REVIEW

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Reunderstanding the classical prescription Banxia Xiexin Decoction: new perspectives from a comprehensive review of clinical research and pharmacological studies



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Abstract

Classical prescriptions of Chinese medicine represent the crystallized wisdom of millennia of clinical practice, enduring as cornerstones of therapeutic intervention due to their demonstrated efficacy across generations. Their evolving role in modern healthcare systems reflects shifting disease patterns, scientific advancements, and global health priorities. Banxia Xiexin Decoction (BXD), formulated by Zhang Zhongjing in the *Treatise on Febrile and Miscellaneous Diseases (Shanghanlun)*, is a time-honored classical prescription renowned for its therapeutic versatility in managing gastrointestinal disorders, both in China and internationally. Recent advancements in clinical research and pharmacological studies on BXD underscore the necessity for a comprehensive bibliometric analysis to summarize and elucidate its specific clinical benefits. Through an extensive literature review of publications from the Web of Science, Pub-Med, Scopus, and the China National Knowledge Infrastructure (CNKI) between 1997 and 2024, 11 major categories of clinical applications for BXD were identified, along with an analysis of the potential pharmacological mechanisms, such as chronic gastritis, functional dyspepsia, and inflammatory bowel disease. We believe this review will provide new insights into the understanding of clinical value of BXD and identify potential future perspectives for its research and development.

Keywords Banxia Xiexin Decoction, Classical prescription, Gastric ulcer, Gastritis, Bibliometric analysis

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Introduction

Classical prescriptions of Chinese medicine are one of the primary carriers that embody the holistic perspective and individualized treatment of traditional Chinese medicine (TCM), which are quintessential aspects of TCM wisdom. Particularly, classical prescriptions exemplified by those formulated by Zhang Zhongjing in the Han Dynasty serve as foundational remedies for treating diseases, and their unique therapeutic effects have been validated over millennia. However, with the increasing precision in medical treatment, the development of classical prescriptions encounters challenges such as difficulties in quality control, unclear



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mechanisms of action, and undefined clinical positioning. Among these, clinical value is the core prerequisite and driving force for the development of classical prescriptions, as well as the guide for whole-process quality control. Therefore, it is necessary to conduct systematic literature review and analysis to identify and analyze the clinical advantages of classical prescriptions, thereby providing precise guidance for their clinical application.

Banxia Xiexin Decoction (BXD), originating from the Treatise on Febrile and Miscellaneous Diseases (Shanghanlun), is primarily used to treat "Xinxiapi," a condition characterized by fullness and tightness in the epigastrium that is soft and non-painful upon pressure. Historical records indicate that BXD has been employed to treat a variety of ailments, with the most common being spleen and stomach system disorders. Its applications extend to hepatobiliary diseases, lung diseases, kidney diseases, heart diseases, brain diseases, exogenous diseases, and surgical conditions, encompassing a wide range of clinical issues. Since the Tang Dynasty (618 A.D.–907 A.D.), BXD has been utilized for treating cholera, dysentery, diarrhea, among other conditions. By the Ming (1368 A.D.-1644 A.D.) and Qing (1616 A.D.-1912 A.D.) Dynasties, the use of BXD reached its zenith in treating ailments such as diarrhea and jaundice, further expanding its therapeutic scope [1]. BXD has also been widely used in Japan as a Kampo medicine, specifically as Hangeshashinto, since the sixteenth century, due to its beneficial effects on gastritis, inflammatory diarrhea, and oral mucositis [2].

With the continuous deepening of the clinical application of BXD, its therapeutic scope has expanded beyond the primary symptoms it was originally designed to address. BXD is now widely used to treat and alleviate a variety of conditions, including gastric ulcers, ulcerative colitis, Helicobacter pylori infection, polycystic ovary syndrome, diabetic gastroparesis, insulin resistance, gastrointestinal cancer, and other diseases [1]. This expansion goes far beyond the original scope of treatment as described in the *Treatise on Febrile Diseases and Miscellaneous Diseases*. The broadened applications of BXD not only enhance its clinical utility but also offer new perspectives for researchers in the utilization of classical prescriptions.

The publication of "Catalogue of Ancient Classical Prescriptions (First Batch)" specifies the composition and usage of BXD, in which BXD consists of 7 herbs with the following dosages: 0.5 *sheng* of Pinelliae Rhizoma (Banxia), 3 *liang* of Scutellariae Radix (Huangqin), 3 *liang* of Zingiberis Rhizoma (Ganjiang), 3 *liang* of Glycyrrhizae Radix et Rhizoma Praeparata cum Melle (Gancao) and Ginseng Radix et Rhizoma (Renshen), 1 *liang* of Coptidis Rhizoma (Huanglian), and 12 counts of Jujubae Fructus (Dazao) in the preparation of the decoction [3].

Recent advancements in clinical research and pharmacological studies on BXD highlight the necessity for a comprehensive bibliometric analysis to summarize and elucidate its specific clinical benefits. To achieve this, this review is designed to first employ bibliometric analysis to summarize the articles in the field of global trends in BXD research and development, encompassing temporal distribution and spatial coordination. Subsequently, based on the screened literature, we categorized current clinical studies into 11 categories according to the practical applications of BXD and analyzed the corresponding pharmacological mechanisms. This approach aims to provide a comprehensive overview of the field, highlight current research hotspots, and suggest future directions for BXD research.

Chemical composition and quality control of BXD

BXD, a prescription comprising 7 Chinese herbal medicines, namely Pinelliae Rhizoma, Coptidis Rhizoma, Scutellariae Radix, Zingiberis Rhizoma, Glycyrrhizae Radix et Rhizoma, Jujubae Fructus, and Ginseng Radix et Rhizoma, exhibits a complex and multifaceted chemical composition. A thorough understanding of the constituents of these medicinal herbs is essential for both the quality control and the elucidation of their pharmacological mechanisms.

Pinelliae Rhizoma, the principal herb of the prescription, is the dried tuber of Pinellia ternata (Thunb.) Breit [4]. It mainly contains organic acids, nucleosides, flavonoids, alkaloids. Organic acids have been identified as the bioactive constituents from *P. ternata* (Thunb.) Breit, and the content is positively correlated with the antitussive effect, such as homogentisic acid (1), protocatechualdehyde (2) and vanillic acid (3) [4]. Alkaloids are generally considered to be the main bioactive ingredients of Pinelliae Rhizoma and exert important pharmacological effects. The ephedrine (4) is the first alkaloid isolated and identified as the active principle of Pinelliae Rhizoma (Fig. 1A) [5]. Coptidis Rhizoma, the dried rhizome of Coptis chinensis Franch., Coptis deltoidei C. Y. Cheng et Hsiao, or Coptis teeta Wall, is primarily characterized by its content of alkaloids, including notable compounds such as berberine (5), jatrorrhizine (6), coptisine (7) and palmatine (8) (Fig. 1B) [6]. Scutellariae Radix is the dried root of Scutellaria baicalensis Georgi, and its flavonoids, especially baicalin (9), baicalein (10), wogonin (11) and oroxylin A (12) (Fig. 1C), are widely recognized as its principal bioactive constituents [7]. Zingiberis Rhizoma, also known as dry ginger, is the dried rhizome of Zingiber officinale Roscoe, commonly used as both a medicinal and dietary additive. A variety of active components have



Fig. 1 Seven Chinese herbal medicines comprising BXD and their representative compounds. Representative active compounds of Pinelliae Rhizoma (**A**), Coptidis Rhizoma (**B**), Scutellariae Radix (**C**), Zingiberis Rhizoma (**D**), Glycyrrhizae Radix et Rhizoma (**E**), Jujubae Fructus (**F**), and Ginseng Radix et Rhizoma (**G**)

been identified in dry ginger, with 4-gingerol (13), 6-gingerol (14), 8-gingerol (15) and 10-gingerol (16) (Fig. 1D) being extensively studied for their medicinal properties [8]. Glycyrrhizae Radix et Rhizoma, commonly known as licorice, is the dry root and rhizome of Glycyrrhiza uralensis Fisch., Glycyrrhiza inflata Bat, or Glycyrrhiza glabra L. It mainly contains flavonoid glycosides, triterpenoid saponins, and phenolic compounds, such as glycyrrhizic acid (17), glycyrrhetinic acid (18) and liquiritin (19) (Fig. 1E) [9]. Jujubae Fructus, commonly referred to as jujube, is the dry ripe fruit of Ziziphus jujuba Mill. The principal biologically active constituents of Jujubae Fructus encompass cyclic adenosine monophosphate, phenolics, flavonoids, triterpenic acids, and polysaccharides, among which oleanolic acid (20), betulinic acid (21) and jujuboside B (22) are notable (Fig. 1F) [10]. Ginseng Radix et Rhizoma, the rhizome and root of Panax ginseng C. A. Meyer, contains a variety of active constituents, including ginsenosides, volatile oils, amino acids, peptides, polysaccharides, nitrogen compounds and polyacetylenes. Among these, ginseng saponins such as ginsenosides Rg₃ (23), Rh₁ (24) and Rh₂ (25) (Fig. 1G), have been identified as the principal and most active constituents [11, 12].

However, considering the chemical reactions that may exist in the decoction process, the chemical constituents of BXD cannot be regarded as a simple superposition of the constituents of the seven Chinese herbal medicines. Combining chemical compositional studies of individual herbs and prescription, the main chemical constituents of BXD were found to be alkaloids, flavonoids, and saponins [13]. The complexity and diversity of the chemical composition of BXD present significant challenges for the quality control of this prescription. As of the latest edition, the Chinese Pharmacopoeia does not provide specific guidelines for the quality control of BXD. However, the Japanese Pharmacopoeia provides detailed specifications for the quality control of BXD (Hangeshashinto). For qualitative analysis, thin-layer chromatography (TLC) is used for the identification of six herbs, including Scutellariae Radix, licorice, processed ginger, ginger, ginseng, and Coptidis Rhizoma. In terms of content limits, baicalin, glycyrrhizic acid, and berberine are used to establish limits for Scutellariae Radix, licorice, and Coptidis Rhizoma. Additionally, specifications for heavy metals, arsenic, loss on drying, and total ash are also included. However, the Japanese Pharmacopoeia does not provide qualitative or quantitative analysis for Pinelliae Rhizoma and jujube [14].

With the rapid development of modern analysis technology, many researchers established qualitative and quantitative detection methods for BXD. 18 active components in BXD are accurately quantitated by a validated UPLC-MS/MS method, including liquiritin, coptisine, jatrorrhizine, scutellarin, berberine, palmatine, isoliquiritin, liquiritigenin, baicalin, wogonoside, ginsenoside Rg₁, ginsenoside Re, isoliquiritigenin, baicalein, wogonin, oroxylin A, glycyrrhizic acid and ginsenoside Rb₁ [13]. By using UPLC/Q-TOF-MS, a total of 74 compounds are detected and characterized in BXD, including flavonoids, triterpenoid saponins, alkaloids and glycosides [15]. In addition, TLC and DESI-MSI are also applied in the quality control and chemical composition study of BXD, as well as 15 batches BXD are used to establish the HPLC-fingerprints [16, 17].

Bibliometric analysis

Bibliometric analysis, introduced by Pritchard in 1969 [18], uses statistical methods to evaluate publication trends, authorship patterns, and research impacts across scientific fields [19]. Tools like CiteSpace and VOSviewer are widely employed for such analyses. CiteSpace identifies emerging research trends and visualizes knowledge domains over time [20, 21], while VOSviewer maps influential journals, authors, and collaborative networks [22]. Both tools will be applied here to analyze evolving trends and emerging directions in BXD research.

Data source, screening and collection

Following PRISMA guidelines, data were retrieved from Web of Science (WoS), PubMed, Scopus, and CNKI, with separate strategies for WOS/PubMed/Scopus and CNKI due to language differences (CNKI contains Chinese articles). For WOS, PubMed, and Scopus, variations of "Banxia Xiexin Decoction" (e.g., "Banxiaxiexintang," "Hangeshashinto," "Banha-sasim-tang") were searched in titles, abstracts, and keywords. Inclusion criteria included English-language publications, high relevance to BXD, sufficient data for analysis, and publications from 1997 (earliest BXD record) to June 2024, with no restrictions on gender, age, or ethnicity. The screening process began with 653 articles, narrowed to 583 after keyword screening, and further reduced to 473, 210, and finally 165 eligible articles (Fig. 2). These 165 articles were exported in "Full record and Cited References" (Plain Text) format for CiteSpace analysis, including titles, authors, abstracts, citations, and publication dates.

To capture the extensive research history of BXD, first documented in the *Treatise on Febrile and Miscellaneous Diseases* (Eastern Han Dynasty), this study also incorporates data from the China National Knowledge Infrastructure (CNKI), the largest Chinese-language academic database covering >99% of Chinese journals [23]. CNKI searches used the terms TI=('Banxiaxiexintang'-'Jia')' (Jiajian'-'Jian') AND TKA=(('Jizhi') OR ('Jili')) to retrieve articles (1997–2024) meeting criteria: (1) Chinese



Fig. 2 Screening process for publications of BXD using CNKI, WoS, PubMed, and Scopus databases

language; (2) focus on BXD's pharmacological mechanisms; (3) sufficient data for analysis. Initial screening identified 399 articles, reduced to 240 eligible entries after excluding non-Chinese publications, reviews, dissertations, and conference papers (Fig. 2). These were formatted for CiteSpace to analyze BXD's research dynamics comprehensively.

Data visualization and data analysis

We further employed CiteSpace (v6.3.R1) and VOSviewer for bibliometric analysis to map research trends and collaborations in BXD studies. CiteSpace,

configured with a 1997–2024 timeframe, annual time slices, and node types (country/institution/keywords), identifies research hotspots and emerging themes through co-authorship, co-citation, and co-occurrence analyses [24]. These metrics reveal collaborative networks (authors/countries/institutions), conceptual linkages (keyword clusters), and intellectual influences (cited references). VOSviewer complements this by visualizing knowledge domain structures and collaboration density [25]. Using 405 screened publications, temporal trends were assessed via annual publication counts and keyword evolution, while spatial

cooperation networks highlighted global and institutional collaboration patterns.

Time distribution and keyword clusters

The chronological analysis of BXD-related publications reveals distinct patterns across international and Chinese databases. In international databases (WoS, PubMed, Scopus), the earliest study on BXD was published in 1998, followed by sporadic outputs until 2013, after which annual publications demonstrated sustained growth (Fig. 3A). Notably, temporary declines occurred in 2015 and 2022, but a significant surge began in 2014, with publication numbers tripling compared to the previous year. Subsequent growth rates remained robust, peaking at 333.3% in 2023. In contrast, the CNKI database documented an earlier inception of BXD research, with the first publication in 1997. However, outputs remained limited (35 cumulative articles) until 2013, after which Chinese scholars exhibited accelerated interest, producing 205 publications by 2024, including over 20 annual publications in the past 5 years. Cross-database comparisons highlight that Chinese researchers initiated BXD studies earlier (1997 vs. 1998), yet sustained growth in international databases lagged, commencing in 2017 compared to CNKI's 2013 trajectory.

Keyword burst analysis underscores thematic shifts in BXD research. International databases exhibited early emphasis on phytochemical compounds such as "baicalin" and "berberine" (2006–2014), followed by a transition to clinical and methodological topics like "mucositis," "double blind," and "Western blotting" (2015-2017). Post-2020, emerging hotspots included "network pharmacology," "apoptosis," and "chronic atrophic gastritis," while "rats" persisted as a consistent keyword since 1998 (Fig. 3B). In CNKI, long-term foci such as "experimental research," "prescription decomposition," and "gastritis" dominated for over a decade. Recent trends (2020–2024) shifted toward mechanistic explorations, including "gastric cancer," "gut flora," and "molecular docking" (Fig. 3C). Strikingly, only "network pharmacology" and "gastritis" overlapped as shared burst keywords between CNKI and international databases, reflecting divergent regional priorities.

It is obvious that CNKI demonstrates a significant advantage in publication volume (240 articles versus 165 international publications), but its lower keyword burst intensity indicates a narrower thematic focus, predominantly on pharmacological studies. This contrasts with the broader thematic diversity observed in global research. Meanwhile, distinct regional disparities in research priorities are apparent: Chinese scholarship emphasizes experimental and mechanistic investigations, as evidenced by high-frequency keywords such as "gut flora" and "molecular docking," whereas international studies prioritize clinical methodologies (e.g., "double blind") and cross-cultural applications. Moreover, non-Chinese regions exhibit a predominant focus on non-clinical BXD research, revealing a critical deficit in clinical validation efforts. Collectively, these findings underscore the imperative for a strategic integration of regional expertise to bridge methodological and translational gaps, thereby enhancing both mechanistic rigor and the clinical applicability of BXD research.

Country network and co-occurrence analysis

The country and institutional collaboration networks (Fig. 4A) reveal a fragmented global research landscape for BXD. China dominates with 95 screened publications (57.57% of total) from WoS, PubMed, and Scopus—exclusive of CNKI data. Japan and South Korea follow with 50 and 16 publications, respectively. Despite this output disparity, all three countries exhibit isolated nodes with minimal interconnections, reflecting limited international collaboration.

Author co-occurrence analysis (Fig. 4B) further highlights sparse domestic collaboration, particularly in China. Despite China's publication dominance, institutional cooperation within the country remains underdeveloped: only three Chinese authors met the cooccurrence threshold (\geq 10 collaborations), compared to 24 in Japan. Lowering the threshold revealed more Chinese authors but underscored weaker collaborative networks relative to Japan.

Analysis of 165 screened publications identified three distinct author clusters corresponding to China, Japan, and South Korea. These clusters show negligible crossborder linkages, reinforcing the lack of global synergy. Notably, Japan's robust intra-cluster collaboration contrasts sharply with China's fragmented institutional networks, suggesting divergent research cultures in BXD studies.

Co-citation analysis

To map the intellectual foundations of BXD research, we performed a co-citation analysis of 3267 cited references. By applying a citation threshold of \geq 14 citations per reference to ensure analytical precision, 14 highly cited references were identified and categorized into two thematic clusters (Fig. 5A).

The first cluster centers on BXD's therapeutic applications for gastrointestinal diseases, particularly gastritis and chronic ulcerative colitis. A series of studies by Kase (1997–2004) established the foundational role of Hangeshashinto (TJ-14, a BXD formulation) in accelerating intestinal healing and mitigating chemotherapyinduced gastrointestinal toxicity [26–31]. These findings



Fig. 3 A Annual number of BXD-related publications retrieved from CNKI, WoS, PubMed, and Scopus; B keywords with the strongest citation burst among BXD-related publications indexed in WoS, PubMed, and Scopus; C keywords with the strongest citation burst among BXD-related publications indexed in CNKI.



Fig. 4 Country network and co-occurrence analysis of BXD studies in WoS, PubMed, and Scopus. A Global research landscape for BXD. B Author co-occurrence analysis of BXD

were further corroborated by Chen et al. who demonstrated BXD's anti-inflammatory and antioxidant effects in alleviating experimental colitis [32]. Recent work by Cao et al. [33] reinforced BXD's clinical superiority over combined traditional and Western therapies, while Wang et al. [34] expanded its potential by exploring the material basis of BXD's efficacy in gastrointestinal disorders.

Cluster 2 highlights BXD's clinical utility in managing oral mucositis. Early research by Kono revealed the effectiveness of topical TJ-14 application in chemotherapy-induced oral mucositis (COM) management [35], a discovery later refined through multicomponent analyses of its PGE2-regulating properties [36]. Clinical trials by Aoyama [37] and Matsuda et al. [38] provided robust evidence for TJ-14's preventive effects in gastric and head/neck cancer patients, respectively, with Yamashita [39] further validating its capacity to reduce mucositis severity during chemoradiation.

Notably, the most frequently cited references—Matsuda et al. (2015, 61 citations) [38], Kono et al. (2014, 58 citations) [36], and Kase et al. (1998, 44 citations) [28] span both clusters, reflecting their dual contributions to mechanistic and clinical research (Fig. 5B). Collectively, these findings illustrate a bifurcation in BXD scholarship: one strand advances mechanistic understanding of gastrointestinal therapies, while the other prioritizes clinical validation for oral mucositis. This dichotomy underscores the need for interdisciplinary collaboration to bridge



Fig. 5 A Clusters of number of cited references. B Clusters of number of most cited authors

preclinical insights with translational applications, ultimately enhancing BXD's therapeutic potential.

Function classification of BXD and pharmacological mechanism

To further focus on the analysis of the clinical efficacy of BXD, a systematic review of clinical studies was conducted. The search and screening process, executed in September 2024, adhered to predefined inclusion/exclusion criteria. Studies employing BXD as an adjuvant therapy or lacking explicit documentation of its primary clinical application were excluded. This yielded 121 eligible articles from CNKI (Fig. 6) and 25 articles from international databases (Web of Science, PubMed, Scopus) (Fig. 7). Data extraction followed a standardized protocol to ensure methodological consistency. Key parameters included study title, objectives, trial design, duration, sample size, patient demographics, functional classification, formulation specifications (prescription details), treatment protocols (administration route, dosage), and clinical outcomes (efficacy, adverse effects, and effect size). Discrepancies in data interpretation were resolved through iterative consensus—building discussions among the research team.

All BXD—related clinical studies were categorized according to 11 clinical indications, including gastritis, functional dyspepsia, diabetes, reflux disease, tumor—associated conditions, and oral mucositis (Fig. 8). Evidently, digestive tract disorders such as gastritis represent the domains with the highest concentration of BXD clinical research. Subsequently, we conducted a more indepth analysis of the efficacy and underlying mechanisms of BXD across these 11 clinical classifications.

Gastritis

Gastritis, defined as inflammation of the gastric mucosa, arises from a variety of etiologic factors, including *Helicobacter pylori* infection, nonsteroidal anti-inflammatory drug (NSAID) use, alcohol consumption, chronic stress, and autoimmune disorders [40]. Among these, gastritis is the most common clinical indication for Banxia Xiexin Decoction (BXD), which has demonstrated therapeutic efficacy across multiple subtypes of this condition.

BXD demonstrates robust clinical efficacy in the staged, comprehensive treatment of refractory Helicobacter



Fig. 6 Screening process of the clinical application publications of BXD from CNKI

pylori infection (RHPI), thereby significantly enhancing patient compliance through targeted therapeutic action [41]. Mechanistic studies reveal BXD's potent inhibitory effects on *H. pylori* proliferation, underpinning its high efficacy in treating *H. pylori*-positive gastritis [42–46]. Clinical trials further corroborate BXD's anti-inflammatory properties, evidenced by its ability to markedly reduce serum levels of hs-CRP and IL-6 in patients with *H. pylori*-associated gastritis [47, 48].

BXD also exhibits multifaceted benefits in chronic atrophic gastritis (CAG) management (Supplementary Table 2). Clinical observations indicate that BXD alleviates core symptoms, mitigates gastric mucosal inflammation, and promotes mucosal repair through mechanisms including increased gastric gland proliferation and partial reversal of precancerous lesions [49–51]. Notably, BXD enhances biochemical markers of gastric function (e.g., G-17, PGI, PGII) and elevates *H. pylori* clearance rates, thereby reducing nausea, vomiting, and other symptomatic burdens [52–63].

Beyond pathogen-targeted therapy, BXD demonstrates broad utility in ameliorating chronic superficial gastritis (CSG), a condition characterized by plasma cell and lymphocyte infiltration of the gastric mucosa [64]. Randomized trials have confirmed that BXD effectively alleviated dyspeptic symptoms—such as acid reflux, epigastric pain, and belching—thereby warranting further largescale clinical validation [65, 66]. However, while existing evidence underscores BXD's therapeutic versatility, critical gaps persist. Current studies remain inconclusive regarding BXD's capacity to mitigate adverse effects associated with sulfasalazine therapy [67], highlighting the need for mechanistic investigations into drug-herb interactions.

Emerging evidence elucidates the therapeutic mechanisms of BXD in managing drug-resistant *H. pylori*associated gastritis (MIC=256–512 μ g/mL). BXD exerts multimodal action through immune activation, bactericidal enhancement, suppression of pathogen colonization, and attenuation of gastric mucosal inflammatory



Fig. 7 Screening process of the clinical application publications of BXD from WoS, PubMed and Scopus

damage [68]. Additionally, preclinical studies in ethanolinduced gastritis models have shown that intragastric administration of BXD significantly ameliorates chronic gastric injury in rats, accompanied by reductions in proinflammatory mediators (TNF- α , IL-2, IL-8) and lactate dehydrogenase (LDH) levels [69].

The therapeutic potency of BXD is further underpinned by the synergistic activities of its component herbs. For example, extracts of Rhizoma Coptidis have been shown to modulate multiple inflammation-associated targets in *N*-methyl-*N*'-nitro-*N*-nitrosoguanidine (MNNG)-induced CAG murine models [70], at the molecular level, bioactive compounds within BXD contribute to its anti-gastritis effects. Specifically, ginsenoside Rg1 alleviates CAG by suppressing pyroptosis via the NF- κ B/NLRP3/GSDMD signaling pathway [71], and palmatine mitigates MNNG-induced CAG through STAT1/CXCL10 pathway regulation [72].

Peptic ulcer

Peptic ulcer, an acid-peptic disorder, involves the erosion of the protective mucosal barrier in the stomach, proximal duodenum, or esophagus [73, 74]. BXD demonstrates significant therapeutic efficacy and favorable safety in the treatment of peptic ulcers [75–82]. BXD mitigates mucosal injury by reducing gastrin and motilin



Fig. 8 Classification of clinical application of BXD

release, thereby alleviating local hypoperfusion and accelerating inflammatory resolution to promote ulcer healing [83]. Meanwhile, BXD can improve sleep quality in patients with peptic ulcers, addressing a common comorbidity of the condition [84].

Mechanically, BXD enhances gastric lymphatic pumping, alleviating the accumulation of inflammatory mediators and metabolic waste in the stomach, a critical mechanism in resolving stress-induced gastric ulceration [85]. BXD modulates the TGF- β /Smad signaling pathway by suppressing transforming growth factor-beta 1 (TGF- β 1) and Smad3 expression while upregulating Smad7 in peptic ulcer patients [86]. Additionally, BXD inhibits excessive apoptosis of gastric mucosal epithelial cells by upregulating Bcl-2 mRNA expression and downregulating the apoptotic executor Caspase-3, thereby preserving mucosal integrity and mitigating injury [87]. BXD further reduces gastric inflammation by lowering levels of proinflammatory cytokines, including interleukin (IL)-2, IL-8, and tumor necrosis factor-alpha (TNF- α), in preclinical ulcer models [88].

Functional dyspepsia (FD)

Functional dyspepsia (FD) is a chronic gastrointestinal disorder characterized by persistent dyspeptic symptoms in the absence of identifiable organic, systemic, or metabolic pathology [89]. BXD has demonstrated significant clinical efficacy in FD management. Specifically, it can elevate the fasting plasma motilin levels in patients, with an overall efficacy comparable to that of metoclopramide [90–95]. It may surpass conventional treatments in alleviating clinical symptoms such as epigastric pain and

postprandial discomfort [96]. BXD is particularly effective in vulnerable populations, including the elderly and pediatric patients, where it ameliorates FD symptoms in individuals with compromised digestive function [97, 98]. Furthermore, BXD exhibits therapeutic benefits in nonulcer dyspepsia (NUD), underscoring its broad applicability in functional gastrointestinal disorders [99].

Korean scholars have also expanded the evidence base for BXD (termed Banha-sasim-tang or BST) for the treatment of FD since 2010. A 2021 study by Sul-Ki Kim et al. identified plasma ghrelin modulation as a key mechanism underlying BST's efficacy [100], with additional clinical trials corroborating its potential to improve FD symptoms [101–104].

Preclinical studies in FD rat models have elucidated BXD's multifaceted mechanisms. BXD enhances gastric emptying and small intestinal propulsion rates, likely mediated by increased gastric mucin and substance P levels, alongside reduced gastrointestinal sensitivity [105, 106]. It also restores gut microbiota homeostasis by promoting probiotic proliferation, suppressing pathogenic bacteria, and preserving the colonic mucosal immune barrier post-microbiota disruption [107, 108]. Additionally, BXD modifies the ultrastructure of interstitial cells of Cajal (ICCs), critical regulators of gastrointestinal motility, further explaining its therapeutic impact on FD [109]. Recent research employing high-resolution mass spectrometer analysis in conjunction with multiple databases and molecular docking techniques, identified a total of 11 active compounds in BXD, especially berberine, could activate TAS2R38 and contributed to the amelioration of inflammation in the duodenum of FD mice [110]. Furthermore, certain constituent herbs or active compounds within BXD have also demonstrated therapeutic efficacy in the treatment of FD, with ginger serving as a notable example [111]. These findings collectively position BXD as a holistic intervention addressing both symptom relief and underlying pathophysiology in FD.

Diabetes

Although BXD is extensively employed in glycemic management, it exhibits significant potential in attenuating diabetes-induced multi-organ damage. Clinical studies highlight its efficacy in addressing diabetic gastroparesis (DGP), a condition characterized by delayed gastric emptying. BXD alleviates DGP symptoms, including nausea, vomiting, abdominal distension, and early satiety, by enhancing gastric motility, shortening gastric emptying time, and modulating gastrointestinal hormone and inflammatory factor levels [112–116]. Furthermore, BXD improves metabolic parameters in diabetic non-alcoholic fatty liver disease (NAFLD), significantly reducing blood glucose, lipid levels, and hepatic dysfunction markers [117–119]. Comparative studies in type 2 diabetes management reveal that BXD, when integrated into treatment regimens, achieves superior clinical outcomes compared to conventional pharmacotherapy alone, underscoring its adjunctive therapeutic value [120].

Preclinical studies have also demonstrated the therapeutic potential and mechanism of BXD in addressing diabetes-related conditions. In diabetic mouse models, BXD significantly improved glucose and lipid metabolism while promoting insulin secretion [121]. In diabetic gastroparesis (DGP) models, BXD enhanced blood glucose regulation and accelerated gastric emptying. Mechanistically, these effects were attributed to the inhibition of advanced glycation end products (AGEs) production and receptor for AGE (RAGE) expression, coupled with the upregulation of neuronal nitric oxide synthase (nNOS). This modulation facilitated the proliferation of ICCs and ICC stem cells (ICC-SCs), thereby improving gastric motility [122]. In type 2 diabetes mellitus (T2DM) rat models, BXD regulated blood glucose homeostasis by altering serum bile acid metabolism profiles, upregulating farnesoid X receptor (FXR) expression, and modulating the secretion of serum and pancreatic glucagon-like peptide-1 (GLP-1) [123]. Additionally, BXD exhibited protective effects in pre-diabetes rats induced by 3-deoxyglucosone (3DG). Its mechanisms included reducing protein carbonylation levels, reactive oxygen species (ROS) levels, and inflammatory factor concentrations in the colon and serum [124]. Furthermore, BXD's therapeutic efficacy in prediabetes was linked to its ability to modulate gut microbiota composition [125].

Reflux disease

BXD demonstrates therapeutic efficacy in the management of several reflux-related disorders, including reflux esophagitis (RE), reflux gastritis, and gastroesophageal reflux disease (GERD). RE, a prevalent clinical gastrointestinal condition, remains incompletely understood in terms of pathogenesis [126, 127]. BXD alleviates RE symptoms such as epigastric pain, acid reflux, and gastric discomfort by promoting gastric emptying, reducing reflux stimulation, protecting the gastric mucosa, modulating gastric acid secretion, and enhancing gastrointestinal motility [128, 129]. Similarly, BXD exhibits clinical utility in GERD, a syndrome characterized by retrograde flow of gastrointestinal contents into the esophagus, manifesting as heartburn and acid regurgitation. Studies report that modified BXD formulations significantly improve GERD symptoms, including gastroesophageal reflux cough, with robust therapeutic outcomes [130-134]. Furthermore, BXD shows marked efficacy in treating reflux gastritis, underscoring its broad applicability in reflux disorders [135, 136]. Notably, complementary therapies such as Hangeshashinto may benefit patients with proton-pump inhibitor (PPI)-refractory GERD, particularly non-obese, non-elderly individuals with dyspepsia [137].

Mechanistic studies in a rat model of RE revealed that BXD reduces gastric acid secretion, regulates calcitonin gene-related peptide (CGRP) synthesis [138], protects esophageal mucosal integrity, and modulates neurotensin synthesis and secretion [139]. These findings highlight BXD's multifaceted mechanisms in mitigating reflux pathology, combining mucosal protection, neuromodulation, and acid suppression to restore gastrointestinal homeostasis. Meanwhile, the active compounds present in BXD have also demonstrated notable bioactivity in the context of reflux disease. For instance, berberine has been shown to inhibit the production of pro-inflammatory cytokines in a rat model of GERD [140].

Inflammatory bowel disease (IBD)

Inflammatory bowel disease (IBD) is a general term for chronic or remitting/relapsing inflammatory diseases of the intestinal tract and generally refers to ulcerative colitis (UC) and Crohn's disease (CD) [141]. Due to the complex etiology of inflammatory bowel disease (IBD) and the limitations of current treatment options, Banxia Xiexin Decoction (BXD) has demonstrated unique advantages in the management of IBD [142, 143]. A meta-analysis incorporating 10 randomized controlled trials (RCTs) involving 768 patients revealed that BXD exhibited significantly higher efficacy (P<0.00001) and reduced serum TNF- α levels (P=0.001) compared to control groups. However, no significant difference was observed in the incidence of adverse reactions (P = 0.23) [144]. Clinical observations have indicated that the therapeutic efficacy of BXD in the treatment of UC is, at least in part, contingent upon its regulatory influence on the intestinal microbiota of patients [145].

Numerous studies have elucidated the mechanisms by which BXD exerts its therapeutic effects on UC, highlighting its multifaceted actions, including immune regulation, anti-inflammatory activity, intestinal barrier repair, oxidative stress reduction, and tissue repair through stem cell mobilization. BXD has been shown to promote ulcer healing by modulating immune cell balance. In dextran sulfate sodium (DSS)-induced UC mouse models, BXD restored the equilibrium between Th17/ Treg [146] and Th1/Th2 immune cells [147], thereby suppressing excessive immune responses. Additionally, BXD exerts anti-inflammatory effects by regulating the levels of pro-inflammatory factors and anti-inflammatory factors, modulating the relevant signaling pathways, and attenuating the inflammatory damage [148-152]. In trinitrobenzene sulfonic acid (TNBS)-induced UC mouse models, BXD elevated the expression of ZO-1 and occludin in the colon, reduced intestinal mucosal permeability, and decreased d-lactic acid levels, indicating its role in maintaining colonic mucosal tight junction integrity and repairing the damaged intestinal mucosal barrier [153]. Furthermore, BXD attenuates oxidative stress by restoring superoxide dismutase (SOD) activity and intervening in the Nrf2 signaling pathway in DSS-induced UC mouse models [32]. Furthermore, BXD facilitated the homing of mesenchymal stem cells (MSCs) to the colonic mucosa, promoting tissue repair and improving the histopathological condition of the colon in TNBS-induced UC rat models [154].

Irritable bowel syndrome (IBS)

Irritable bowel syndrome (IBS) is a functional gastrointestinal disorder characterized by abdominal pain or discomfort, accompanied by alterations in bowel habits. Currently, effective treatment options for IBS remain limited [155]. Several clinical studies have demonstrated the potential of BXD in alleviating abdominal pain, discomfort, and diarrhea associated with IBS [156–159]. In a prospective, randomized, controlled trial, although a 4-week treatment with BXD did not show a statistically significant difference compared to the control group in patients with diarrhea-predominant IBS (D-IBS), it significantly modulated ghrelin secretion, which may contribute to improved gastrointestinal function [156]. Another study reported that a modified BXD formulation achieved an overall effectiveness rate of 93.3% in treating D-IBS, significantly higher than the 75.0% observed in the control group [157].

Through a systems pharmacology approach, researchers identified 36 active compounds in BXD, including wogonin, glycyrrhetinic acid, berberine, and ginsenoside Rh4. The study revealed that the cross-talk interactions among the TNF signaling pathway, dopaminergic synapse, and cGMP-PKG signaling pathway may synergistically influence the pathogenesis and treatment of IBS [160]. Additionally, numerous studies have highlighted the therapeutic potential of individual active compounds derived from BXD for IBS management, such as berberine [161], Coptisine [162], and 6-Shogaol [163]. These findings underscore the multifaceted mechanisms through which BXD and its components may exert beneficial effects in IBS treatment.

Oral mucositis

Oral mucositis is a frequent and clinically significant side effect in cancer patients undergoing chemotherapy or radiation therapy. Japanese researchers have widely investigated the therapeutic effect of Hangeshashinto (TJ-14) on COM. Among the seven selected clinical trials evaluating the treatment of oral mucositis, all relevant studies originated Japan. The earliest clinical study, conducted in 2013, involved a double-blind trial of 91 patients who received either Hangeshashinto or placebo for 2 to 6 weeks [37]. The results indicated that while Hangeshashinto treatment did not significantly reduce the incidence of ≥ 2 COM in patients developing mucositis during gastric cancer chemotherapy, it tends to lower the risk of COM in patients with grade 1 COM during the screening cycle. The study pointed out that follow-up phase III studies with larger sample sizes are necessary to elucidate the protective effect of Hangeshashinto on COM. A 2014 study involving 80 patients demonstrated that Hangeshashinto was effective in ameliorating oral mucositis induced by radiation therapy in patients with head and neck cancer. Hangeshashinto was associated with improved completion rates of cisplatinbased chemoradiotherapy [39]. Other studies have shown that, although the incidence of grade ≥ 2 oral mucositis was lower in patients treated with Hangeshashinto compared to those receiving a placebo, the difference was not statistically significant [38, 164, 165]. However, Hangeshashinto showed significant efficacy compared with placebo in the treatment of grade ≥ 2 mucositis in patients with colorectal cancer. Studies also suggest that Hangeshashinto cannot prevent the occurrence of COM [166], but it can reduce its severity [167]. Another preliminary study showed that the combination of Hangeshashinto and cryotherapy may be effective in treating radiation induced oral stomatitis [168].

Despite the widespread reporting of Hangeshashinto's effectiveness in managing oral mucositis, the underlying mechanisms of action remain to be fully elucidated. Some studies explored the ingredient-specific pharmacological actions of Hangeshashinto. For instance, 6-gingerol and 6-shogaol, two bioactive compounds derived from Hangeshashinto, have been shown to alleviate pain associated with oral ulcerative mucositis through modulation of Na⁺ channels [169]. A randomized clinical trial demonstrated that a licorice-based mucoadhesive film, containing herb of Hangeshashinto, significantly reduced pain severity and mitigated the progression of radiationinduced mucositis [170].

Tumor-related conditions

BXD has demonstrated significant potential as a widely applicable adjuvant therapy in cancer treatment. Clinically, it effectively addresses gastric precancerous lesions and liver-spleen disharmony following colorectal cancer surgery. Studies have shown that BXD reduces serum carcinoembryonic antigen (CEA) levels, accelerates postoperative recovery, and alleviates surgical complications [171, 172]. Additionally, Hangeshashinto has been shown to reduce the risk of afatinib-induced diarrhea, a common adverse effect in cancer therapy [173], and effectively mitigates chemotherapy-related gastrointestinal symptoms, such as nausea and vomiting, in patients with digestive tract tumors [174]. Furthermore, BXD exhibits broad-spectrum anti-tumor activity, showing therapeutic benefits in colon cancer and hepatocellular carcinoma (HCC) [175, 176]. When combined with chemotherapy, modified BXD formulations not only alleviate chemotherapy-induced clinical symptoms but also significantly prolong disease-free survival (DFS) in patients with stage III colon cancer [177], gastric cancer (GC) [178], and duodenal cancer [179].

BXD exhibits multifaceted anti-tumor effects across various cancer models, including inhibition of tumor growth, suppression of invasion, delay of cancer progression, and modulation of drug sensitivity through the regulation of multiple cancer-related signaling pathways. In GC models, BXD significantly inhibits tumor growth and delays disease progression, potentially mediated by the regulation of the PI3K-Akt signaling pathway [180]. Similarly, in colitis-associated cancer (CAC) models, BXD impedes the colitis-to-cancer transition by suppressing the E-cadherin/β-catenin pathway, particularly through inhibition of Fusobacterium nucleatum FadA activity [181]. BXD also enhances drug sensitivity in gastric cancer cells by regulating MGMT expression through the IL-6/JAK/STAT3-mediated PD-L1 signaling axis [182]. This mechanism underscores BXD's potential to overcome chemoresistance and improve therapeutic outcomes.

Polycystic ovary syndrome (PCOS)

Polycystic ovary syndrome (PCOS) is a prevalent endocrine and metabolic disorder affecting women of reproductive age, characterized by oligo-anovulation, hyperandrogenism, polycystic ovarian morphology, and metabolic dysregulation, including abdominal obesity and insulin resistance (IR) [183]. Emerging clinical evidence suggests that modified BXD demonstrates therapeutic efficacy in ameliorating insulin sensitivity and restoring reproductive endocrine balance in patients with PCOS-associated IR (PCOS-IR). These improvements correlate with enhanced clinical outcomes, such as restoration of spontaneous menstruation, elevated pregnancy rates, and metabolic normalization, potentially mediated through IR correction and endocrine stabilization [184]. In PCOS patients with hyperinsulinemia (PCOS-HI) presenting with traditional Chinese medicine (TCM) syndromes of stomach heat and spleen deficiency, BXD exhibits comparable efficacy to metformin in reducing fasting insulin (FINS) levels and enhancing insulin sensitivity. Notably, modified BXD surpasses metformin in restoring spontaneous ovulation rates and alleviating oligomenorrhea, effects attributed to its capacity to modulate FINS levels [185, 186].

Mechanistic studies indicate that BXD may restore sex hormone equilibrium in PCOS by modulating gut microbiota composition, including enrichment of beneficial taxa, suppression of pathogenic species, and reestablishment of intestinal microecological homeostasis [187]. Preclinical studies utilizing a letrozole and high-fat dietinduced PCOS-IR rat model further demonstrate that modified BXD formulations attenuate IR and metabolic dysfunction via gut microbiota regulation [188, 189]. Additionally, modified BXD improves IR and endocrine parameters in PCOS-IR rats, potentially through activation of the PI3K/Akt/GLUT4 signaling pathway [190]. Another recent study highlights BXD's role in suppressing ovarian granulosa cell proliferation and inflammation in PCOS models by upregulating miR-20b-5p and inhibiting the TLR4/IL-6 axis [191].

Meanwhile, emerging evidence highlights the pharmacological efficacy of bioactive constituents in BXD PCOS intervention. Notably, berberine, a key alkaloid of BXD, ameliorates PCOS-associated inflammation through downregulation of hyaluronan synthase 2 (HAS2) [192], while concurrently enhancing ovulation rates and endometrial receptivity [193]. Similarly, 6-gingerol, a primary bioactive phytochemical in ginger, exhibits therapeutic promise in PCOS models. In estradiol valerate-induced PCOS rats, 6-gingerol attenuates pathological increases in body weight, ovarian hypertrophy, and sex steroid dysregulation. These effects correlate with suppression of cyclooxygenase-2 (COX-2) expression, suggesting a mechanism involving modulation of inflammatory pathways [194].

Other conditions

In addition to its well-documented efficacy in the 10 primary disease classifications, BXD has demonstrated therapeutic potential across a broad spectrum of clinical conditions. These include diarrhea, ventricular premature beats, sleep disorders, chronic gastric issues, respiratory-related pneumonia, chronic subjective dizziness, impaired fasting blood sugar, and chronic cough.

BXD has been shown to prevent and control irinotecan (CPT-11)-induced delayed diarrhea, with its efficacy validated in clinical studies [195]. Additionally, Hangeshashinto is effective in managing acute radiation-induced enteritis (ARE) [196]. BXD could also alleviate postprandial distress syndrome (PDS) [197] and reduces the incidence and severity of postoperative sore throat in patients undergoing laparoscopic surgery [198]. Furthermore, given the role of *H. pylori* in halitosis, BXD has shown significant efficacy in treating *H. pylori*-related halitosis [199].

Preclinical studies suggest that BXD may have therapeutic potential for migraine, as it reduces plasma levels of neuropeptides [e.g., calcitonin gene-related peptide (CGRP) and substance P (SP)], increases endothelin (ET) levels, and downregulates earlyresponse genes (e.g., C-FOS and C-JUN) in experimental migraine models [200]. These findings provide a promising research direction for BXD's clinical application in migraine management (Fig. 9).



Fig. 9 Clinical application of BXD and related mechanism

Discussion and perspectives

Since September 2020, the National Medical Products Administration of China has implemented new registration categories for TCM, categorizing classical prescription preparations as one of the four types of new drugs. This initiative has significantly spurred the development of classical prescriptions. To date, over a dozen classical prescription preparations, such as Linggui Zhugan Decoction, have received approval for marketing. However, since most classical prescriptions are formulated to address specific TCM syndromes, their expression in TCM terminology may encounter substantial challenges in clinical application and market promotion, hindering the full realization of their clinical value. Consequently, clarifying clinical indications and accurately reflecting applicable diseases in drug labeling are critical and unavoidable issues for classical prescription products.

Over the past 25 years, the enthusiasm for the research and development of BXD has continued to grow, and literature reviews have provided valuable insights into evolving research trends. China, Japan, and South Korea are the leading countries in advancing BXD research. Notably, while Japanese scholars initially published a higher number of papers, by 2018, the number of publications from China had surpassed that of Japan, positioning China as the most prolific contributor in this field. The most productive research institutions are primarily located in Japan and China. However, the citation counts for Chinese researchers still lag behind those of their Japanese counterparts, suggesting that the quality and impact of their research need further enhancement. We propose that with the accelerated development of BXD R&D and increased international and institutional collaborations, the research network will become increasingly complex and interconnected. However, we believe that the development of BXD should still prioritize the following aspects.

The stability and reliability of quality are fundamental prerequisites for the clinical efficacy of classical prescription preparations. Ensuring every detail, including the quality of herbs, decoction pieces, and manufacturing processes, is essential for maintaining the stability and reliability of these preparations. This meticulous attention to detail is both critical and an inevitable requirement for ensuring their quality. For example, He's study emphasized the impact of decoction methods on the chemical composition and pharmacological activity of BXD [201]. Simultaneously, the clear delineation of critical quality attributes is indispensable for attaining cohesive control across various stages, thus guaranteeing comprehensive quality control throughout the entire process. However, given the complex composition of BXD, the quality control marker for Pinelliae Rhizoma and jujube remain undefined. Consequently, advanced analytical techniques are required to perform in-depth characterization of their constituents and establish correlations with relevant biological activities, thereby identifying critical quality attributes. It is imperative to underscore that the enhancement of quality is inherently linked to increased manufacturing expenses, which further demands that the product possess significant clinical and market value [202].

In the context of clinical research, significant challenges arise from inconsistencies in BXD dosing and administration protocols, as well as the variable quality of studies, which hinder the comprehensive analysis and synthesis of BXD's clinical benefits. For example, as per the key information of BXD issued by the National Medical Products Administration and the National Administration of Traditional Chinese Medicine of China, BXD comprises seven herbal ingredients, with the cumulative dosage amounting to 83.3 g. Conversely, within the Japanese Pharmacopoeia, there are three distinct prescriptions for BXD (Hangeshashinto). These are categorized into versions containing either processed ginger or ginger, and the dosages specified therein are significantly lower than those in the officially published Chinese version, which range from 18.5 to 22 g. Moreover, in the Japanese Pharmacopoeia, both Pinelliae Rhizoma and Glycyrrhizae Radix et Rhizoma are presented in their unprocessed forms. The disparities in prescriptions and dosages pose challenges in directly comparing and evaluating the clinical efficacy of BXD. Consequently, future research endeavors should focus on conducting systematic investigations into the dose-response relationships of BXD preparations for various diseases. This approach will facilitate a more comprehensive understanding of the optimal utilization of BXD in clinical practice.

BXD has exhibited promising therapeutic efficacy in the management of various gastrointestinal disorders, including gastritis, IBD, and FD. Our findings indicate that the majority of clinical investigations on BXD have predominantly centered on these conditions. Simultaneously, recent studies have revealed that BXD demonstrates unique therapeutic potential in other clinical domains. For instance, since 2020, research exploring the application of BXD in PCOS and peptic ulcers has emerged, marking a notable shift as prior to this period, BXD was scarcely utilized in these areas. Furthermore, BXD has been shown to possess distinct therapeutic properties in the treatment of oral mucositis, as evidenced by multiple clinical studies. However, current research on BXD in this context has largely focused on mucositis induced by chemotherapy or radiotherapy, with conventional forms of mucositis remaining underexplored. We propose that this represents a promising avenue for future research and development.

Simultaneously, given that BXD is frequently employed in the management of chronic gastrointestinal disorders, including chronic gastritis and IBD, and considering that Pinelliae Rhizoma, an ingredient in BXD, exhibits mild toxicity, the safety profile of BXD emerges as a critical aspect that demands due attention. Generally speaking, BXD is widely recognized for its safety, and clinical studies have not reported any substantial adverse effects. Nevertheless, in the absence of a comprehensive and systematic assessment of its toxicity, long-term and indiscriminate use of BXD is not advisable. In subsequent research, it is imperative to conduct high-quality randomized controlled clinical trials following rigorous scientific protocols. These trials will play an indispensable role in generating more reliable and conclusive evidence to support the clinical application of BXD.

Supplementary Information

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Supplementary Material 1

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Author contributions

CL, PG and XL drafted and revised the manuscript; MK, HX, and YW performed data analysis. WL and SW conceived and designed the review, and revised the manuscript; all authors read and approved the final manuscript.

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Data availability

The study's original data can be obtained from the corresponding authors upon reasonable request.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that there are no competing interests.

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