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Nanomaterials Targeting Ferroptosis Opens New Avenues for Osteoarthritis Therapy: A Systematic Review of In Vivo and In Vitro Studies

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ADMINISTRATIVE INFORMATION

Support - None.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 27 July 2025 and was last updated on 27 July 2025.

INTRODUCTION

Review question / Objective Nanomaterials targeting ferroptosis offer a novel treatment approach for osteoarthritis. This systematic review has two main aims. First, it aims to comprehensively search, screen, and analyze relevant studies on treating osteoarthritis by targeting ferroptosis with nanomaterials. Second, it aims to clarify the research status, core mechanisms, and key technical breakthroughs in this field. To our knowledge, this is the first comprehensive systematic review on this subject.

Condition being studied Osteoarthritis (OA) is a common degenerative joint disease. It is characterized by progressive cartilage degradation, subchondral bone remodeling, and synovial inflammation. Despite progress in understanding its pathophysiology, therapeutic strategies mainly focus on symptom management. There is no cure for structural repair. Recent studies have shown that ferroptosis, a regulated form of cell death driven by iron-dependent lipid peroxidation and oxidative stress, plays a crucial role in OA progression. Ferroptosis disrupts chondrocyte homeostasis. It does this by depleting glutathione peroxidase 4, increasing reactive oxygen species, and promoting extracellular matrix degradation. These findings suggest that ferroptosis could be a promising therapeutic target for OA. However, conventional small-molecule drugs targeting ferroptosis face problems. These include poor bioavailability, systemic toxicity, and limited tissue specificity. Nanomaterials, with their adjustable physicochemical properties and multifunctional capabilities, offer a new platform for precision medicine in OA. Currently, research on using nanomaterials to target ferroptosis for OA treatment is in a rapid development phase. The number of relevant studies has increased significantly, and research directions are diverse. They cover aspects like nanomaterial design and synthesis, screening of ferroptosis regulatory targets, and evaluation of in vitro and in vivo treatment effects. But different studies vary in experimental methods, material selection, and evaluation indicators. This challenges the

comparability and reproducibility of research results. Thus, there is an urgent need to integrate and analyze existing evidence through systematic review methods. Based on this, this systematic review has two main aims. First, it will comprehensively search, screen, and analyze relevant studies on using nanomaterials to target ferroptosis for OA treatment. Second, it will clarify the research status, core mechanisms, and key technical breakthroughs in this field. The significance of this study is two-fold. Firstly, by systematically organizing existing evidence, it provides standardized research perspectives and methodological references for researchers. This helps reduce the heterogeneity among studies. Secondly, by summarizing the advantages and limitations of using nanomaterials to target ferroptosis for OA treatment, it offers a theoretical basis and practical guidance for clinical translation. This can promote the transformation of new treatment strategies from basic research to clinical application, ultimately providing more effective treatment options for OA patients.

METHODS

Search strategy A systematic search of Embase, Ovid, ProQuest, PubMed, Scopus, the Cochrane Library, and Web of Science was carried out from the inception of the database to July 27th, 2025. The following Medical Subject Headings terms and free words were used: (("ferroptosis"[Mesh]) OR ("iron death" [Title/Abstract])) AND ((((((((("osteoarthritis"[Mesh]) OR (osteoarthritides[Title/Abstract])) OR (osteoarthrosis[Title/Abstract])) OR (osteoarthroses[Title/Abstract])) OR (arthritis, degenerative[Title/Abstract])) OR (arthritides, degenerative[Title/Abstract])) OR (degenerative arthritides[Title/Abstract])) OR (degenerative arthritis[Title/Abstract])) OR (arthrosis[Title/Abstract])) OR (arthroses[Title/Abstract])) OR (osteoarthrosis deformans[Title/Abstract]) AND ("nano*"[Title/Abstract]).

Participant or population Experimental studies at the cellular and/or animal level on the use of nanodrug delivery systems to target ferroptosis for the prevention and treatment of osteoarthritis.

Intervention Not Applicable.

Comparator Not Applicable.

Study designs to be included (1) Literature regarding the utilization of nanodrug delivery systems to target ferroptosis for the prevention and treatment of osteoarthritis. (2) It is required to include cell and/or animal experiments.

Eligibility criteria The inclusion criteria were as follows: (1) Literature regarding the utilization of nanodrug delivery systems to target ferroptosis for the prevention and treatment of osteoarthritis. (2) Studies must contain cell and/or animal experiments. (3) The literature must be in English. The exclusion criteria were as follows: (1) Review papers, dissertation papers, letters, commentaries, editorials, conference abstracts, meta-analyses, case reports, and bibliometric/scientometric analyses. (2) The same studies published in different journals under the same or different titles. (3) Studies with inaccessible full-text.

Information sources The research relied on multiple information sources, namely: Embase, Ovid, ProQuest, PubMed, Scopus, the Cochrane Library, and Web of Science.

Main outcome(s) The following data were collected: author (year), country, cell type and source, animal species, animal age, weight and gender, sample size, core study design, approaches of nano drug delivery systems, duration of intervention, and pivotal discovery.

Data management Studies collected from the initial search were imported into NoteExpress (ANGEAN SEA Technology, Beijing, China) to organize the related literature and eliminate duplicate references. The final eligibility of the retrieved papers was determined by two adjudicators, who independently scrutinized the titles and abstracts of the papers. Discrepancies were addressed via consensus with a third reviewer.

Quality assessment / Risk of bias analysis The risk of bias evaluation for in vivo studies was performed independently by two researchers. They used Review Manager 5.3 (Cochrane Collaboration, Oxford, UK) according to the Systematic Review Centre for Laboratory animal Experimentation (SYRCLE)'s risk of bias tool. For in vitro studies, the same two researchers who evaluated the in vivo studies independently assessed the bias risk using a table for cellular experiments adapted from previous studies. All discrepancies were resolved through discussion and adjudication by a third researcher.

Strategy of data synthesis Not Applicable.

Subgroup analysis Not Applicable.

Sensitivity analysis Not Applicable.

Language restriction English.

Country(ies) involved People's Republic of China.

Keywords nanomedicine; osteoarthritis; ferroptosis; systematic review.

Contributions of each author

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