European Journal of Pharmacology 974 (2024) 176604

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Therapeutic effects of ginsenosides on osteoporosis for novel drug applications

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ARTICLE INFO

Keywords:
Ginsenosides
Osteoporosis
Osteoblasts
Osteoclasts
Bone marrow stromal cells

ABSTRACT

Osteoporosis (OP) is a metabolic bone disease with a high incidence rate worldwide. Its main features are decreased bone mass, increased bone fragility and deterioration of bone microstructure. It is caused by an imbalance between bone formation and bone resorption. Ginsenoside is a safe and effective traditional Chinese medicine (TCM) usually extracted from ginseng plants, having various therapeutic effects, of which the effect against osteoporosis has been extensively studied. We searched a total of 44 relevant articles with using keywords including osteoporosis, ginsenosides, bone mesenchymal cells, osteoblasts, osteoclasts and bone remodeling, all of which investigated the cellular mechanisms of different types of ginsenosides affecting the activity of bone remodeling by mesenchymal stem cells, osteoblasts and osteoclasts to counteract osteoporosis. This review describes the different types of ginsenosides used to treat osteoporosis from different perspectives, providing a solid theoretical basis for future clinical applications.

1. Introduction

Osteoporosis (OP) is a metabolic bone disease characterized by decreased bone mass and destruction of bone tissue microstructure, leading to increased bone fragility and susceptibility to fractures (Gopinath, 2023). A global epidemiological survey on osteoporotic vertebral fractures showed that one in three women and one in five men over the age of 50 will be directly affected by osteoporosis for the rest of their lives (Laird et al., 2023). A study on the prediction of hip fractures in Asia estimated that by 2050, the direct cost of osteoporotic fractures in Asia alone may reach at least $15 billion per year (Cheung et al., 2018). Therefore, early detection and treatment of osteoporosis is crucial for preventing fractures and reducing the burden on the global health care system.

Normal bone homeostasis in the human body is mainly maintained by osteoblasts differentiated from bone marrow mesenchymal stem cells (BMSCs) and osteoclasts produced by the fusion of monocytes and macrophages (Guo et al., 2023; Kular et al., 2012), which participate in bone reconstruction and exert the sequential function of absorbing old bone and forming new bone (Harris et al., 2023; Iantomasi et al., 2023) (Fig. 1). The main cause of OP is aging, while secondary causes include genetic diseases, endocrine diseases, gastrointestinal diseases, blood diseases, neurological diseases, rheumatism and autoimmune diseases (Patel and Wairkar, 2023). In addition, lifestyle changes, such as vitamin D and calcium deficiency, high salt intake, alcohol consumption, and smoking, also significantly increase the risk of osteoporosis. These factors can lead to an imbalance in bone cell activity and disrupt the dynamic cycle of bone formation and absorption, thereby affecting bone homeostasis and exacerbating OP (Beekman et al., 2023).

The drugs used to treat and prevent the development of osteoporosis are divided into two categories. The first category is bone resorption inhibitors, and the second category is bone-promoting drugs (LeBoff et al., 2022). Although many clinical drugs targeting osteoporosis are effective in restoring bone strength, they unintentionally reduce bone strain (Patel and Wairkar, 2023). In addition, some clinical drugs are expensive, require long-term use and have serious side effects (Sugiyama et al., 2015). For example, excessive treatment with bisphosphonates may lead to bone fractures, while hormone therapy may lead to serious complications such as thromboembolism (Lewiecki et al., 2019).

Ginseng is a valuable medicinal plant with thousands of years of

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https://doi.org/10.1016/j.ejphar.2024.176604
Received 21 February 2024; Received in revised form 12 April 2024; Accepted 18 April 2024
Available online 20 April 2024

history in Asian countries. It is a food homologous and famous medicinal herb with many pharmacological components, including saponins, polysaccharides, oligosaccharides, polyacetylene, peptides, and bioactive proteins (Ding et al., 2023). Ginsenoside is one of the active ingredients of ginseng, accounting for only a small portion of the compounds isolated from ginseng roots (Paik et al., 2023), and can be classified into two categories: protopanaxadiol (PPD) and protopanaxatriol (PPT). For example, ginsenosides of the PPD type include Rb1, Rb2, Rb3, Rc, Rd, Rh2, Rg3, and F2, whereas those of the PPT type include Re, Rf, Rg1, Rg2, and Rh1, which are considered to have potential value in treating various diseases (Li et al., 2023; Qi et al., 2022).

In recent years, an increasing number of cell experiments, animal experiments, and clinical studies have confirmed that many types of ginsenosides can exhibit therapeutic effects on osteoporosis by regulating the activity of osteoclasts and osteoblasts (He et al., 2019; Jung et al., 2021; Li et al., 2021; Wang et al., 2017; Zhang et al., 2022). Therefore, this review will further elucidate the mechanism of ginsenoside in treating osteoporosis from four aspects: signal pathways, bone mesenchymal cells, osteoblasts, and osteoclasts, to determine the goals of new methods for treating OP.

2. Specific varieties of ginsenoside ingredients

The active ingredients associated with the ginsenosides used in treating OP are shown in Table 1 and Fig. 2.

3. Bone marrow stromal cells (BMSCs)

BMSCs are MSCs located in the bone marrow that have various differentiation potentials, become osteoblasts, adipocytes, or chondrocytes, and play an important role in maintaining normal bone stability (Hu et al., 2018). There is evidence to suggest that changes in proliferation and differentiation, as well as changes in the quantity and function of BMSCs, are also key causes of osteoporosis (Kiernan et al., 2017) (Fig. 3).

3.1. Promoting osteogenic differentiation of bone marrow stromal cells

When the differentiation of BMSCs into osteoblasts is relatively low, this transformation leads to a decrease in bone formation. Therefore, many scholars have conducted the following experimental studies on this key cellular mechanism. The research results of Bei et al. (2018) showed that when Rb1 cultured BMSCs for 7 days, alkaline phosphatase activity (ALP) and calcium deposition increased in a dose- and concentration-dependent manner with increasing Rb1 dose and concentration. In addition, their results also showed that Rb1 significantly promoted the expression level of osteogenesis-related proteins such as osteopontin and osteoprotegerin, thereby promoting osteoblast differentiation. Since previous study explored periodontal regulation using hydrogels loaded with ginsenoside Rg1 (Guo et al., 2021), so it would be relevant to discuss the role of ginsenoside Rg1 in bone tissue repair. Cell experiments showed that Rg1 not only significantly promoted the proliferation of BMSCs but also inhibited their apoptosis (Gu et al., 2016). Rg1 increases the expression of osteogenic differentiation-related genes, including ALP, collagen I (COL1), bone morphogenetic protein-2 (BMP-2) and Runt-related transcription factor-2 (Runx2), through the BMP-2/Smad signaling pathway. Animal experimental results showed that rats in the Rg1 treatment group had a higher bone trabecular ratio, bone trabecular number (Tb. N), bone trabecular thickness (Tb. Th), bone mineral density (BMD), and bone volume percentage (BV/TV), while the number of bone trabecular separations (Tb. SP) was significantly reduced.

The Wnt signaling pathway is an evolutionarily conserved signaling pathway that determines cell fate, proliferation, and differentiation. Therefore, improper modification of Wnt signaling can result in feared diseases such as cancer, osteoporosis, and congenital disability (Niehrs, 2012). The mechanism of ginsenoside in treating osteoporosis has been studied via the Wnt signaling pathway. Chen found that PNS stimulates bone formation by promoting the proliferation and osteogenic differentiation of BMSCs, including enhancing osteoprotegerin (OPG), β-MRNA expression of catenin, and cyclin D1, while reducing the mRNA expression of RANKL and PPARγ2 (Chen et al., 2012). On the other hand, through the Wnt/β-catenin signaling pathway, the expression of

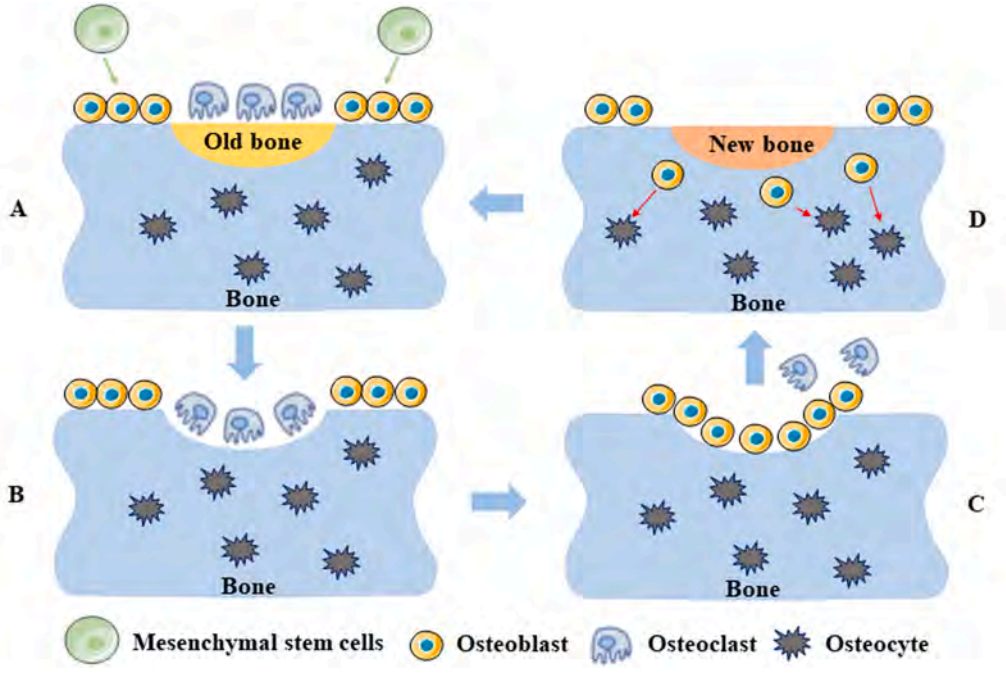

Fig. 1. Bone remodeling process under physiological conditions. **A** Mesenchymal stem cells differentiate into osteoblasts and osteoclasts. **B** Osteoclasts migrate to the surface of old bone for bone resorption. **C** After the osteoclasts leave, osteoblasts migrate to the surface to form bone. **D** New bone replaces old bone to maintain bone quality and strength.

Table 1
Detailed information on the beneficial ginsenoside properties in the treatment of osteoprosis.

Ginsenosides	BMSCs	Osteoblast	Osteoclast	Signal path or receptor	References
Rb1		✓		AHR/PRELP/NF-κB	Zhang et al. (2022)
		✓		Wnt/β-catenin	Zhou et al. (2018)
			✓	RANKL/JNK/p38MAPKs/NF-κB	Cheng et al. (2012)
		✓			Zhu et al. (2016)
	✓				Bei et al. (2018)
Rb2			✓	RANKL/NF-κb/STAT3	Cong et al. (2017)
		✓	✓		Liu et al. (2020)
		✓		RANKL	Huang et al. (2014)
	✓			Ras-ERK1/2	Gao et al. (2015)
Rb3			✓	ERK/NF-κB	Sun et al. (2023)
Rg1		✓			Lin et al. (2012)
				NF-κB	Du et al. (2011)
		✓			Gong et al. (2006)
	✓			BMP-2/SMAD	Gu et al. (2016)
Rg2			✓	MAPK/RANKL	Lee et al. (2023)
Rg3			✓	Cat-K/RANKL/NF-κB	Siddiqi et al. (2015)
				BMP-2/BMPR1A/Runx2	Zhang et al. (2016)
		✓		TGF-β1/BMP-2/IGF-I/CBF-α1	Song et al. (2020)
		✓		AMPK/mTOR	Zhang et al. (2020)
		✓			Siddiqi et al. (2015)
Rg5		✓		BMP-2/Runx2	Siddiqi et al. (2014)
Rh1		✓		BMP-2/Runx2	Siddiqi et al. (2014)
Rh2(S)		✓		PKD/AMPK	Kim et al. (2011)
			✓	RANKL/NF-κB/ERK	He et al. (2012)
Rh2(R)			✓		Liu et al. (2009)
Rk1		✓		BMP-2/Runx2	Siddiqi et al. (2014)
Rc		✓		Wnt/β-catenin	Yang et al. (2022)
Rd		✓		AMPK/BMP-2/Smad	Kim et al. (2012)
Re		✓	✓	Runt-2	Kim et al. (2016)
			✓	RANKL/NF-κB	Park et al. (2016)
NGR1		✓		MAPK and JAK1/STAT3	Wang et al. (2019)
			✓	RANKL/MAPKs	Zhao et al. (2017)
		✓			Liu et al. (2016)
		✓		JNK	Li et al. (2021)
		✓		ERs	Wang et al. (2015)
PNS	✓			Wnt/β-catenin	Chen et al. (2012)
	✓			PPARγ2	Li et al. (2011)
GCK	✓			Wnt/β-catenin	Ding et al. (2022)
GDNs			✓	RANKL/IκBα/c-JUN	Seo et al. (2023)

*NGR1, Notoginsenoside R1; PNS, Panax notoginseng saponins; GCK, Ginsenoside Compound K; GDNs, Ginseng-derived exosome-like nanovesicles.

RANKL/OPG is decreased to reduce bone resorption and protect the skeletal system, which is consistent with the results of Li (Li et al., 2011). There are also research findings confirming that ginsenoside Compound K (CK) can also activate the Wnt/β-catenin signaling pathway to promote osteogenic differentiation in BMSCs (Ding et al., 2022).

3.2. Inhibiting the apoptosis of bone marrow stromal cells

Like other cells, BMSCs also follow aging because their primary culture does not grow indefinitely but grows in a limited manner. Therefore, inhibiting the apoptosis of BMSCs is also a key mechanism for treating osteoporosis. To date, only Gao et al. (2015) have studied the mechanism of ginsenosides. In 2015, their experimental research results showed that Rb2 can protect BMSCs from dexamethasone-induced cell apoptosis through the Ras-ERK1/2 signaling pathway, and this response is dose dependent.

In summary, the differentiation and aging apoptotic changes in BMSCs are potential targets for the treatment of osteoporosis. Transplanting normal BMSCs, inhibiting their apoptosis, altering their differentiation ability, and eliminating aging BMSCs can effectively treat osteoporosis (Qadir et al., 2020), which can serve as innovative points for future research.

4. Osteoblast

Osteoblasts undergo four stages in the process of bone formation: osteoblast proliferation, extracellular matrix maturation, extracellular matrix mineralization, and osteoblast apoptosis (Fischer and Haffner-Luntzer, 2022). During the proliferation phase of osteoblasts, the number of osteoblasts increases to form multiple layers of cells and synthesize and secrete type I collagen, ultimately allowing for mineralization to form a new bone matrix (Song et al., 2022) (Fig. 4).

4.1. Promoting the activity of osteoblasts

Rb1 can significantly increase the upregulation of Runx2, osteopontin (OPN), and osteocalcin (OCN) proteins in osteoblasts, increasing the number of mineralization and calcium nodules. In addition, the above regulatory mechanism is achieved by activating AHR/PRELP and inhibiting nuclear factor kappa-B (NF-κB) by mining three database genes (Zhang et al., 2022). There is also literature confirming that three derived microorganisms isolated from Rb1 fermentation, including a known 229-ketone derivative and two new dehydrogenation

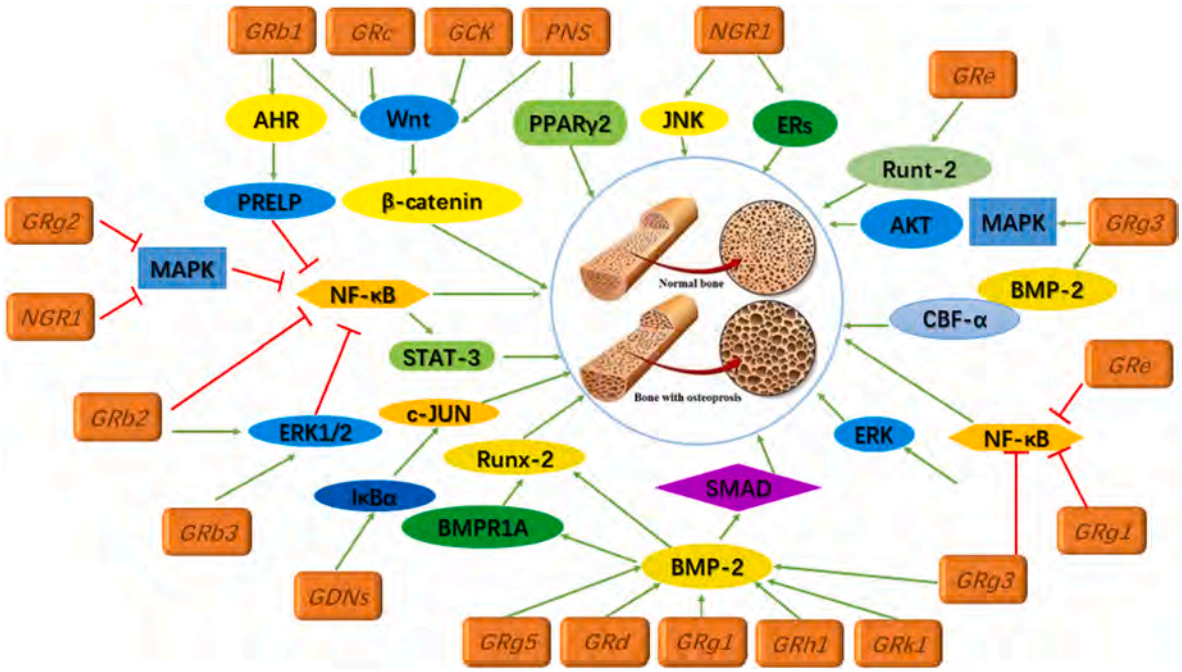

Fig. 2. Different kinds of ginsenosides play a role in the signaling pathway and key factors of the anti-osteoporosis mechanism.

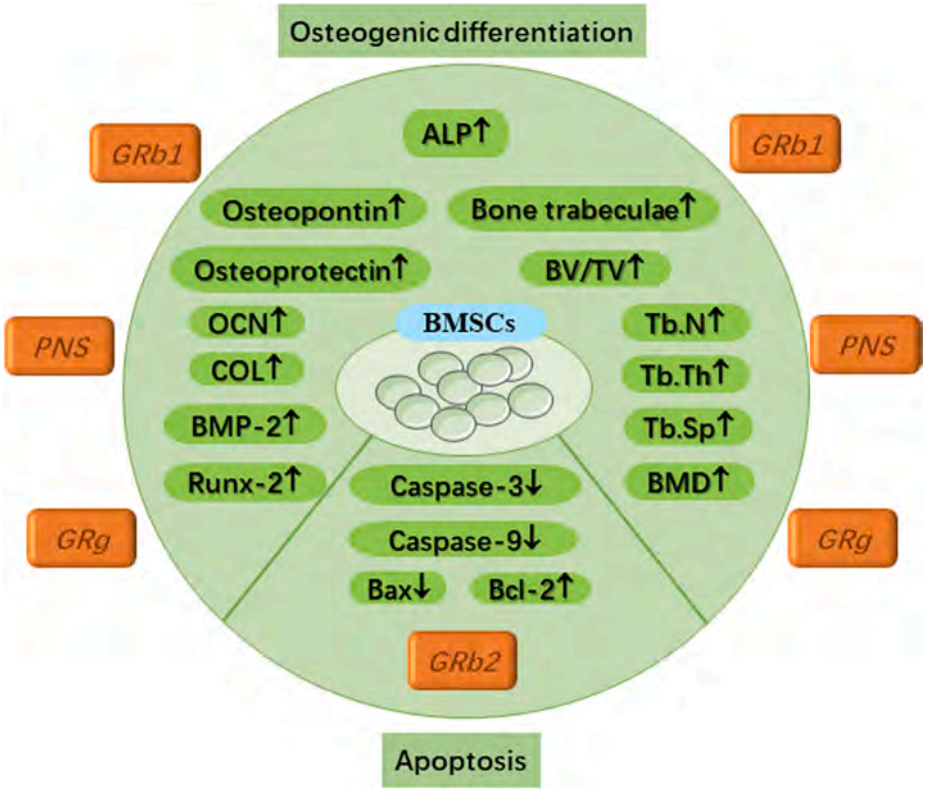

Fig. 3. Different kinds of ginsenosides play a specific role in promoting bone differentiation and anti-apoptosis through BMSCs.

metabolites, can be obtained through Wnt/β-catenin signaling, which enhances some markers of osteoblast differentiation in a dose-dependent manner (Zhou et al., 2018). In addition to Rb1, Rb2 also exhibits significant anti-osteoporosis effects in other Rb families. Some studies have shown that Rb2 treatment significantly reduced bone loss in cancellous bone and maintained biomechanics, with the bone volume fraction of rats increasing from 2.2% to 6.0%. At the same time, Rb2 increased the expression of bone alkaline phosphatase (BALP) in serum, decreased the expression of tartrate-resistant acid phosphatase (TRACP), upregulated OCN and downregulated TRAP and PPAR-γ. Compared with cathepsin K, Rb2 effectively maintained the biomechanical strength of cancellous bone, delayed bone loss, inhibited the bone resorption process, and induced osteogenic differentiation, providing evidence for the alternative treatment of osteoporosis with ginsenosides (Liu et al., 2020).

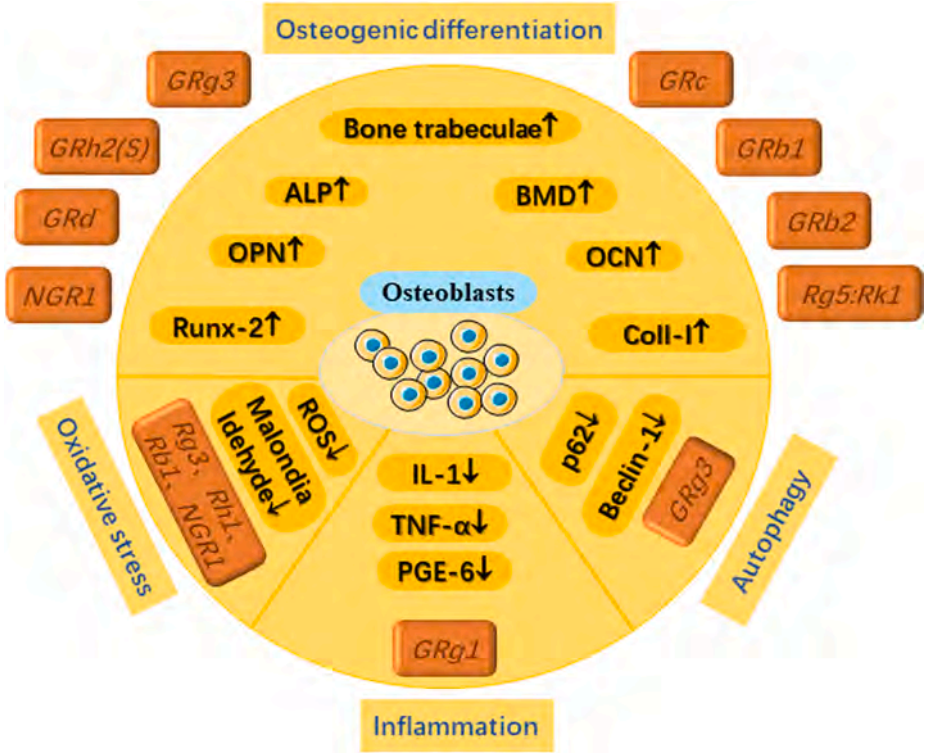

Fig. 4. Different ginsenosides play specific roles in osteogenic differentiation, anti-oxidative stress, anti-inflammation and anti-autophagy through osteoblasts.

In 2014, Siddiqi (Siddiqi et al., 2014) found that the Rg5: Rk1 mixture increased the activity of proteins related to osteoblast growth and differentiation in a dose-dependent manner, including various osteoblast markers, such as ALP activity, Coll-I, calcium deposition, extracellular mRNA expression of bone morphogenetic protein-2, and levels of Runx2. In 2015, Siddiqi's team found that Rg3 significantly improved bone formation and differentiation in MC3T3-E1 cells (Siddiqi et al., 2015) but did not clarify the specific signaling pathway. Another study (Zhang et al., 2016) filled this gap, and their results showed that Rg3 effectively prevented dexamethasone-induced weight and BMD reduction through the BMP-2/BMPR1A/Runx2 signaling axis, enhanced the secretion of bone formation markers, and reduced bone resorption markers. Rg1 exhibits the same effect: on the one hand, it can increase the number of osteoblasts, ALP activity, and intercellular cAMP concentration, and on the other hand, it can offset the decrease in BMD of the lumbar spine and tibia in ovariectomized rats (Gong et al., 2006).

In addition to some common ginsenosides mentioned above, some scholars have also selected parts from other lower content ginsenoside races for research. In 2011, Kim et al. (2011) reported that Rh2 (S) can induce differentiation and mineralization in MC3T3-E1 cells by activating the PKD/AMPK signaling pathway. Ginsenoside Re promotes osteoblast differentiation while also inhibiting osteoclast differentiation, which is regulated by the key signaling protein Runt-2 (Kim et al., 2016). In 2011, the research team also conducted basic experiments on Rd, and the results showed that Rd can induce the differentiation and mineralization of MC3T1-E2 cells by activating the AMPK/BMP-3/Smad signaling pathway (Kim et al., 2012). Another study showed that Rc can significantly inhibit the decrease in bone density, bone volume fraction, and trabecular meshwork, as well as the increase in trabecular meshwork separation, and promote the expression of bone formation-related genes through Wnt/β-regulation of the catenin signaling pathway (Yang et al., 2022).

Notoginsenoside R1 (NGR1) is a natural triterpenoid saponin compound derived from the traditional Chinese medicine Panax notoginseng and has a strong ability to promote osteoblast differentiation. Currently, two key protein targets have been identified for the study of this saponin. One of them is miR-23a (Wang et al., 2019), and NGR1 can cause overexpression of miR-23a in a concentration-dependent manner, positively regulating the expression of Runx2 and Osx, as well as ALP activity. This mechanism is achieved through the mitogen-activated protein kinase (MAPK) and JAK23/STAT1 pathways, which effectively promote osteoblast differentiation. Another key target is estrogen receptors (ERs) (Wang et al., 2015), which have been reported to have estrogenic properties. NGR1 induces ER in osteoblasts by activating the transcriptional activity of phosphorylated estrogen response element (pERE)-luciferase-α phosphorylation, which promotes the expression level of biomarkers for osteoblast differentiation, including alkaline phosphatase activity and the transcription of osteoblast genes, such as COL1, osteonectin, osteocalcin (OC), Runx2, and osterix. On the other hand, it also promotes the mineralization process of osteoblasts, which is consistent with findings of Liu et al. (2016).

Most ginsenosides still exert their anti-osteoporosis effects by promoting the activity of osteoblasts, with different signaling pathways and key protein targets. To conduct further and better research, I believe that bioinformatics technology can be chosen to explore the vast gene database.

4.2. *Inhibiting oxidative stress in osteoblasts*

Due to the energy needed for osteoblast differentiation, osteoblast precursor cells often undergo metabolic transformation to increase mitochondrial respiration levels and ATP production to ensure sufficient energy supply. However, excessive reactive oxygen species (ROS) levels reduce osteoblast differentiation, leading to a decrease in antioxidant capacity and an increase in ROS levels, leading to a decrease or loss of osteoblast differentiation potential (Zhu et al., 2022). Numerous scholars have conducted experimental demonstrations on this key mechanism. The results of Song et al. (2020) showed that Rg3 can reduce the levels of ROS and malondialdehyde while increasing the activities of glutathione peroxidase and superoxide dismutase, inhibiting oxidative stress in rat bones. On the other hand, Rg3 can promote bone formation, inhibit bone resorption, and significantly upregulate or

downregulate related proteins. The former includes bone alkaline phosphatase activity in serum, COL-I, osteocalcin, and osteopontin, while the latter includes the content of N-terminal cross-linked peptide and C-terminal cross-linked peptide of COL-I, and tartrate-resistant acid phosphatase activity in serum. Therefore, it is concluded that Rg3 can effectively alleviate AlCl3-induced osteoporosis. For this animal model, Zhu et al. (2016) also conducted research and reached consistent conclusions, but they used Rb1 and found that Rb1 can significantly promote the expression of osteoblast growth regulatory factor mRNA and the ultrastructural characteristics of osteoblasts and inhibit AlCl3-induced oxidative stress. In addition, whether in cell experiments or animal experiments, Rh1, Rb2, and NGR1 can promote the expression of related osteogenic markers by inhibiting the level of oxidative stress in osteoblasts, such as ALP, Col-I, and OCN (Huang et al., 2014; Li et al., 2021; Siddiqi et al., 2014), making them promising drugs for the treatment of OP.

4.3. Inhibiting the inflammation of osteoblasts

Osteoblasts are key bone-building cells that maintain bone homeostasis, and inflammatory stimulation can inhibit osteogenesis and activate inflammatory responses. Previous studies have confirmed that high levels of inflammation in osteoblasts significantly inhibit osteogenesis and mineralization levels (Zhang et al., 2019). Ti particles can induce a significant increase in inflammation levels in osteoblasts, and the use of different concentrations of Rg1 can significantly reduce prostaglandin 6 (PGE6) and TNF-α in osteoblasts (Lin et al., 2012). The expression of IL-1 is between that of control cells and cells cultured solely with Ti particles. Currently, there is relatively little research on the level of inflammation in osteoblasts, which is also one of the directions for future research. It is possible to explore the ability of inhibiting the inflammatory expression of osteoblasts at a deeper level to promote osteogenic differentiation and increase the expression of osteogenic-related proteins.

4.4. Inhibiting autophagy in osteoblasts

Cellular autophagy is a very important biological phenomenon that participates in various processes, such as biological development and growth. Autophagy refers to the formation of autophagosomes by a membrane enveloping part of the cytoplasm and organelles, proteins, etc., that needs to be degraded within the cell and form so-called autophagic endosomes with endosomes. Finally, the autophagic endosome fuses with lysosomes to form autophagic lysosomes, which degrade the contents they contain to achieve cell homeostasis and organelle renewal (Yoshida et al., 2022). Currently, the autophagy level of osteoblasts plays an important role in their differentiation and mineralization, and scholars unanimously believe that activating autophagy levels in osteoblasts can better stabilize bone metabolism levels (Wang et al., 2019). Rg3 significantly alleviated the increase in BW, decrease in BMD, and histological changes in femoral tissue induced by ovariectomy (OVX), significantly promoting osteogenesis and autophagy levels. Besides, Rg3 may weaken OVX-induced osteoporosis through the AMPK/mTOR signaling pathway (Zhang et al., 2020).

5. Osteoclast

Osteoclasts are multinucleated giant cells formed by the fusion of mononuclear macrophages derived from myeloid progenitor cells in the bone marrow. Early immature proliferative mononuclear phagocytes are called osteoclast precursors. These osteoclast precursors enter the bloodstream under the action of chemical factors and then enter the bone structure cavity under the action of signaling factors released by basal multicellular units. Under the stimulation of various chemical factors, transcription factors, cytokines, and other signaling factors, the osteoclast precursors fuse into multinucleated cells and ultimately activate osteoclasts. Osteoclasts, also known as bone resorbing cells, are a type of bone tissue component that performs the function of bone resorption. Osteoclasts and osteoblasts correspond functionally. The synergy between the two plays an important role in the development and formation of bones (Da et al., 2021). Osteoclasts are specialized multinucleated macrophages in the bone microenvironment composed of NF-κB ligand receptor activator (RANKL) and macrophage colony stimulating factor (M-CSF) that stimulate monocyte differentiation (Chen et al., 2023; Wu et al., 2023). Therefore, many scholars at home and abroad have used osteoclasts to study the mechanism of action of ginsenosides in the treatment of osteoporosis (Fig. 5).

5.1. Single ginsenoside

To date, most studies have only focused on different single ginsenosides, including Rb1, Rb2, Rg3, Rh2, and Re. In 2012, Cheng et al. (2012) suggested that Rb1 can inhibit RANKL-induced c-Jun N-terminal kinase (JNK), p38 MAPK, and NF-κB. Activation of the pathway inhibits the formation of Raw264.7 osteoclasts, thereby restraining the gene expression of c-Fos and nuclear factor of activated T cells (NFATc1) in osteoclasts, which is one of the effective ingredients for combating osteoporosis. Similarly, Re, Rb3, and NGR1 all inhibit osteoclast differentiation by inhibiting the RANKL-induced MAPK pathway (Lee et al., 2023; Park et al., 2016; Sun et al., 2023; Zhao et al., 2017). Cong et al. (2017) believe that Rb2 also dose-dependently inhibits the expression of nuclear factors of osteoclast marker genes NFATc2, c-Fos and cathepsin K, but this mechanism of action is through inhibition of RANKL-induced NF-κB activation of the and transcription protein 3 (STAT3) signaling pathways. In addition to the aforementioned signaling pathways, Siddiqi et al. (2015) found that Rg3 reduces RANKL-induced osteoclast-specific markers by downregulating the p38, extracellular signal-regulated kinase, and JNK pathways. In addition to the key protein factors mentioned above, regulating the phosphorylation of ERK is also a key mechanism of ginsenoside's anti-osteoporosis effect. He et al. (2012) believed that Rh2 (S-type) can inhibit RANKL-mediated MAPK and ERK phosphorylation to inhibit osteoclasts and is not cytotoxic. Liu et al. (2009) believed that Rh2 (R-type) also had an inhibitory effect on osteoclasts.

5.2. Ginsenoside mixture

Currently, there are only a few studies on the osteogenesis of ginsenoside mixtures. The research results of Seo et al. (2023) showed that GDN contains a high proportion of Rb1 and Rg1, which are more effective in inhibiting osteoclast differentiation than single using. In a lipopolysaccharide-induced bone resorption mouse model, GDNs were expressed through RANKL/IκBα. The c-JUN signaling pathway has a significant inhibitory effect on osteoclast differentiation. In addition, Lee et al. (2015) reported that six ginseng soap mixtures consisting of 0.04% Rf, 0.07% Rc, 0.12% Rb2, 0.57% Rg1, 0.64% Re and 1.19% Rb1 significantly inhibited the activity of osteoclasts. This mixture can reduce the number of osteoclasts on the one hand, and on the other hand, it stimulates the expression of mRNAs of calcium receptor (Cal-R) and estrogen receptor-α (ER-α) to affect bone structure and biochemical properties, thereby regulating bone density and bone mineral content.

6. Prospects of ginsenosides in the treatment of osteoporosis

To date, numerous studies have shown that ginsenosides have great potential in the treatment of osteoporosis, and to some extent, their related mechanisms have been revealed. However, as a therapeutic strategy, the application of ginsenosides is still limited. On the one hand, most scholars only apply a single variety of ginsenosides in both cell experiments and animal experiments, with limited research on multiple drugs. On the other hand, we need to deepen our research on the specific concentration comparison of ginsenosides in bone and whether they can cause toxic side effects in other organs of animals. In addition, many new

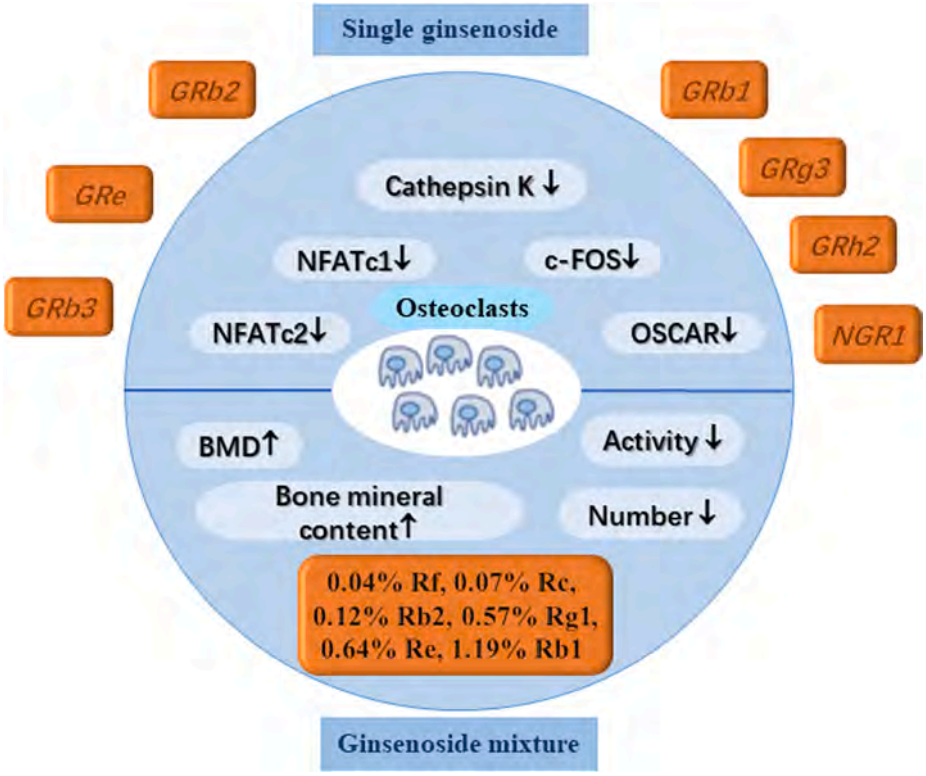

Fig. 5. Single ginsenosides and different ginsenosides exert anti-osteoporosis mechanism through osteoclasts.

biochemical materials have emerged in recent years, and we should combine ginsenosides with them to improve their pharmacological effects.

7. Conclusion

In recent years, there has been increasing research on the treatment of osteoporosis with ginsenosides. Therefore, this review describes the possible mechanisms of different types of treatment for osteoporosis from three aspects, BMSCs, osteoblasts, and osteoclasts, and summarizes their specific signaling pathways or key factor mechanisms. However, this treatment method is still in the initial stage of clinical transformation, and there are still many obstacles between its experimental results and clinical application, such as in terms of combination therapy, drug delivery pathways, bioavailability, and combination with biochemical materials. With increasing attention given to the role of ginsenosides in bone reconstruction, ginsenosides may become a new drug for treating osteoporosis and promoting fracture healing and a powerful candidate for cytokines in tissue engineering bone.

Funding

This research is supported by Tianjin Natural Science Foundation (S24YBL069).

Ethics approval and consent to participate

None.

CRediT authorship contribution statement

Rui Liu: Writing – original draft. **Li-Xia Xu:** Writing – review & editing. **Lin-Jian Tong:** Writing – review & editing. **Hai-Yang Wu:** Writing – review & editing. **Qiang Guo:** Writing – review & editing. **Zhi-Ming Sun:** Writing – review & editing. **Hua Yan:** Writing – review & editing.

Declaration of competing interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability

No data was used for the research described in the article.

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