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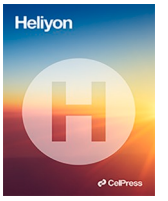

Review article

Review on effects and mechanisms of plant-derived natural products against breast cancer bone metastasis

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ABSTRACT

Bone metastasis is the prevalent form of metastasis in breast cancer, resulting in severe pain, pathological fractures, nerve compression, hypercalcemia, and other complications that significantly impair patients' quality of life. The infiltration and colonization of breast cancer (BC) cells in bone tissue disrupt the delicate balance between osteoblasts and osteoclasts within the bone microenvironment, initiating a vicious cycle of bone metastasis. Once bone metastasis occurs, conventional medical therapy with bone-modifying agents is commonly used to alleviate bone-related complications and improve patients' quality of life. However, the utilization of bone-modifying agents may cause severe drug-related adverse effects. Plant-derived natural products such as terpenoids, alkaloids, coumarins, and phenols have anti-tumor, anti-inflammatory, and anti-angiogenic pharmacological properties with minimal side effects. Certain natural products that exhibit both anti-breast cancer and anti-bone metastasis effects are potential therapeutic agents for breast cancer bone metastasis (BCBM). This article reviewed the effects of plant-derived natural products against BCBM and their mechanisms to provide a reference for the research and development of drugs related to BCBM.

1. Introduction

Breast cancer is the most prevalent malignancy and the leading cause of cancer-related deaths among women globally [1]. In 2020, approximately 2.3 million new cases of female breast cancer were reported worldwide, accounting for 11.7 % of all cancer diagnoses and ranking as the fifth leading cause of cancer mortality, with 685,000 deaths [2]. Although more than 90 % of breast cancer cases do not exhibit metastasis at diagnosis, 20%–30 % of cases progress to secondary metastasis [3,4]. Bone is the primary site of breast cancer metastasis, affecting over 70 % of patients with metastatic disease [5]. Bone metastasis is significantly more common than primary

Abbreviations: AG, andrographolide; AIL, ailanthone; ART, artemisinin; BA, betulinic acid; BC, breast cancer; BCBM, breast cancer bone metastasis; BRU, brucine; CTCs, circulating tumor cells; CTSK, cathepsin K; CUR, curcumin; DTCs, disseminated tumor cells; EMT, epithelial-to-mesenchymal transition; EPI, epiberberine; EVs, extracellular vesicles; hAJs, heterotypic adherens junctions; HI, hypericin; KS, kadsurenone; MMPs, generate matrix metalloproteinases; MSCs, mesenchymal stem cells; OPG, osteoprotegerin; OS, osthole; PB, plumbagin; PMN, pre-metastatic niche; PNC, punicalin; PO, pogostone; PS, psoralen; PTHrP, parathyroid hormone-related peptide; QOL, quality of life; RA, rosmarinic acid; RANK, receptor activator of NF-κB; RANKL, receptor activator of NF-κB ligand; SIN, sinomenine; SREs, skeletal-related occurrences; TGF-β, transforming growth factor-β; TME, tumor microenvironment; TRAP, tartrate-resistant acid phosphatase; WDL, wedelolactone.

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bone cancer in adults and is typically considered incurable, leading to a grim life expectancy of only 2–3 years post-diagnosis [6,7]. A comprehensive retrospective study of 6482 breast cancer patients with bone metastases indicated that the predominant age range for those affected was between 50 and 70 years, with peak incidence occurring around age 60 [8]. Although bone metastases are difficult to cure, disease progression can be managed over an extended period by combining systemic anti-cancer therapies with a holistic multidisciplinary supportive care approach [9].

Bone is a highly dynamic system that maintains a dynamic equilibrium through the interaction of osteoblasts and osteoclasts [10]. BCBM results from complex interactions between cancer cells, bone marrow entities, and intrinsic bone structures. In the bone metastasis microenvironment, tumor cells secrete cytokines and growth factors that stimulate the abnormal production of osteoclasts and osteoblasts within the bone matrix [11]. These interactions disrupt the equilibrium of bone homeostasis, typically increasing osteoclast and osteoblast activity, culminating in a series of skeletal-related events (SREs) that persist over extended periods in individuals with BCBM [12]. Common SREs include pathological fractures, hypercalcemia, and spinal cord compression [13]. The prognosis for patients with BCBM depends not only on the presence of SREs but also on other factors such as age, ethnicity, marital status, and the presence of metastases to other organs [8]. Once bone metastasis occurs, treatment strategies primarily focus on palliative interventions, including bone-modifying agents, surgical procedures, and radiotherapy [14]. However, bone-modifying agents, mainly bisphosphonates and denosumab, may cause severe drug-related adverse reactions while providing relief from SREs. Therefore, the search for safe and effective drugs to combat BCBM remains an urgent issue warranting resolution within the medical community.

Natural products with broad pharmacological activity are important sources for modern drug discovery. It is estimated that 25%–50 % of current pharmaceuticals stem from plant-derived natural products sourced [15]. Terpenoids, alkaloids, phenolics, and quinones are effectively utilized to manage breast cancer (BC) due to their milder side effects and lower risk profiles [16]. Certain compounds within these phytoconstituents demonstrate potential anti-bone metastasis effects while inhibiting BC. This review summarized the effects of natural products against BCBM and their mechanisms of action, to provide valuable references for the development of relevant drugs and clinical studies.

2. Mechanism of breast cancer bone metastasis

The classical model of cancer metastasis, known as the “seed and soil” theory, was proposed by Stephen Paget in 1889 [17]. According to this theory, the development of cancer metastasis depends on specific interactions between cancer cells and particular organ microenvironments that are predisposed to metastasis. Metastasis occurs exclusively in specific organs and follows a series of steps: invasion, embolization, survival in circulation, arrest in distant capillary beds, and extravasation into and proliferation within organ parenchyma [18]. Although the “seed and soil” theory is widely accepted regarding the mechanism of BCBM, further research is needed to elucidate the exact mechanisms involved.

2.1. Tumor microenvironment and pre-metastatic niche

Throughout the progression of metastatic cancer, the tumor microenvironment (TME) significantly influences the dissemination and colonization of cancer cells in secondary sites [19]. Various stromal cells within the breast cancer TME, including fibroblasts, macrophages, adipocytes, immune cells, and mesenchymal stem cells (MSCs), play pivotal roles in facilitating epithelial-to-mesenchymal transition (EMT) at primary sites [19,20]. During EMT, these stromal cells acquire a pro-tumoural phenotype when they interact reciprocally with tumor cells, ultimately facilitating the metastatic spread of BC cells [21]. Initiation of the pre-metastatic niche (PMN) is manifested by clot formation and vascular rupture, further facilitated by localized increases in cytokines of tumor and stromal origin [22]. The survival and proliferation of cancer cells within the metastatic niche are sustained by the evolving PMN, influenced by the complex interplay of tumor-secreted factors and extracellular vesicles (EVs) acting on tumor-seeding organs [22]. EVs are essential for mediating communication between cancer cells involved in EMT and other cells [23]. EVs released from primary cancer cells disseminate to distant metastatic sites [24]. Upon reaching the PMN, EVs reprogram niche cells to promote subsequent metastatic growth and invasion, fostering bidirectional communication between niche and cancer cells [25].

2.2. Invasion and migration

Angiogenesis, triggered by cancer cells at the primary tumor site, facilitates the infiltration of tumor cells into the blood or lymphatic vessels [18]. The recruitment and activation of osteoclasts through paracrine signaling between cancer cells and osteoblasts are critical features of BCBM [26]. In bone metastases, chemokines produced by cancer cells induce leukocytes to generate matrix metalloproteinases (MMPs), which assist cancer cells in breaching the basement membrane [27].

Circulating tumor cells (CTCs) are neoplastic cells that stem from primary tumors, recurrences, or metastatic sites and circulate freely within the peripheral blood [28]. CTCs consist of epithelial tumor cells, epithelial-to-mesenchymal transition cells, hybrid (epithelial/EMT) tumor cells, irreversibly transitioned EMT tumor cells, and circulating tumor stem cells [29]. EMT can promote the generation of CTCs by enhancing tumor cell invasiveness, intravasation, and survival in the peripheral system [30]. Certain CTCs from BC migrate into the bone, penetrate the vascular basement membrane into the blood vessels, and transform into disseminated tumor cells (DTCs) within the bone microenvironment [31,32]. The successful colonization of DTCs is associated with the formation of heterotypic E-cadherin junctions with osteoblasts [33]. These heterotypic adherens junctions (hAJs) involving cancer-derived E-cadherin and osteogenic N-cadherin mediate niche interactions, and the formation of hAJs is the primary initiation step of bone

colonization [34].

Although parathyroid hormone-related peptide (PTHrP) in bone is predominantly stemmed from osteoblasts, tumor-associated PTHrP can also prompt osteoblasts to produce receptor activator of NF-kappaB ligand (RANKL), which induces osteoclastogenesis and osteoclast activation, leading to an increase in bone turnover [35–37]. Osteoclast-mediated bone matrix resorption releases transforming growth factor-β (TGF-β) and insulin-like growth factors, which interact with cancer cells and further prompt disease progression [38–40]. Ultimately, these processes collectively establish a "vicious cycle" of bone metastasis [26,41] (Fig. 1).

3. Conventional treatments of breast cancer bone metastasis

Complications arising from bone metastases include pain, diminished performance status, reduced quality of life (QOL), and SREs [42]. The management of BCBM primarily aims to alleviate pain, restore function, control tumor growth, prevent and treat SREs, and improve patients' QOL [43]. The clinical treatment of BCBM mainly includes the systemic administration of radiopharmaceuticals, antiresorptive agents, and local treatments such as surgery, radiofrequency ablation, and radiation therapy [44]. Different treatment approaches can be chosen based on the condition of patients with BCBM [43]. Bisphosphonates have been demonstrated to be effective in preventing and postponing SREs [45–47]. Supported by substantial data from randomized clinical trials, bisphosphonates have been integrated into clinical practice guidelines as standard therapeutic agents [48–54]. Among these interventions, drug therapy is the most cost-effective option for patients. However, the availability of alternative medications is limited, underscoring the urgent need for the development of additional safe and effective drugs. Natural products may serve as a promising source of these alternative drugs.

4. Inhibitory effects of natural compounds on breast cancer bone metastasis

Breast cancer bone metastasis presents distinct types including osteolytic, osteosclerotic, and mixed variants based on histological

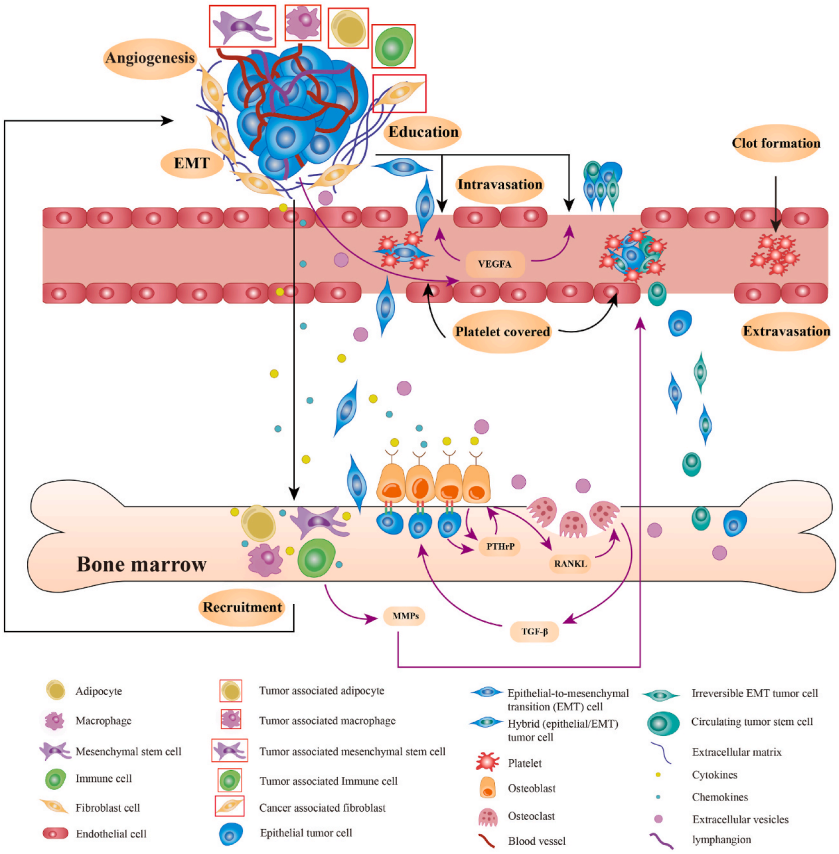

Fig. 1. The mechanism of breast cancer bone metastasis. EMT causes primary BC cells to acquire a mesenchymal phenotype with migratory and invasive capabilities; in response to cytokines, BC cells undergoing EMT intravasate into the blood vessels and become CTC cells; some of the CTC cells exude from the blood vessels and are transformed into DTC cells; DTC cells enter the bone microenvironment and ultimately colonize the bone through interactions with osteoblasts and osteoclasts. EMT, epithelial-to-mesenchymal transition; MMPs, matrix metalloproteinases; VEGFA, vascular endothelial growth factor A; PTHrP, parathyroid hormone-related peptide; RANKL, receptor activator of NF-κB ligand; TGF-β, transforming growth factor beta.

and clinical features. Among these, osteolytic metastasis, driven by a "vicious cycle" of tumor-stroma interactions, is the predominant form [55]. Natural products are crucial resources for modern drug discovery and have garnered significant attention as potential therapeutic agents for various diseases. Natural products influence cellular activities by targeting different signaling pathways [56]. Current research on natural products in BCBM primarily focuses on inhibiting specific signaling pathways within the "vicious cycle." Preclinical studies have indicated the potential of certain natural products to inhibit bone metastasis in breast cancer and have

Table 1
Inhibitory effects of natural products on breast cancer bone metastasis.

Natural product	Phytochemicals classification	Type of Study	Cell lines/animal	Signaling pathway	Effects	References
Betulinic acid	terpenoids	in vitro, in vivo	MDA-MB-231; male ICR mice	TGF-β	prevent bone resorption; mitigate BC cell-mediated bone loss.	[66]
Ailanthone	terpenoids	in vitro, in vivo	MDA-MB-231; BALB/c female, nude mice	MAPK, PI3K/AKT, NF-κB	inhibit the BC-induced osteolytic bone metastasis; decrease the osteoclast cell differentiation and functioning; inhibit the growth, migration, and infiltration of the BC cells; suppress the osteolytic bone damage.	[74]
Artemisinin	terpenoids	in vitro, in vivo	MDA-MB-231,BMM; male C57BL/6 mice	NF-κB	inhibit differentiation of osteoclast precursor cells; inhibit osteoclast-induced soluble bone destruction and MDA-MB-231 cell proliferation within bone; inhibit bone resorption; promote apoptosis of MDA-MB-231 cells.	[81]
Pogostone	terpenoids	in vitro, in vivo	MDA-MB-231, RAW264.7; female C57BL/6 mice	NF-kB, JNK	inhibit osteoclast differentiation, and bone resorption; suppress invasion and migration of BC cells; promote apoptosis of BC cells; inhibit osteoclast formation; inhibit BC-induced osteolysis.	[91]
Andrographolide	terpenoids	in vitro, in vivo	MDA-MB-231, RAW264.7; female BALB/c nu/nu mice	NF-κB, ERK	attenuate BC-induced osteoclastogenesis; inhibit bone destruction; inhibit the metastasis of BC cells to bone.	[102,103]
Wedelolactone	coumarins	in vitro	MDA-MB-231	Akt/mTOR	inhibit BC-mediated osteoclastogenesis; suppress osteoclast differentiation and activity;	[123]
Osthole	coumarins	in vitro, in vivo	MDA-231BO; female BALB/c nu/nu mice	TGF-β	inhibit BC cell growth, migration, and invasion; induce apoptosis of BC cells; inhibit BC metastasis to bone.	[127]
Psoralen	coumarins	in vivo	MDA-231BO; female BALB/c nu/nu mice	RANKL/RANK	inhibit bone metastases in mice; inhibit BC cell growth in the bone microenvironment; regulate the function of osteoblasts and osteoclasts in tumor-bearing mice.	[132]
Brucine	alkaloids	in vitro, in vivo	MDA-MB-231, RAW264.7; female BALB/c nu/nu mice	RANKL/RANK, Jagged1/Notch1	inhibit osteoclastogenesis and bone resorption.	[143,144]
Sinomenine	alkaloids	in vitro, in vivo	MDA-MB-231, RAW264.7; female BALB/c nu/nu mice	c-Fos/NFATc1	reduce BC cell-induced bone loss; inhibit osteoclastogenesis and bone resorption; inhibit osteoclast-related gene expression.	[154]
Epiberberine	alkaloids	in vitro, in vivo	MDA-MB-231,4T1; female Balb/c mice	Akt/c-Fos	reduce BC cell-induced bone loss; inhibit the differentiation and function of osteoclasts; attenuate BC induced-the differentiation and function of osteoclasts.	[163]
Curcumin	phenols	in vitro, in vivo	MDA-MB-231, 4T1; female C57BL/6J mice	TGF-β	inhibit BC TGFβ-mediated Smad signaling driving osteolysis in bone.	[166,167]
Rosmarinic acid	phenols	in vitro	MDA-MB-231BO	RANKL/RANK	inhibit the migration of MDA-MB-231BO human bone-homing BC cells.	[172]
Hypericin	quinones	in vitro, in vivo	MDA-MB-231, MCF-7, RAW264.7; female C57BL/6	NFATc1	inhibit the invasion and migration of BC cells; inhibit osteoclast differentiation and function.; reduce osteolysis.	[180]
Plumbagin	quinones	in vitro, in vivo	MDA-MB-231; female BALB/c nu/nu mice	RANKL/RANK	inhibit the migration and invasion of BC cells; inhibit the expression of osteoclast-activating factors; inhibit cancer cells-induced osteoclastogenesis and the secretion of osteoclast-activating factors.	[187]
Kadsurenone	lignans	in vitro	MDA-MB-231, RAW 264.7	NF-κB	inhibit BC cells or RANKL-induced osteoclastogenesis.	[194]
Punicalin	tannins	in vitro, in vivo	MDA-MB-231, RAW 264.7; female C57BL/6 mice	NF-κB	suppress the BC-induced osteoclastogenesis, proliferation, migration, and osteolysis; inhibit the invasion of BC cells.	[201]
Raddeanin A	saponins	in vitro, in vivo	MDA-MB-231; female BALB/c nu/nu mice	Akt/mTOR	inhibit osteoclast formation, bone resorption, and osteolysis; inhibit cancer cell invasion; induce cancer apoptosis.	[228]

explored their underlying mechanisms (Table 1). The chemical structures of these natural products are detailed in Fig. 2.

4.1. Terpenoid compounds

Among the prevalent natural compounds, terpenoids have various pharmacological activities, such as antiviral, anti-inflammatory, antibacterial, antimalarial, and antitumor effects [57]. Based on the number of isoprene units, terpenoids are categorized into monoterpenes, sesquiterpenes, diterpenes, triterpenes, and tetraterpenes. Additionally, terpenoids are classified into acyclic, monocyclic, bicyclic, tricyclic, and tetracyclic terpenes according to carbon ring count. Since many terpenes are oxygenated derivatives, they can be subdivided into alcohols, aldehydes, ketones, carboxylic acids, esters, and glycosides. Regarding the anti-tumor activity of terpenoids, paclitaxel is a representative terpenoid compound successfully applied in clinical practice. Studies have shown that certain terpenoids have therapeutic effects on BC and BCBM.

Betulinic acid (BA), a lupine-type pentacyclic triterpenoid, can be isolated from *Diospyros leucomelas*, *Tovomita krukovii*, *Rosmarinus officinalis*, and *Rosa canina* [58,59]. The primary natural source of BA is the outer bark of white birch trees, which contains approximately 0.002–2% of BA [60]. However, the naturally derived BA falls short of demand, necessitating reliance on chemically synthesized and biologically transformed BA as the primary source [60]. BA exhibits diverse pharmacological activities, including antidiabetic, anti-inflammatory, antiviral, and antitumor effects [61]. BA could inhibit the proliferation of BC cells, induce tumor cell apoptosis, inhibit tumor growth, and enhance the sensitivity of BC cells to chemotherapy drugs [62–65]. In BCBM models, BA could exert bone-protective effects by inhibiting osteoclast production and reducing bone loss [66]. To improve the bioavailability and solubility of BA, Xu et al. developed a heterocyclic condensed derivative of BA [67]. This derivative inhibits osteoclastogenesis by suppressing the mRNA expression of tartrate-resistant acid phosphatase (TRAP) and cathepsin K (CTSK), exhibiting more effectiveness than BA.

Ailanthone (AIL) is a pentacyclic diterpenoid lactone compound derived from *Ailanthus altissima* (called “Chou chun” in China) [68]. In addition to its anti-inflammatory, anti-ulcer, anti-allergic, and anti-malaria effects, AIL has been shown to have anticancer effects against various types of cancer, such as breast, lung, colorectal, and gastric cancers [68–73]. AIL could inhibit MCF-7 cell proliferation, arrest the cell cycle, and induce apoptosis by upregulating Bax protein expression and downregulating Bcl-2 protein expression [68]. Research by Wang et al. demonstrated that AIL inhibited the generation and absorption of osteoclasts induced by MDA-MB-231 CM and RANKL in vitro, inhibiting the expression of osteoclast-related genes and proteins, including TGF-β, CDH11, RUNX2, CXCR4, PTHrP, NFATc1, MMP9, CTSK, TRAP, and DCSTAMP [74]. These effects were related to the fact that AIL could inhibit the signal transduction of PI3K-AKT and NF-κB pathways. Notably, in vivo studies revealed that doses of 10 mg/kg and 15 mg/kg of AIL significantly suppressed bone metastasis and osteolysis in mice within a BCBM model.

Artemisinin (ART) is a sesquiterpene lactone derived from *Artemisia annua* L (annual mugwort) [75]. ART is a lipid-soluble compound with high oral bioavailability [76]. ART serves as a vital medication against malaria and boasts a range of biological activities, including antiviral, anti-fungal, anti-microbial, anti-parasitic, anti-arrhythmias, anti-schistosomiasis, and anti-cancer [77,78]. ART has been shown to inhibit cell proliferation and progression of BC by acting on T cells, regulatory T cells, and MDSCs to produce anti-tumor immune responses [79]. In a nude mouse model induced by MDA-MB-231 cells, ART could inhibit tumor growth by blocking the Notch signaling pathway [80]. Additionally, in the MDA-MB-231-induced bone metastasis model, ART inhibited osteoclast formation, differentiation, and bone resorption by modulating the RANKL and NF-κB pathways [81]. A derivative of ART, dihydroartemisinin (DHA)—an active metabolite of ART—exhibited greater efficacy in inhibiting both proliferation and migration of

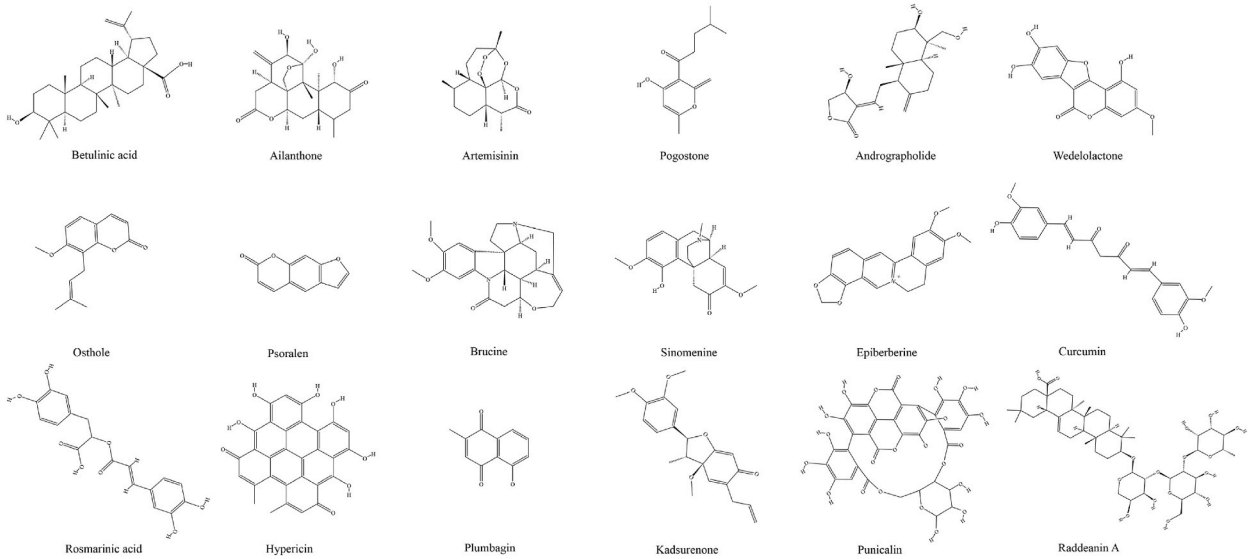

Fig. 2. The chemical construct of natural products with inhibitory effects on breast cancer bone metastasis.

BC cells than ART alone [82]. DHA could inhibit angiogenesis in BC, induce cell apoptosis, and inhibit the formation of the F-actin ring, osteoclast differentiation, bone resorption, and osteolysis by regulating the AKT signaling pathway [83–86].

Pogostone (PO), a terpenoid compound identified in the volatile oil of the traditional Chinese medicine *Pogostemon cablin* (Guang huoxiang), possesses the activities of antiviral, anti-fungal, anti-inflammatory, antibacterial, and anticancer, along with high oral bioavailability [87–90]. PO could induce apoptosis in MDA-MB-231 cells while inhibiting cell invasion and migration [91]. PO could also inhibit cancer cell migration in BCBM model mice and osteoclast formation, bone resorption, and osteolysis [91].

Andrographolide (AG), a diterpenoid compound isolated from *Andrographis paniculata*, has low solubility in water and poor oral bioavailability [92]. As the primary active component in the traditional Chinese medicine "Chuan xin lian", AG exhibits diverse pharmacological effects, including immune modulation, glucose and lipid metabolism regulation, antivirus effects, anti-inflammatory responses, anticancer activities, and bone protection effects [93–99]. AG regulated the differentiation and function of tumor-associated macrophages through the Wnt/β-catenin signaling pathway and suppressed angiogenesis via the VEGF pathway, thereby impeding BC progression [100,101]. In addition, AG inhibited BC cell-induced osteoclast differentiation by blocking the NF-κB signaling pathway, effectively mitigating osteolysis and bone loss initiated by cancer cells [102,103].

4.2. Coumarin compounds

Coumarins are aromatic compounds found in large quantities in plants, with some also originating from microorganisms and animal sources. Coumarins possess a fundamental structure comprising benzoic acid α-pyranone and exist either in a free state or in the form of glycosides formed by combining with sugar [104]. Based on the type of substituents and linkage methods within their basic structure, coumarin compounds are categorized as simple coumarins, pyranocoumarins, furan coumarins, isocoumarins, and other coumarins. While free coumarins have limited water solubility, their solubility increases when forming glycosides with sugars. Coumarin compounds exhibit high bioavailability and a wide range of pharmacological benefits, including antioxidant, antiviral, antibacterial, anti-inflammatory, anti-HIV, anticonvulsant, and anti-tumor [105,106].

Wedelolactone (WDL), a coumarin derived from *Wedelia chinensis* and *Eclipta prostrata*, has poor solubility and limited bioavailability and is primarily absorbed through the gastrointestinal tract following oral intake [107–109]. WDL exhibits diverse pharmacological effects, including anti-inflammatory, anti-virus, anti-tumor, anti-osteoporosis, and anti-diabetes [110–116]. In vitro and in vivo studies have demonstrated WDL's promising antitumor effects against several solid tumors, including breast cancer, ovarian cancer, mantle cell lymphoma, prostate cancer, and neuroblastoma [117–121]. Elevated PI3K/mTOR protein levels in human BCBM are associated with cancer progression and bone degradation [122]. WDL could inhibit BCBM by inhibiting osteoclast differentiation and regulating the interaction between osteoclasts and osteoblasts mediated by breast cancer cells [123].

Osthole (OS), a natural coumarin derivative, is predominantly found in the plant of Umbelliferae, Rutaceae, Compositae, and Leguminosae. The primary source of osthole is the fruit of the Umbelliferae plant *Cnidium monnieri* (L.) known as *Fructus Cnidii* [124]. The pharmacological properties of OS have been extensively studied, such as anti-cancer, anti-hyperglycemia, antiplatelet, antioxidant, and neuroprotective activities [125]. OS has been shown to inhibit the growth, migration, and invasion of BC cells, and induce the apoptosis of BC cells [126]. In a mouse model of BCBM, treatment with OS at a dosage of 5.25 mg/kg twice weekly for six weeks resulted in a 40 % reduction in the average bone metastasis rate and approximately a 57 % decrease in the number of metastatic lesions compared to controls [127].

Psoralen (PS), a plant-derived furocoumarin, is principally isolated from *Cullen corylifolium* (known as babchi) and is also found in other vegetables and fruits, such as *Apium graveolens* and *Ficus carica* [128]. PS induced cell cycle arrest in breast cancer MCF-7 and MDA-MB-231 cell lines by modulating the Wnt/β-catenin pathway in cells [129]. As a phytoestrogen, PS could enhance osteoblast proliferation through the NF-κB pathway [130]. Furthermore, PS could accelerate bone fracture healing in tibial fracture rats by regulating the production of osteoclasts and osteoblasts via the ERK pathway [131]. In a mouse model of BCBM, PS inhibited the interactions between cancer cells, osteoblasts, and osteoclasts in tumor-bearing mice by upregulating osteoprotegerin (OPG) expression and downregulating the expression of IL-8, M-CSF, PTHrP, and RANKL in bone lesions [132].

4.3. Alkaloid compounds

Alkaloids, nitrogen-containing organic compounds predominantly alkaline in nature, are primarily found within the plant kingdom. Alkaloids often share the same core structures in plants belonging to identical families and genera, such as Papaveraceae, Amaryllidaceae, Menispermaceae, Ranunculaceae, Loganiaceae, and Solanaceae [133]. Alkaloids are categorized based on their chemical structure into steroids, pyrrolidines, purines, isoquinolines, diterpenoids, indoles, imidazoles, and organic amines [134]. The solubility of alkaloids is closely related to their form of existence. Free alkaloids consist of lipophilic and hydrophilic varieties, while alkaloid salts have high water solubility. Alkaloids with complex ring structures often exhibit significant and distinctive biological activities, such as antifungal, analgesic, anticancer, antimalarial, anti-diabetes, and anti-Alzheimer's disease [135,136].

Brucine (BRU), an indole alkaloid compound isolated from the seeds of *Strychnos nux-vomica* (known as nux vomica), is recognized as the primary bioactive and principal toxic element of nux vomica [137]. BRU is commonly utilized as an anti-inflammatory and analgesic agent for its effectiveness in reducing inflammation and alleviating pain [138]. The anti-tumor properties of BRU have been investigated in liver, colorectal, and breast cancers [139–141]. In vitro studies indicated that BRU inhibited migration, invasion, and angiogenesis in MDA-MB-231 cells by regulating the expression of EPH receptor A2, MMP-9, and MMP-2 [141]. In a mouse model of BCBM, BRU inhibited BCBM progression by reducing tumor vascular endothelial growth factor (VEGF) expression and angiogenesis [142]. In a co-culture system with MDA-MB-231 cells, brucine inhibited osteoclast formation by blocking the Notch1 pathways and

maintained bone metabolic equilibrium by modulating the RANKL/RANK signaling pathways [143,144].

Sinomenine (SIN) is a monomer alkaloid isolated from Chinese medicine *Sinomenium acutum* or *Caulis Sinomenii*, belonging to the isoquinoline alkaloid class [145]. Due to its limited solubility, SIN is commonly utilized for medicinal purposes in the form of hydrochloride salts [146]. Given its effective anti-inflammatory properties, SIN has received regulatory approval in China for the treatment of acute arthritis and rheumatoid arthritis. Moreover, SIN exhibits diverse pharmacological benefits, including analgesia, immune regulation, anti-tumor activity, cardiac protection, and neuroprotection [147–151]. In vitro studies showed that SIN inhibited the growth, invasion, and migration of MDA-MB-231 and MCF7 cells, and induced cell apoptosis [152]. Additionally, research by Song et al. revealed that under hypoxic conditions, SIN inhibited the invasion and migration of MDA-MB-231 side population cells by the PI3K/Akt/mTOR pathway [153]. Zhang et al. found that SIN inhibited osteoclast formation and bone resorption by reducing the expression of osteoclast-related genes OSCAR and TRAP, consequently ameliorating cancer-induced bone destruction in mouse models [154].

Epiberberine (EPI), a bioactive protoberberine alkaloid isolated from *Coptis chinensis*, *Corydalis turtschaninovii*, and *Sinomenium acutum*, is rapidly absorbed and metabolized after oral administration, but its bioavailability is low [155]. As a berberine isomer, EPI presents pharmacological effects spanning anti-cancer, anti-dyslipidemia, antibacterial, anti-inflammatory, anti-adipogenesis, and anti-Alzheimer's disease [156–161]. EPI could inhibit the growth, invasion, and migration, and induce cell apoptosis of MCF-7 and MDA-MB-231 cells [162]. The effects of EPI on BC cells involved activating the Wnt/β-Catenin signaling pathway and reversing the EMT process [162]. Research by Wei et al. found that EPI could inhibit osteoclast differentiation and function, thereby reducing bone loss induced by BC cells [163]. Moreover, the combined use of EPI and docetaxel mitigated BC-induced osteolysis in vivo, providing a protective effect on bones [163].

4.4. Other compounds

Some other natural compounds like quinones, phenols, saponins, lignans, and tannins contained in plants also have the pharmacological activity of inhibiting bone metastasis of breast cancer, such as hypericin, plumbagin, curcumin, rosmarinic acid, raddeanin A, kadsurenone, and punicalin.

Curcumin (CUR), primarily derived from the rhizomes of *Curcuma* longa L. (known as turmeric), is a natural polyphenolic compound. Turmeric is widely used as a traditional medicine, a food preservative, an aromatic stimulant, and a coloring material in China, India, and Southeast Asia [164]. Numerous studies highlighted the effects of CUR in addressing various conditions, including cancers, infectious diseases, inflammatory diseases, neurological diseases, metabolic diseases, cardiovascular diseases, and skin diseases [165]. The suppressive impact of CUR on BCBM was attributed to its ability to inhibit TGF-β-stimulated PTHrP secretion and decrease osteolytic bone destruction by blocking the TGF-β signaling pathway [166,167].

Rosmarinic acid (RA), another natural polyphenolic acid, is derived from approximately 162 plants, such as *S. deserta Schang*, *S. miltiorrhiza Bunge*, *S. przewalskii Maxim*, and *S. miltiorrhiza Bunge* [168]. RA induced apoptosis and cell cycle arrest in MDA-MB-231 cells [169]. Additionally, RA regulates bone metabolism by promoting osteoblastic differentiation while inhibiting osteoclastic differentiation [170,171]. Notably, RA could inhibit the migration of MDA-MB-231BO cells and increase the activity of alkaline phosphatase (ALP) in murine bone marrow stromal cells. RA exerted anti-BCBM effects mainly by regulating the RANKL/RANK pathway and inhibiting IL-8 expression [172].

Hypericin (HI), a polycyclic aromatic naphthodianthrone, is distributed widely in the Hypericum genus plants, such as *H. perforatum.*, *H. aegypticuml.*, *H. androsaemuml.*, *H. australe Ten.*, *H. hircinuml.*, and *H. triquetrifolium Turra.*, among which *H. perforatum* contains more HI than other species [173]. HI exhibits diverse pharmacological effects, including anti-inflammatory, antimicrobial, antiviral, anti-diabetic, and anti-cancer activities [174–178]. HI could induce cell apoptosis by regulating the P53 overexpression in BC cells [179]. Moreover, HI has shown potential for the prevention and treatment of BCBM. In vitro studies demonstrated that HI could suppress RANKL-induced osteoclastogenesis in an early stage and inhibit BC-induced osteoclast differentiation and function by downregulating the NFATc1 pathway and attenuating Ca^{2+} oscillation [180]. In vivo, HI could reduce osteolysis and bone metastasis in MDA-MB-231 BC-bearing mice, and improve survival rates of mice [180].

Plumbagin (PB), a naphthoquinone compound extracted from the roots of *Plumbago zeylanica,* is also found in other plant families such as Plumbaginaceae, Droseraceae, and Juglandaceae [181]. The anticancer activities of PB have been investigated in different cancers, such as breast, pancreatic, liver, lung, and cervical cancers [182–186]. PB could inhibit BCBM and osteolysis by modulating the tumor-bone microenvironment. These effects were attributed to PB's capacity to suppress osteoclast-activating factor expression, modulate the RANKL/OPG ratio induced by cancer cells in osteoblasts, and inhibit cancer cell and RANKL-stimulated osteoclastogenesis by inhibiting the activation of IκBα kinase, IκBα phosphorylation, and degradation [187,188]. Additionally, PB inhibited BC cell invasion and migration and reduced osteolytic bone metastases by downregulating the mRNA expression of IL-1α, TGF-β, MMP-2, and MMP-9 [189].

Kadsurenone (KS), a neolignan extracted from the stems of *Piper kadsura*, has limited research on its pharmacological effects. Platelet-activating factor (PAF) could enhance osteoclast motility and absorption activity and plays a crucial role in tumor neovascularization by activating NF-κB [190–193]. KS could inhibit BC cell-induced or PAF-stimulated osteoclastogenesis and downregulate the expression of osteoclast differentiation markers [194].

Punicalin (PNC), a natural ellagitannin primarily sourced from the husk of *Punica granatum* L. (known as pomegranate), exhibits diverse pharmacological benefits, including anti-inflammation, antibacterial, antioxidant, anti-hepatotoxic, anti-hepatitis B virus, and anti-cancer properties [195–200]. PNC could protect against BC-associated osteolysis by inhibiting osteoclast formation, F-actin ring formation, bone resorption, and osteoclast-related gene expression through NF-κB signaling pathway suppression [201]. In vitro, PNC

inhibited BC-induced osteoclastogenesis, proliferation, migration, and invasion while enhancing apoptosis in a dose-dependent manner. In vivo, PNC inhibited BC-induced osteolysis and associated bone metastasis [201].

5. Mechanism of natural compounds against breast cancer bone metastasis

5.1. Inhibiting RANK/RANKL signaling pathway

The RANK/RANKL signaling pathway is pivotal in regulating bone homeostasis [202]. Osteoblasts express RANKL, which controls the differentiation and proliferation of osteoclasts [203]. RANK expressed by BC cells acts as the receptor for RANKL [204]. The binding of RANK and RANKL recruits TNF receptor-associated factor 6 (TRAF6), triggering the activation of the NF-κB, PI3K, and MAPK pathways, which culminates in the maturation of osteoclast precursors [205]. OPG acts as a decoy receptor for RANKL, mediating bone remodeling by blocking RANK-RANKL interaction [206]. PTHrP produced by BC cells is a balance regulator between RANKL and OPG, which can promote the formation of osteoclasts by up-regulating the expression of RANKL in osteoblasts and down-regulating the expression of OPG [207]. Furthermore, metastatic BC cells can directly produce RANKL or stimulate osteoblasts to produce RANKL, which promotes the release of bone-derived cytokines and growth factors, leading to osteolysis and the migration of cancer cells to bone [208].

NFATc1 and c-Fos are crucial regulators of osteoclasts, influencing osteoclast differentiation and function by regulating the expression of osteoclast-related genes TRAF6, CTR, V-ATPase-d2, and tissue protease-K [209–211]. The NF-κB and MAPK signaling pathways are vital for osteoclast differentiation. In the cytoplasm, the dimer formed by NF-κB and IκBα prevents NF-κB entering the nucleus [212]. Following RANKL stimulation, extracellular signals are transmitted to the nucleus through the NF-κB and MAPK pathways, ultimately leading to the differentiation and maturation of osteoclasts [213]. Natural compounds can inhibit osteoclast differentiation and maturation induced by BC cells by blocking the RANKL/RANK signaling pathway and downstream signal transduction, thereby exerting osteoprotective effects (Fig. 3). Research showed that parthenolide could inhibit the expression of NF-κB, NFATc1, p38, and ERK within the RANKL/RANK signaling pathway, reduce the stability of c-Fos, and block the signal transduction of this pathway, thereby reducing the differentiation and osteolytic activity of osteoclasts [214]. Punicalin and germacrone inhibited NF-κB activation by inhibiting the phosphorylation of IκBα, thereby blocking the transduction of NFB signals and reducing the formation of osteoclasts [201,215]. Pogostone could downregulate osteoclast-related genes TRAF6, NFATc-1, CTR, and V-ATPase-d2 expression, inhibit NF-κB and JNK signaling pathways by regulating these genes and the phosphorylation of IκBα, thus inhibiting the migration of BC cells to bone [91].

5.2. Inhibiting TGF-β signaling pathway

TGF-β, belonging to the polypeptide growth factor family, can induce EMT of BC cells [216]. EMT enables epithelial tumor cells to obtain a mesenchymal phenotype with migration and invasion capabilities, accompanied by the secretion of cytokines that promote metastasis, leading to breast cancer progression and subsequent metastasis [217,218]. As a pivotal agent in BCBM, TGF-β discharged

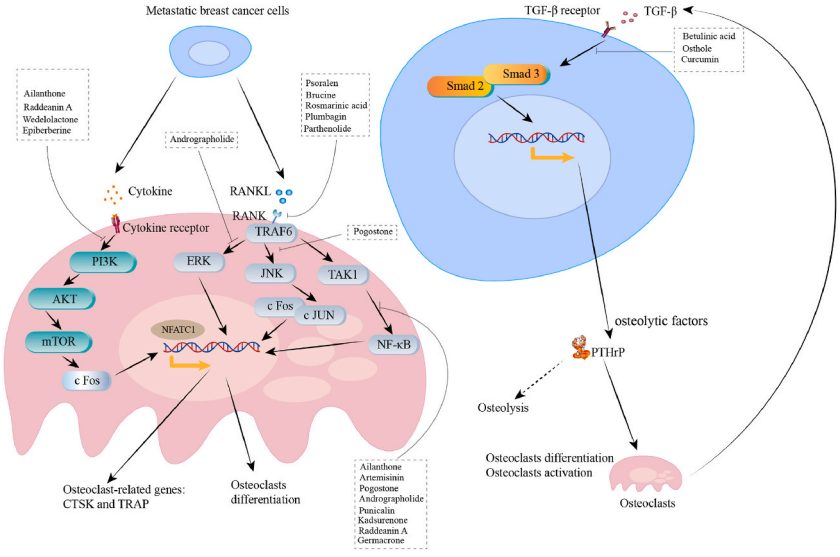

Fig. 3. Natural products inhibit breast cancer bone metastasis by the RANKL/RANK, PI3K/AKT/mTOR, and TGF-β signaling pathway. AKT, protein kinase B; ERK, extracellular signal-regulated kinase; JNK, c-Jun N-terminal kinase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-B; PI3K, phosphoinositide 3-kinase; PTHrP, parathyroid hormone-related peptide; TAK1, transforming growth factor-beta-activated kinase 1; TGF-β, transforming growth factor beta; TRAF6, TNF receptor-associated factor 6.

due to bone resorption by osteoclasts can enhance the secretion of PTHrP in osteoblasts, activate the RANKL receptor in osteoblasts, and diminish OPG expression [219]. High levels of RANKL and low levels of OPG can lead to enhanced osteolytic activity and the release of TGF-β. The TGF-β released during this process, in turn, promotes the expression of PTHrP, forming a feedback loop [220]. Therefore, blocking TGF-β signal transduction can effectively reduce BMCM (Fig. 3). Curcumin has been shown to inhibit TGF-β stimulated Smad activation. By blocking TGF-β/Smad signal transduction, curcumin could inhibit the secretion of PTHrP by TGF-β stimulating metastatic BC cells, thereby inhibiting the progress of osteolysis and bone metastasis [221]. The inhibitory effect of osthole on BCBM involves TGF-β and RANKL/RANK signaling pathways. Osthole could inhibit the expression of TGF-β and Smad in BC cells, and regulate RANKL/RANK signal transduction between cancer cells and bone cells by downregulating PTHrP and M-CSF expression and upregulating OPG expression, thus inhibiting the metastasis of BC cells to bone [127].

5.3. Inhibiting PI3K/AKT/mTOR signaling pathway

The PI3K/AKT/mTOR signaling pathway is crucial in various cells, maintaining fundamental cellular functions such as proliferation, metabolism, and survival [222]. Dysregulation of signal transduction within this pathway is implicated in numerous cancers [223]. In BC, the PI3K-AKT-mTOR pathway is often excessively activated, promoting cancer cell proliferation, invasion, and migration [224,225]. The activity of PI3K/mTOR protein plays an important role in the occurrence and bone metastasis of breast cancer and is related to osteolysis in the process of metastasis [122]. Blocking the PI3K-AKT-mTOR signal transduction can inhibit osteoclast formation and osteolysis during breast cancer progression and bone metastasis (Fig. 3) [226]. By impeding M-CSF/RANKL-induced Akt/mTOR activation, wedelolactone could reduce BC cell-mediated osteoclast differentiation and bone resorption, counteracting the reinforcement of the Akt/mTOR signaling pathway by BC and reinstating the equilibrium in osteoblast-osteoclast interaction [123]. In addition, wedelolactone could also enhance osteoblastogenesis from bone marrow mesenchymal stem cells by inducing JNK- and ERK-mediated expression of bone morphogenetic protein and Smad phosphorylation [227]. Raddeanin A, isolated from the roots of *Anemone raddeana Regel,* could inhibit the proliferation and invasion of BC cells, and alleviate osteolysis induced by metastatic BC cells by inhibiting AKT/mTOR and SRC/AKT pathway [228].

6. Conclusion and prospective

Although bone metastasis rarely poses a direct threat to the lives of breast cancer patients, it significantly impacts their quality of life. Current pharmacologic treatments for BCBM are primarily bone-modifying agents, such as bisphosphonates and denosumab. However, the potential risks of jaw osteonecrosis and nephrotoxicity associated with these agents cannot be disregarded. The incidence of medication-related jaw osteonecrosis following the bone-modifying agents intake is approximately 1 %–9 % [229]. Specifically, the reported incidence rates of jaw osteonecrosis attributed to bisphosphonates and denosumab are about 1.2 % and 1.6 %, respectively [230]. Research revealed that the incidence of renal function impairment in patients with breast cancer bone metastasis taking zoledronic acid for less than 2 years was about 0.7 %, and the incidence for more than two years was about 1.1 % [231]. Natural products have the advantages of abundant sources, diverse structures, and fewer side effects compared to conventional medications, making them an important treasure trove for drug discovery. Plant-derived natural products, such as terpenoids, alkaloids, coumarins, and phenols, exhibit diverse anti-tumor activities with fewer adverse reactions. In the bone metastatic niches, metastatic tumor cells can sustainably produce various factors and release them into the bone microenvironment, activating osteoclasts and bone resorption. Denosumab and bisphosphonates primarily target osteoclast activity but have a limited effect on tumor growth at metastatic sites. In contrast, in addition to inhibiting osteoclast activation and bone resorption, natural products can also inhibit tumor cell proliferation, invasion, and migration. Mechanistically, natural products inhibit the production of osteoclast-associated cytokines to counteract BC-induced bone destruction mainly by blocking the signaling of the RANKL/RANK pathway, PI3K/AKT/mTOR pathway, and TGF-β pathway. Therefore, natural products with anti-BC and osteoprotective effects may be a potential source of drugs for the prevention and treatment of BCBM.

The low solubility and bioavailability of plant-derived natural products is a major challenge in their transition to clinical applications. Structural modification of natural products in combination with biosynthetic and computer technologies to improve their solubility, bioavailability, and in vivo pharmacokinetic profiles will become an important direction for natural product research in the future. In addition, nanotechnology offers promising strategies for improving the bioavailability of these natural products. Nanoparticles modified with targeting agents can prepare nanoparticles with targeted functions. After loading the active compounds onto targeted nanoparticles, the targeted delivery of natural products to bone metastatic niches can be achieved, increasing the molecular concentration and therapeutic index of the active ingredients in the lesion localization. This targeted delivery system can also load different active compounds simultaneously to play a synergistic role, which is a promising research direction for future targeted therapy of BCBM.

With a further understanding of the molecular subtypes of breast cancer, future research will pay more attention to the formulation of personalized treatment strategies. In combination with biomarkers for bone metastasis, screening natural products that are sensitive to specific breast cancer subtypes can provide personalized treatment methods for patients and achieve precision treatment of BCBM. In future research, natural product screening with artificial intelligence will facilitate the discovery of relevant drugs. Due to the large quantity of natural products, extensive experimental evaluation of their actions and mechanisms is impractical. By constructing specific models, powerful artificial intelligence with machine learning capabilities can help researchers predict the biological activity, structure-activity relationship, and mechanism of action of natural products based on their chemical structures. On the other hand, natural products are characterized by multi-target action, which makes it difficult to elucidate the mechanism of action of natural

products. The application of artificial intelligence will also facilitate the in-depth analysis of the multi-target mechanism of action of natural products. However, the application of artificial intelligence in natural product screening is currently limited by the lack of relevant large-scale and high-quality datasets. In addition, some experimental studies have confirmed the inhibitory effect of certain natural products on BCBM and explored their mechanism of action. Future studies should focus on exploring the structure-activity relationships of these natural products to discover more compounds that are effective against BCBM, which can then be validated in clinical trials to facilitate the development of relevant drugs.

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Compliance with ethics guidelines

This article is based on publicly published research and does not include any new research conducted by the author on human participants or animals.

Data availability statement

All data obtained during this study are included in the manuscript, and no data were used for the research described in the article.

CRediT authorship contribution statement

Xiaolei Zhang: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Jinxin Miao:** Writing – review & editing, Writing – original draft. **Yagang Song:** Writing – review & editing, Writing – original draft. **Jiawen Zhang:** Writing – review & editing, Visualization. **Mingsan Miao:** Writing – review & editing, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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