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Review Article

Role of ginsenosides in bone remodelling: A narrative review on molecular mechanism

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ABSTRACT

Osteoporosis (OP) is a metabolic bone disease that impacts a large number of humanity. Degeneration of the bone microstructure, loss of mass, and heightened fragility are symptoms. The primary reason is because the rates of bone formation and resorption are different. Extensive research on the effects of ginsenoside, a component of ginseng used in traditional Indian medicine, on osteoporosis has shown promising results. There were forty-four articles written about ginsenosides, osteoblasts, osteoclasts, osteoporosis, and bone mesenchymal cells. The effects of ginsenosides on osteoblast, osteoclast, and mesenchymal stem cell activity in bone remodelling and their potential role in preventing osteoporosis were the focus of these studies. This in-depth study sheds light on the several ginsenosides used to treat osteoporosis from different perspectives, paving the way for potential therapeutic applications in the future.

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1. Introduction

Osteoporosis (OP), a metabolic bone disease, reduces bone density and microstructure, hence increasing the vulnerability of bones to fractures. A worldwide epidemiological study on spinal osteoporotic fractures indicates that half of males and one-third of women over the age of 50 will eventually suffer with osteoporosis.^{1,2} Studies on the matter estimate that osteoporotic hip fractures in Asia would cost more than \$15 billion annually by 2025.³ Reducing the load on worldwide healthcare systems and avoiding fractures depend on early identification and treatment of osteoporosis.

These cells remove damaged bone and simultaneously produce new bone in a sequential manner, therefore

assisting in bone healing. Bone marrow mesenchymal stem cells (BMSCs) become osteoblasts; monocyte-macrophage fusion generates osteoclasts.^{4–6}

A range of secondary ailments, including autoimmune diseases, rheumatism, gastrointestinal difficulties, blood disorders, neurological conditions, ageing, and endocrine problems, can also induce OP. Figure 1 Additional major risk factors for osteoporosis are lifestyle choices including inadequate vitamin D and calcium intake, too much salt consumption, too much alcohol usage, and smoking.⁷ These components could upset the fine equilibrium between bone cell activity and the dynamic cycle of bone formation and absorption. This can aggravate both osteostasis and OP.⁸

A. The final end-products of mesenchymal stem cell differentiation are osteoblasts and osteoclasts. B. As they are the ones in charge of resorbing bone, osteoclasts migrate to the surface of deteriorating bone. C. Osteoblasts rush

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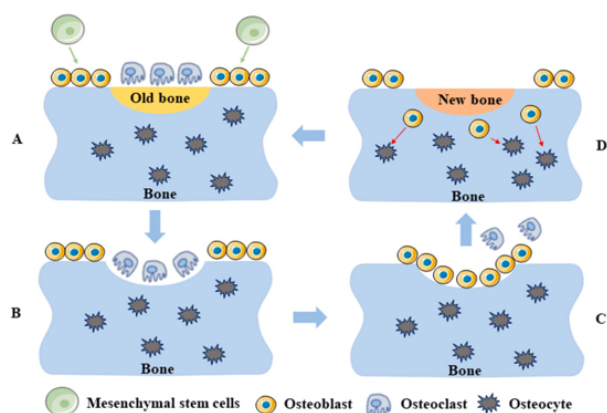


Figure 1: The process of bone remodelling under physiological settings.

to the surface to initiate bone creation the second the osteoclasts depart. a. In order to maintain the bone's quality and strength, new bone is used to replace old bone.

In terms of the drugs used to treat or prevent osteoporosis, there are essentially two main classifications. The first group includes medications that prevent bone resorption, whereas the second group includes conditions that encourage bone formation.⁹ Research has shown that several osteoporosis drugs effectively restore bone strength; nevertheless, some treatments also lower bone strain unintentionally.¹⁰ In addition, there are a number of expensive and time-consuming clinical drugs that come with serious side effects and necessitate long-term use.¹¹ Take bisphosphonates as an example; they can cause bone fractures if used in excess, and hormone therapy can have serious side effects including thrombosis.¹² Traditional Asian medicine has made extensive use of the miraculous ginseng plant for thousands of years for a wide variety of medical issues. It is a popular medical herb with many different pharmacological components; it is also a food related herb. Among these ingredients are bioactive proteins, peptides, polyacetylene, oligosaccharides, and saponins. Ginsenosides can be grouped into two types: protopanaxadiol (PPD) and proto-panaxatriol (PPT).¹³ Although ginsenoside is one of the active components of ginseng, it is just one of many chemicals extracted from the root of the plant.¹⁴ An example of a ginsenoside is Rb1, followed by Rb2, and so on along the chain to Rb3, Rc, Rd, Rh2, Rg3, and finally F2. However, there are ginsenosides of the PPT type, such as Re, Rf, Rg1, Rg2, and Rh1, that are believed to provide therapeutic promise for a range of diseases.^{15,16} The number of ginsenosides may have therapeutic benefits on osteoporosis by controlling the activity of osteoclasts and osteoblasts, according to an increasing amount of cell tests, animal experiments, and clinical investigations conducted in recent years.^{17–30} The results of recent scientific studies

corroborate these conclusions. Thus, from the perspectives of signal pathways, bone mesenchymal cells, osteoblasts, and osteoclasts, this investigation will delve more into the mechanism of action of ginsenoside in the treatment of osteoporosis. The goal of this review is to outline the objectives of new ways of treating osteoporosis.

2. Different types of ginsenoside compounds

nd Figure 2 respectively present the active components that are connected with the ginsenosides that are utilised in the treatment of OP.

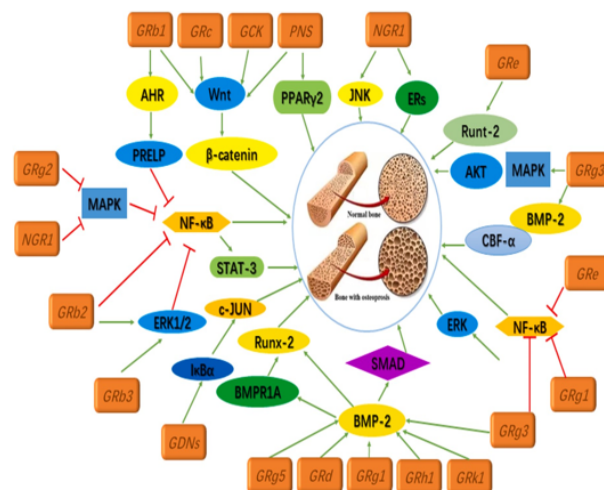


Figure 2: Different ginsenosides affect different parts of the anti-osteoporosis mechanism's signalling pathway.

3. Bone marrow stromal cells (BMSCs)

Mesenchymal stem cells (MSCs) found in bone marrow are known as bone marrow stem cells (BMSCs).⁵⁹ The capacity of these MSCs to develop into osteoblasts, adipocytes, or chondrocytes is crucial for their function in preserving normal bone stability. It has been demonstrated that osteoporosis develops in part because of changes in bone marrow stem cell (BMSC) proliferation and differentiation, quantity, and function.⁶⁰ (Figure 3).

3.1. Supporting the process of bone marrow stromal cell osteogenic differentiation

The outcome of this transformation is a decrease in bone production, which happens when the differentiation of osteoblasts from bone marrow stem cells (BMSCs) is relatively low. This crucial biological function has thus been the subject of several experimental investigations, some of which are described below. Calcium deposition and alkaline phosphatase activity (ALP) in BMSCs cultured with Rb1 for seven days increased in a concentration- and dose-dependent manner.⁶¹ This happened when the

Table 1: Ginsenoside properties in the treatment of osteoporosis.

Ginsenosides	BMSCs	Osteoblast	Osteoclast	Signal path or receptor	References
Rb1	√	√	√	AHR/ PRELP/NF-κB	22
		√		Wnt/β-catenin	23
				RANKL/JNK/p38MAPKs/NF-κB	31
		√			24
					25
Rb2			√	RANKL/NF-κB/STAT3	26
		√	√		27
		√		RANKL	28
				Ras-ERK1/2	29
Rb3				ERK/NF-κB	30
Rg1		√			32
				NF-κB	33
		√			34
	√			BMP-2/SMAD	35
Rg2			√	MAPK/ RANKL	36
Rg3			√	Cat-K/RANKL/NF-κB	37
				BMP-2/BMPRI A/Runx2	38
		√		TGF-β1/BMP-2/IGF-1/CBF-α1	39
		√		AMPK/mTOR	40
		√			41
Rg5		√		BMP-2/Runx2	42
Rh1		√		BMP-2/Runx2	42
Rh(S)		√		PKD/AMPK	43
			√	RANKL/NF-κB/ERK	44
Rh2(R)			√		45
Rk1		√		BMP-2/Runx2	42
Rc		√		Wnt/β-catenin	46
Rd		√		AMPK/BMP-2/Smad	47
Re		√	√	Runt-2	48
			√	RANKL/NF-κB	49
NGR1		√		MAPK and JAK1 / STAT3	50
			√	RANKL/MAPKs	51
					52
		√		JNK	53
		√		ERs	54
PNS				Wnt/β-catenin	55
	√			PPARγ2	56
GCK	√			Wnt/β-catenin	57
GDNs			√	RANKL/IκBα/c-JUN	58

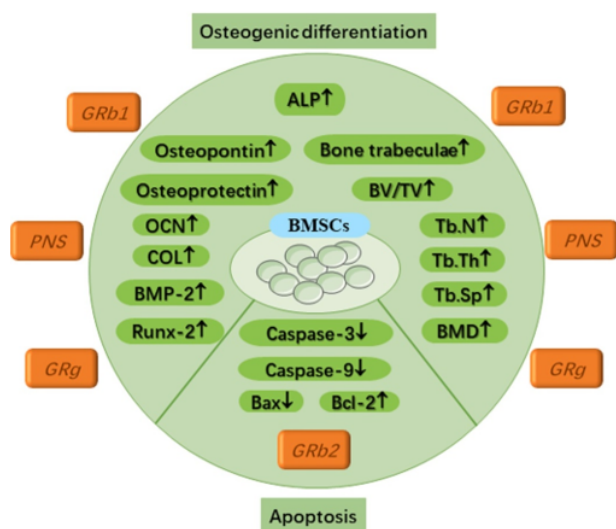


Figure 3: Certain ginsenosides activate BMSCs in a way that promotes bone development and inhibits cell death.

dosage and concentration of Rb1 were raised. Furthermore, their study's results showed that Rb1 induced osteoblast differentiation by significantly raising the expression levels of osteogenesis-related proteins such osteopontin and osteoprotegerin. It is appropriate to address the function of ginsenoside Rg1 in bone tissue restoration in light of a recent study that examined the regulation of periodontal tissue using hydrogels loaded with Rg1.⁶² Cellular research shown that Rg1 inhibited cell death (apoptosis) and significantly facilitated the growth of bone marrow stem cells (BMSCs).⁶³ Increased expression of genes linked to osteogenic differentiation is a consequence of Rg1's role in the BMP-2/Smad signalling pathway. The following genes are part of this set: ALP, COL1, BMP-2, and Runt-related transcription factor-2 (Runx2). The results of the animal studies showed that rats given Rg1 had much higher levels of bone trabecular ratio, trabecular number, trabecular thickness, bone mineral density, and bone volume % compared to rats given a placebo. The number of bone trabecular separations (Tb. SP) was, however, markedly reduced.

Evolution has spared several signalling pathways, and the Wnt signalling system is one such them. Cell proliferation, differentiation, and destiny are all controlled by this pathway. Illnesses including cancer, osteoporosis, and congenital disability can arise when Wnt signalling is manipulated in an improper way. To learn how ginsenoside works to treat osteoporosis, researchers have looked into the Wnt signalling pathway.⁶⁴ By promoting the proliferation and osteogenic differentiation of bone marrow stem cells (BMSCs), the peripheral nervous system (PNS) contributes to the stimulation of bone production. Osteoprotegerin (OPG), β -MRNA synthesis

of catenin, and cyclin D1 are all improved, however RANKL and PPAR γ 2 mRNA expression are decreased.⁶⁵ The Wnt/ β -catenin signalling pathway, in contrast, reduces the expression of RANKL/OPG.⁶⁶ This decrease in expression aids in protecting the skeletal system by limiting bone resorption. Furthermore, studies have shown that ginsenoside compound K (CK) can stimulate osteogenic differentiation in bone marrow stem cells (BMSCs) via activating the Wnt/ β -catenin signalling pathway.⁶⁷

3.2. Inhibiting the apoptosis of bone marrow stromal cells

Figure 1 shows a schematic of the physiologically-driven bone remodelling process. Differentiation begins with mesenchymal stem cells and culminates in osteoblasts and osteoclasts. B. Bone resorption occurs when osteoclasts, the cells responsible for the process, move to the surface of dead bone. C. The initial phase in making new bone, known as osteoblast migration to the surface, occurs immediately after osteoclasts depart. a. Removing and replacing old bone with new bone is necessary to keep the bone's quality and strength.

Bone marrow stem cells (BMSCs) are potential therapeutic targets for osteoporosis due to age-related changes in cell death and differentiation. Bone marrow stem cell (BMSC) transplantation, apoptosis inhibition, BMSC modification of differentiation capacity, and BMSC elimination are all successful treatments for osteoporosis. Future research can build on these discoveries in innovative ways.⁶⁸

4. Osteoblast

There are four stages that osteoblasts go through as they produce bone: proliferation, maturation of the extracellular matrix, mineralisation of the extracellular matrix, and apoptosis.⁶⁹ The process culminates in apoptosis. As the number of osteoblasts increases during proliferation, new bone matrix is formed, type I collagen is synthesised and secreted, and many layers of cells are formed (Figure 4).⁷⁰

4.1. Promoting the activity of osteoblasts

An increase in the number of calcium nodules and consequent mineralisation can be achieved by Rb1 by a dramatic overexpression of Runx2, osteopontin (OPN), and osteocalcin (OCN) proteins in osteoblasts. In addition, the regulatory approach mentioned earlier is carried out by using three genes from the database to activate the AHR/PRELP pathway and inhibit the nuclear factor kappa-B (NF- κ B) route.⁷¹ Furthermore, several studies have shown that the Wnt/ β -catenin signalling pathway can be used to acquire three microorganisms produced from Rb1 fermentation. Among these microbes, you can find two novel dehydrogenation metabolites and

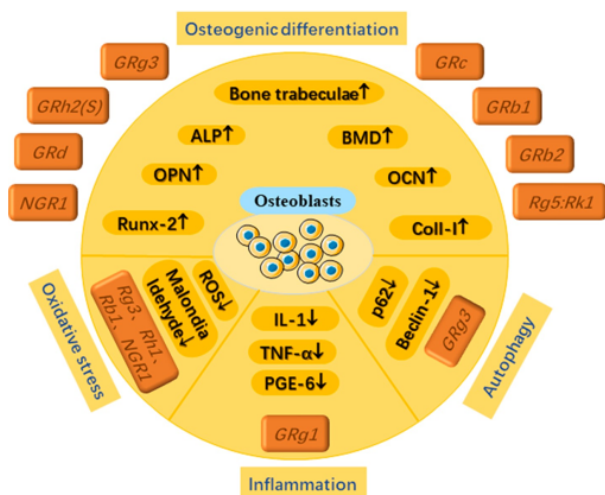


Figure 4: Different ginsenosides play specific roles in osteogenic differentiation, anti-oxidative stress, anti-inflammation and anti-autophagy through osteoblasts.

a well-known 229-ketone derivative. These microbes improve osteoblast differentiation indicators in a way that depends on the dosage.⁷² Beyond Rb1, further members of the Rb family, such as Rb2, have demonstrated strong anti-osteoporosis properties. Several studies have shown that Rb2 therapy significantly reduced bone loss in cancellous bone while retaining biomechanics. Consequently, rat bone volume fraction went raised from 2.2% to 6.0%. While Rb2 increased serum levels of bone alkaline phosphatase (BALP), decreased levels of tartrate-resistant acid phosphatase (TRACP), increased levels of octanoin (OCN), and decreased levels of tyrosine phosphatase (TRAP) and PPAR- γ , these changes occurred simultaneously. Also, Rb2 did a better job than cathepsin K of preserving cancellous bone's biomechanical strength, postponing bone loss, blocking bone resorption, and inducing osteogenic differentiation. These findings provide credence to the idea that ginsenosides can be used as an alternate treatment for osteoporosis.⁷³

There was a dose-dependent increase in the activity of proteins involved in osteoblast development and differentiation by the Rg5: Rk1 combination. Calcium deposition, extracellular mRNA expression of bone morphogenetic protein-2, levels of Runx2, and ALP activity were among the proteins that comprised this set of osteoblast indicators.⁷⁴ Rg3 significantly boosted MC3T3-E1 cell bone formation and differentiation. There was a lack of specificity regarding the signalling route that was involved, though.⁷⁵ Rg3 effectively counteracted dexamethasone's effects on bone mineral density and weight loss via the BMP-2/BMPRII/Runx2 signalling pathway. Furthermore, Rg3 lowered markers of bone resorption and raised those of bone growth. Similarly,

Rg1 can increase osteoblast numbers, ALP activity, and intercellular cAMP concentration, and it can compensate for the loss of BMD in the lumbar spine and tibia of rats that have undergone ovariectomy.^{75,76}

Furthermore, other researchers have used components from different ginsenoside races with lower composition for their studies, in addition to the common ginsenosides already mentioned. According to research published in 2011 by Kim et al., Rh2 (S) can activate the PKD/AMPK signalling pathway, which in turn stimulates mineralisation and differentiation in MC3T3-E1 cells. While limiting osteoclast differentiation, ginsenoside Re promotes osteoblast differentiation, a process regulated by the crucial signalling protein Runt-2. Fundamental studies were also conducted on Rd in 2011 by the study team.⁷⁷ Through stimulating the AMPK/BMP-3/Smad signalling cascade, our experiments showed that Rd may promote mineralisation and differentiation of MC3T1-E2 cells. According to another study, Rc can greatly prevent bone density loss, bone volume percentage, and trabecular meshwork from decreasing and trabecular meshwork separation from increasing. In addition, it can regulate the catenin signalling system through the Wnt/ β pathway, which implies it can enhance the expression of genes associated with bone production.⁷⁸

Panax notoginseng, a plant used in traditional Chinese medicine, is the source of the natural triterpenoid saponin molecule known as notoginsenoside R1, or NGR1. It may stimulate the formation of osteoblasts with great efficacy. Two key protein targets have been identified so far for this saponin's investigation. The capacity of NGR1 to induce concentration-dependent overexpression of miR-23a regulates Runx2 and OsX expression, ALP activity, and other genes in a positive way. In 2019, Wang et al. found one of these microRNAs, miR-23a. This technique is accomplished by utilising the mitogen-activated protein kinase (MAPK) and JAK2/STAT1 pathways, which are known to promote osteoblast growth successfully. The oestrogen receptors (ERs), which have been found to have osteogenic properties, are another significant target.⁷⁹ "Oestrogen receptors" are another key area of focus. NGR1 activates the transcriptional activity of phosphorylated oestrogen response element (pERE)-luciferase- α phosphorylation, which in turn induces endoplasmic reticulum (ER) in osteoblasts. The transcription of osteoblast genes (such as COL1, osteonectin, osteocalcin (OC), Runx2, and osteriX) and alkaline phosphatase activity are both enhanced by this action, which is a biomarker for osteoblast development. Plus, it promotes osteoblast mineralisation.⁸⁰

Most ginsenosides still fight osteoporosis by getting osteoblasts to work more by hitting many targets and signalling pathways crucial for protein expression. I believe that bioinformatics might be chosen to explore the large

gene database in order to carry out more effective and broad research.

4.2. Preventing Osteoblast Oxidative Stress

In order to increase the levels of mitochondrial respiration and ATP generation, osteoblast precursor cells often undergo metabolic changes. This is because osteoblast growth is energy intensive. In order to make sure there's enough power, this is done. However, when ROS levels are high, osteoblast differentiation is reduced, antioxidative ability is decreased, and ROS levels are increased. This vicious cycle continues until the osteoblast differentiation potential is lost or reduced.⁸¹ A large number of researchers have conducted experiments to prove this crucial mechanism. Rg3 can reduce malondialdehyde and reactive oxygen species (ROS) levels while increasing glutathione peroxidase and superoxide dismutase activity, which inhibits oxidative stress in rat bones.⁸² In contrast, Rg3 can promote bone formation and prevent bone resorption in addition to significantly up- or down-regulating associated proteins. Sera COL-I, osteocalcin, osteopontin, and bone alkaline phosphatase activity make up the first group. The second group includes tartrate-resistant acid phosphatase activity in serum and the N-terminal and C-terminal cross-linked peptide content of COL-I. As a result, Rg3 likely has the potential to alleviate AIC13-induced osteoporosis. Research by Zhu et al. (2016) using the same animal model yielded similar results.⁸³ Nevertheless, by utilising Rb1, they learnt that Rb1 can greatly enhance osteoblast ultrastructural features and the expression of osteoblast growth regulating factor mRNA. Additionally, oxidative stress generated by AIC13 was discovered to be inhibited by Rb1. Also, studies have shown that Rh1, Rb2, and NGR1 can reduce oxidative stress in osteoblasts, which in turn increases the production of associated osteogenic markers. The ALP, Col-I, and OCN markers are among them. These medications show great promise in treating osteoporosis (OP).^{84–86}

4.3. Reducing osteoblast inflammation

The balance of bone mass is ensured by osteoblasts, which are cells that are vital for the formation of new bone. Simultaneously inhibiting osteogenesis and activating inflammatory responses are possible outcomes of inflammatory stimulation. The inhibitory effects of osteogenesis and mineralisation are significantly affected by the high levels of inflammation in osteoblasts.⁸⁷ The levels of prostaglandin (PGE6) and TNF- α in osteoblasts can be significantly decreased by using various amounts of Rg1.⁸⁸

Titanium particles can cause osteoblasts to experience a dramatic rise in inflammatory levels. Similar levels of IL-1 expression were seen in cells cultured just with titanium particles and in control cells. Inflammation levels

in osteoblasts have been the subject of very little research up to this point. One of the areas where future research will concentrate on this as well. Investigating the potential of limiting the inflammatory expression of osteoblasts at a deeper level can improve osteogenic differentiation and boost the production of proteins relevant to osteogenesis.

4.4. Preventing autophagy in osteoblasts

The process of cellular autophagy is crucial to many biological processes, including the development and maintenance of living things. A process called "autophagy" involves the breakdown of various components within the cell, including organelles, proteins, and cytoplasm, into smaller structures called "autophagic endosomes" that are housed within endosomes. Finally, autophagic lysosomes are formed when autophagic endosomes combine with lysosomes. To achieve cellular homeostasis and organelle renewal, these lysosomes must degrade the materials they carry.⁸⁹ All the experts agree that a better way to stabilise bone metabolism is to activate autophagy levels in osteoblasts. The current state of osteoblast differentiation and mineralisation is greatly influenced by their autophagy level, which is why this is the case. The effects of ovariectomy (OVX) on body weight gain, bone mineral density decrease, and femoral tissue histological abnormalities were significantly mitigated by Rg3. Osteogenesis and autophagy were also significantly enhanced by Rg3. Rg3 may mitigate OVX-induced osteoporosis via the AMPK/mTOR signalling pathway.

5. Osteoclast

Large, multinucleated cells called osteoclasts are made in the bone marrow by merging mononuclear macrophages with myeloid progenitor cells. Precursors of osteoclasts are proliferative early immature mononuclear phagocytes. These early-stage osteoclasts enter the bloodstream in response to chemical cues. Finally, they enter the bone structure cavity, where basal multicellular units emit signalling substances that affect them. A wide range of pharmacological substances, transcription factors, cytokines, and other signalling factors can activate osteoclasts by causing their progenitors to fuse into multinucleated cells. The process of bone resorption is carried out by a particular type of cell in bone tissue called bone resorbing cells, often called osteoclasts. There is no difference in function between osteoclasts and osteoblasts. When it comes to bone growth and formation, the interplay between the two is crucial.⁹⁰ The bone microenvironment contains osteoclasts, which are macrophages with many nuclei. The components that make them up are M-CSF and NF- κ B ligand receptor activator (RANKL), both of which are recognised as drivers of monocyte growth.^{91,92} As a result, numerous researchers in the US and abroad

have studied the efficacy of ginsenosides as an osteoporosis treatment by manipulating osteoclasts (Figure 5).

5.1. Single ginsenoside

Most studies done thus far have focused on specific ginsenosides, such as Rb1, Rb2, Rg3, Rh2, and Re. Rb1 can block the activities of NF- κ B, p38 MAPK, and RANKL-induced c-Jun N-terminal kinase (JNK).⁹³ (In order to combat osteoporosis, it is necessary to activate a pathway that stops the formation of Raw264.7 osteoclasts by limiting the gene expression of c-Fos and nuclear factor of activated T cells (NFATc1) in these cells. The RANKL-induced MAPK pathway is blocked by Re, Rb3, and NGR1, which in turn limits osteoclast differentiation. According to previous research, Rb2 has a dose-dependent effect on the expression of NFATc2, c-Fos, and cathepsin K, which are genes that are known to be osteoclast marker genes. The suppression of the STAT3 signalling pathways and RANKL-induced NF- κ B activation is linked to this mode of action, though. By downregulating the p38, extracellular signal-regulated kinase, and JNK pathways, Siddiqi et al. (2015) found that Rg3 reduces RANKL-induced osteoclast-specific markers. On top of the signalling channels already covered, here is another one.^{94–96} The modulation of ERK phosphorylation is one of the essential mechanisms via which ginsenoside exerts its anti-osteoporosis effect. Not only that, but this method supplements the previously mentioned critical protein factors.⁹⁷ The non-cytotoxic Rh2 (S-type) can inhibit osteoclasts by suppressing RANKL-mediated MAPK and ERK activation.⁹⁸ It was also believed that Rh2 (R-type) inhibited osteoclasts.

5.2. Ginsenoside mixture

The osteogenesis of ginsenoside combinations is an area that has seen very little investigation thus far. Rb1 and Rg1 are more effective together than individually in blocking osteoclast differentiation, and the GDN has a high concentration of both. In a mouse model of lipopolysaccharide-induced bone resorption, GDNs were expressed by means of RANKL/ $\text{I}\kappa\text{B}\alpha$ expression. The c-JUN signalling pathway has a long-lasting inhibitory effect on osteoclast formation.⁹⁹ A combination of siX ginseng soaps containing 0.04% Rf, 0.07% Rc, 0.12% Rb2, 0.57% Rg1, 0.64% Re, and 1.19% Rb1 successfully inhibited osteoclast activity. First, this combination can reduce the number of osteoclasts. Additionally, it can enhance the production of mRNAs for the calcium receptor (Cal-R) and the oestrogen receptor- α (ER- α). This, in turn, influences the biochemical characteristics and structure of bones, leading to regulation of bone density and mineral content.¹⁰⁰

6. Prospects of ginsenosides in the treatment of osteoporosis

The osteogenesis of ginsenoside combinations is an area that has seen very little investigation thus far. Rb1 and Rg1 are more effective in inhibiting osteoclast differentiation when present in GDN in substantial fractions compared to when used alone. In a mouse model of lipopolysaccharide-induced bone resorption, GDNs were expressed by means of RANKL/ $\text{I}\kappa\text{B}\alpha$ expression. The c-JUN signalling pathway has a long-lasting inhibitory effect on osteoclast formation.⁹⁹ A combination of siX ginseng soaps containing 0.04% Rf, 0.07% Rc, 0.12% Rb2, 0.57% Rg1, 0.64% Re, and 1.19% Rb1 successfully inhibited osteoclast activity. Their analysis confirmed this. First, this combination can reduce the number of osteoclasts. Additionally, it can enhance the production of mRNAs for the calcium receptor (Cal-R) and the oestrogen receptor- α (ER- α). This, in turn, influences the biochemical characteristics and structure of bones, leading to regulation of bone density and mineral content.¹⁰⁰

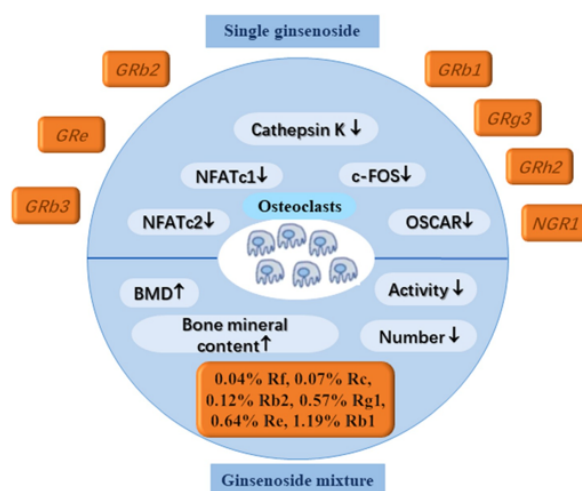


Figure 5: Single ginsenosides and different ginsenosides exert anti-osteoporosis mechanism through osteoclasts.

7. Conclusion

There has been a rise in the amount of research conducted in recent years regarding the use of ginsenosides as a therapy for osteoporosis. A summary of the distinct signalling pathways or key factor mechanisms that are associated with bone marrow stem cells (BMSCs), osteoblasts, and osteoclasts is provided in this review. As a result, this review covers the possible mechanisms of various types of treatment for osteoporosis from three different perspectives. However, this treatment method is still in the preliminary stages of clinical transformation, and there are still a great deal of obstacles that

stand between its experimental results and its clinical application. These obstacles include combination therapy, drug delivery pathways, bioavailability, and the combination of biochemical materials. Ginsenosides have the potential to become a new medicine for the treatment of osteoporosis and the promotion of fracture healing. Additionally, they serve as a powerful candidate for cytokines in tissue engineering bone. This is due to the growing attention that is being paid to the role that ginsenosides play in bone rebuilding.

8. Source of Funding

None.

9. Conflict of Interest

None.

References

- Gopinath V, Kovalenko VM, Korzh MO, Tatarchuk TF, Dedukh NV. Guideline for diagnostic, prevention and treatment of postmenopausal osteoporosis. *Osteoporosis Med Clin*. 2023;107(3):213–25.
- Laird C, Benson H, Williams KA. Pharmacist interventions in osteoporosis management: a systematic review. *Osteoporosis Int*. 2023;34(2):239–54.
- Cheung CL, Ang SB, Chadha M, Chow ES, Chung YS, Hew FL, et al. An updated hip fracture projection in Asia: The Asian Federation of Osteoporosis Societies study. *Osteoporosis Sarcopenia*. 2018;4(1):16–21.
- Guo D, Zhao M, Xu W, He H, Li B, Hou T. Dietary interventions for better management of osteoporosis: an overview. *Crit Rev Food Sci Nutr*. 2023;63(1):125–44.
- Harris K, Zagar CA, Lawrence KV. Osteoporosis: common questions and answers. *Am Fam Physician*. 2023;107(3):238–46.
- Iantomasi T, Romagnoli C, Palmieri G, Donati S, Falsetti I, Miglietta F. Oxidative stress and inflammation in osteoporosis: molecular mechanisms involved and the relationship with microRNAs. *Int J Mol Sci*. 2023;24(2):3772.
- Patel D, Wairkar S. Bone regeneration in osteoporosis: opportunities and challenges. *Drug Deliv Transl Res*. 2023;13(2):419–32.
- Beekman KM, Duque G, Corsi A, Tencerova M, Bisschop PH, Paccou J. Osteoporosis and bone marrow adipose tissue. *Curr Osteoporosis Rep*. 2023;21(1):45–55.
- Leboff MS, Greenspan SL, Insogna KL, Lewiecki EM, Saag KG, Singer AJ, et al. The clinician's guide to prevention and treatment of osteoporosis. *Osteoporosis Int*. 2022;33(10):2049–102.
- Patel D, Wairkar S. Bone regeneration in osteoporosis: opportunities and challenges. *Drug Deliv Transl Res*. 2023;13:419–32.
- Sugiyama T, Kim YT, Oda H. Osteoporosis therapy: a novel insight from natural homeostatic system in the skeleton. *Osteoporosis Int*. 2015;26(2):443–7.
- Lewiecki EM, Dinavahi RV, Lazaretti-Castro M, Ebeling PR, Adachi JD, Miyauchi A, et al. One year of romosozumab followed by two years of denosumab maintains fracture risk reductions: results of the FRAME extension study. *J Bone Miner Res*. 2019;34(3):419–28.
- Ding L, Qi H, Wang Y, Zhang Z, Liu Q, Guo C, et al. Recent advances in ginsenosides against respiratory diseases: therapeutic targets and potential mechanisms. *Biomed Pharm*. 2023;158:114096.
- Paik S, Song GY, Jo EK. Ginsenosides for therapeutically targeting inflammation through modulation of oxidative stress. *Int Immunopharm*. 2023;121:110461.
- Li J, Li F, Jin D. Ginsenosides are promising medicine for tumor and inflammation: a review. *Am J Chin Med*. 2023;51(4):883–908.
- Qi L, Zhang J, Wang J, An J, Xue W, Liu Q, et al. Mechanisms of ginsenosides exert neuroprotective effects on spinal cord injury: a promising traditional Chinese medicine. *Front Neurosci*. 2022;16:969056.
- He J, Li X, Wang Z, Bennett S, Chen K, Xiao Z, et al. Therapeutic anabolic and anticatabolic benefits of natural Chinese medicines for the treatment of osteoporosis. *Front Pharmacol*. 2019;10:1344.
- Jung SJ, Oh MR, Lee DY, Lee YS, Iantomasi T, Romagnoli C, et al. Oxidative stress and inflammation in osteoporosis: molecular mechanisms involved and the relationship with microRNAs. *Int J Mol Sci*. 2023;24(4):3772.
- Li X, Lin H, Zhang X, Jaspers RT, Yu Q, Ji Y, et al. Noto-ginsenoside R1 attenuates oxidative stress-induced osteoblast dysfunction through JNK signalling pathway. *J Cell Mol Med*. 2021;25(23):11278–89.
- Wang T, Liu Q, Tjhi W, Zhao J, Lu A, Zhang G, et al. Therapeutic potential and outlook of alternative medicine for osteoporosis. *Curr Drug Tar*. 2017;18:1051–68.
- Zhang D, Du J, Yu M, Suo L. Ginsenoside Rb1 prevents osteoporosis via the AHR/PRELP/NF- κ B signaling axis. *Phytomedicine*. 2022;104:154205.
- Zhou W, Huang H, Zhu H, Zhou P, Shi X. New metabolites from the biotransformation of ginsenoside Rb1 by *Paecilomyces bainieri* sp.229 and activities in inducing osteogenic differentiation by Wnt/ β -catenin signaling activation. *J Ginseng Res*. 2018;42(2):199–207.
- Cheng B, Li J, Du J, Lv X, Weng L, Ling C. Ginsenoside Rb1 inhibits osteoclastogenesis by modulating NF- κ B and MAPKs pathways. *Food Chem Toxicol*. 2012;50(5):1610–5.
- Bei J, Zhang X, Wu J, Hu Z, Xu B, Lin S, et al. Ginsenoside Rb1 does not halt osteoporotic bone loss in ovariectomized rats. *PLoS One*. 2018;13(9):e0202885.
- Cong F, Liu J, Wang C, Yuan Z, Bi L, Liang J, et al. Ginsenoside Rb2 inhibits osteoclast differentiation through nuclear factor-kappaB and signal transducer and activator of transcription protein 3 signaling pathway. *Biomed Pharm*. 2017;92:927–34.
- Liu Q, Zhou J, Yang Z. The ginsenoside exhibits antiosteoporosis effects in ketogenic-diet-induced osteoporosis via rebalancing bone turnover. *Front Pharmacol*. 2020;11:593820.
- Huang Q, Gao B, Jie Q, Wei BY, Fan J, Zhang HY. Ginsenoside-Rb2 displays anti-osteoporosis effects through reducing oxidative damage and bone-resorbing cytokines during osteogenesis. *Bone*. 2014;66:306–14.
- Gao B, Huang Q, Jie Q, Zhang HY, Wang L, Guo YS, et al. Ginsenoside-Rb2 inhibits dexamethasone-induced apoptosis through promotion of GPR120 induction in bone marrow-derived mesenchymal stem cells. *Stem Cell Dev*. 2015;24(6):781–90.
- Sun M, Ji Y, Zhou S, Chen R, Yao H, Du M. Ginsenoside Rb3 inhibits osteoclastogenesis via ERK/NF- κ B signaling pathway in vitro and in vivo. *Oral Dis*. 2023;29(8):3460–71.
- Lin Y, Wu Y, He J, Huang Y, Lin Y. Effects of ginsenosides rg1 on osteoblasts cultured with ti particles. *Biomol Ther (Seoul)*. 2012;20(1):75–80.
- Zhu Y, Hu C, Zheng P, Miao L, Yan X, Li H, et al. Effect of 17beta-oestradiol and ginsenoside on osteoporosis in ovariectomized rats. *J Asian Nat Prod Res*. 2016;8:649–56.
- Gong YS, Chen J, Zhang QZ, Zhang JT. Effect of 17beta-oestradiol and ginsenoside on osteoporosis in ovariectomized rats. *J Asian Nat Prod Res*. 2006;8:649–56.
- Gu Y, Zhou J, Wang Q, Fan W, Yin G. Ginsenoside Rg1 promotes osteogenic differentiation of rBMSCs and healing of rat tibial fractures through regulation of GR-dependent BMP-2/SMAD signaling. *Sci Rep*. 2016;6:25282.
- Lee SH, Park SY, Kim JH, Kim N, Lee J. Ginsenoside Rg2 inhibits osteoclastogenesis by downregulating the NFATc1, c-Fos, and MAPK pathways. *BMB Rep*. 2023;56(10):551–6.
- Siddiqi MH, Siddiqi MZ, Kang S, Noh HY, Ahn S, Simu SY, et al. Inhibition of osteoclast differentiation by ginsenoside Rg3 in RAW264.7 cells via RANKL, JNK and p38 MAPK pathways

- through a modulation of cathepsin K: an in silico and in vitro study. *Phytother Res.* 2015;29(9):1286–94.
36. Zhang X, Chen K, Wei B, Liu X, Lei Z, Bai X. Ginsenosides Rg3 attenuates glucocorticoid-induced osteoporosis through regulating BMP-2/BMPRII/Runx2 signaling pathway. *Chem Biol Interact.* 2016;256:188–97.
 37. Song M, Jia F, Cao Z, Zhang H, Liu M, Gao L. Ginsenoside Rg3 attenuates aluminum-induced osteoporosis through regulation of oxidative stress and bone metabolism in rats. *Biol Trace Elem Res.* 2020;198(2):557–66.
 38. Zhang X, Huang F, Chen X, Wu X, Zhu J. Ginsenoside Rg3 attenuates ovariectomy-induced osteoporosis via AMPK/mTOR signaling pathway. *Drug Dev Res.* 2020;81:874–85.
 39. Siddiqi MH, Siddiqi MZ, Kang S, Noh HY, Ahn S, Simu SY, et al. Inhibition of osteoclast differentiation by ginsenoside Rg3 in RAW264.7 cells via RANKL, JNK and p38 MAPK pathways through a modulation of cathepsin K: an in silico and in vitro study. *Phytother Res.* 2015;29(9):1286–94.
 40. Siddiqi MH, Siddiqi MZ, Ahn S, Kim YJ, Yang DC. Ginsenoside Rh1 induces mouse osteoblast growth and differentiation through the bone morphogenetic protein 2/runt-related gene 2 signalling pathway. *J Pharm Pharm.* 2014;66(12):1763–73.
 41. Siddiqi MZ, Siddiqi MH, Kim YJ, Jin Y, Huq MA, Yang DC. Effect of fermented red ginseng extract enriched in ginsenoside Rg3 on the differentiation and mineralization of preosteoblastic MC3T3-E1 cells. *J Med Food.* 2015;18(5):542–8.
 42. Kim DY, Park KH, Jung MS, Huang B, Yuan HD, Quan HY. Cinnamaldehyde prevents adipocyte differentiation and adipogenesis via regulation of peroxisome proliferator-activated receptor- γ (PPAR γ) and AMP-activated protein kinase (AMPK) pathways. *J Agric Food Chem.* 2011;59(8):3666–73.
 43. He L, Lee J, Jang JH, Lee SH, Nan MH, Oh BC. Ginsenoside Rh2 inhibits osteoclastogenesis through down-regulation of NF- κ B, NFATc1 and c-Fos. *Bone.* 2012;50(6):1207–13.
 44. Liu J, Shiono J, Shimizu K, Yu H, Zhang C, Jin F, et al. (R)-ginsenoside Rh2, not 20(S), is a selective osteoclastogenesis inhibitor without any cytotoxicity. *Bioorg Med Chem Lett.* 2009;19:3320–3.
 45. Yang N, Zhang X, Li L, Xu T, Li M, Zhao Q, et al. Ginsenoside Rc Promotes Bone Formation in Ovariectomy-Induced Osteoporosis In Vivo and Osteogenic Differentiation In Vitro. *Int J Mol Sci.* 2022;23(11):6187.
 46. Kim DY, Park YG, Quan HY, Kim SJ, Jung MS, Chung SH. Ginsenoside Rd stimulates the differentiation and mineralization of osteoblastic MC3T3-E1 cells by activating AMP-activated protein kinase via the BMP-2 signaling pathway. *Fitoterapia.* 2012;83:215–22.
 47. Kim HM, Kim DH, Han HJ, Park CM, Ganipiseti SR, Arasu MV, et al. Ginsenoside Re promotes osteoblast differentiation in mouse osteoblast precursor MC3T3-E1 cells and a zebrafish model. *Molecules.* 2016;22(1):42.
 48. Park CM, Kim HM, Kim DH, Han HJ, Noh H, Jang JH, et al. Ginsenoside Re inhibits osteoclast differentiation in mouse bone marrow-derived macrophages and zebrafish scale model. *Mol Cell.* 2016;39(12):855–61.
 49. Wang L, Heckmann BL, Yang X, Long H. Osteoblast autophagy in glucocorticoid-induced osteoporosis. *J Cell Physiol.* 2019;234(4):3207–15.
 50. Zhao S, Yan L, Li X, Zhang Z, Sun Y, Wang J, et al. Notoginsenoside R1 suppresses wear particle-induced osteolysis and RANKL mediated osteoclastogenesis in vivo and in vitro. *Int Immunopharm.* 2017;47:118–25.
 51. Liu Y, Lin Z, Guo J, Xu G, Li Y, Xu T, et al. Notoginsenoside R1 significantly promotes in vitro osteoblastogenesis. *Int J Mol Med.* 2016;38:537–44.
 52. Liu Q, Zhou J, Yang Z. The ginsenoside exhibits antiosteoporosis effects in ketogenic-diet-induced osteoporosis via rebalancing bone turnover. *Front Pharmacol.* 2020;11:593820.
 53. Wang T, Wan D, Shao L, Dai J, Jiang C. Notoginsenoside R1 stimulates osteogenic function in primary osteoblasts via estrogen receptor signaling. *Biochem Biophys Res Commun.* 2015;466(1):232–9.
 54. Cheng B, Li J, Du J, Lv X, Weng L, Ling C. Ginsenoside Rb1 inhibits osteoclastogenesis by modulating NF- κ B and MAPKs pathways. *Food Chem Toxicol.* 2012;50(5):1610–5.
 55. Li XD, Wang JS, Chang B, Chen B, Guo C, Hou GQ. Panax notoginseng saponins promotes proliferation and osteogenic differentiation of rat bone marrow stromal cells. *J Ethnopharmacol.* 2011;134(2):268–74.
 56. Ding L, Gu S, Zhou B, Wang M, Zhang Y, Wu S, et al. Ginsenoside compound K enhances fracture healing via promoting osteogenesis and angiogenesis. *Front Pharmacol.* 2022;13:855393.
 57. Seo K, Yoo JH, Kim J, Min SJ, Heo DN, Kwon IK. Ginseng-derived exosome-like nanovesicles extracted by sucrose gradient ultracentrifugation to inhibit osteoclast differentiation. *Nanoscale.* 2023;15(12):5798–808.
 58. Hu L, Yin C, Zhao F, Ali A, Ma J, Qian A, et al. Mesenchymal stem cells: cell fate decision to osteoblast or adipocyte and application in osteoporosis treatment. *Int J Mol Sci.* 2018;19(2):360.
 59. Kiernan J, Davies JE, Stanford WL. Concise review: musculoskeletal stem cells to treat age-related osteoporosis. *Stem Cells Transl Med.* 2017;6:1930–9.
 60. Bei J, Zhang X, Wu J, Hu Z, Xu B, Lin S, et al. Ginsenoside Rb1 does not halt osteoporotic bone loss in ovariectomized rats. *PLoS One.* 2018;13(9):e0202885.
 61. Guo H, Huang S, Yang X, Wu J, Kirk TB, Xu J. Injectable and self-healing hydrogels with double-dynamic bond tunable mechanical, gel-sol transition and drug delivery properties for promoting periodontium regeneration in periodontitis. *ACS Appl Mater Interf.* 2021;13(51):61638–52.
 62. Gu Y, Zhou J, Wang Q, Fan W, Yin G. Ginsenoside Rg1 promotes osteogenic differentiation of rBMSCs and healing of rat tibial fractures through regulation of GR-dependent BMP-2/SMAD signaling. *Sci Rep.* 2016;6:25282.
 63. Niehrs C. The complex world of WNT receptor signalling. *Nat Rev Mol Cell Biol.* 2012;13(12):767–79.
 64. Chen B, Li XD, Liu DX, Wang H, Xie P, Liu ZY, et al. Canonical Wnt signaling is required for Panax notoginseng saponin-mediated attenuation of the RANKL/OPG ratio in bone marrow stromal cells during osteogenic differentiation. *Phytomedicine.* 2012;19(11):1029–34.
 65. Li XD, Wang JS, Chang B, Chen B, Guo C, Hou GQ. Panax notoginseng saponins promotes proliferation and osteogenic differentiation of rat bone marrow stromal cells. *J Ethnopharmacol.* 2011;134(2):268–74.
 66. Ding L, Gu S, Zhou B, Wang M, Zhang Y, Wu S, et al. Ginsenoside compound K enhances fracture healing via promoting osteogenesis and angiogenesis. *Front Pharmacol.* 2022;13:855393–855393.
 67. Qadir A, Liang S, Wu Z, Chen Z, Hu L, Qian A, et al. Senile osteoporosis: the involvement of differentiation and senescence of bone marrow stromal cells. *Int J Mol Sci.* 2020;21(1):349.
 68. Fischer V, Haffner-Luntzer M. Interaction between bone and immune cells: implications for postmenopausal osteoporosis. *Semin Cell Dev Biol.* 2022;123:14–21.
 69. Song S, Guo Y, Yang Y, Fu D. Advances in pathogenesis and therapeutic strategies for osteoporosis. *Pharmacol Ther.* 2022;237:108168.
 70. Zhang D, Du J, Yu M, Suo L. Ginsenoside Rb1 prevents osteoporosis via the AHR/PRELP/NF- κ B signaling axis. *Phytomedicine.* 2022;104:154205.
 71. Zhou W, Huang H, Zhu H, Zhou P, Shi X. New metabolites from the biotransformation of ginsenoside Rb1 by *Paecilomyces bainier* sp.229 and activities in inducing osteogenic differentiation by Wnt/ β -catenin signaling activation. *J Ginseng Res.* 2018;42(2):199–207.
 72. Liu Q, Zhou J, Yang Z. The ginsenoside exhibits antiosteoporosis effects in ketogenic-diet-induced osteoporosis via rebalancing bone turnover. *Front Pharm.* 2020;11:593820.
 73. Siddiqi MH, Siddiqi MZ, Ahn S, Kang S, Kim YJ, Veerappan K, et al. Stimulative effect of ginsenosides Rg5:Rk1 on murine osteoblastic

- MC3T3-E1 cells. *Phytother Res.* 2014;28:1447–55.
74. Siddiqi MH, Siddiqi MZ, Ahn S, Kim YJ, Yang DC. Ginsenoside Rb1 induces mouse osteoblast growth and differentiation through the bone morphogenetic protein 2/runt-related gene 2 signalling pathway. *J Pharm Pharm.* 2014;66(12):1763–73.
 75. Zhang X, Chen K, Wei B, Liu X, Lei Z, Bai X. Ginsenosides Rg3 attenuates glucocorticoid-induced osteoporosis through regulating BMP-2/BMPRII/Runx2 signaling pathway. *Chem Biol Interact.* 2016;256:188–97.
 76. Gong YS, Chen J, Zhang QZ, Zhang JT. Effect of 17 β -oestradiol and ginsenoside on osteoporosis in ovariectomised rats. *J Asian Nat Prod Res.* 2006;8(7):649–56.
 77. Kim HM, Kim DH, Han HJ, Park CM, Ganipiseti SR, Arasu MV, et al. Ginsenoside Re promotes osteoblast differentiation in mouse osteoblast precursor MC3T3-E1 cells and a zebrafish model. *Molecules.* 2016;22(1):42.
 78. Yang N, Zhang X, Li L, Xu T, Li M, Zhao Q. Ginsenoside Rc Promotes Bone Formation in Ovariectomy-Induced Osteoporosis In Vivo and Osteogenic Differentiation In Vitro. *Int J Mol Sci.* 2022;23(11):6187.
 79. Wang T, Wan D, Shao L, Dai J, Jiang C. Notoginsenoside R1 stimulates osteogenic function in primary osteoblasts via estrogen receptor signaling. *Biochem Biophys Res Commun.* 2015;466(2):232–9.
 80. Liu Y, Lin Z, Guo J, Xu G, Li Y, Xu T, et al. Notoginsenoside R1 significantly promotes in vitro osteoblastogenesis. *Int J Mol Med.* 2016;38:537–44.
 81. Zhu C, Shen S, Zhang S, Huang M, Zhang L, Chen X. Autophagy in bone remodeling: a regulator of oxidative stress. *Front Endocrinol.* 2022;13:898634.
 82. Song M, Jia F, Cao Z, Zhang H, Liu M, Gao L. Ginsenoside Rg3 attenuates aluminum-induced osteoporosis through regulation of oxidative stress and bone metabolism in rats. *Biol Trace Elem Res.* 2020;198:557–66.
 83. Zhu Y, Hu C, Zheng P, Miao L, Yan X, Li H, et al. Ginsenoside Rb1 alleviates aluminum chloride-induced rat osteoblasts dysfunction. *Toxicology.* 2016;368:183–8.
 84. Huang Q, Gao B, Jie Q, Wei BY, Fan J, Zhang HY, et al. Ginsenoside-Rb2 displays anti-osteoporosis effects through reducing oxidative damage and bone-resorbing cytokines during osteogenesis. *Bone.* 2014;66:306–314.
 85. Li X, Lin H, Zhang X, Jaspers RT, Yu Q, Ji Y, et al. Notoginsenoside R1 attenuates oxidative stress-induced osteoblast dysfunction through JNK signalling pathway. *J Cell Mol Med.* 2021;25:11278–89.
 86. Siddiqi MH, Siddiqi MZ, Ahn S, Kang S, Kim YJ, Veerappan K, et al. Stimulative effect of ginsenosides Rg5:Rk1 on murine osteoblastic MC3T3-E1 cells. *Phytother Res.* 2014;28:1447–55.
 87. Zhang Y, Gu X, Li D, Cai L, Xu Q. METTL3 regulates osteoblast differentiation and inflammatory response via smad signaling and MAPK signaling. *Int J Mol Sci.* 2019;21(1):199.
 88. Lin Y, Wu Y, He J, Huang Y, Lin Y. Effects of ginsenosides rg1 on osteoblasts cultured with ti particles. *Biomol Ther.* 2012;20(1):75–80.
 89. Yoshida G, Kawabata T, Takamatsu H, Saita S, Nakamura S, Nishikawa K, et al. Degradation of the NOTCH intracellular domain by elevated autophagy in osteoblasts promotes osteoblast differentiation and alleviates osteoporosis. *Autophagy.* 2022;18(10):2323–32.
 90. Da W, Tao L, Zhu Y. The role of osteoclast energy metabolism in the occurrence and development of osteoporosis. *Front Endocrinol.* 2021;12:675385.
 91. Chen M, Fu W, Xu H, Liu CJ. Pathogenic mechanisms of glucocorticoid-induced osteoporosis. *Cytokine Growth Factor Rev.* 2023;70(1):54–66.
 92. Wu Y, Ai H, Xi Y, Yin P, Qu Y, Xu J, et al. Reduced osteoclast-derived apoptotic bodies in bone marrow characterizes the pathological progression of osteoporosis. *Cell Death Dis.* 2023;9(1):135.
 93. Cheng B, Li J, Du J, Lv X, Weng L, Ling C. Ginsenoside Rb1 inhibits osteoclastogenesis by modulating NF- κ B and MAPKs pathways. *Food Chem Toxicol.* 2012;50(1):1610–5.
 94. Lee SH, Park SY, Kim JH, Kim N, Lee J. Ginsenoside Rg2 inhibits osteoclastogenesis by downregulating the NFATc1, c-Fos, and MAPK pathways. *BMB Rep.* 2023;56:551–556.
 95. Park CM, Kim HM, Kim DH, Han HJ, Noh H, Jang JH, et al. Ginsenoside Re inhibits osteoclast differentiation in mouse bone marrow-derived macrophages and zebrafish scale model. *Mol Cell.* 2016;39:855–861.
 96. Sun M, Ji Y, Zhou S, Chen R, Yao H, Du M. Ginsenoside Rb3 inhibits osteoclastogenesis via ERK/NF- κ B signaling pathway in vitro and in vivo. *Oral Dis.* 2023;29(2):3460–71.
 97. Cong F, Liu J, Wang C, Yuan Z, Bi L, Liang J, et al. Ginsenoside Rb2 inhibits osteoclast differentiation through nuclear factor-kappaB and signal transducer and activator of transcription protein 3 signaling pathway. *Biomed Pharmacoth.* 2017;92:927–34.
 98. He L, Lee J, Jang JH, Lee SH, Nan MH, Oh BC, et al. Ginsenoside Rh2 inhibits osteoclastogenesis through down-regulation of NF- κ B, NFATc1 and c-Fos. *Bone.* 2012;50(6):1207–13.
 99. Seo K, Yoo JH, Kim J, Min SJ, Heo DN, Kwon IK, et al. Ginseng-derived exosome-like nanovesicles extracted by sucrose gradient ultracentrifugation to inhibit osteoclast differentiation. *Nanoscale.* 2023;15(12):5798–808.
 100. Lee HY, Park SH, Chae SW. Aqueous ginseng extract has a preventive role in RANKL-induced osteoclast differentiation and estrogen deficiency-induced osteoporosis. *J Funct Foods.* 2015;13:192–203.

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