover, studies using animal models or human samples can be conducted to corroborate natural products key targets and validate natural product effects on the treatment progress.

5 | CONCLUSION

In summary, by adopting new research strategies, researchers will be able to gain a deeper understanding of the effects and mechanisms of natural products in prevention and disease treatment, thereby paving the way for discovering new therapeutic targets.

Looking ahead, we remain committed to supporting and publishing ground-breaking natural product work that not only meets but exceeds our standards. We encourage authors to take advantage of the insights and feedback provided through the editorial process to enrich their research contributions. Our goal is to advance the field of natural product research by disseminating research of the highest quality and of significant impact on the scientific community and beyond.

As we move forward, we are optimistic that the collective efforts of our contributors will continue to push the boundaries of what is possible in natural product research. Together, we can build on the progress achieved thus far, ensuring that the BJP remains at the forefront of publishing innovative and influential research in this ever-important area of pharmacological science.

5.1 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in the IUPHAR/BPS Guide to PHARMACOLOGY http://www.guidetopharmacology.org and are permanently archived in the Concise Guide to PHARMACOLOGY 2023/24 (Alexander, Kelly, Mathie, Peters, Veale, Armstrong, Buneman, Faccenda, Harding, Spedding, Cidlowski, et al., 2023; Alexander, Fabbro, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Davies, Amarosi, et al., 2023; Alexander, Fabbro, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Davies, Annett, et al., 2023; Alexander, Fabbro, Kelly, Mathie, Peters, Veale, Armstrong, Faccenda, Harding, Davies, Beuve, et al., 2023).

AUTHOR CONTRIBUTIONS

X. Wang: Conceptualization; writing—original draft. **A. A. Izzo:** Writing—review and editing. **A. Papapetropoulos:** Writing—review and editing. **S. P. H. Alexander:** Writing—review and editing. **M. Cortese-Krott:** Writing—review and editing. **D. A. Kendall:** Writing—review and editing. **K. A. Martemyanov:** Writing—review and editing. **C. Mauro:** Writing—review and editing. **R. A. Panettieri:** Writing—review and editing. **H. H. Patel:** Writing—review and editing. **R. Schulz:** Writing—review and editing. **B. Stefanska:** Writing—review and editing. **G. J. Stephens:** Writing—review and editing. **M. M. Teixeira:** Writing—review and editing. **N. Vergnolle:** Writing—review and editing. **P. Ferdinandy:** Writing—review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflict of interest.

DATA AVAILABILITY STATEMENT

N/A-Review.

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