Saudi Pharmaceutical Journal 32 (2024) 102209

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Saudi Pharmaceutical Journal

journal homepage: www.sciencedirect.com

Drug delivery for age-related bone diseases: From therapeutic targets to common and emerging therapeutic strategies

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ARTICLE INFO

Keywords:
Drug delivery
Nanotechnology
Age-related bone diseases
Cell senescence
Anti-aging

ABSTRACT

With the accumulation of knowledge on aging, people have gradually realized that among the many factors that cause individual aging, the accumulation of aging cells is an essential cause of organ degeneration and, ultimately, age-related diseases. Most cells present in the bone microenvironment gradually age over time, leading to an imbalance of osteogenesis, osteoclastogenesis, adipogenesis, and chondrogenesis. This imbalance contributes to age-related bone loss and the development of age-related bone diseases, such as osteoporosis. Bone aging can prolong the lifespan and delay the development of age-related diseases. Nanoparticles have controllable and stable physical and chemical properties and can precisely target different tissues and organs. By preparing multiple easily modified and biocompatible nanoparticles as different drug delivery carriers, specifically targeting various diseased tissues for controlled-release and sustained-release administration, the delivery efficiency of drugs can be significantly improved, and the toxicity and side effects of drugs can be substantially reduced, thereby improving the therapeutic effect of age-related bone diseases. In addition, other novel anti-aging strategies (such as stem cell exosomes) also have significant scientific and practical significance in anti-aging research on age-related bone diseases. This article reviews the research progress of various nano-drug-loaded particles and emerging anti-aging methods for treating age-related bone diseases, offering new insights and directions for precise targeted clinical therapies.

1. Introduction

Aging is an irreversible degenerative change in the structure and function of various tissues and organs under the influence of multiple factors, such as heredity, mental stress, and environmental pollution, both *in vivo* and *in vitro* (Corrêa, 2018). The bone is the first aging tissue in the human body. Osteoblasts mediate bone formation, osteoclasts mediate bone resorption, adipocytes mediate fat formation, chondrocytes mediate cartilage formation, and mechanical transduction of osteocytes regulates bone resorption and formation. An imbalance in these five aspects leads to bone aging, and further degradation leads to age-related bone diseases [such as osteoporosis, osteoarthritis (OA), rheumatoid arthritis (RA), and periodontitis] (Rachner et al., 2011; Gao et al., 2021; Salhotra, 2020). Notably, age-related loss of trabecular and cortical bone, changes in the content of various components in bone tissue, and their interactions with various cells can lead to a decrease in bone biological and mechanical properties, increasing the risk of age-related bone diseases in the elderly, and even affecting lifespan (Burr, 2019; Curtis, 2016). Therefore, research on the pathogenesis and treatment of age-related bone diseases has gradually become an important and difficult topic in current research.

In the process of individual aging, senescent cells gradually accumulate in tissues, leading to the loss of tissue repair capacity and the occurrence of dysfunction (Di Micco, 2021; Gruber, et al., 2007). Simultaneously, senescent cells activate various inflammatory factors that lead to the deterioration of the tissue microenvironment via

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https://doi.org/10.1016/j.jsps.2024.102209
Received 12 September 2024; Accepted 22 November 2024
Available online 24 November 2024

paracrine signaling, promote the aging of adjacent cells, and recruit immune cells to eliminate senescent cells (da Costa, 2016; Biran and Krizhanovsky, 2015; Contrepois, 2017). These inflammatory factors include proinflammatory cytokines, chemokines, proteases, growth factors, and other peptides and proteins known as the senescence-associated secretory phenotype (SASP) (Coppé, 2008). The efficiency of clearance of senescent cells by immune cells gradually decreases with age, and senescent cells accumulate through replicative, programmed, and stress-induced premature senescence (Burton and Krizhanovsky, 2014). The continuous accumulation of senescent cells and increased SASP secretion are the main factors that lead to aging-related diseases (Wei and Ji, 2018). Increasing evidence shows that treatment strategies targeting senescent cells can reduce the age-dependent degradation of tissues and organs (Baker, 2011; Baker, 2016). Therefore, in addition to inhibiting aging, another new method is to specifically target and selectively remove senescent cells and prevent their accumulation to delay the occurrence and development of aging-related diseases, which is the most popular and vital research in the field of aging. In recent years, nanoparticles (NPs) have been used as a new drug delivery system for the targeted therapy of age-related bone diseases. Small-molecule drugs or cell-surface molecular inhibitors can be loaded with controllable nanomaterials owing to the high selectivity and good drug-loading ability of NPs in specific cells or tissues. Through nano-drug delivery systems, drugs can specifically target and regulate a disordered immune system or block abnormally activated signal transduction pathways in age-related bone diseases, effectively controlling the development of diseases, reducing clinical symptoms, and overcoming the toxicity and side effects caused by the distribution of conventional drugs in normal tissues (Chaturvedi, 2022).

Although various anti-aging methods have made exciting and substantive progress in the study of aging and aging-related diseases, these strategies require a large number of long-term clinical studies before they can be applied to humans. In addition, there is a lack of systematic summaries and reviews of research progress on the therapeutic targets and application status of these common and emerging anti-aging strategies in age-related bone diseases. Therefore, this article systematically reviews the characteristics of senescent cells, the potential application of senescent cells as therapeutic targets in age-related bone diseases, and common and emerging anti-aging strategies for age-related bone diseases in recent years. The limitations and future developmental directions of current anti-aging methods (such as anti-inflammatory drug therapy) in the treatment of age-related bone diseases are discussed to provide a reference for the clinical promotion of precise anti-aging treatments within the context of precision medicine.

2. The role of cell senescence in age-related bone diseases

2.1. Molecular characteristics of senescent cells

Senescent cells are characterized by increased cell volume, flattened morphology, increased senescence-associated β-galactosidase (SA-β-gal) activity, accumulation of SASP, activation of DNA damage response (DDR), increased expression of cyclin-dependent kinase (CDK) inhibitors p16 (CDKN2A) and p21 (CDKN1A), telomere dysfunction, and formation of senescence-associated heterochromatin lesions (SAHF) (Goldstein, 1990; Bunz, 1998; Sedivy, 1998; Kuilman, 2010; Hernandez-Segura et al., 2018). Permanent cell cycle arrest is an essential feature of senescent cells and an indispensable indicator of cell senescence *in vitro* (Kuilman, 2010; Hernandez-Segura et al., 2018). SA-β-gal is expressed in many types of human senescent cells and can be used as a biomarker of senescent cells (Dimri, 1995). Moreover, some features are not common to senescent cells, such as SAHF, whose formation may not be observed under certain conditions or may not exist in certain cell types (Kosar, 2011). Therefore, it is necessary to maintain a combination of phenotypes to identify senescent cells.

Gorgoulis et al. (Gorgoulis, 2019) proposed a three-step method for identifying senescent cells. First, evaluate SA-β-gal activity and lipofuscin accumulation (via SBB or GL13 staining). Second, perform co-staining with other markers common in senescent cells, such as p16Ink4a and p21WAF1/Cip1, or markers without proliferation activity, such as lamin B1. Third, determine the factors that may be altered in a specific aging environment (SASP, DDR, etc.). This multi-label workflow identified senescent cells with the highest accuracy. In addition, Yosef et al. (Yosef, 2016) showed that the resistance of senescent cells to apoptosis can promote their survival, which may be mediated by increasing the expression of anti-apoptotic Bcl-2 family proteins, known as senescent cell anti-apoptotic pathways. Owing to the heterogeneity of senescence, accurate characterization of the occurrence of cell senescence using a single feature is difficult. Therefore, a combination of these elements is often used to identify senescent cells (Fig. 1).

2.2. Accumulation of senescent cells in vivo

Recent studies have shown that the adverse effects of cell senescence in the body are mainly achieved through the accumulation of senescent cells and the deterioration of the tissue microenvironment (Fig. 1) (He and Sharpless, 2017). The accumulation of senescent cells is closely associated with the development of age-related bone diseases. The accumulated senescent cells lose their original physiological functions and affect tissue functions (Gruber, et al., 2007; Krishnamurthy, 2004). Simultaneously, the SASP secreted by senescent cells deteriorates the cell microenvironment (Acosta, 2013). In addition, senescent cells can consolidate their senescent phenotype through autocrine or paracrine signaling, promote senescence of adjacent cells, hinder tissue regeneration and remodeling, and promote aging-related diseases (Childs, 2015). The positive effect of cell senescence on the body occurs mainly in the short term. Cells withdraw from the cell cycle after injury, limit tissue damage to a specific range, and avoid tumorigenesis by exiting the cell cycle, which is considered a tumor suppressor mechanism (Demaria, 2014; Aravinthan, 2015). Senescence occurs in a programmed manner during normal tissue development and regeneration. Studies have reported that senescent cells are produced during the revival of salamanders, and adequate clearance by immune cells is necessary for salamanders to achieve regeneration (Yun et al., 2015). Notably, a dynamic balance exists between the production and clearance of decidualized senescent cells during the menstrual cycle, which may play an essential role in maintaining homeostasis in luteal phase tissues (Brighton, 2017). Therefore, cell senescence is either stressful or programmed. Avoiding the adverse effects of tissue function decline and the inflammatory microenvironment caused by the accumulation of cellular senescence is an important entry point for studying cell senescence and age-related bone diseases.

2.3. Pathophysiological mechanism of bone aging and bone remodeling

The skeleton is a metabolically active organ in the human body, which undergoes a continuous cycle of bone reconstruction in human life. An increasing number of studies have shown that osteocytes play an indispensable role in bone aging and loss caused by aging. The mechanisms of osteocytes associated with bone aging include, but are not limited to, impaired mechanical sensitivity, accumulation of cell senescence, dysfunction in osteocyte lacuna remodeling, and degradation of the lacunar tubule network (Schurman et al., 2021; Javaheri and Pitsillides, 2019; Yee, 2019; Farr, 2020). Age-related bone disease is caused by an imbalance in bone remodeling due to bone resorption, which exceeds bone formation. Bone remodeling is essential for bone homeostasis and involves the balance and coordination of bone formation and resorption (Zhao, 2025). In general, bone remodeling can be divided into five stages: 1) Activation stage: bone remodeling is initiated by local mechanical or hormonal signals. Osteocytes are thought to sense these signals and convert them into biological reactions in bones (Komori, 2013). 2) Resorption stage: mature osteoclasts secrete matrix

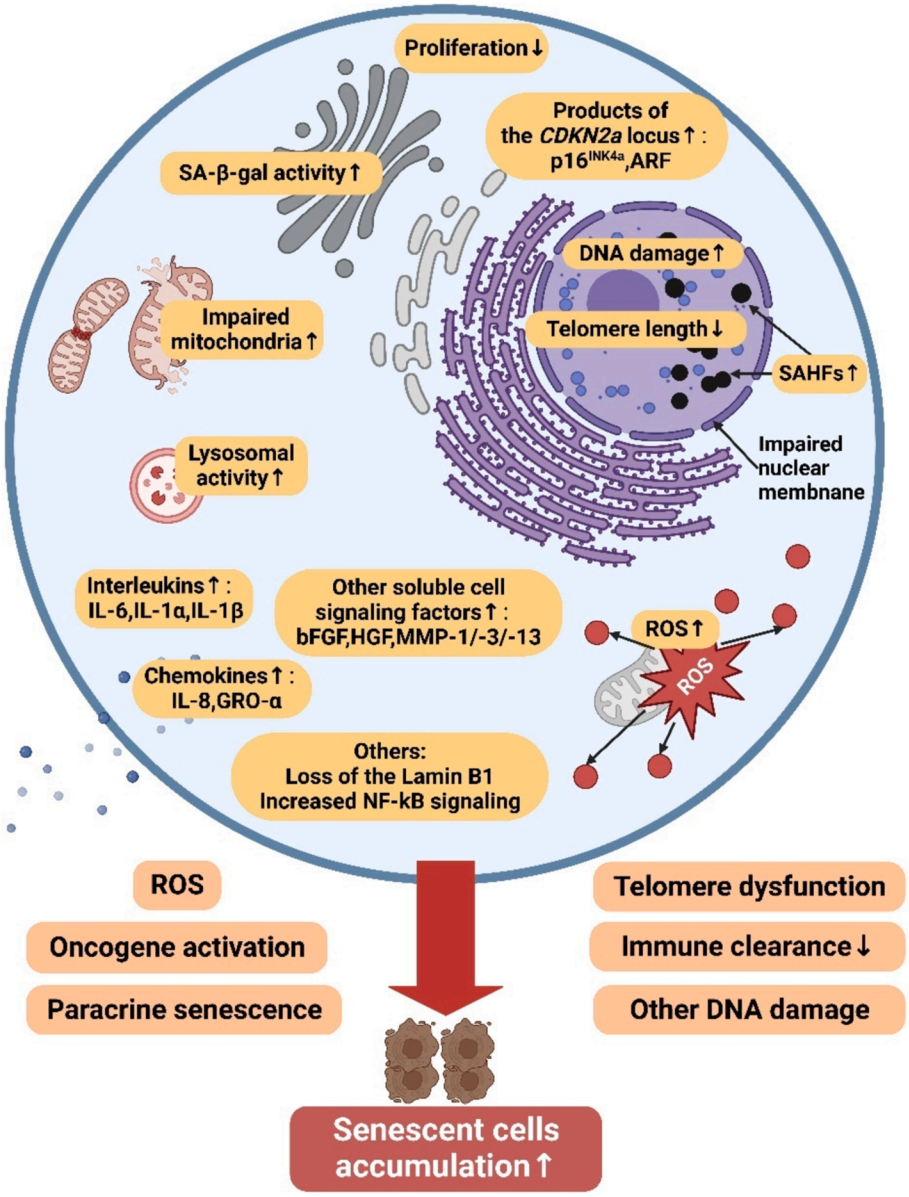

Fig. 1. Characteristics and accumulation mechanisms of senescent cells. Senescent cells exhibit permanent cell cycle arrest, increased expression of CDKN2a site products (p16INK4a and ARF), and characteristic changes in cell structure and protein expression (increased expression of various cytokines, chemokines, and other soluble signaling molecules). In vitro aging cells exhibit changes in cell morphology and SA- β- Increased activity of galactosidase and several other biomarkers (such as telomere shortening, reduced proliferation, activated NF-kB, DNA damage response, and increased SAHFs) have also been shown to be associated with cell senescence. The loss of laminin B1 is an emerging aging biomarker under research. The rate of senescent cell accumulation increases with age, which may be related to an increase in ROS, activation of oncogenes, DNA damage, telomere dysfunction, and / or a decrease in immune system clearance of senescent cells, leading to an increase in the rate of senescent cell production. In addition, senescent cells can also induce the formation of other senescent cells through paracrine pathways. bFGF: basic fibroblast growth factor; HGF: hepatocyte growth factor.

metalloproteinases (MMPs) to digest minerals and organic matrices. During this stage, Howship's lacunae form beneath canopy cells (Ono and Nakashima, 2018). 3) Reversal stage: mature osteoclasts undergo apoptosis, and osteoblasts are directed to the bone resorption sites. Local molecules, such as transforming biochemical factor (TGF)-β, are released to induce osteoblasts and initiate bone formation (Tang, 2009). 4) Osteogenic stage: osteoblasts dominate the bone remodeling process, which usually takes 4–6 months (Katsimbri, 2017). Various local and systemic regulators, such as Wnt, sclerostin, and parathyroid hormone (PTH), promote osteoblastogenesis. The organic bone matrix (osteoid), which is composed of different proteins (such as type I collagen), begins to deposit until full compensation for bone resorption is achieved (Katsimbri, 2017). 5) Termination stage: bone matrix resorption and formation are balanced, marking the end of the formation phase. Osteoblasts either undergo apoptosis or form new osteocytes (Raggatt and Partridge, 2010). Bone mineralization begins and is completed at this stage (Bala, 2010). Osteoclasts, osteoblasts, and osteocytes are three important bone tissue cells directly involved in bone remodeling. At the same time, bone formation is coordinated by bone resorption of osteoblasts derived from mesenchymal stem cells (MSCs) and osteoclasts derived from tissue-specific macrophages to maintain bone mineral homeostasis and strength (Boyle et al., 2003). Bone aging and age-related bone diseases may be caused by the dysfunction of each cell type.

2.4. Senescent cells as a therapeutic target for age-related bone diseases

Senescent cells play essential roles in several physiological processes, including bone remodeling. Therefore, anti-aging therapies targeting senescent cells have great clinical value for the treatment of aging-related bone loss. Sufficient evidence suggests that eliminating senescent cells or inhibiting SASP secretion can prevent the occurrence and development of age-related bone diseases. For example, Farr et al. (Farr, 2017) established a mouse model of senile osteoporosis in different ways and eliminated senescent cells using transgenic methods, producing senescent cell scavengers or Janus kinase inhibitors that inhibit SASP secretion. They found that the mice had increased bone mass, clear bone structure, and reduced bone resorption after the targeted removal of senescent cells. Similarly, the administration of ganciclovir to remove senescent cells delayed the occurrence and development of osteoarthritis in p16-3MR transgenic mice, reduced knee pain, and accelerated cartilage regeneration (Jeon, 2017). We also used a new senescence scavenger, UBX0101, to remove senescent cells. UBX0101 promotes cartilage regeneration and improves joint function by inducing apoptosis in senescent cells and reducing SASP secretion (Jeon, 2017). *In vitro* studies confirmed this hypothesis. After treatment with UBX0101, the expression levels of matrix metalloproteinase (MMP)-13, IL-6, and IL-1β in primary chondrocytes were substantially reduced. UBX0101 can also improve functional indicators in osteoarthritis mice models, increase polysaccharide and type II collagen levels, and improve joint-bearing capacity (Jeon, 2017). These results suggest that UBX0101 has clinical transformation potential.

Childs et al. (Childs, 2016) found that foamy macrophages with aging markers accumulate in the subcutaneous space at the beginning of atherosclerosis and drive the pathology by increasing the expression of key cytokines and chemokines that cause atherosclerosis and inflammation. Low-density lipoprotein receptor-deficient (Ldlr-/-) mice are prone to atherosclerosis, and ganciclovir can reduce p16Ink4a-positive senescent cells in Ldlr-/- mice can treat atherosclerosis. Using this transgenic mouse model, other research groups have reported that clearing p16Ink4a-positive senescent cells prevents the development of post-traumatic osteoarthritis, treats degenerative joint disease (Jeon, 2017) and age-related intervertebral disc degeneration (Patil, 2019), and improves obesity-induced metabolic dysfunction (Palmer, 2019). These results confirmed that senescent cells can be used as therapeutic targets to delay the occurrence and development of age-related diseases. However, not all the cells with high p16Ink4a expression were senescent (Hall, 2017; Okuma, 2017). Therefore, these transgenic mouse models have certain limitations in terms of their specificity and sensitivity for killing senescent cells.

Recently, compounds that eliminate senescent cells have been discovered. They targeted the anti-apoptotic pathways of senescent cells and selectively eliminated them using p16Ink4a-independent methods (Kirkland and Tchkonia, 2017; Zhu, 2015). These compounds are known as 'senolytics.' The senolytics identified in this study included dasatinib, quercetin, navitoclax (N; ABT-263), piperlongumine, fisetin, A1331852, A1155463, and EF24 (Table 1) (Palmer, 2019; Zhu, 2017; Li, 2019). Simultaneously, an increasing number of new compounds have been shown to have effects similar to senolytics, such as epigallocatechin-3-gallate (Kumar, 2019). Notably, each senolytic is effective only on specific tissue-derived aging cells; therefore, different senolytics may be required for various age-related diseases. Animal studies have shown that the removal of some aging cells is sufficient to produce a substantial anti-aging effect. Senolytics only affect existing senescent cells without affecting their formation, which means that the tumor suppressor function of the senescent cells themselves can still be retained (Chang, 2016).

Therefore, compared with other anti-aging strategies, direct targeted elimination of aging cells has the following advantages. First, in theory, only the regular application of senolytics to eliminate aging cells plays a role in delayed aging, which can reduce or prevent adverse reactions.

Table 1
Senolytic agents and the potential drug targets.

Senolytic agents	Drug targets	References
Dasatinib (D)	Receptor-dependent/ Src kinase/ tyrosine kinase	(Zhu, 2015; Gore, 2018; Xu, 2018)
Quercetin (Q)	Bcl-2 family, p53/ p21/ serpine and PI3K/ AKT	(Yosef, 2016; Zhu, 2015; Xu, 2018)
Venetoclax (ABT-199)	The Bcl-2 family (Bcl-2)	(Roberts, 2016; Peris, 2023; Whittle, 2020)
A1331852	The Bcl-2 family (Bcl-xL)	(Zhu, 2017; Carrington, 2021)
A1155463		(Zhu, 2017; Chang, 2016)
Navitoclax (ABT-263)	The Bcl-2 family (Bcl-2, Bcl-xL, Bcl-W)	(Childs, 2016; Chang, 2016; Pan, 2017)
ABT-737		(Yalniz and Wierda, 2019; Haston, 2023; Thompson, 2019)
UBX0101	MDM2/ p53	(Jeon, 2017)
Fisetin (FIS)	PI3K/ AKT	(Zhu, 2017; Yousefzadeh, 2018)
17-DMAG		(Hassan and Bhatwadekar, 2022; Fuhrmann-Stroissnigg, 2017; Strong, 2020)
FOXO4-DRI peptide	Bcl-2 family and p53/ p21/ serpine	(Born, 2023; Meng, 2021; Krimpenfort and Berns, 2017)
Piperlongumine (PL)	p53/ p21, Bcl-2 family, antioxidant protein 1 (OXR1)	(Wang, 2016; Zhang, 2018)
EF24	Unknown	(Li, 2019; He, 2018)

Second, unlike cancer treatment, the prevention and treatment of age-related diseases do not require the removal of all aging cells from tissues. Additionally, SASP is an essential anti-aging therapy. For example, metformin, rapamycin, and various inflammatory factor antibodies can inhibit the SASP phenotype of aging cells by inhibiting aging-related signaling pathways (Childs, 2017); thus playing a specific role in delaying aging.

3. Common anti-aging strategies in the treatment of age-related bone diseases

3.1. Nanomaterial-mediated anti-aging strategies

Abnormal immune system disorders during aging play important roles in the occurrence and development of age-related bone diseases. Currently, commonly used treatment methods mainly reduce disease activity by inhibiting the abnormal expression of immune cells and inflammatory factors (Abbasi, 2019). However, the shortcomings of conventional drugs, such as narrow safety windows, serious systemic side effects, and short half-lives, greatly limit their clinical application. In the past decade, the rapid development of nanomedicine has optimized the therapeutic impact on age-related bone diseases. Specific aggregation of nano-drug delivery systems at the targeted site can reduce tissue damage caused by off-target effects of drugs. In addition, its unique drug protection ability prolongs the half-life of the drug in circulation and reduces toxic effects while improving drug bioavailability (Yang, 2017).

3.1.1. The classification and general properties of NPs

Currently developed nanoparticles can be divided into organic and inorganic nanoparticles, which have unique physical and chemical properties and thus show excellent application potential in the biomedical field (Singh, 2019). Different types of nanoparticles, such as metals, liposomes, polymers, and biomimetic NPs have been used as diagnostic tools and anti-aging treatments for age-related chronic diseases (Fig. 2 and Table 2) (Boisselier and Astruc, 2009; Flores, 2020; Kraft, 2014; Liu, 2019).

Inorganic nanoparticles

Owing to their unique and stable physical, chemical, and photothermal properties, inorganic nanoparticles are often loaded with small-molecule drugs for the anti-inflammatory treatment of age-related chronic diseases. Metals, metal oxides, silica, and other inorganic substances are the basic materials commonly used as inorganic nanoparticle

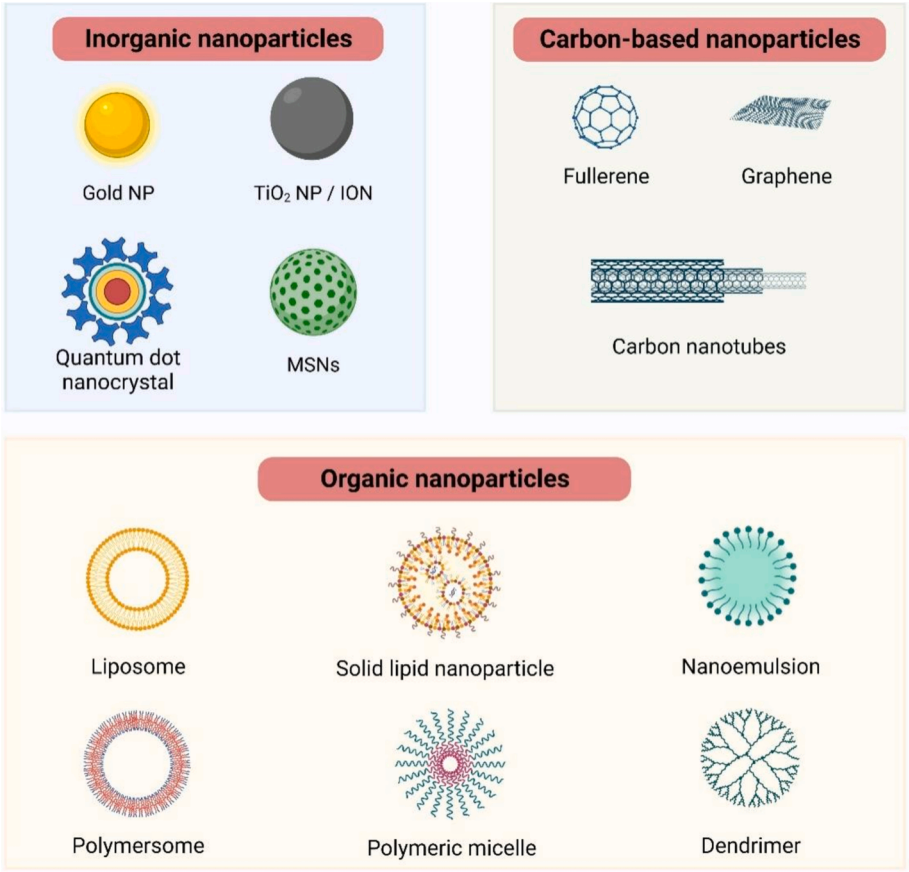

Fig. 2. Schematic diagram of different types of nanoparticles. Mainly inorganic nanoparticles (gold nanoparticles, iron oxide/ titanium dioxide nanoparticles, mesoporous silica nanoparticles, quantum dots), carbon-based nanoparticles (fullerene, graphene, carbon nanotubes), and organic nanoparticles (lipid-based nanoparticles and polymer nanoparticles).

carriers (Wang, 2021).

Mesoporous silica nanocarriers (MSNs) have the advantages of good biocompatibility, free pore size regulation, and functional modification of surface genes (Wang, 2015). Xiaonan et al. used cell-penetrating peptide (CADY) and phase change material (PCM)-modified MSN to load gene-targeted drugs and triptolide (TP) to construct CADY-MSNs@ miRNA and MSNs@ PEG@ PCM@ TP nano-drug delivery systems to treat RA by targeting biomolecules to inhibit the overactive immune system and abnormal proliferation of rheumatoid arthritis synovial fibroblasts (Zhang, 2020). The results showed that the modified MSNs were more targeted and that using excitation light to control the release of drugs significantly improved the symptoms of collagen-induced arthritis in rats (Zhang, 2020). Therefore, using silica NPs as a drug carrier and a variety of exogenous stimulation signals to regulate the release of drugs in a specific time and space may have a positive effect on the treatment of age-related bone diseases such as RA.

Additionally, a small number of inorganic nanoparticles can directly mediate related biological processes *in vivo*, such as autophagy, apoptosis, necrosis, and other cell death pathways, owing to their physical and chemical properties (Mohammadinejad, 2019). For example, Ag silver nanoparticles have been reported to regulate apoptosis (Yang, 2021). The gold nanoparticle drug delivery system has also been shown to cause reactive oxygen (ROS) quenching, reduce immune stress response, and reduce RANKL-induced osteoclast formation and inflammatory cytokines (IL-1, IL-6, TNF-α, etc.), which plays a vital role in the precise targeted anti-inflammatory treatment of RA (Koushki, 2021).

Liposome nanoparticles

Liposomal nanoparticles (LNPs) have received increasing attention in the treatment of age-related bone diseases. Common LNPs are small spherical particles spontaneously formed by one or more bimolecular layers through the dispersion of natural or synthetic amphiphilic lipids in water, which can encapsulate drugs on the surface of a carrier matrix or solid nucleus to achieve drug delivery (Scioli Montoto et al., 2020). The structure of LNP is relatively simple and has the advantages of controllable physical and chemical properties, good biocompatibility, high bioavailability, and the ability to carry macromolecular drugs, which makes them a broad application prospect for the treatment of age-related bone diseases (Wen, 2023; Chuang, 2018).

In recent years, researchers have continuously improved the properties or surface modifiers of LNPs to improve their drug encapsulation rate and cycle half-life and to optimize targeted therapy. Methotrexate (MTX) is the first-line drug for the conventional treatment of RA; however, its clinical application is limited because of its low specificity and bioavailability. To broaden the safe therapeutic window of MTX and solve the problems of poor stability and easy dumping of single-layer liposome-loaded drugs, Verma et al. (Verma, 2019) developed double-layer liposome-loaded particles loaded with prednisolone (PRD) and MTX. Endosomes containing PRD and MTX were coated in the core of the double-layered liposome, and the folic acid-modified outer liposome maintained the stability and targeting of the drug-loading system. Compared to single-layer drug-loaded liposomes, double-layer drug-loaded liposomes not only have a greater loading amount but also better protect the drug from biodegradation, prolong the circulation half-life of the drug in the body, and achieve better therapeutic effects (Verma, 2019).

Polymer nanoparticles

Polymeric nanoparticles (PNPs) are biodegradable polymers with

Table 2
Classification and characteristics of nanoparticles for the study of bone aging-related diseases.

Types of nanoparticles	Subclasses	Advantages	Disadvantages	Reference
Inorganic nanoparticles	ION	Superparamagnetism, tissue permeability, biocompatibility, colloid stability, environmentally friendly	Toxicity problems, high technical sensitivity of preparation, high production cost	(Jeon, 2021)
	AuNP	Good optical properties and biocompatibility, plasma properties, stable physical and chemical properties, good surface chemical properties, and versatility	Toxicity problems	(Jadzinsky, 2007)
	QD	High quantum yield, good chemical stability, and light stability, size-tunable light emission	The impact on the environment, high preparation cost, toxicity problems, human clearance rate	(Alaghmandfard, 2021; Molaei, 2019)
	MSN	Narrow pore size distribution, wide range, highly uniform pore channels, and large surface area	Potential genetic toxicity, drug degradation rate, and time-consuming preparation process	(Li et al., 2019; Antonelli et al., 1996)
Carbon-based nanoparticles	Fullerene	Good water solubility, high specific surface area, highly specialized nanostructures, and electron affinity	Distribution and toxicity issues within organisms	(Kazemzadeh and Mozafari, 2019)
	Graphene	Excellent mechanical properties, light transmittance, conductivity, and optical performance	Impact on cell viability and toxicity issues	(Syama and Mohanan, 2016; Liao et al., 2018)
	CNT	Large specific surface area, excellent adsorption ability, unique fluorescence, and Raman spectroscopy in the near-infrared region	Poor solubility, low biodegradability and dispersibility, and toxicity issues	(Negri, 2020)
	CQD	Strong chemical inertia, stable optical performance, and good water dispersibility	Biocompatibility issues (concentration-dependent)	(Nekoueian, 2019)
Lipid-based nanoparticles	Liposome	Hydrophilicity and lipophilicity, good solubility, increased half-life, targeted delivery, excellent biocompatibility, and biodegradability	Technical issues (high cost, rapid clearance, sterility, shelf life, etc.), toxicology, and inflammatory effects	(Hu, et al., 2022; Bowey et al., 2012)
	NCL	Good solubility, high drug encapsulation efficiency and stability, high drug loading capacity, and low drug discharge during storage	Stability, polymorphism, and storage issues	(Dhiman, 2021; Xu, 2022)
	SLN	High surface area, small size, good biocompatibility and biodegradability, stable physicochemical properties	Low drug loading and uncomplicated discharge of drugs during storage	(Dhiman, 2021; Xu, 2022)
	Nanoemulsion	Good stability and affinity, good taste experience, easy storage, long shelf life, and high bioavailability	Biosafety and toxicity issues	(Singh, 2017)
Polymeric nanoparticles	Polymersomes	High stability and cargo detention efficiency	Difficult preparation and low drug encapsulation efficiency	(Leong, 2018)
	Dendrimer	High solubility and penetrability, high bioavailability of drugs, and targeted distribution	Various toxicity issues (including cytotoxicity, hematological and immunological toxicity, neurotoxicity)	(Chis, 2020)
	Micelles	High structural stability and water solubility, customizable according to specific needs	In some cases, there may be issues such as poor drug incorporation and immune toxicity	(Hwang et al., 2020; Hwang, 2021)
Biomimetic nanoparticles	Cell-membrane coated nanoparticles	Long system circulation time, immune escape, specific targeting effect, high biocompatibility, and low drug side effects	May induce or exacerbate inflammation	(Liu, 2019; Ferreira-Faria, 2022)
	Natural protein-based nanoparticles	Good biocompatibility and biodegradability, easy particle surface modification, and size control	Fast degradation, high cost, low yield, and significant differences between batches	(Hong, 2020)
	Nanoparticles with targeting ligands	Excellent binding affinity, specificity, good biocompatibility, low immunogenicity	High cost, poor stability, and penetration	(Sousa, 2017)
Virus/ Virus-like nanoparticles	/	Natural nanoscale particle size and immune regulatory effects	Potential danger, possibility of mutation, strong immune cascade reaction	(Jeevanandam et al., 2019; Di Gioacchino, 2020; Zampieri, 2020)

low cytotoxicity that are ideal drug delivery platforms. The semi-solid hydrophobic core of PNPs can load drugs with different relative molecular masses into the polymer core or accumulate on the polymer core via surface adsorption (Zielińska, 2020); which can optimize treatment strategies for age-related bone diseases. For example, some therapeutic drugs for RA and OA can be stably loaded with PNPs owing to their hydrophobic properties. Its unique structure and properties can promote the phagocytosis of drug-loaded particles by activated macrophages in the RA immune microenvironment, allowing the carrier to stably release the drug, prolonging the residence time of the drug in the inflamed joint, and ensuring its drug release rate. Adjusting the drug composition, stability, responsiveness, and surface charge allows the drug-loading effect and release kinetics to be accurately controlled (Saeedi et al., 2020).

Virus nanoparticles

A virus is a relatively simple microorganism, and its natural nanoscale particle size makes it an ideal biological carrier. Relevant regulatory genes or molecules are incorporated by removing the genetic material from the viral protein capsid to produce an empty capsid. The virus was then used to transfect the cells. Regulatory molecules are delivered to cells to promote the expression of target proteins, thus playing a role in regulating cellular function (Jeevanandam et al., 2019). Therefore, using viral vectors to load regulatory genes to treat age-related bone diseases at the molecular level can effectively prevent the side effects of drug therapy. Recently, virus-like nanoparticles have been increasingly used in nanomedicine. They do not contain genetic material and are, therefore, not infectious. They are suitable materials for constructing nano-drug delivery systems but can still cause immune solid cascades (Di Gioacchino, 2020). Therefore, owing to the risk of viral vectors and the possibility of mutations, biosafety, efficient delivery, and stability should be considered when selecting or preparing vectors.

Cell membrane-coated nanoparticles

Most drugs carried by nanoparticles cannot reach the target organs through the systemic circulatory system after entering the body, which limits their wide application in clinical practice. Cell membrane-coated nanoparticles (CMCNPs) represent a promising drug delivery strategy owing to their low immunogenicity, long half-life, low toxicity, and innate targeting (Fang, 2018). The commonly used cell membrane

sources include red blood cells, neutrophils, tumor cells, platelets, natural killer cells, exosomes, and stem cells. Different cell membrane types exhibit unique characteristics. Coated NPs can mimic the biological features and functions of innate immune cells and can be used to diagnose and treat various diseases (Fang, 2018; Fang, 2017; Beh, 2021). Currently, platelet membranes are used for targeted therapy of vascular injury caused by many factors, such as atherosclerosis (AS), cancer, RA, and other diseases, owing to the repair of damaged vascular endothelium (Kunde and Wairkar, 2021). In addition, in transgenic mouse models and collagen-induced mouse models, drug-loaded CMCNPs (neutrophil membrane) can not only neutralize pro-inflammatory cytokines and inhibit inflammatory responses but also penetrate the cartilage matrix to provide vital protection for the cartilage and prevent joint damage (Zhang, 2018), showing a significant therapeutic effect in inhibiting the severity of RA.

3.1.2. Nanoparticle-based anti-inflammatory therapy

The cause and pathogenesis of age-related bone diseases remain unclear; however, excessive ROS levels can lead to oxidative stress. The oxidative stress-inflammatory response plays an essential role in the occurrence and development of bone aging-related inflammatory diseases (Papaconstantinou, 2019). Therefore, anti-inflammatory therapy may be an effective strategy for managing age-related bone diseases. Compared with the shortcomings of traditional therapeutic drugs, the selective delivery of drugs to the inflammatory site using nanoparticles as carriers can improve the pharmacokinetics of drugs in the body, increase the rate of cell internalization, and reduce the side effects at non-lesion sites (Jeong and Park, 2021). Triptolide (TP), a traditional Chinese medicinal extract, has excellent therapeutic effects as an immunosuppressant in RA. However, its clinical application is limited because of its hepatorenal solid toxicity (Zhou, 2021). Zhou et al. used the characteristics of folic acid receptor overexpression on the surface of activated macrophages during RA development to construct an FA-modified liposome-loaded TP drug delivery system. Targeting the folic acid receptor on the surface of macrophages increases the cell internalization rate of TP and prolongs the residence time of drugs at the inflammatory site. Simultaneously, the toxicity and side effects of TP on the liver, kidneys, and other organs were reduced (Zhou, 2021). Similarly, Yang et al. targeted synovial macrophages by constructing folic acid-silver nanoparticles (FA-Ag NPs) that bind to the folic acid receptor on the surface of synovial macrophages and are endocytosed into the cells. Under intracellular glutathione, AgNPs release Ag^{+} to mediate apoptosis and ROS clearance of M1 macrophages and synergistically induce the repolarization of M1 macrophages to M2 macrophages to reduce the inflammatory response. The results showed that it was safer and more effective than MTX treatment (Yang, 2021).

Cartilage degeneration caused by joint injury or OA involves two inflammatory cytokines, TNF-α and IL-1, expressed in the acute phase of OA and are the primary triggers of the inflammatory cascade. Celecoxib (CXB) is a highly selective non-steroidal anti-inflammatory drug. It can inhibit the activation of the NF-κB pathway by inhibiting the synthesis of cyclooxygenase-2 (COX-2) and related inflammatory cytokines, thus exerting anti-inflammatory and analgesic effects on OA. However, the commonly used oral administration method substantially reduces local drug concentration in the joints, resulting in decreased efficacy (Cruz, 2022). Studies have shown that intra-articular drug delivery systems (DDS) are suitable for treating OA. The DDS effectively avoids the side effects associated with systemic therapy. Nano-drug delivery systems can increase the area under the plasma concentration–time curve of CXB and the retention time of the drug in the blood, thereby prolonging its half-life (Mehta et al., 2021). As OA is an age-related chronic disease characterized by changes in inflammatory intensity, researchers have attempted to use CXB-loaded polyesteramide (PEA) microspheres to treat OA-related pain. The results showed that the degradation of microspheres in the OA-induced knee joint was substantially higher than that in the contralateral healthy knee joint. Simultaneously, CXB had a substantial inhibitory effect on the degradation of microspheres (Liu, 2019); suggesting that this was an auto-regulated drug release system with anti-inflammatory effects *in vitro* and *in vivo*.

In addition, the effects of resveratrol on mammalian aging and lifespan have been reported (Marchal et al., 2013) In vitro experiments have shown that resveratrol can down-regulate the expression of inflammatory factors IL-1β, IL-6, IL-8, and TNF-α in a dose-dependent manner (Li, 2021). *In vivo* experiments have also confirmed that resveratrol can reduce the level of reduced nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, upregulate the expression of sirtuin 1 (SIRT1) and superoxide dismutase (SOD) to reduce the oxidative stress in rats with periodontitis caused by cigarette smoke inhalation and reduce the degree of periodontal tissue damage (Corrêa, 2019). Therefore, resveratrol may serve as a therapeutic agent for age-related bone diseases through the inhibition of inflammation. To improve the poor water solubility and low bioavailability of resveratrol, the therapeutic resveratrol liposome system (Lipo-RSV), developed by Shi et al., has good biocompatibility and can recover macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory M2 phenotype (Shi, 2021). In addition, Lipo-RSV can effectively remove ROS, reduce the expression of pro-inflammatory cytokines such as IL-1β, IL-6, and TNF-α, and increase the level of anti-inflammatory factor IL-10, thereby improving the inflammatory state of periodontal tissue (Shi, 2021). Notably, resveratrol has therapeutic effects on systemic diseases related to periodontitis (such as diabetes, atherosclerosis, osteoporosis, etc.). However, the specific mechanism of action requires further investigation.

Precise targeted anti-inflammatory therapy for age-related bone diseases has been a hot topic in the medical field. Although several NP-based anti-inflammatory drugs have been developed, their targeted therapeutic effects require further investigation. Research on the mechanism of drug action remains insufficient, and many drugs have clinical applications. Therefore, further research is needed to explore ways to improve the bioavailability of nano-anti-inflammatory medicines and enhance their therapeutic effects in age-related bone diseases.

3.1.3. Nanomaterials for immune regulation

With an increase in age, aging of the immune system initiates a process of chronic inflammation, making the elderly vulnerable to infectious diseases, malignant tumors, age-related bone diseases, and other chronic diseases. This physiological decline in immune function is known as immunosenescence (Barbé-Tuana, 2020). Therefore, effective regulation of the functional status of the immune system through various technological means may be a potential treatment option for age-related bone diseases. Induction of antigen-specific immune tolerance can avoid the toxic side effects of traditional non-specific immunosuppressive agents and is a hot topic in the treatment of autoimmune or age-related inflammatory diseases (Millozzi, et al., 2023). In recent years, the development of nanotechnology has revolutionized the diagnosis and treatment of diseases in modern medicine. NPs combined with specific autoantigens restore peripheral immune tolerance, remove excess circulating inflammatory mediators, and reduce immunopathological damage in various models of autoimmune and inflammatory diseases (Smith et al., 2013).

Several studies have shown that immune cell-mediated immune responses are regulated by the chemical composition, structure, and bioactive molecules of nanomaterials (Lee, 2019). For example, to simulate the ECM of bone, Qiu et al. (Qiu, 2020) prepared an injectable periosteal extracellular matrix hydrogel that was beneficial for angiogenesis, promoted macrophage recruitment transformation from M1 to M2, and further enhanced bone regeneration. Therefore, based on the composition of the natural bone tissue, it is important to explore the effects of the chemical composition of nanomaterials on the immune responses of macrophages from a bionic perspective. Interestingly, the surface morphology of the nanomaterials can directly affect macrophage polarization. The ordered intrafibrillar-mineralized collagen prepared

by Jin et al. (Jin, 2019) simulated the morphology of the surface of natural bone tissue, promoted the transformation of macrophages to an anti-inflammatory phenotype, and promoted the osteogenic differentiation of bone mesenchymal stem cells by secreting IL-4, substantially promoting mandibular regeneration. In addition, the hydroxyapatite nanoparticle structure modified on the titanium surface promotes M2 macrophage polarization more effectively than the nanorod structure, which is beneficial for bone immune regulation, angiogenesis, and bone formation (Bai, 2018). Similarly, the micro/nano-scale titanium dioxide fiber network structure prepared on the surface of titanium implants also has a comparable effect (Bai, 2021). With advancements in nanomaterial technology, the surface structure size, hydrophilicity, and roughness have become easier to control. Therefore, the difficulty in obtaining a more favorable bone microenvironment by modifying the surface structure of the NPs has been significantly reduced.

Notably, metal ions with immunomodulatory activity can be loaded onto nanomaterials to form single- or multi-loaded nanorelease systems, which are also important for bone regeneration. Studies have shown that silver-loaded titanium dioxide nanotubes can control the release of ultralow doses of Ag^{+}, increase autophagy in macrophages, remove ROS, inhibit inflammatory responses, and promote new bone formation (Chen, 2020). Similarly, nanomaterials loaded with Zn^{2+}, $Cu^{2+,}$ or Mg^{2+} can stimulate bone-tissue regeneration by regulating the immune responses of macrophages (Chen, 2020; Wang, 2022; Huang, 2019).

Therefore, NP-based immune regulation can achieve effectiveness, timing, and synergy of immune cell behavior regulation in the treatment of age-related bone diseases. However, it is necessary to strictly control the degree of immune cell-mediated immune response to achieve effective bone tissue repair and regeneration.

3.1.4. Nanomaterial-mediated tissue regeneration strategy

Bone defects and insufficient bone mass caused by aging are common clinical phenomena. With increasing age, the number of aging bone marrow mesenchymal stem cells (BMSCs) remains unchanged, but the number of mature osteoblasts decreases, which impairs the osteogenic differentiation ability of BMSCs and the ability of bone remodeling and micro-damage repair, resulting in bone loss and increased probability of fracture (Lerner et al., 2019). Improving the osteogenic differentiation of BMSCs in patients with age-related bone diseases may provide a new treatment strategy for bone microdamage repair and fracture prevention. Various bone biomaterials have been developed for bone tissue regeneration with specific results (Li and Liu, 2017). Recently, researchers observed that the local immune microenvironment plays a crucial role in bone tissue regeneration. Therefore, the development of bone biomaterials with immunomodulatory properties has become a popular research topic. Thus, the role of macrophages in bone tissue regeneration is noteworthy (Schlundt, 2021). Many studies have shown that when there is chronic inflammation in the body, too many M1 macrophages produce many pro-inflammatory cytokines and inhibit bone tissue regeneration by inhibiting the osteogenic differentiation of BMSCs and enhancing osteoclast formation (Schlundt, 2021). Therefore, the conversion of M1 macrophages to M2 macrophages is crucial during the late stages of bone tissue regeneration.

Because macrophages respond differently to complex environments, they are expected to achieve good bone tissue regeneration in targeted therapy of age-related bone diseases based on strategies such as nanomaterials to regulate their biological behavior. For example, hydroxyapatite is the main component of natural bone tissue. Bone-mimicking nano-hydroxyapatite particles prepared by Mahon et al. (Mahon, 2020) promoted osteogenic differentiation and mineral formation in BMSCs by enhancing the secretion of IL-10 by macrophages. Strontium-containing nanonodules have been shown to inhibit the inflammatory response caused by M1 macrophages and provide a favorable microenvironment for the early healing stage of bone tissue (Choi and Park, 2018). To explore the related mechanism, Xu et al. (Xu, 2021) found that strontium-modified surfaces can activate the extracellular regulatory protein kinase signaling pathway, thereby promoting the M2 polarization of macrophages. Similarly, cerium-ion-modified titanium surfaces scavenge ROS in macrophages, inhibit the production of inflammatory mediators, and promote the transformation of macrophages into anti-inflammatory phenotypes (Li, 2018). Other researchers have found that the surface of hydroxyapatite bioceramics with a needle-like nanomorphology or the surface of nanomaterials with an appropriate pore size (such as 30 nm) can effectively inhibit the M1-type transformation of macrophages and show good osteogenic effects (Yang, 2019; Ma, 2018). These results show that designing nanomaterials with appropriate components based on the immune microenvironment of bone tissue healing and regeneration is an effective way to regulate the behavior of macrophages during bone tissue regeneration, which affects the morphology, polarization, and secretory function of macrophages.

Other studies have reported that carrying bioactive molecules onto nanomaterials can achieve precise positioning in space and time, which is conducive to prolonging their release time, reducing dosage, reducing adverse reactions, and promoting bone tissue regeneration in coordination with the materials (Gu, 2013). Wei et al. (Wei, 2019) loaded bone morphogenetic protein-2-stimulated macrophage exosomes into titanium dioxide nanotubes, effectively avoiding ectopic osteogenesis caused by high-dose use and promoting osteogenic differentiation by activating BMSCs autophagy, improving bone tissue regeneration, and enhancing safety. In addition, extracellular matrix-derived peptides and dexamethasone have been loaded into nanomaterials to achieve multiple functions, including anti-infection, anti-inflammatory, and bone regeneration (Shao, 2019). Moreover, it is suggested that the anti-inflammatory medium can be loaded into nanomaterials to achieve anti-inflammatory and tissue regeneration through multiple effects. Notably, multiloading metal ions through a nano-drug delivery system can also exert a synergistic enhancement effect. For example, a micro-nano hierarchical drug delivery system with Ag^{+} and Sr^{2+} double loading can resist bacteria, directly promote osteoblast differentiation, indirectly enhance osteogenic differentiation by promoting M2 polarization of macrophages, and ultimately synergistically improve bone regeneration (Li, 2019).

Therefore, the chemical composition of nanomaterials or bioactive molecules can regulate the behavior of immune cells and construct an immune microenvironment conducive to bone tissue regeneration and promote bone tissue regeneration, providing a research basis and new ideas for improving the therapeutic effect of age-related bone diseases.

3.1.5. Nanomaterials for targeted clearance of senescent cells

Some studies have shown that nanosenolytics or new galactooligosaccharide-coated nanomaterials that can reduce SASP drugs can precisely remove senescent cells without damaging adjacent normal cells, which is expected to improve the biological targeting of senescent cell scavengers (Table 3). Several nanodelivery systems that effectively target senescent cells *in vitro* and *in vivo* have been proposed (Muoz-Espín, 2019). For example, quercetin surface-functionalized Fe_3O_4 nanoparticles exhibit catalase-like activity in cells, which can eliminate premature senescence of human fibroblasts (induced by hydrogen peroxide) *in vitro* and reduce senescence-mediated pro-inflammatory responses, showing good senolytic activity (Lewinska, 2020). Similarly, B2M (β2-microglobulin) nano-molecularly imprinted nanoparticles (MIPs) loaded with dasatinib can target the removal of senescent bladder cancer cells (Ekpenyong-Akiba, 2019). In addition, nano-MIPs may have diagnostic, prognostic, and therapeutic potential in age-related diseases and are non-toxic after single-dose injections (Ekpenyong-Akiba, 2019).

Nanotechnology-based removal of senescent cells or blocking SASP secretion may be a potentially effective strategy for treating age-related bone diseases. However, there are still many challenges to achieving this strategy. First, cell senescence benefits the body through physiological processes, and the time, location, and treatment methods using senescent cell scavengers must be carefully considered. Secondly, more

Table 3
The types and mechanisms of nanomaterials targeting senescent cells.

Nanomaterials	Senescence Models	Effects and Mechanisms	Reference
LR-CD9mAb CD9 monoclonal antibody conjugated to PEGylated liposomes	Adriamycin-induced aging; Human dermal fibroblasts (HDF)	Cell proliferation potential ↑, β-Galactosidase activity and p53/ p21 expression ↓, cell migration ↑	(Nguyen, 2017)
CD9-Lac/ $CaCO_3$/ Rapa NPs CD9 monoclonal antibody-conjugated lactose-wrapped calcium carbonate nanoparticles loaded with rapamycin	Reproductive aging and doxorubicin-induced aging; Human dermal fibroblasts (HDF)	β- Galactosidase activity ↓, p53/ p21/ CD9/ Cyclin D1 expression ↓, cell proliferation and migration ability ↑, population doubling time ↓, to prevent G1 cell cycle arrest	(Thapa, 2017)
MoS_2 NPs molybdenum disulfide mesoporous silica nanoparticles	Stress-induced premature aging; Human aortic endothelial cells (HAEC)	γ- H2AX phosphorylation ↓, inhibits upregulation of p16, p21, and p53, activates autophagy, improves autophagy flux, and prevents lysosomal and mitochondrial dysfunction	(Ke, 2018)
GalNP (dox) 6-mer galacto-oligosaccharide encapsulated doxorubicin	Bleomycin-induced pulmonary fibrosis; Mice	Improving lung function	(Muñoz-Espín, 2018)
GalNP (nav) 6-mer galacto-oligosaccharide encapsulated navitoclax	Paboxil-induced aging; Melanoma (SK-MEL-103)	Apoptosis of senescent cells	
GalNP (dox) 6-mer galacto-oligosaccharide encapsulated doxorubicin GalNP (nav) 6-mer galacto-oligosaccharide encapsulated navitoclax	Paboxil-induced tumor aging; Mice carrying SK-MEL-103 tumor xenograft	Clearing senescent cells and inducing tumor xenograft regression	
DSAs Docetaxel-tannic acid self-assemblies (DSAs)-based nanoparticles	Prostate cancer cells (C4-2 and PC-3) PC-3 tumor xenograft in mice	Aging related TGF β R1, FOXO1, and p21 proteins ↓, activation of cell apoptosis ↓ By blocking TGF β R1/ p21 mediated activation of aging signaling and cell apoptosis induces regression of tumor xenografts	(Nagesh, 2019)
NanoMIPs molecularly-imprinted nanoparticles	Bladder cancer cells with tetracycline (tet) regulated p16 expression system (EJp16)	Decreased number of aging cancer cells	(Xu et al., 2021)
MNPQ quercetin surface-functionalized Fe_3O_4 nanoparticles	Hydrogen peroxide-induced aging; Human foreskin fibroblasts (BJ)	AMPK activation, induction of non-apoptotic cell death, SASP components ↓ (IL-6 and IFN- β)	(Lewinska, 2020)
GalNP (nav)	Palbociclib-induced aging; Triple negative breast cancer mice models	Tumor growth and metastasis ↓, systemic toxicity of Navitoclax, and apoptosis of aging cancer cells (senolytic activity)	(Galiana, 2020)

targeted studies are required to explore the modification effects of nanotechnology on drugs to increase the selective impact of medications on senescent cells and reduce their cytotoxicity to non-target cells. Finally, designing safer and more effective nanosenescent cell scavengers for different tissue cell types and senescent cell accumulation characteristics is necessary because of the different origins and susceptibilities of senescent cells in various tissues.

3.2. Biotherapy

In addition to anti-aging drugs, various other anti-aging technologies have been developed to combat aging in terms of appearance and body shape, and new drugs targeting senescent cells have been developed. However, owing to the progression of cell aging and the heterogeneity of tissues and organs, there are still no specific and universal senescent cell markers and drug targets. This field still has a significant knowledge gap that requires further study. Fig. 3 and Table 4 summarize the potential anti-aging strategies for the age-related bone diseases mentioned in this review.

3.2.1. Stem cell transplantation

Adipose-derived stem cells (ADSCs) and BMSCs are commonly used in anti-aging stem cell transplantation. These two types of stem cells are characterized by minor tissue damage, convenient sampling, strong differentiation abilities, and lasting effects. They secrete various growth- and inflammation-related factors, improve the body's ability to resist free radicals, inhibit inflammation, and accelerate wound healing to achieve anti-aging effects (Zhao and Zhang, 2016). After intravenous injection of allogeneic ADSCs in aging rat models, the level of SOD increased, indicating that the antioxidant capacity of rats was enhanced and the aging process was delayed (Zhou, 2019). In addition, Zhang et al. (Zhang, 2015) found that BMSCs transplantation could improve age-related osteoporosis, Parkinson's disease, and atherosclerosis by differentiating into cardiomyocytes, exerting immunosuppressive activity, secreting protective factors or cytokines, notably improving the damaged heart function of aging rats, and restoring their physical and cognitive functions, thus showing a strong anti-aging effect.

3.2.2. Fecal microbiota transplantation

As age increases, the body's immunity decreases and the intestinal physiological function and diet structure change, resulting in a decrease in the number and diversity of beneficial bacteria in the intestinal flora and an increase in facultative anaerobes (Gupta et al., 2016). Changes in aging-related intestinal flora affect the brain-gut axis through the enteric nervous system, which can hinder nerve, endocrine, and immune signals, leading to central nervous system diseases such as Alzheimer's disease and Parkinson's syndrome (Gupta et al., 2016). Fecal microbiota transplantation (FMT) refers to the transplantation of functional flora from the feces of healthy individuals into the gastrointestinal tract of patients to reconstruct new intestinal flora and treat intestinal and extraintestinal diseases (Biazzo and Deidda, 2022). FMT is an effective and safe anti-aging method that has been used to treat Clostridium difficile infections, stress bowel disease, and hepatic encephalopathy (Dinan and Cryan, 2017). For example, Kelly et al. (Kelly, 2016) found that increased diversity of the gut microbiota reduces the risk of heart disease. In addition, the intestinal flora of African medaka larvae were transplanted into elderly medaka, and their lifespan was prolonged by 41 % (Callaway, 2017). However, its clinical application and ethical issues must be addressed.

3.2.3. Application of stem cell exosomes in age-related bone diseases

In recent years, stem cell-based therapies have shown that stem cells inhibit inflammation, regulate immune responses, prevent apoptosis, and replace and promote the repair of damaged sites. At the same time, studies have shown that the main beneficial effects are not due to the 'homing,' proliferation, and differentiation of stem cells at the injury

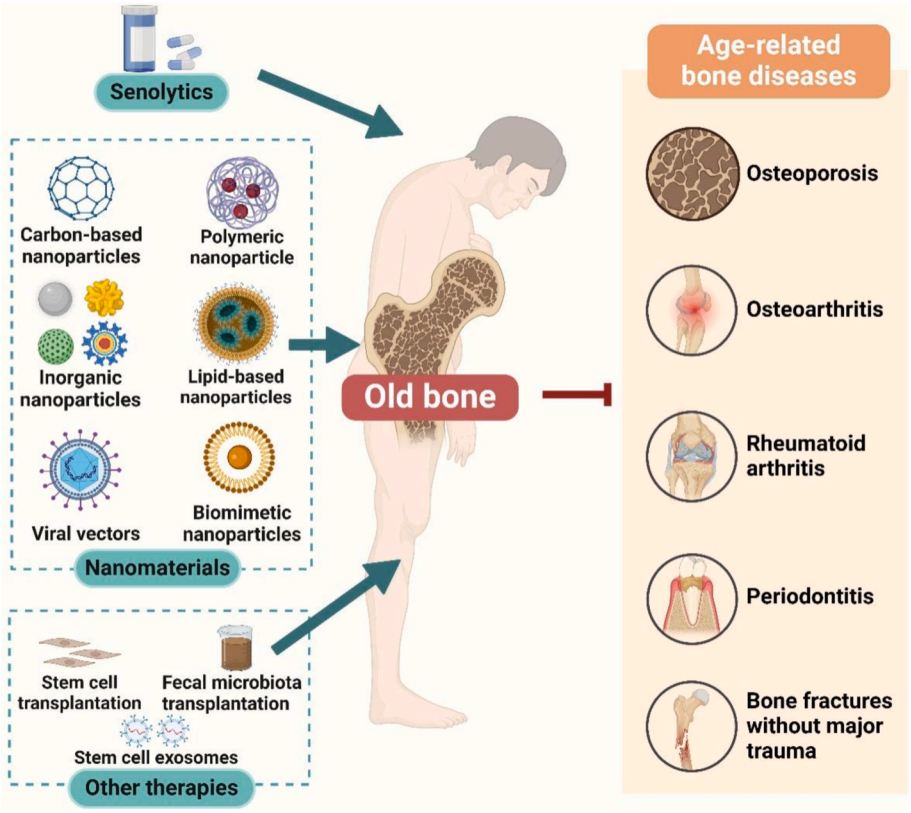

Fig. 3. Potential anti-aging strategies of age-related bone diseases. Senolytics, nanomedicines with multiple functions, and other new therapies (including stem cell exosomes) can effectively improve the therapeutic effects of age-related bone diseases such as osteoporosis, osteoarthritis, rheumatoid arthritis, periodontitis, and bone fractures without major trauma.

Table 4
Anti-aging strategies for age-related bone diseases.

Bone Diseases	Treatment Strategies	Classification
Osteoporosis, osteoarthritis, rheumatoid arthritis, periodontitis, non-traumatic fracture, bone-related cancer	Senolytics	Dasatinib (D) Quercetin (Q) Venetoclax (ABT-199) A1331852 A1155463 Navitoclax (ABT-263) ABT-737 UBX0101 Fisetin (FIS) 17-DMAG FOXO4-DRI peptide Piperlongumine (PL) EF24
	Nanomaterial-mediated strategies	Anti-inflammatory therapy Immunomodulation therapy Tissue regeneration therapy Targeted clearance therapy of senescent cells
	Biotherapy	Stem cell transplantation Fecal microbiota transplantation Stem cell exosomes

site, but rather are mediated by paracrine effects (Lin, 2022; Wang, 2024). Cells can synthesize and secrete a wide range of soluble factors (cell growth factors and chemokines, etc.) in their life activities and can also secrete extracellular vesicles (EVs). Soluble factors can have a particular impact on the surrounding cells, whereas EVs affect various signaling pathways through paracrine or endocrine effects. Exosomes, the most widely studied subtype of extracellular vesicles, are immunomodulatory, promote cell proliferation and migration, and act as anti-aging biomaterials for tissue repair and regeneration. At the same time, exosomes have the advantages of repeated administration, low immunogenicity, and no ethical restrictions and have attracted great interest in regenerative medicine (Hassanzadeh, 2021).

Osteoporosis

With age, the osteogenic differentiation ability of BMSCs in older people is impaired. Compared with young people, the content of galectin-3 in the plasma EVs of older people is reduced, and osteogenic differentiation is inhibited (Weilner, 2016). In the serum exosomes of young rats, high miRNA-19b-3p expression improved the decreased osteogenic ability of senescent BMSCs and reduced the expression of PTEN (phosphatase and tensin homolog deleted on chromosome ten) (Weilner, 2016). Abundant anti-aging signals have also been found in exosomes isolated from stem cell-conditioned medium. In 2021, Lei et al. (Lei, 2021) found that after incubation of senescent BMSCs with hUC-Exo, the proportion of S-phase cells in senescent BMSCs^{EV+} was much higher than that in the control group and was proportional to the dose. Additionally, colony formation ability was enhanced, aging-related SA-β-Gal activity decreased, and the protein levels of IL-6, IL-8, monocyte chemoattractant protein-1 (MCP-1), and the phosphorylated form of H2AX histone variant (γ-H2AX) were reduced. Animal studies also showed that senescent BMSCs^{EV+} had higher osteogenic ability *in vivo*. Diabetes, a common disease in the elderly, is associated with inflammation, which is one of the causes of osteoporosis. Overexpression of miR-146a-Exo in hADSCs inhibits proinflammatory factors and helps repair bone loss in rats with diabetic osteoporosis (Zhang, 2022).

Osteoarthritis

OA is a degenerative disease with a high incidence in the elderly

population. It is characterized by an imbalance in the synthesis and catabolism of chondrocytes and extracellular matrix, leading to articular cartilage damage. Chondrocyte senescence is a critical factor in the development of OA. Stem cell-derived exosomes promoted chondrocyte proliferation and inhibited apoptosis (Zhang, 2018; Gupta, 2021). Exosomes have made significant progress in basic and clinical studies on cartilage repair. For example, miR-92a-3q contained in the exosomes of human bone marrow mesenchymal stem cells (BMSC-Exos) can directly target Mnt5a, increase the expression of chondrocyte markers (such as type II collagen and SOX9), and reduce the expression of catabolic markers (such as MMP-13 and RUNT-related transcription factor 2), thereby increasing chondrocyte proliferation and inhibiting chondrocyte apoptosis (Mao, 2018). The exosomes obtained by the hypoxic pretreatment of BMSCs may stimulate the proliferation and migration of cartilage through the miRNA-18-3P/JAK/STAT or miRNA-181c-5P/MAPK signaling pathways, inhibit chondrocyte apoptosis, and promote cartilage repair. Similarly, Rong et al. (Rong, 2021) found that exosomes derived from hypoxia-preconditioned BMSCs mediate cartilage repair through miR-216a-5P. It is worth noting that lncRNA is involved in regulating cell growth, proliferation, differentiation, and apoptosis. The lncRNA KLF3-AS1 in BMSC-Exos and lncRNA H19 in hUC-Exos can promote cartilage repair by promoting cell proliferation, migration, and inhibiting apoptosis (Liu, 2018; Yan et al., 2021), suggesting that lncRNAs in mesenchymal stem cell-derived exosomes can inhibit the translation of mRNA and can be used as a new biomarker and therapeutic target for various diseases (including age-related bone diseases) (Yan et al., 2021).

4. Discussion

4.1. Cell senescence and tumor therapy

Multiple myeloma (MM) is a plasma cell disease characterized by clonal proliferation of malignant plasma cells in the bone marrow. Its incidence ranks second among hematological tumors and is increasing as the world population enters an aging stage (Dimopoulos, 2021). MM has the highest incidence of bone invasion among all malignant tumors and a high disability rate, which seriously affects the quality of life of patients and is the main cause of death (Emkey and Epstein, 2014). Osteoporosis and osteolytic destruction are the most common clinical symptoms of MM. Bone pain is the first symptom and the reason for treatment (Mumford et al., 2015. 2015.). The occurrence of bone disease is multicellular and multifactorial, which leads to the uncoupling of bone remodeling; that is, the enhancement of bone resorption function and decrease in formation function, resulting in bone loss and osteolytic lesions (Terpos et al., 2019). Increased bone resorption is an independent risk factor for overall survival in patients (Mukkamalla and Malipeddi, 2021). Therefore, the timely diagnosis and treatment of the potential causes of secondary osteoporosis in MM can effectively reduce the risk of fractures and improve patient survival and quality of life.

Various cancer treatment strategies have been proposed based on the heterogeneous effects of cell senescence on tumor cells. For example, senolytic therapy is an anti-aging therapy that removes senescent tumor cells by selectively inducing their apoptosis. Senomorphic therapy, another anti-aging therapy, reduces the adverse effects of senescent cells by inhibiting the harmful effects of SASP factors they secrete. Senolytic therapy has great potential for removing senescent cells, reducing the adverse effects of cell senescence, and improving the therapeutic effect on cancer (Kirkland and Tchkonia, 2020). Several senolytics have been tested in clinical trials. Compared to senolytic drugs, senomorphic drugs cannot directly remove senescent cells; therefore, long-term administration is required to maintain efficacy. Therefore, senomorphic drugs have not yet entered the clinical trial stage, and the use of such drugs will interfere with the progress of some key signaling pathways, which may result in greater risks and adverse reactions (Song, 2020). Additionally, because senescent cells can escape immune surveillance by secreting SASP factors, researchers have developed immunotherapies that promote immune cells to target senescent cells. Chimeric antigen receptor T (CAR-T) cells are generated by the gene editing of T cells so that they can specifically recognize and bind to proteins upregulated on the surface of senescent cells, thereby promoting their clearance of senescent cells (Qu, 2022; Ai, 2024). For example, the CD19 transmembrane glycoprotein expressed only in B cell lines is upregulated in most malignant B cell tumors. Axicabtagene ciloleucel, lisocabtagene maraleucel, and tisagenlecleucel are FDA-approved drugs that target CD19 for the treatment of relapsed or refractory diffuse large B-cell lymphoma with good therapeutic effects (Qu, 2022).

4.2. Other potential anti-aging therapeutic targets

In addition to the known targets for senescent cells to resist apoptosis, the development of other senescent cell clearance methods is worthy of future attention. For example, Kim et al. (Kim, 2017) reported that DPP4 (CD26) is highly expressed in senescent human fibroblasts and that senescent cells are preferentially cleared by NK cells that recognize anti-DPP4 antibodies, which is instructive for developing senescent cell clearance methods. In addition, new drug targets targeting senescent cells have been established. However, owing to the progressive nature of cell senescence and the heterogeneity of tissues and organs, there are still no precise and universal senescent cell markers and drug targets.

It is worth noting that several studies in recent years have shown that the use of anti-inflammatory drugs such as metformin, aspirin, rapamycin, and ibuprofen can effectively delay the progression of age-related chronic diseases (Weng, 2022; Rodas-Junco, 2024; Zhu, 2023). For example, metformin can reduce chronic inflammation and improve the health of patients by acting on possible targets such as IKK/NF-κB in patients with type 2 diabetes (Moiseeva, 2013), as well as GPX7/NRF2338 (Fang, 2018) and the recently discovered target PEN2 (Ma, 2022). Additionally, aspirin delays replicative aging by reducing oxidative stress. Recent studies have shown that CD36 is key to SASP-related mechanisms. Silencing CD36 in senescent muscle tissue cells using CD36-specific short interfering RNA reduces SASP secretion in these cells (Moiseeva, 2023). Therefore, it is important to study the regulatory pathways of anti-inflammatory treatments in age-related bone diseases. Based on the existing literature, our research group is committed to using the non-steroidal anti-inflammatory drug flufenamic acid (FFA) to develop a new composite nanomaterial with anti-inflammatory, anti-aging, anti-osteoclast, and osteogenic effects to help treat periodontal bone regeneration (Liu, 2019; Rouzer and Marnett, 2020; Zhang, 2020); to optimize its application in biomedicine. However, the regulatory process of anti-inflammatory drugs in chronic inflammatory bone disease remains unclear, and the signaling molecules and regulatory networks involved are still not fully elucidated. Therefore, there is still a large knowledge gap in this field, and more basic and clinical experiments are required in the future.

5. Conclusion, limitations, and prospects

In summary, considerable knowledge has been accumulated regarding many fundamental scientific problems in age-related bone diseases, and the development of safe and specific anti-aging methods remains a significant future research direction. Recent studies have confirmed that inflammation is closely associated with various age-related bone diseases, including osteoporosis, osteoarthritis, rheumatoid arthritis, and periodontitis. Although SASP secreted by senescent cells is an important feature, no specific inflammatory factor has been found to accurately reflect cell senescence; therefore, it is difficult to quantify or distinguish it from other types of inflammation. In future research, different models must be used to observe the occurrence and development of senescent cells and the SASP and to explore personalized medication regimens.

Nanoparticle-mediated drug delivery systems effectively improve drug delivery efficiency, and their targeting and safety can compensate for the shortcomings of existing traditional drugs in treating age-related bone diseases. However, the cytotoxicity and biocompatibility of nanocarriers introduced by targeted therapy require further improvement. Second, the load capacity, targeting, carrier stability, and methods to reduce the accumulation of nondegradable materials in the body are still worthy of further exploration. However, the application of nanotargeted therapy in clinical treatment still requires a large amount of experimental data to prove its safety. In addition, although new therapeutic strategies such as stem cell exosomes have made exciting progress in the anti-aging treatment of bone diseases, many problems still require further study. On the one hand, the components of exosomes derived from different stem cells are highly heterogeneous, and their biological activities are not the same. Moreover, the mechanism of action of exosomes in various diseases is complex and remains challenging to elucidate. However, the preparation and quality control of exosomes requires considerable clinical data. These factors affect the transformation of the clinical applications.

In the future, we need more in-depth analyses to solve the clinical application of new anti-aging strategies, such as nanotechnology, and to establish a complete set of operating procedures for preparing drug carriers for clinical application. It is expected to improve the mechanisms of action of these precisely targeted therapies for related diseases through many clinical applications, significantly compensate for the shortcomings of existing clinical treatments, and improve patient cure and survival rates.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent for publication

All authors agreed to publication.

Funding

This work was supported by Scientific Research and Cultivation Project of Stomatological Hospital, Southern Medical University (Grant no., PY2021018 and PY2022013).

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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.

Acknowledgments

The authors would like to thank all the reviewers who participated in the review and thank Editage (www.editage.cn) for English language editing. Biorender.com (Toronto, Ontario) tool was used to create the figures.

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