Astaxanthin and Osteoarthritis: A Survey on Its Role in Modulating Signaling Pathways and Protecting Chondrocytes

www.surveyx.cn

Abstract

Osteoarthritis (OA) is a prevalent degenerative joint disease characterized by cartilage deterioration and inflammation. This survey explores the potential role of astaxanthin, a potent antioxidant, in modulating signaling pathways to mitigate oxidative stress and inflammation in OA. The paper delves into how astaxanthin influences key pathways such as NFB and MAPK, crucial in OA pathogenesis, and highlights its protective effects on chondrocytes, which are vital for cartilage health. Astaxanthin's ability to reduce oxidative stress and modulate inflammatory responses positions it as a promising candidate for OA management. The survey integrates findings from various studies, emphasizing astaxanthin's therapeutic potential in addressing limitations in current OA treatments, including cartilage regeneration challenges and the accumulation of senescent cells. The review also considers the broader implications of astaxanthin's integration into OA treatment strategies, evaluating its efficacy, safety, and potential for enhancing current therapeutic approaches. Despite promising findings, the complexity of OA necessitates further research to fully elucidate astaxanthin's therapeutic potential and develop targeted, individualized treatment strategies. The survey underscores the need for continued exploration of astaxanthin's role in OA to improve patient outcomes and quality of life.

1 Introduction

1.1 Focus of the Paper

This paper investigates the role of astaxanthin in modulating signaling pathways to alleviate oxidative stress and inflammation in osteoarthritis (OA). Recognized for its potent antioxidant properties, astaxanthin has shown promise in treating conditions related to oxidative stress and inflammation [1]. The study elucidates how astaxanthin influences critical signaling pathways, such as NFB and MAPK, integral to the inflammatory response and oxidative stress mechanisms in OA [2]. By focusing on these pathways, the paper provides insights into astaxanthin's protective effects on chondrocytes, which are essential for maintaining cartilage health and are often compromised in OA [3]. Furthermore, the potential of astaxanthin in addressing current OA treatment challenges, including limitations in cartilage regeneration and the accumulation of senescent cells in joint tissues, is explored [4]. The survey integrates findings from various studies that elucidate the mechanisms governing chondrocyte proliferation and differentiation, emphasizing the regulatory factors involved in cartilage homeostasis and repair [5]. A comprehensive review of literature and recent advances in OA research highlights astaxanthin's therapeutic potential and its integration into OA treatment strategies. Additionally, the paper discusses erythropoietin's effects on mitigating cartilage degeneration through inflammatory response modulation [6] and the role of oxidative stress in mitochondrial dysfunction. The involvement of Pink1-mediated mitophagy and the balance

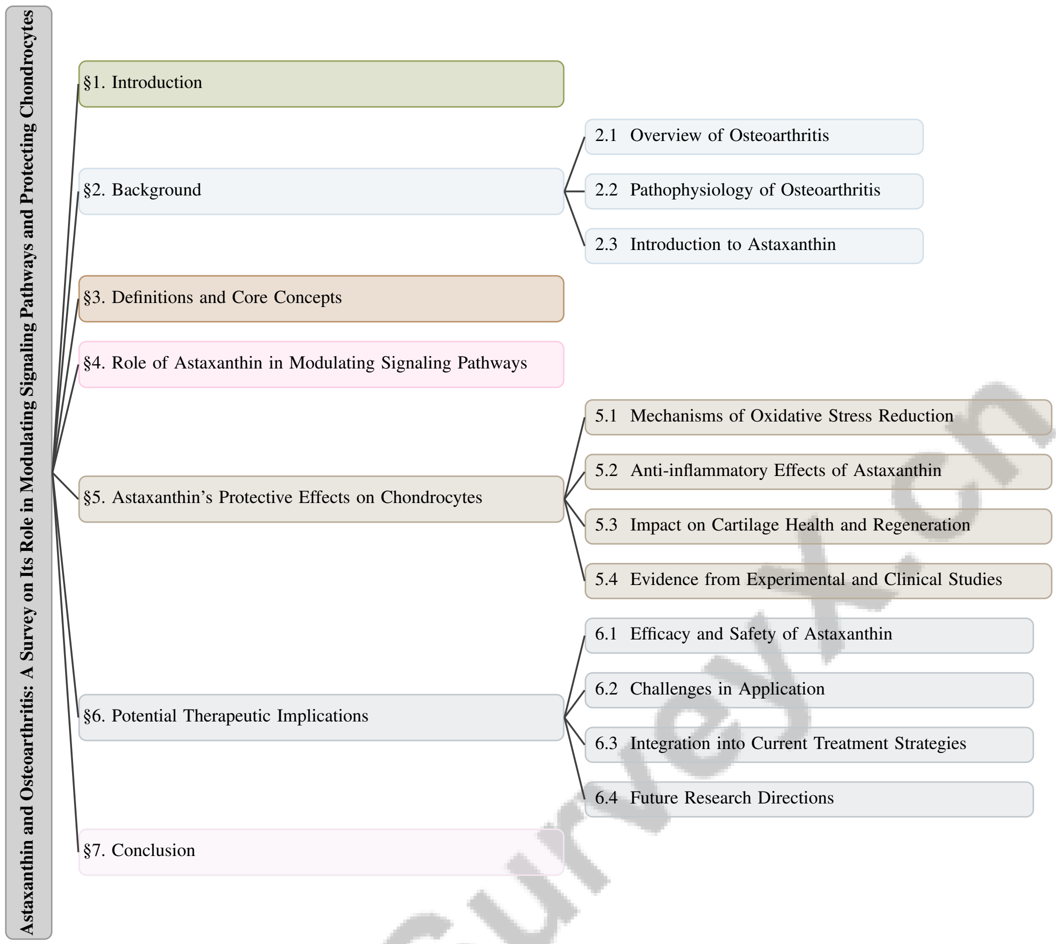


Figure 1: chapter structure

between pro-inflammatory and anti-inflammatory cytokines are also considered to provide a holistic understanding of OA pathogenesis and treatment [7].

1.2 Structure of the Survey

This survey offers a comprehensive analysis of astaxanthin's role in osteoarthritis (OA) management, focusing on its effects on signaling pathways and chondrocyte protection. The paper begins with an **Introduction** that outlines astaxanthin's therapeutic potential in OA, followed by a detailed **Focus of the Paper** that establishes primary objectives and research questions. The **Background** section provides foundational knowledge of OA, its pathophysiology, and introduces astaxanthin's antioxidant properties.

The core of the survey is the **Role of Astaxanthin in Modulating Signaling Pathways**, where specific pathways influenced by astaxanthin, such as NFB, MAPK, TGF, and Wnt, are explored concerning oxidative stress and inflammation. The section titled **Astaxanthin's Protective Effects on Chondrocytes** presents an in-depth analysis of the biochemical mechanisms through which astaxanthin mitigates oxidative stress, exhibits anti-inflammatory properties, and enhances cartilage health and regeneration. This review is supported by a comprehensive array of experimental and clinical studies, emphasizing astaxanthin's role in activating antioxidant response elements, modulating inflammatory cytokines, and promoting mitochondrial function in chondrocytes, which are critical for maintaining cartilage integrity and preventing degeneration associated with conditions such as osteoarthritis [8, 9, 3].

The survey then discusses the **Potential Therapeutic Implications** of astaxanthin in OA treatment, evaluating its efficacy, safety, and the challenges of its application. This section also considers how

AI-generated, for reference only.

astaxanthin can be integrated into current treatment strategies and highlights future research directions. Finally, the **Conclusion** summarizes key findings, emphasizing astaxanthin's potential benefits and the need for further research to fully elucidate its therapeutic potential in OA.The following sections are organized as shown in Figure 1.

2 Background

2.1 Overview of Osteoarthritis

Osteoarthritis (OA) stands as the most prevalent arthritis form, notably impairing the quality of life for millions, especially the elderly. In the United States, knee OA affects approximately 20-40% of those over 65, underscoring its widespread nature and the lack of a definitive cure [10]. This degenerative joint disease primarily targets weight-bearing joints like the knee and hip, leading to significant disability and healthcare expenses. The increasing rates of overweight and obesity further intensify OA's prevalence, marking it as a pressing public health concern [11]. Current single-component lipid models fall short in accurately replicating natural synovial joint lubrication, highlighting the demand for advanced research [12].

OA pathogenesis is driven by a complex interplay of biochemical and mechanical factors resulting in articular cartilage degeneration and joint structural modifications [13]. Traditional non-steroidal anti-inflammatory drugs (NSAIDs) are commonly employed, yet their efficacy is limited, necessitating alternative treatments that address underlying causes rather than merely alleviating symptoms.

Progress in quantitative magnetic resonance imaging (qMRI) mapping of cartilage offers promising avenues for early detection of degenerative changes before significant clinical symptoms emerge [14]. However, variability in mechanical testing protocols complicates cross-study comparisons, potentially leading to misinterpretations of native tissue properties [15]. Addressing these issues is crucial for developing clinically applicable methods to predict OA progression based on individual anatomical and loading conditions [16]. This survey also aims to summarize current understanding of in vitro and in vivo OA models, elucidating disease pathophysiology, classification, and the urgent need for accurate segmentation techniques amid rising OA prevalence [17, 18].

2.2 Pathophysiology of Osteoarthritis

Osteoarthritis (OA) pathophysiology involves the progressive degradation of articular cartilage, crucial for smooth joint movement and load distribution. This degenerative process is marked by an intricate interplay of mechanical and biochemical factors that exacerbate cartilage degeneration and joint inflammation [13]. Chondrocytes, the sole cellular components of cartilage, are vital for maintaining the extracellular matrix and responding to mechanical loads. However, their limited regenerative capacity, due to cartilage's avascular nature, impedes effective tissue repair, contributing to OA's chronic progression.

Mechanical stress, including shear stress, exacerbates cartilage degradation by activating mechano-inflammatory pathways within chondrocytes [19]. Mitochondrial dysfunction in chondrocytes leads to apoptosis, further aggravating cartilage degeneration [3]. The unique mechanical properties and low regenerative potential of articular cartilage, alongside subchondral bone alterations, present significant repair and regeneration challenges [20, 21].

Current therapeutic interventions primarily focus on symptom relief rather than addressing underlying pathophysiological mechanisms. Despite NSAIDs' common use for managing OA symptoms, they often fail to prevent cartilage and subchondral bone degradation, resulting in suboptimal outcomes. The diverse patient phenotypes and underlying cartilage degeneration mechanisms further complicate treatment strategies, underscoring the need for targeted interventions promoting cartilage regeneration [22, 23]. Traditional diagnostic methods, such as X-rays, are limited to detecting advanced disease stages, whereas advanced quantitative MRI techniques offer opportunities for earlier intervention by measuring early cartilage matrix composition changes.

Addressing OA's multifaceted nature requires therapies capable of modulating biological mechanoresponses and counteracting cartilage breakdown under chronic loading conditions. Such approaches aim to alleviate symptoms while targeting cartilage degradation's root causes, potentially reversing or halting OA progression. Ongoing research continues to explore novel therapeutic targets, including inflammation and synovitis roles, significantly influencing disease progression and patient symptoms [2].

2.3 Introduction to Astaxanthin

Astaxanthin, a naturally occurring carotenoid, is renowned for its potent antioxidant properties and diverse biological activities, extensively studied in contexts such as neuroprotection, cardiovascular health, and cancer prevention [1]. Primarily sourced from Haematococcus pluvialis, petrochemicals, and genetically-modified yeast, it offers various forms with potential therapeutic benefits [7]. Astaxanthin's capacity to effectively neutralize free radicals positions it as a promising candidate for managing oxidative stress, a critical factor in osteoarthritis (OA) pathogenesis [13].

Astaxanthin's unique molecular structure enables it to integrate into cell membranes, providing robust protection against lipid peroxidation and maintaining cellular integrity under stress. This capability is particularly relevant in OA, where oxidative stress significantly contributes to cartilage degradation and chondrocyte apoptosis [24]. Its anti-inflammatory properties are noteworthy, as it modulates inflammatory signaling pathways such as NFB and MAPK, potentially reducing inflammation and slowing OA progression.

Astaxanthin also influences various cellular signaling pathways crucial for regulating chondrocyte function and cartilage homeostasis. Its impact on NFB and MAPK pathways is significant, as these are pivotal in the inflammatory response and oxidative stress mechanisms associated with OA [1]. By modulating these pathways, astaxanthin not only protects chondrocytes from oxidative damage but also supports cartilage repair and regeneration, presenting a promising avenue for OA management [5].

The application of astaxanthin in OA treatment is further supported by its favorable safety profile and low toxicity, making it a viable candidate for long-term therapeutic use. Its ability to cross the blood-brain barrier and accumulate in tissues enhances its potential as a systemic antioxidant, providing protective effects beyond joint health. As research continues to elucidate the molecular mechanisms underlying astaxanthin's protective effects, its integration into OA treatment strategies holds promise for improving patient outcomes and quality of life [25].

In examining the complexities of osteoarthritis (OA), it is essential to understand the interplay between its core concepts and the signaling pathways involved in its pathogenesis. Figure 2 illustrates the hierarchical structure of these concepts, providing a clear visual representation that highlights key definitions such as cartilage degeneration and various pathogenesis factors. Furthermore, the figure delineates the significance of critical signaling pathways, emphasizing important pathways like NFB, MAPK, and TGF. This comprehensive overview also includes potential therapeutic strategies, such as photobiomodulation and targeted molecular interventions, thereby enhancing our understanding of management approaches in OA. By integrating this visual aid, we can better appreciate the multifaceted nature of osteoarthritis and the therapeutic avenues that may arise from a deeper understanding of its underlying mechanisms.

3 Definitions and Core Concepts

3.1 Key Definitions and Concepts

Osteoarthritis (OA) is characterized by the degeneration of articular cartilage, alterations in subchondral bone, and synovial inflammation, leading to joint pain and stiffness [26]. The complexity of correlating structural changes with pain perception complicates OA management [27]. Chondrocytes, which are crucial for maintaining the extracellular matrix (ECM) and cartilage integrity, often exhibit phenotypic instability in OA, shifting to hypertrophic or fibroblastic forms that produce defective ECM, thus promoting disease progression [28].

Cartilage degeneration results from mechanical and biochemical disruptions affecting anabolic and catabolic processes. Due to its avascular nature, cartilage has limited repair capacity, which hinders recovery and reduces the efficacy of surgical interventions [29]. Oxidative stress, marked by an imbalance between oxidants and antioxidants, is a critical factor in OA pathogenesis, causing molecular damage and disrupting redox signaling pathways [30]. This exacerbates cartilage degradation and chondrocyte apoptosis, underscoring the importance of antioxidant strategies in OA management.

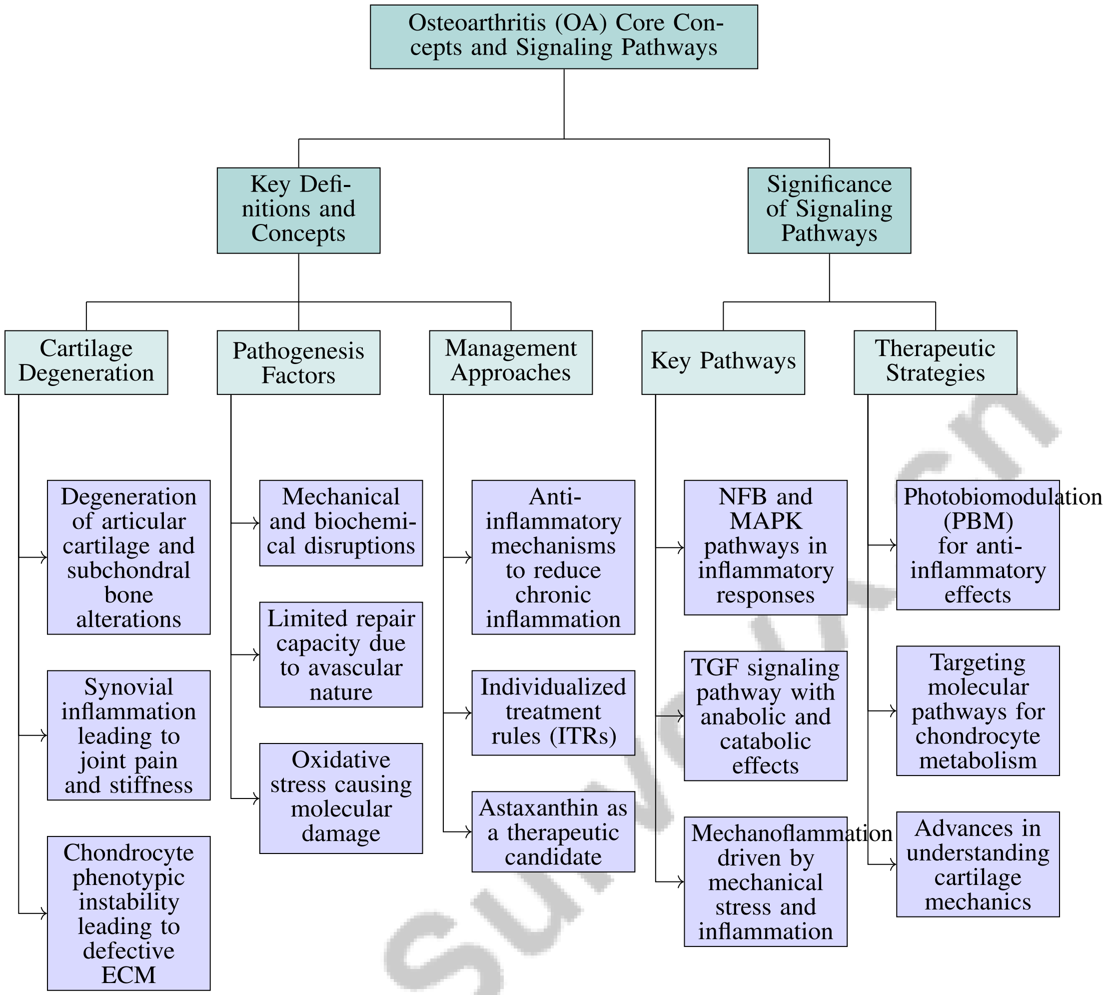


Figure 2: This figure illustrates the hierarchical structure of core concepts and signaling pathways in osteoarthritis (OA), highlighting key definitions such as cartilage degeneration and pathogenesis factors, alongside management approaches. It also delineates the significance of signaling pathways, emphasizing key pathways like NFB, MAPK, and TGF, and potential therapeutic strategies including photobiomodulation and targeted molecular interventions.

Anti-inflammatory mechanisms are vital for reducing chronic inflammation, which accelerates cartilage degradation and contributes to OA-related pain and disability. A comprehensive management approach addressing both oxidative and inflammatory components is required, potentially through individualized treatment rules (ITRs) tailored to patient-specific characteristics [11]. Astaxanthin emerges as a promising therapeutic candidate due to its potential to modulate these pathological processes and improve patient outcomes.

3.2 Significance of Signaling Pathways

Signaling pathways are integral to OA progression, mediating the biochemical and mechanical interactions that lead to cartilage degradation and joint inflammation. The NFB and MAPK pathways are central to inflammatory responses and oxidative stress mechanisms that exacerbate OA [1]. These pathways, activated by mechanical stress and inflammatory cytokines, upregulate catabolic enzymes and pro-inflammatory mediators, contributing to cartilage matrix breakdown and chondrocyte apoptosis [31].

As illustrated in Figure 3, which highlights the key signaling pathways involved in osteoarthritis progression, the figure underscores the significance of inflammatory pathways like NFB and MAPK, as

AI-generated, for reference only.

well as the dual role of the TGF pathway and potential therapeutic approaches such as photobiomodulation. The transforming growth factor-beta (TGF) signaling pathway significantly influences OA through a complex feedback mechanism that can have anabolic or catabolic effects on chondrocytes, depending on the disease context and stage [32]. This dual role complicates therapeutic targeting, necessitating a nuanced understanding of TGF's regulatory dynamics.

Mechanoflammation, driven by mechanical stress and inflammation, initiates inflammatory signaling cascades and matrix degradation, adding complexity to OA's signaling landscape [31]. The interaction between mechanical forces and biochemical signals highlights the need for therapeutic strategies that modulate these pathways to mitigate their detrimental effects on joint tissues.

Photobiomodulation (PBM) has emerged as a potential therapeutic tool, with studies exploring its anti-inflammatory effects and promotion of cellular healing [33]. By influencing signaling pathways involved in inflammation and repair, PBM offers a novel approach to modulating pathological processes in OA.

Identifying critical molecular pathways that regulate chondrocyte metabolism and matrix homeostasis is essential for developing targeted therapies [34]. Advances in understanding cartilage mechanics and underlying signaling pathways have improved diagnostic and treatment strategies for OA [35]. Ongoing research into these pathways holds promise for developing interventions that effectively alter disease progression and enhance patient outcomes.

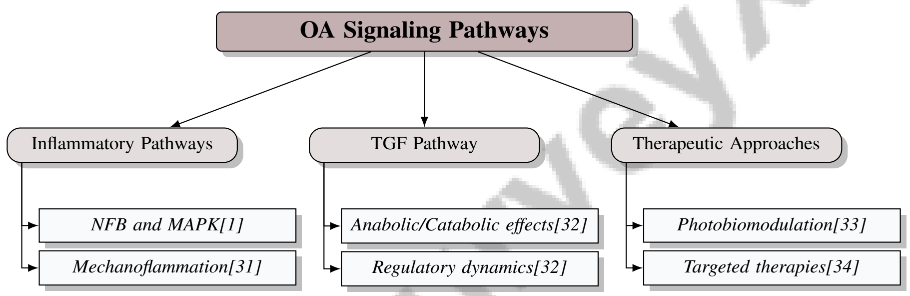


Figure 3: This figure illustrates the key signaling pathways involved in osteoarthritis (OA) progression, highlighting inflammatory pathways like NFB and MAPK, the dual role of the TGF pathway, and potential therapeutic approaches such as photobiomodulation.

4 Role of Astaxanthin in Modulating Signaling Pathways

Category	Feature	Method
Overview of Signaling Pathways in Osteoarthritis	Predictive Modeling Techniques	ASKBC[18]
Astaxanthin's Influence on NFB and MAPK Pathways	Antioxidant Pathway Modulation	pMPC-LUVs[19], CTS[36]
Impact on TGF and Wnt Signaling	Therapeutic Pathway Strategies	T-FACT[37], HPIP-shRNA[38]

Table 1: This table summarizes the key methods and features associated with various signaling pathways influenced by astaxanthin in the context of osteoarthritis. It highlights predictive modeling techniques and therapeutic strategies employed to understand and modulate pathways such as NFB, MAPK, TGF, and Wnt, which are crucial for inflammation reduction and cartilage integrity. The referenced methods provide insights into the potential for targeted interventions in osteoarthritis management.

Astaxanthin significantly influences osteoarthritis (OA) by interacting with key signaling pathways that regulate disease progression. These pathways orchestrate inflammatory responses and cellular processes linked to cartilage degradation and joint dysfunction. Table 1 presents a comprehensive overview of the methods and features related to signaling pathways in osteoarthritis, emphasizing the role of astaxanthin in modulating these pathways for therapeutic purposes. This section explores the primary signaling pathways involved in OA and examines how astaxanthin modulates these pathways, focusing on the NFB and MAPK pathways, crucial for reducing inflammation and maintaining cartilage integrity.

4.1 Overview of Signaling Pathways in Osteoarthritis

OA involves articular cartilage degradation and joint inflammation, regulated by a complex network of signaling pathways. The NFB and MAPK pathways are central to OA pathogenesis, activated by mechanical stress and pro-inflammatory cytokines such as IL-1 and TNF, leading to increased catabolic enzymes and pro-inflammatory mediators that exacerbate cartilage breakdown and chondrocyte apoptosis [2]. The transforming growth factor-beta (TGF) pathway also plays a critical role, exhibiting both anabolic and catabolic effects on chondrocytes, requiring nuanced understanding for therapeutic targeting [36]. The Wnt signaling pathway is vital for chondrocyte proliferation and differentiation, influencing cartilage homeostasis and repair. Mechanical load-induced mechanoradicals contribute to reactive oxygen species (ROS) formation, exacerbating oxidative stress in cartilage, emphasizing the need for antioxidant strategies to preserve chondrocyte health [5]. Emerging research has identified additional interconnected pathways influencing cartilage degeneration, enhancing OA progression understanding.

Advancements in imaging technologies, such as quantitative T 1 mapping, enhance the study of these pathways, providing sensitive biomarkers for cartilage degeneration and facilitating early diagnosis and intervention in OA [18]. These techniques enable high-resolution imaging of molecular distributions within cartilage, elucidating the underlying molecular mechanisms of OA progression. Ongoing research into these signaling pathways offers potential for interventions that can effectively mitigate OA progression and improve patient outcomes. Template-based modeling methods streamline knee cartilage analysis and predict degeneration, enhancing diagnostic methods and fostering personalized treatment strategies, allowing for targeted interventions [22, 34].

4.2 Astaxanthin's Influence on NFB and MAPK Pathways

Astaxanthin, known for its potent antioxidant properties, modulates key signaling pathways such as NFB and MAPK, pivotal in OA's inflammatory processes. The NFB pathway regulates pro-inflammatory cytokines and catabolic enzymes contributing to cartilage degradation. Astaxanthin's ability to reduce NFB activation is crucial for lowering inflammation and preserving cartilage integrity, especially against ROS that exacerbate NFB signaling [19]. Similarly, the MAPK pathway, activated by mechanical stress and inflammatory stimuli, upregulates inflammatory mediators worsening OA progression. Astaxanthin's modulation of MAPK signaling suggests its potential in reducing inflammation and protecting cartilage from degeneration, possibly by attenuating TAK1-dependent mechanisms involved in mechanoflammation and pain signaling in OA [36].

Astaxanthin's protective influence on chondrocytes is enhanced by its role in maintaining mitochondrial health, as selective degradation of damaged mitochondria is vital for cellular homeostasis. Derived from the microalga Haematococcus pluvialis, astaxanthin enhances mitochondrial function, mitigating oxidative stress and inflammation associated with OA. Research indicates astaxanthin exhibits 14 to 90 times greater antioxidant activity compared to synthetic alternatives, contributing to reduced ROS levels and modulation of inflammatory pathways, supporting joint health and improving OA management outcomes [8, 7]. Incorporating astaxanthin into OA therapeutic strategies may benefit from identifying additional molecular targets, including the regulation of chondrocyte function through critical signaling pathways and transcription factors. This framework could facilitate targeted interventions leveraging astaxanthin's anti-inflammatory and antioxidant properties, particularly from natural sources like Haematococcus pluvialis, to preserve cartilage integrity and enhance chondrocyte viability, ultimately improving OA management outcomes [8, 23, 21, 29, 7].

4.3 Impact on TGF and Wnt Signaling

Astaxanthin's influence extends to the TGF and Wnt pathways, both critical for cartilage health and homeostasis. The TGF pathway plays a pivotal role in cartilage metabolism and cell differentiation, with significant implications for OA pathogenesis. Modulating TGF signaling through astaxanthin may enhance chondrocyte function and cartilage repair, offering a therapeutic avenue for OA management [32]. In the context of Wnt signaling, astaxanthin's therapeutic potential is highlighted by its capacity to modulate this pathway, integral to chondrocyte proliferation and differentiation. The interaction between hematopoietic pre-B-cell leukemia transcription factor-interacting protein (HPIP) and Wnt signaling pathways has been implicated in cartilage degeneration, suggesting that targeting these interactions could mitigate OA progression [38]. By influencing these pathways, astaxanthin may contribute to preserving cartilage integrity and delaying degenerative processes characteristic of OA.

The interplay between metabolic regulation and mitochondrial biogenesis in chondrocytes, mediated by the PPAR/PGC-1 pathway, underscores mitochondrial health's importance in cartilage maintenance. Astaxanthin's antioxidant properties may support mitochondrial function, enhancing chondrocyte resilience against oxidative stress and promoting cartilage health [39]. Advanced imaging techniques, such as the T-FACT model, provide accurate representations of T1rho relaxation in articular cartilage, capturing tissue complexities and facilitating the assessment of astaxanthin's impact on cartilage health [37]. These insights underscore astaxanthin's potential to modulate critical signaling pathways, offering promising strategies for improving cartilage health and managing OA.

5 Astaxanthin's Protective Effects on Chondrocytes

Astaxanthin plays a crucial role in enhancing chondrocyte health and mitigating osteoarthritis (OA) effects by protecting these vital cartilage cells. Chondrocytes are integral to maintaining cartilage integrity, and their dysfunction is a key factor in OA progression. This section delves into the mechanisms through which astaxanthin reduces oxidative stress—an important contributor to chondrocyte apoptosis and cartilage degeneration—highlighting its broader implications in OA management.

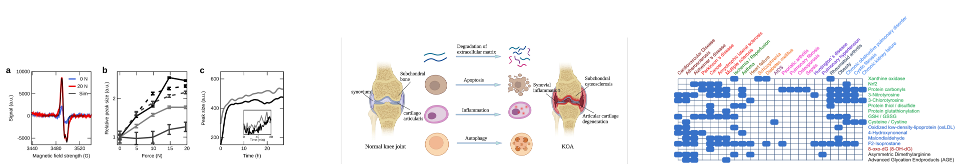
5.1 Mechanisms of Oxidative Stress Reduction

Astaxanthin, a potent antioxidant, significantly mitigates oxidative stress in chondrocytes, a critical factor in OA pathogenesis. Excessive reactive oxygen species (ROS) in cartilage lead to cellular damage and degeneration. Astaxanthin's unique molecular structure effectively neutralizes free radicals, protecting chondrocytes from apoptosis [8]. This antioxidative action modulates signaling pathways, notably NFB, which is influenced by oxidative stress [40]. By attenuating NFB activation, astaxanthin reduces inflammation and preserves cartilage integrity.

Astaxanthin counteracts mechanoradicals produced under mechanical stress, such as those from collagen under tensile load, which convert to hydrogen peroxide, exacerbating oxidative stress [41]. In OA, mechanical loading increases ROS production, highlighting the importance of antioxidants in reducing oxidative damage [42]. Furthermore, astaxanthin supports mitochondrial health, crucial for reducing oxidative stress in chondrocytes. By maintaining mitochondrial function, astaxanthin enhances cellular resilience, promoting chondrocyte survival and function. Mitochondrial dysfunction in OA chondrocytes is linked to increased apoptosis and decreased type II collagen secretion, underscoring mitochondrial health's importance in cartilage preservation [3].

The removal of dysfunctional organelles through Pink1-mediated autophagy complements astaxanthin's effects, as Pink1 initiates protective processes against chondrocyte apoptosis [43]. Inhibiting the mTOR pathway with rapamycin restores autophagy and reduces apoptosis in chondrocytes, protecting cartilage integrity [44]. Additionally, the regulation of asporin expression by proinflammatory cytokines is crucial for understanding oxidative stress mechanisms in chondrocytes [45].

Astaxanthin's antioxidative mechanisms offer a promising strategy for mitigating OA progression and improving outcomes. Research highlights the anti-inflammatory and immunomodulatory effects of polyphenols, contributing to their protective roles against chronic diseases [1]. The therapeutic implications of targeting oxidative stress in OA are underscored by models indicating its significant impact on cartilage health [46]. These insights emphasize astaxanthin's potential in OA management, preserving cartilage health and function.



(a) ERROR!!![41] (b) ERROR!!![47] (c) ERROR!!![30]

Figure 4: Examples of Mechanisms of Oxidative Stress Reduction

AI-generated, for reference only.

As shown in Figure 4, astaxanthin's protective effects on chondrocytes offer insights into how this antioxidant mitigates oxidative stress. The imbalance between ROS production and detoxification is critical in chondrocyte degeneration. The figure illustrates the biochemical pathways and cellular interactions through which astaxanthin protects chondrocytes. By neutralizing ROS and enhancing cellular resilience, astaxanthin helps preserve cartilage integrity and function, making it a promising candidate for therapeutic interventions in OA.

5.2 Anti-inflammatory Effects of Astaxanthin

Astaxanthin exhibits significant anti-inflammatory properties essential in mitigating OA progression, characterized by chronic inflammation and cartilage degradation. Understanding the inflammatory mechanisms in OA is crucial for developing targeted therapies to improve outcomes [26]. Astaxanthin modulates inflammatory signaling pathways, such as NFB and MAPK, reducing pro-inflammatory cytokines and catabolic enzymes responsible for cartilage breakdown and joint inflammation.

Astaxanthin's integration into therapeutic strategies is further supported by its synergistic effects with other treatments. For instance, combining low-intensity pulsed ultrasound (LIPUS) with human umbilical cord mesenchymal stem cell (hUC-MSC) transplantation enhances cartilage repair and reduces inflammation, offering a novel, non-invasive approach to OA management [48]. This synergistic approach underscores the potential of combining astaxanthin with other interventions to amplify its anti-inflammatory effects and promote cartilage health.

Astaxanthin also modulates the immune response, balancing pro-inflammatory and anti-inflammatory mediators, crucial for preventing chronic inflammation that exacerbates OA. By enhancing cartilage integrity and reducing pain, astaxanthin not only improves joint function but also addresses the underlying cellular mechanisms disrupted by ROS. This multifaceted approach offers a promising strategy for effective OA management, particularly in aging populations where the incidence of this condition is rising [49, 8].

5.3 Impact on Cartilage Health and Regeneration

Astaxanthin enhances cartilage health and promotes regeneration through its antioxidant and anti-inflammatory properties. Its ability to modulate oxidative stress and inflammatory signaling pathways, such as NFB and MAPK, is crucial for preserving cartilage integrity and creating a favorable environment for cartilage repair [19]. These effects are significant given the interplay of mechanical forces and biochemical responses contributing to cartilage degradation and post-traumatic osteoarthritis (PTOA) development [50].

Advancements in scaffold materials demonstrate improved biocompatibility and mechanical stability, essential for supporting chondrogenesis and achieving better outcomes in cartilage repair [51]. Hybrid scaffolds, combining polyvinyl alcohol (PVA) with natural materials, enhance mechanical properties and biocompatibility, facilitating cartilage regeneration [20]. These scaffolds mimic native cartilage properties, providing a suitable microenvironment for chondrocyte culture [52].

The rigidity percolation framework predicts how compositional changes in cartilage influence shear mechanics, offering insights into disease progression and potential diagnostic applications [53]. This understanding is critical for developing therapeutic strategies leveraging astaxanthin and advanced biomaterials to restore cartilage function.

Integrating high-performance natural hydrogels into cartilage repair strategies holds promise, as these materials enhance cartilage regeneration, necessitating further optimization to improve mechanical properties and integration with surrounding tissues [54]. Continued research into the synergistic effects of astaxanthin and innovative biomaterials may lead to comprehensive therapeutic approaches that mitigate cartilage degradation and promote regeneration, improving outcomes for OA patients.

5.4 Evidence from Experimental and Clinical Studies

Astaxanthin's protective roles in OA are substantiated by various experimental and clinical studies, highlighting its therapeutic potential. Advanced imaging techniques and computational models enhance understanding of cartilage health and OA progression. For example, the CMT approach balances accuracy and full-thickness cartilage loss (FCL) region coverage, crucial for assessing

AI-generated, for reference only.

astaxanthin's impact on cartilage integrity [55]. Additionally, PS-OCT combined with mechanical indentation differentiates between healthy and early degenerative cartilage, providing valuable diagnostic information for early OA assessment and informing astaxanthin's efficacy in intervention strategies [56].

The template-based modeling approach serves as a clinical prediction tool for OA, categorizing subjects into Kellgren-Lawrence (KL) grade groups based on 4-year follow-up data [16]. This predictive capability is instrumental in identifying patients who may benefit from astaxanthin supplementation as part of a personalized OA management plan. Furthermore, the HA-4AR hydrogel significantly preserves subchondral bone plate tissue mineral density compared to HA alone, indicating enhanced osteoprotective benefits in treating OA, aligning with astaxanthin's role in supporting joint health [21].

In cartilage regeneration, studies highlight multilayer scaffolds' superior performance over single-layer designs in promoting repair, suggesting that combining astaxanthin with advanced scaffold materials could enhance regenerative outcomes [29]. The identification of hydration lubrication as a critical mechanism for achieving low friction in cartilage underscores the importance of molecular interactions in joint health, providing insights into how astaxanthin might contribute to improved cartilage lubrication and function [5].

Astaxanthin's integration into OA management strategies is supported by evidence emphasizing the need for standardized methodologies and a better understanding of mechanotransduction pathways involved in chondrocyte responses to dynamic loading. By modulating these pathways, astaxanthin may enhance chondrocyte resilience to mechanical stress, promoting cartilage repair and regeneration. Evidence from both experimental and clinical studies highlights astaxanthin's diverse protective effects in OA, suggesting its potential as a therapeutic agent. Notably, astaxanthin has demonstrated significant antioxidant properties, with natural sources like Haematococcus pluvialis exhibiting up to 90 times greater efficacy than synthetic alternatives. These findings indicate that astaxanthin may help mitigate oxidative stress, reduce inflammation, and support joint health, underscoring the necessity for further research to comprehensively explore and validate its therapeutic applications in OA management [8, 34, 7].

6 Potential Therapeutic Implications

6.1 Efficacy and Safety of Astaxanthin

Astaxanthin demonstrates substantial efficacy in osteoarthritis (OA) treatment through its antioxidant and anti-inflammatory properties, which modulate oxidative stress and inflammatory pathways integral to OA pathogenesis. By reducing reactive oxygen species (ROS) in chondrocytes, astaxanthin mitigates oxidative damage, thereby preserving cartilage integrity [19]. It further supports cartilage health by modulating key signaling pathways such as NFB and MAPK, reducing inflammation [25]. Its favorable safety profile, marked by low toxicity and beneficial pharmacokinetics, supports its suitability for long-term OA management [25]. The ability to cross the blood-brain barrier enhances systemic antioxidant effects, extending benefits beyond joint health. Synergistic effects with other therapeutic agents, such as injectable hydrogels, not only provide mechanical support but also inhibit matrix metalloproteinases (MMPs), enhancing astaxanthin's therapeutic potential [57]. Astaxanthin promotes autophagy and protects chondrocytes from apoptosis, with evidence suggesting that targeting the mTOR pathway with agents like rapamycin enhances autophagy and protects against cytokine-induced apoptosis [44]. This strategy underscores the potential of combining astaxanthin with other interventions to amplify its therapeutic efficacy in OA. Despite promising attributes, further investigation into astaxanthin's long-term effects on joint health and OA progression is necessary [19]. Personalized treatment strategies leveraging unbiased estimates of treatment effects may enhance therapeutic outcomes [11]. Integrating astaxanthin into comprehensive OA treatment strategies shows promise for improving patient outcomes, necessitating ongoing research to elucidate its full therapeutic potential.

6.2 Challenges in Application

Integrating astaxanthin into OA treatment strategies involves several challenges that must be addressed to optimize its therapeutic potential. Reduced effectiveness in advanced stages of cartilage degeneration, where chondrocytes' regenerative capacity is compromised, highlights the need for early intervention strategies [25]. The complexity of inflammatory pathways complicates effective modulation with astaxanthin, as seen in existing treatments involving erythropoietin (EPO) [58]. A comprehensive understanding of the molecular mechanisms underlying astaxanthin's effects is essential for successful integration into OA treatment protocols. Computational demands of advanced imaging techniques used to assess cartilage health and monitor treatment efficacy present another challenge. While these methods provide insights into cartilage degeneration and therapeutic impacts, their application in large-scale datasets requires further optimization [18]. Addressing this barrier is crucial for widespread clinical adoption of astaxanthin, facilitating precise monitoring of its effects on cartilage health. Additionally, long-term effects of astaxanthin supplementation on joint health and potential side effects require thorough investigation. Similar to concerns surrounding rapamycin, understanding long-term implications of astaxanthin treatment is vital to ensure safety and efficacy [44]. Comprehensive clinical trials and longitudinal studies are necessary to assess sustained impact on cartilage health and joint function.

6.3 Integration into Current Treatment Strategies

Integrating astaxanthin into existing OA treatment strategies requires a multifaceted approach leveraging its antioxidant and anti-inflammatory properties to complement conventional therapies. Current OA management focuses on symptom relief through non-steroidal anti-inflammatory drugs (NSAIDs) and physical therapies, often neglecting underlying pathophysiological mechanisms [13]. Incorporating astaxanthin could enhance outcomes by targeting oxidative stress and inflammatory pathways, slowing disease progression and promoting cartilage health. Astaxanthin's modulation of signaling pathways such as NFB and MAPK provides strategic advantages in reducing inflammation and oxidative damage, potentially creating synergistic effects with existing pharmacological treatments. This interaction may allow lower dosages, minimizing side effects, particularly relevant in chronic inflammatory conditions [33, 11, 1, 25]. Using astaxanthin alongside advanced biomaterials like hydrogels and scaffolds could further enhance cartilage regeneration outcomes. These materials provide structural support and foster optimal microenvironments for chondrocyte proliferation and differentiation, crucial for successful cartilage repair and OA prevention [23, 28, 9, 29, 51]. Incorporating astaxanthin into these biomaterials localizes protective effects to affected joints, enhancing therapeutic impact and facilitating targeted delivery. Developing personalized treatment plans incorporating astaxanthin, tailored to individual patient characteristics and disease stages, aligns with precision medicine in OA management [11]. Advanced imaging techniques and computational models can assist in monitoring treatment efficacy and adjusting strategies, ensuring optimal outcomes.

6.4 Future Research Directions

Future research on astaxanthin in OA should prioritize exploring novel therapeutic targets and mechanisms, particularly enhancing mitochondrial health across cartilage layers and investigating agents improving mitochondrial function in OA chondrocytes [3]. Investigating interactions between lubricating molecules and developing synthetic lubricants inspired by biological systems present promising avenues for joint health improvement, necessitating clinical trials to evaluate efficacy [5]. Modifying biomaterial surfaces to reduce fibronectin adsorption and exploring innovative treatments like nano-medicines for biofilm-associated infections warrant further investigation [6]. Understanding combined effects of mechanical stimuli amplitude and frequency on chondrocyte responses, alongside potential interventions targeting Piezo2, could provide insights into cartilage mechanobiology and inform therapeutic strategies [36]. Enhancing biodegradability of polyvinyl alcohol (PVA), improving cell adhesion, and exploring new material combinations to mimic native cartilage environments are essential for advancing tissue engineering approaches in OA treatment [20]. Improving computational efficiency, exploring alternative statistical shape models, and integrating shape knowledge into CNN training processes are crucial for refining diagnostic tools and predictive models in OA research [18]. Examining systemic inflammation's role and comorbidities like obesity, alongside personalized treatment strategies based on inflammatory profiles, will be vital in tailoring OA therapies to individual needs [2]. Addressing these research areas will help realize astaxanthin's therapeutic potential in OA, enhancing patient care and outcomes.

7 Conclusion

Astaxanthin emerges as a promising candidate in osteoarthritis (OA) management, demonstrating a capacity to modulate oxidative stress and inflammation, which are pivotal in OA pathogenesis. By impacting signaling pathways such as NFB and MAPK, astaxanthin contributes to reducing inflammation and enhancing cartilage health, thereby underscoring its therapeutic potential. Its antioxidant properties play a crucial role in maintaining chondrocyte integrity, offering protection to cartilage. Given the complex nature of OA, there is a need for personalized treatment strategies and the advancement of therapies that target specific pathways. Addressing inflammation remains a priority in OA treatment development, highlighting the necessity for research focused on targeted therapies. Additionally, exploring the gut-joint axis and genetic influences could provide valuable insights into OA pathogenesis and inform treatment innovations. Although astaxanthin holds significant promise, continued research is essential to fully understand its capabilities and incorporate it into effective OA management frameworks.

AI-generated, for reference only.

References

[1] Nour Yahfoufi, Nawal Alsadi, Majed Jambi, and Chantal Matar. The immunomodulatory and anti-inflammatory role of polyphenols. *Nutrients*, 10(11):1618, 2018.

[2] Alexander J Knights, Stephen J Redding, and Tristan Maerz. Inflammation in osteoarthritis: the latest progress and ongoing challenges. *Current opinion in rheumatology*, 35(2):128–134, 2023.

[3] Effect of chondrocyte mitochondr.

[4] M Rocio Servin-Vences, Mirko Moroni, Gary R Lewin, and Kate Poole. Direct measurement of trpv4 and piezo1 activity reveals multiple mechanotransduction pathways in chondrocytes. *elife*, 6:e21074, 2017.

[5] Weifeng Lin and Jacob Klein. Recent progress in cartilage lubrication, 2023.

[6] S Dutta Sinha, P. K. Maiti, and S Tarafdar. Vulnerability of geriatric patients to biomaterial associated infections: in vitro study of biofilm formation by pseudomonas aeruginosa on orthopedic implants, 2015.

[7] Bob Capelli, Shawn Talbott, and Lixin Ding. Astaxanthin sources: Suitability for human health and nutrition. *Functional Foods in Health and Disease*, 9(6):430–445, 2019.

[8] Sajad Fakhri, Fatemeh Abbaszadeh, Leila Dargahi, and Masoumeh Jorjani. Astaxanthin: A mechanistic review on its biological activities and health benefits. *Pharmacological research*, 136:1–20, 2018.

[9] Hui Chen, Xiao-Ning Tan, Shi Hu, Ren-Qin Liu, Li-Hong Peng, Yong-Min Li, and Ping Wu. Molecular mechanisms of chondrocyte proliferation and differentiation. *Frontiers in cell and developmental biology*, 9:664168, 2021.

[10] Kevin A. Thomas, Dominik Krzemiński, Łukasz Kidziński, Rohan Paul, Elka B. Rubin, Eni Halilaj, Marianne S. Black, Akshay Chaudhari, Garry E. Gold, and Scott L. Delp. Open source software for automatic subregional assessment of knee cartilage degradation using quantitative t2 relaxometry and deep learning, 2020.

[11] Xiaotong Jiang, Amanda E. Nelson, Rebecca J. Cleveland, Daniel P. Beavers, Todd A. Schwartz, Liubov Arbeeva, Carolina Alvarez, Leigh F. Callahan, Stephen Messier, Richard Loeser, and Michael R. Kosorok. Technical background for "a precision medicine approach to develop and internally validate optimal exercise and weight loss treatments for overweight and obese adults with knee osteoarthritis", 2020.

[12] Yifeng Cao, Di Jin, Nir Kampf, and Jacob Klein. Multi-lipid synergy in synovial lubrication: natural redundancy vs. natural selection, 2024.

[13] Mohd Heikal Mohd Yunus, Abid Nordin, and Haziq Kamal. Pathophysiological perspective of osteoarthritis. *Medicina*, 56(11):614, 2020.

[14] Junru Zhong, Yongcheng Yao, Fan Xiao, Tim-Yun Michael Ong, Ki-Wai Kevin Ho, Siyue Li, Chaoxing Huang, Queenie Chan, James F. Griffith, and Weitian Chen. A systematic post-processing approach for quantitative $t_{1\rho}$ imaging of knee articular cartilage, 2024.

[15] Jay M Patel, Brian C Wise, Edward D Bonnevie, and Robert L Mauck. A systematic review and guide to mechanical testing for articular cartilage tissue engineering. *Tissue Engineering Part C: Methods*, 25(10):593–608, 2019.

[16] Utilizing atlas-based modeling t.

[17] Hasmik Jasmine Samvelyan, David Hughes, Craig Stevens, and Katherine Ann Staines. Models of osteoarthritis: relevance and new insights. *Calcified tissue international*, 109(3):243–256, 2021.

[18] Felix Ambellan, Alexander Tack, Moritz Ehlke, and Stefan Zachow. Automated segmentation of knee bone and cartilage combining statistical shape knowledge and convolutional neural networks: Data from the osteoarthritis initiative. *Medical image analysis*, 52:109–118, 2019.

[19] Linyi Zhu, Weifeng Lin, Monika Kluzek, Jadwiga Miotla-Zarebska, Vicky Batchelor, Matthew Gardiner, Chris Chan, Peter Culmer, Anastasios Chanalaris, Ronit Goldberg, Jacob Klein, and Tonia L. Vincent. Liposomic lubricants suppress shear-stress induced inflammatory gene regulation in the joint in vivo, 2023.

[20] Silvia Barbon, Martina Contran, Elena Stocco, Silvia Todros, Veronica Macchi, Raffaele De Caro, and Andrea Porzionato. Enhanced biomechanical properties of polyvinyl alcohol-based hybrid scaffolds for cartilage tissue engineering. *Processes*, 9(5):730, 2021.

[21] Romain Rieger, Sema Kaderli, and Caroline Boulocher. In vivo impact on rabbit subchondral bone of viscosupplementation with a hyaluronic acid antioxidant conjugate, 2024.

[22] Susanne Grässel and Dominique Muschter. Recent advances in the treatment of osteoarthritis. *F1000Research*, 9:F1000–Faculty, 2020.

[23] Sathish Muthu, Jasmijn V Korpershoek, Emanuel J Novais, Gwenllian F Tawy, Anthony P Hollander, and Ivan Martin. Failure of cartilage regeneration: emerging hypotheses and related therapeutic strategies. *Nature Reviews Rheumatology*, 19(7):403–416, 2023.

[24] Gillian A Hawker. Osteoarthritis is a serious disease. *Clin Exp Rheumatol*, 37(Suppl 120):3–6, 2019.

[25] Ruzanna Shkhyan, Ben Van Handel, Jacob Bogdanov, Siyoung Lee, Yifan Yu, Mila Scheinberg, Nicholas W Banks, Sean Limfat, Arthur Chernostrik, Carlos Eduardo Franciozi, et al. Drug-induced modulation of gp130 signalling prevents articular cartilage degeneration and promotes repair. *Annals of the rheumatic diseases*, 77(5):760–769, 2018.

[26] Terence W O'Neill and David T Felson. Mechanisms of osteoarthritis (oa) pain. *Current osteoporosis reports*, 16:611–616, 2018.

[27] Felix Ambellan, Stefan Zachow, and Christoph von Tycowicz. Geodesic b-score for improved assessment of knee osteoarthritis, 2021.

[28] Andrew C Hall. The role of chondrocyte morphology and volume in controlling phenotype—implications for osteoarthritis, cartilage repair, and cartilage engineering. *Current Rheumatology Reports*, 21:1–13, 2019.

[29] Yaima Campos, Amisel Almirall, Gastón Fuentes, Hans L Bloem, Eric L Kaijzel, and Luis J Cruz. Tissue engineering: an alternative to repair cartilage. *Tissue Engineering Part B: Reviews*, 25(4):357–373, 2019.

[30] Helmut Sies. Oxidative stress: Concept and some practical aspects. *Antioxidants*, 9(9):852, 2020.

[31] Tonia L Vincent. Mechanoflammation in osteoarthritis pathogenesis. In *Seminars in arthritis and rheumatism*, volume 49, pages S36–S38. Elsevier, 2019.

[32] Catherine Baugé, Olivier Cauvard, Sylvain Leclercq, Philippe Galéra, and Karim Boumédiene. Modulation of transforming growth factor beta signalling pathway genes by transforming growth factor beta in human osteoarthritic chondrocytes: involvement of sp1 in both early and late response cells to transforming growth factor beta, 2015.

[33] Michael R Hamblin. Mechanisms and applications of the anti-inflammatory effects of photobiomodulation. *AIMS biophysics*, 4(3):337, 2017.

[34] DI Chen, Jie Shen, Weiwei Zhao, Tingyu Wang, Lin Han, John L Hamilton, and Hee-Jeong Im. Osteoarthritis: toward a comprehensive understanding of pathological mechanism. *Bone research*, 5(1):1–13, 2017.

[35] Biao Han, Hadi T Nia, Chao Wang, Prashant Chandrasekaran, Qing Li, Daphney R Chery, Hao Li, Alan J Grodzinsky, and Lin Han. Afm-nanomechanical test: an interdisciplinary tool that links the understanding of cartilage and meniscus biomechanics, osteoarthritis degeneration, and tissue engineering. *ACS biomaterials science & engineering*, 3(9):2033–2049, 2017.

[36] Genlai Du, Li Li, Xinwang Zhang, Jianbing Liu, Jianqing Hao, Jianjun Zhu, Hao Wu, Weiyi Chen, and Quanyou Zhang. Roles of trpv4 and piezo channels in stretch-evoked ca2+ response in chondrocytes. *Experimental Biology and Medicine*, 245(3):180–189, 2020.

[37] Lixian Zou, Haifeng Wang, Yanjie Zhu, Yuanyuan Liu, Jing Cheng, Sen Jia, Caiyun Shi, Shi Su, Xin Liu, Hairong Zheng, and Dong Liang. T1rho fractional-order relaxation of human articular cartilage, 2019.

[38] Quanbo Ji, Xiaojie Xu, Lei Kang, Yameng Xu, Jingbo Xiao, Stuart B Goodman, Xiang Zhu, Wenchao Li, Juan Liu, Xu Gao, et al. Hematopoietic pbx-interacting protein mediates cartilage degeneration during the pathogenesis of osteoarthritis. *Nature communications*, 10(1):313, 2019.

[39] Haochen Wang, Jianbang Su, Minghao Yu, Yang Xia, and Yingliang Wei. Pgc-1α in osteoarthritic chondrocytes: From mechanism to target of action. *Frontiers in Pharmacology*, 14:1169019, 2023.

[40] Krithika Lingappan. Nf-κb in oxidative stress. *Current opinion in toxicology*, 7:81–86, 2018.

[41] Christopher Zapp, Agnieszka Obarska-Kosinska, Benedikt Rennekamp, Davide Mercadante, Uladzimir Barayeu, Tobias P. Dick, Vasyl Denysenkov, Thomas Prisner, Marina Bennati, Csaba Daday, Reinhard Kappl, and Frauke Gräter. Mechanoradicals in tensed tendon collagen as a new source of oxidative stress, 2019.

[42] Xiayi Wang, Bruce P. Ayati, Marc J. Brouillete, Jason M. Graham, Prem S. Ramakrishnan, and James A. Martin. Modeling and simulation of the effects of cyclic loading on articular cartilage lesion formation, 2013.

[43] Hyo Jung Shin, Hyewon Park, Nara Shin, Hyeok Hee Kwon, Yuhua Yin, Jeong-Ah Hwang, Hee-Jung Song, Jinhyun Kim, Dong Woon Kim, and Jaewon Beom. Pink1-mediated chondrocytic mitophagy contributes to cartilage degeneration in osteoarthritis. *Journal of clinical medicine*, 8(11):1849, 2019.

[44] Jiapeng Bao, Zhonggai Chen, Langhai Xu, Lidong Wu, and Yan Xiong. Rapamycin protects chondrocytes against il-18-induced apoptosis and ameliorates rat osteoarthritis. *Aging (Albany NY)*, 12(6):5152, 2020.

[45] Elise Duval, Nicolas Bigot, Magalie Hervieu, Ikuyo Kou, Sylvain Leclercq, Philippe Galéra, Karim Boumediene, and Catherine Baugé. Asporin expression is highly regulated in human chondrocytes, 2015.

[46] Georgi I. Kapitanov, Bruce P. Ayati, and James A. Martin. Modeling the effect of blunt impact on mitochondrial dysfunction in cartilage, 2016.

[47] Xin-An Zhang and Hui Kong. Mechanism of hifs in osteoarthritis. *Frontiers in Immunology*, 14:1168799, 2023.

[48] Yiming Chen, Huiyi Yang, Zhaojie Wang, Rongrong Zhu, Liming Cheng, and Qian Cheng. Low-intensity pulsed ultrasound promotes mesenchymal stem cell transplantation-based articular cartilage regeneration via inhibiting the tnf signaling pathway, 2023.

[49] Richard F Loeser. The role of aging in the development of osteoarthritis. *Transactions of the American Clinical and Climatological Association*, 128:44, 2017.

[50] Georgi I. Kapitanov, Xiayi Wang, Bruce P. Ayati, Marc J. Brouillette, and James A. Martin. Linking cellular and mechanical processes in articular cartilage lesion formation: A mathematical model, 2016.

[51] Monika Wasyłeczko, Wioleta Sikorska, and Andrzej Chwojnowski. Review of synthetic and hybrid scaffolds in cartilage tissue engineering. *Membranes*, 10(11):348, 2020.

[52] Onur Bas, Elena M De-Juan-Pardo, Christoph Meinert, Davide D'Angella, Jeremy G Baldwin, Laura J Bray, R Mark Wellard, Stefan Kollmannsberger, Ernst Rank, Carsten Werner, et al. Biofabricated soft network composites for cartilage tissue engineering. *Biofabrication*, 9(2):025014, 2017.

[53] Thomas Wyse Jackson, Jonathan Michel, Pancy Lwin, Lisa A. Fortier, Moumita Das, Lawrence J. Bonassar, and Itai Cohen. Structural origins of cartilage shear mechanics, 2021.

[54] Wuren Bao, Menglu Li, Yanyu Yang, Yi Wan, Xing Wang, Na Bi, and Chunlin Li. Advancements and frontiers in the high performance of natural hydrogels for cartilage tissue engineering. *Frontiers in chemistry*, 8:53, 2020.

[55] Yongcheng Yao and Weitian Chen. Quantifying knee cartilage shape and lesion: From image to metrics, 2024.

[56] Matthew Goodwin, Bastian Bräuer, Stephen lewis, Ashvin Thambyah, and Frédérique Vanholsbeeck. Quantifying birefringence in the bovine model of early osteoarthritis using polarisation-sensitive optical coherence tomography and mechanical indentation, 2018.

[57] Ziyu Gao, Xuebin Yang, Elena Jones, Paul A. Bingham, Alex Scrimshire, Paul D. Thornton, and Giuseppe Tronci. An injectable, self-healing and mmp-inhibiting hyaluronic acid gel via iron coordination, 2021.

[58] Jason M. Graham, Bruce P. Ayati, Lei Ding, Prem S. Ramakrishnan, and James A. Martin. Reaction-diffusion-delay model for epo/tnf-α? interaction in articular cartilage lesion abatement, 2011.

Disclaimer:

SurveyX is an AI-powered system designed to automate the generation of surveys. While it aims to produce high-quality, coherent, and comprehensive surveys with accurate citations, the final output is derived from the AI's synthesis of pre-processed materials, which may contain limitations or inaccuracies. As such, the generated content should not be used for academic publication or formal submissions and must be independently reviewed and verified. The developers of SurveyX do not assume responsibility for any errors or consequences arising from the use of the generated surveys.

AI-generated, for reference only.