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Review article

Research progress of procyanidins in repairing cartilage injury after anterior cruciate ligament tear

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ABSTRACT

Anterior cruciate ligament (ACL) tear is a common sports-related injury, and cartilage injury always emerges as a serious complication following ACL tear, significantly impacting the physical and psychological well-being of affected individuals. Over the years, efforts have been directed toward finding strategies to repair cartilage injury after ACL tear. In recent times, procyanidins, known for their anti-inflammatory and antioxidant properties, have emerged as potential key players in addressing this concern. This article focuses on summarizing the research progress of procyanidins in repairing cartilage injury after ACL tear. It covers the roles, mechanisms, and clinical significance of procyanidins in repairing cartilage injury following ACL tear and explores the future prospects of procyanidins in this domain. This review provides novel insights and hope for the repair of cartilage injury following ACL tear.

1. Introduction

The anterior cruciate ligament (ACL) serves as a vital stabilizing structure of the knee joint, preventing anterior tibial translation and internal tibial rotation. ACL tear ranks among the most frequent injuries in athletes, accounting for approximately 50% of knee ligament injuries, and is often precipitated by sudden direction changes and impacts on the knee joint [1–5]. Current treatment strategies primarily involve ACL repair and reconstruction [6,7]. However, the evidence supporting the efficacy of ACL reconstruction in preventing cartilage injury remains insufficient. A study has shown that approximately 11.4% of ACL tear patients are diagnosed with cartilage injury [8], accompanied by pain and functional impairments. The resulting pain and loss of function significantly affect individuals' physical well-being, contributing to substantial economic burdens in developed countries, representing 1%–2.5% of the gross domestic product [9].

Cartilage is a type of dense, supportive, resilient connective tissue, consisting of numerous intercellular substances and chondrocytes with cysts [10]. Due to the avascular structure and low metabolic activities of chondrocytes, cartilage generally does not self-repair following an injury [11]. Once damaged, it can lead to joint swelling and pain, accelerating the progression of osteoarthritis [12].

Research indicates a significant role of cytokines, proteases, and inflammatory factors in the progression of knee joint cartilage

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injury after ACL tear. For instance, elevated C3aR1 and C5aR1 expression on synovial cell surfaces following ACL tear enhances local complement-mediated signal transduction, potentially exacerbating inflammation and cartilage injury development [13]. After an ACL tear, the levels of inflammation-related proteins increase, while cartilage-protective protein levels decrease, including CHI3L2 (YKL-39), TNFAIP6/TSG6, DEFA1, SPP1, and CILP [14]. Currently, clinical interventions for cartilage injuries include chondrocyte implantation, microfracture, and osteochondral transplantation. However, rather than restoring cartilage integrity, these methods only postpone further cartilage deterioration [11,15]. Procyanidin, in repairing cartilage injury, emerges as a promising avenue. Procyanidin interacts with cytokines, proteases, inflammatory factors, and specific signaling molecules, inhibiting inflammation and effectively repairing cartilage injury. For example, epigallocatechin gallate (EGCG) reduces inflammation in synovial tissue and cartilage by decreasing cyclooxygenase-2 and matrix metalloproteinase-13 levels. This may activate cell-protective autophagy by reducing mTOR expression and enhancing the expression of microtubule-associated protein light chain 3, Beclin-1, and p62, thereby modulating chondrocyte apoptosis [16].

Although significant progress has been made in studying procyanidin's role in post-ACL tear-induced cartilage injury, research on its repair effects remains in its early stages. The exact mechanisms, roles, and clinical value of procyanidin in repairing cartilage injury require further exploration. This article aims to comprehensively review the current state of research on procyanidin in repairing cartilage injury, focusing on its mechanisms and clinical significance, to shed light on its potential application and drive research progress in this field. This comprehensive review seeks to offer more valuable options for experimental research and clinical repair of cartilage injury involving procyanidin following ACL tear.

2. Overview of procyanidin

Polyphenols, the most abundant secondary metabolites, are widely distributed in nature [17]. As one of the most consumed polyphenols in the human diet, procyanidin is formed by the polymerization of catechins, epicatechins, and epicatechin gallates, with the basic structural unit being a flavan-3-ol [18–20]. Procyanidin can be extracted from sources such as grape seeds, peanut skins, persimmon peels, apples, hawthorn, pine bark, and tea leaves [21–26]. Procyanidin was first discovered and isolated from peanut seed coats by Masquelier, and subsequently, the understanding of the procyanidin family has evolved through ongoing research efforts.

Due to differences in bond characteristics, procyanidins are divided into A-type and B-type procyanidins. Monomers linked by ether bonds at positions C2–*O*–C7/C2–*O*–C5 and C4–C8/C6 are referred to as A-type, while monomers linked by a C4–C8/C6 bond are referred to as B-type. The linkage between C-4 and C-6 is termed "C-type" linkage [27–31]. Procyanidin C falls into the special case of procyanidin B. The monomers constituting procyanidins, including catechins and their derivatives, are also categorized as procyanidins.

The procyanidin family exhibits diverse functions including anti-inflammatory, potent antioxidant, and anti-aging activities. Distinguishing and elucidating the various roles of procyanidins may complement research directions in repairing cartilage injury after ACL tear, broadening the application prospects of procyanidins in this context, and offering new perspectives for clinical cartilage repair.

3. Mechanisms of procyanidins in repairing cartilage injury after ACL tear

3.1. Structural factor

3.1.1. Direct repair effect

After an ACL tear, the cartilage within the joint may suffer damage, leading to reduced surface smoothness of the cartilage and increased friction within the joint. Studies have indicated that nearly half of ACL injury patients also experience articular cartilage damage on the medial and lateral sides of the femur [32]. Mechanical impacts result in elevated expression of cartilage matrix-degrading enzymes and inflammatory cytokines, along with increased apoptosis of cartilage cells [33]. Due to the limited regenerative capacity of cartilage, surface damage can lead to subchondral lesions [34,35]. These factors not only contribute to cartilage degeneration and joint pain but also progressively advance to PTOA [36].

Procyanidins have been shown to enhance the protection and repair of cartilage cells to some extent. They bolster cartilage synthesis and resilience against damage, thereby aiding in decelerating the process of cartilage degeneration. In this context, procyanidins possess anti-inflammatory properties that could help alleviate inflammatory responses and mitigate cartilage degeneration [16]. Existing research indicates that procyanidins can inhibit the NF-κB pathway and reduce cartilage cell SASP and apoptosis triggered by IL-1β, thus ameliorating the progression of PTOA [37,38]. Additionally, procyanidins might exert an anti-apoptotic effect on cartilage cells through the Nrf2/BAX/Bcl-2 pathway, facilitating damaged cell survival and repair, thereby supporting joint recovery and regeneration [38,39]. The articular cartilage solid matrix is mainly composed of collagen [40]. Procyanidins have been shown to prevent collagen from being degraded by collagenase, thereby enhancing cartilage repair [41]. By promoting the generation of essential components of cartilage, such as the cartilage matrix, procyanidins play a pivotal role in cartilage structure and function [42,43]. These compounds notably induce macrophage polarization toward the M2 phenotype within the synovium, reducing the expression of pro-inflammatory cytokines (such as IL-1β, MMP-13, and TNF-α), promoting cartilage matrix formation, and repairing cartilage damage [42]. Studies have confirmed that procyanidins prevent cartilage matrix degradation by stimulating the production of insulin-like growth factor 1 (IGF-1) in human cartilage [43]. Matrix metalloproteinases (MMPs), a group of enzymes involved in cartilage and bone remodeling, are associated with joint cartilage degeneration and bone remodeling [44]. Procyanidins can regulate the expression and activity of MMPs, inhibiting their excessive activation, thereby protecting cartilage and bone from

over-degradation and promoting joint stability and repair [45,46]. This review summarizes the effects and mechanisms of procyanidins on various chondrocyte biomarkers, which are shown in Table 1.

3.1.2. Indirect repair effect

Cartilage injury after anterior cruciate ligament tear is closely related to the "ecological environment" in which the cartilage is located. The "ecological environment" includes subchondral bone, synovium, synovial fluid, joint capsule and anterior cruciate ligament, etc. The destruction of the "ecological environment" will aggravate cartilage damage (Fig. 1). Procyanidins can reduce or even repair the "ecological environment" and thus promote the repair of cartilage injury.

Following an ACL tear, the distribution of forces within the compromised joint may undergo alteration, potentially leading to

Table 1
Effect and mechanism of procyanidins on chondrocyte biomarkers.

Chondrocyte Biomarkers	Action mechanism of biomarkers	Changes of biomarkers in cartilage injury	Effect of Procyanidins	Type or extraction source of Procyanidins	Action mechanism of Procyanidins	References
NF-κB	Regulate cell survival, proliferation and differentiation	Increase	Lower	Procyanidin B2	Block the Nrf2/NF-κB pathway and increase the activity of cartilage cells	[38]
IL-1β	Regulate SASP expression and apoptosis	Increase	Lower	Procyanidin B2	Activation of Nrf 1/HO-2 pathway. Reduced SASP and apoptosis in chondrocytes	[38]
IL-6	Maintain active inflammatory	Increase	Lower	GSPE	Decreased IL-6 mRNA expression	[47]
IL-8	Maintain active inflammatory	Increase	Lower	EGCG	NF-κBInhibition of transcription factor NF-κB	[48]
IL-10	Suppress inflammation	Lower	Increase	Catechin	Enhanced clearance of damaged mitochondriaPromote macrophage polarization	[49,50]
TNF-α	Characteristic proinflammatory cytokines	Increase	Lower	Pine bark extract	Reduced production of TNF-α by macrophages	[51,52]
MMP-1	Degrade collagen and other proteins Mediating inflammation	Increase	Lower	ECG or EGCG	The NOX2/EGFR mechanism downregulates the expression of MMP-9 and MMP-1	[53,54]
MMP-9				ECG or EGCG	Downregulation of MMP-9 and MMP-1 expression by NOX2/EGFR-dependent mechanism	[53,55]
MMP-13				GSPE	Inhibition of p38-MAPK and JNK activation	[56,57]
H2O2	Induce Biomarker apoptosis	Increase	Lower	Procyanidin B3	Regulate the expression of antioxidant enzyme system	[58,59]
iNOS	Synthetic NO Induces oxidative stress in chondrocytes	Increase	Lower	Procyanidin B3	Inhibition of IL-1β mediated mRNA production	[58]
COX-2	Associated with pain, fever and inflammation	Increase	Lower	GSPE	Inhibition of p65 nuclear expression	[56,60]
PGE2	Regulate inflammation and pain responses	Increase	Lower	GSPE	Inhibition of NF-κB pathway	[61,62]
P16	Related to cellular senescence	Increase	Lower	Procyanidin B2	Decreased methylation of P16 gene	[38,63]
Nrf2	Protects cells from oxidative stress	Lower	Increase	Procyanidin B2	Upregulating Nrf2/HO-1 pathway for anti-aging	[38]
PGC-1α	Activate and protect mitochondria	Lower	Increase	apple procyanidin or procyanidin B2 or EGCG	Activation of PGC-1α gene expression	[64,65]
Dipeptidyl Peptidase-4 (DPP4)	Associate with apoptosis and senescence of chondrocytes	Increase	Lower	GSPE	Inhibition of DPP4 reduces cell senescence	[66]
VEGF	Enhance the expression of proinflammatory factors and catabolic mediators	Increase	Lower	Pine bark extract	Inhibit the expression of VEGF and phosphorylation of VEGFR-2 to reduce the pathway VEGF	[51]
Insulin-like Growth Factor 1 (IGF-1)	Inhibit the catabolic breakdown of cartilage matrix	Lower	Increase	Croton palanostigma/ Oligomeric proanthocyanidin	Maintain normal IGF-1 protein and mRNA levels	[43]
Aggrecan	Binding collagen network	Lower	Increase	Procyanidin B3	Reduced inhibition of H2O2	[58]
Col2a1	Encode type II collagen	Lower	Increase	Procyanidin B3	Reduced inhibition of H2O2	[58]

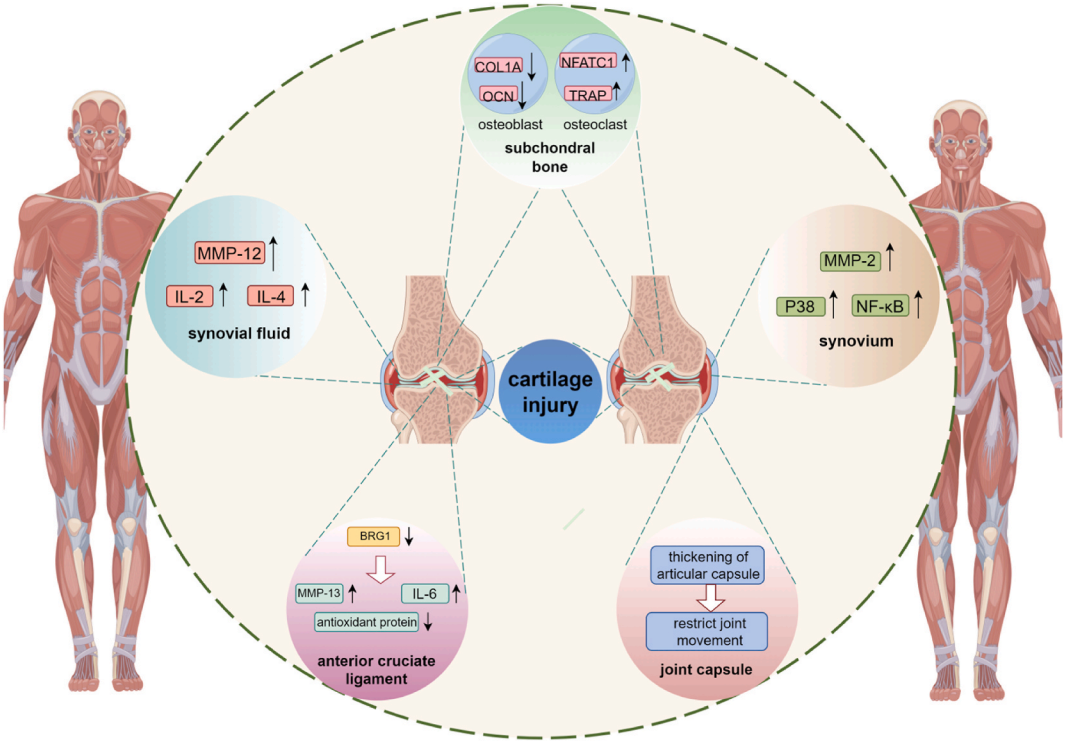

Fig. 1. The connection between cartilage "ecological environment" destruction and cartilage damage after anterior cruciate ligament tear.
Anterior cruciate ligament tear causes changes in the "ecological environment" of cartilage, which in turn causes cartilage damage. The cartilage "ecological environment" may be an important target for repairing cartilage damage. COL1A, collagen type I alpha; OCN, osteocalcin; NFATC1, nuclear factor of activated T cells 1; TRAP, tartrate resistant acid phosphatase; MMP-12, matrix metallopeptidase 12; IL-2, interleukin-2; IL-4, interleukin-4; MMP-2, matrix metallopeptidase 2; P38, p38 mitogen-activated protein kinase; NF-κB, nuclear factor kappa-B; MMP-13, matrix metallopeptidase 13; IL-6, interleukin-6. "↓" indicates downregulation and "↑" indicates upregulation.

osteoporosis. Prolonged osteoporosis renders bones fragile, increasing the risk of fractures and impacting the stability and function of the bone joints [67]. Subchondral bone and overlying articular cartilage are closely associated and function as an "osteo-chondral unit" in the joint [68]. Procyanidins possess the capacity to inhibit osteoclast activity, thereby reducing bone resorption and contributing to skeletal stability [69]. Furthermore, procyanidins can enhance osteoblast activity and function, stimulating new bone formation and mineralization of the bone matrix, thus aiding in bone joint repair and regeneration [70]. Additionally, animal studies have demonstrated that grape seed procyanidin extract can mitigate cartilage cell and proteoglycan loss in rat models, reducing the production of MMP13, nitrotyrosine, and IL-1β, decreasing bone spur formation, and lowering the incidence of subchondral fractures [56].

In recent years, increasing research has focused on the mechanisms underlying synovial fluid-related changes in cartilage injury following ACL tear. The synovium, a thin membrane covering the joint, plays a crucial role in maintaining normal joint movement and lubrication, while synovial fluid functions to reduce friction and impact. After ACL injury, synovial inflammation and hyperplasia may occur, resulting in fluid accumulation within the joint space, leading to swelling and pain. Several animal models have evaluated the synovium after ACL transection, revealing upregulated pro-inflammatory responses, increased expression of both catabolic and anabolic genes, and altered cellular activities [71,72]. Then synovitis promotes cartilage injury to some extent [12].

Alterations in synovial cell activity post-ACL tear can affect their secretion functions and cell signaling. Activation of M1 macrophages, known as major pro-inflammatory cells in cartilage injury progression, leads to the release of pro-inflammatory cytokines such as IL-1β and TNF-α [73]. Moreover, receptors such as chemokine receptor-5 (CCR5), macrophage inflammatory protein-1α and protein-1β (CCL3 and CCL4, respectively), CCL5, and macrophage chemoattractant protein-2/CCL8 are strongly expressed in affected synovial tissues [74]. ACL tear-induced changes in synovial cells result in increased enzyme and protein production, affecting synovial fluid composition [75]. Such changes include imbalances in cell counts, protein content, and levels of inflammatory factors. This might lead to increased viscosity of the synovial fluid, compromising its lubricating and friction-reducing functions [76]. Changes in inflammatory factors of synovial fluid show a strong correlation with cartilage damage, suggesting their potential significance in cartilage injury onset [77]. Furthermore, ACL injury triggers oxidative stress, leading to detrimental effects on the normal function of synovial cells and fluid. This, in turn, affects the stability of the joint microenvironment and contributes to the pathological changes in cartilage [78,79].

Previous evidence has demonstrated the presence of procyanidins in the synovial fluid, supporting the rationalization of clinical

efficacy studies [80]. Procyanidins exhibit anti-inflammatory properties that not only mitigate the actions of inflammatory cells within the synovium and synovial fluid but also disrupt a series of damaging pathways initiated by inflammatory factors, thus alleviating cartilage injury progression [81]. Additionally, Sabrina Fechtner discovered that procyanidins from green tea differentially interfere with the IL-1β signaling pathway, which regulates the expression of pro-inflammatory mediators (IL-6 and IL-8) and Cox-2 in synovial fibroblasts (RASFs) associated with PTOA [82]. Gamal Ramadan and others have shown that tea extracts can counteract PTOA by downregulating synovial tissue CCR5 expression and reducing systemic production of IL-1β and TNF-α [74]. Furthermore, procyanidins regulate the generation and synthesis of joint synovial fluid, thereby enhancing its lubricating function [83]. We summarized the mechanism of procyanidins in the synovium (Fig. 2).

Following an ACL tear, the capsule surrounding the damaged joint may undergo thickening, a normal physiological response aimed at enhancing joint stability. However, excessive capsular thickening can potentially restrict the range of joint motion, leading to joint dysfunction and eventually aggravating cartilage damage [84]. Research suggests that inflammatory factors could trigger excessive proliferation of fibroblast-like synovial cells (FLS), which might play a crucial role in joint diseases such as arthritis and rheumatoid arthritis [85,86]. Procyanidins, on the other hand, may play a role in mitigating the excessive proliferation of FLSs, which in turn could contribute to the prevention of capsular thickening. This benefit is notably apparent in animal models of rheumatoid arthritis, indicating the potential applicability of procyanidins in vivo and therapy [87]. Such applicability may be linked to the development of cartilage injury, although further experimental validation is warranted.

The ACL is a crucial ligament that connects the femur and tibia, restraining anterior translation and rotational forces of the tibia and thereby playing a key role in maintaining joint stability. Tearing of the ACL leads to joint instability, subjecting the bones to abnormal mechanical stress during movement and altering the biomechanical characteristics of the joint [34]. For instance, alterations in load distribution, stress transmission, and joint motion may affect joint stability and function, particularly damaging the cartilage and subchondral bone [88,89]. Studies indicate that procyanidins can regulate the expression and activity of various growth factors, such as transforming growth factor-beta (TGF-β) and bone morphogenetic proteins (BMPs) [90,91], promoting the proliferation and differentiation of bone and cartilage cells, thereby facilitating joint repair and regeneration [92].

The ACL primarily comprises collagen, mainly type I collagen [93], which is the most abundant collagen type in connective tissues and is known for its high tensile strength and stability. Damage to this collagen type could compromise the mechanical support provided by the ligament. Kapoor et al. found that procyanidin treatment significantly upregulated the expression of vascular endothelial growth factor (VEGF) protein, facilitating collagen orientation and maturation to contribute to repair at the wound site, resulting in more compact collagen fibers [94]. Procyanidins play a critical role in stabilizing type I collagen. Experimental evidence demonstrates that collagen fibers treated with procyanidins exhibit a contraction temperature of approximately 70 °C, indicating enhanced thermal stability [94]. Apart from stabilizing and repairing collagen, procyanidins also play a role in reducing collagen degradation to some extent [95]. Furthermore, procyanidins, owing to their unique molecular structure, readily adsorb collagen [96]. This feature enables them to better exert their effects during the treatment process of repairing and protecting collagen, contributing to

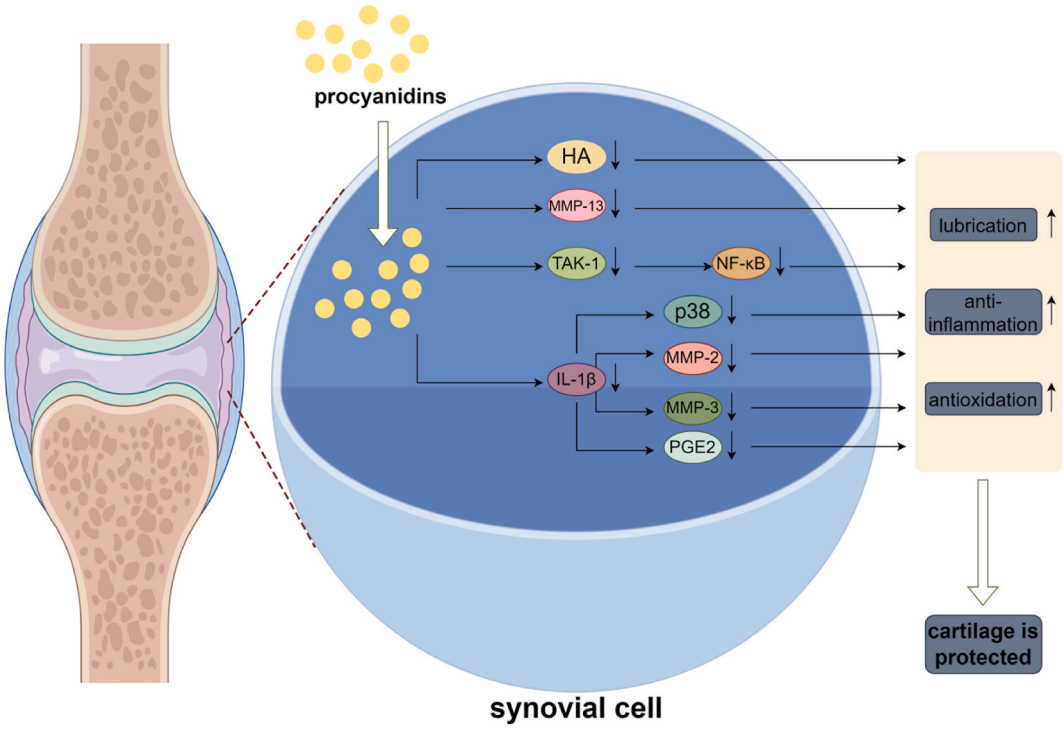

Fig. 2. Schematic diagram of the mechanism of procyanidins in the synovium. "↓" indicates downregulation.

the restoration of ACL function.

3.2. Mechanism of inflammation

The inflammatory response after ACL tear is a major contributor to tissue damage and joint pain [97]. The damaged area triggers a cascade of inflammatory reactions, including the release of inflammatory cells and cytokines such as interleukin-1β (IL-1β), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-17 (IL-17), and tumor necrosis factor-α (TNF-α). These reactions lead to local tissue swelling, redness, pain, and functional impairment, promoting the progression of cartilage injury [98]. For instance, IL-1 downregulates the synthesis of extracellular matrix (ECM) by chondrocytes. IL-6 and IL-17 synergistically accelerate ECM degradation along with IL-1. TNF-α plays a role in augmenting the activity of caspase and the cysteine aspartic acid protease (caspase) pathway. The elevated levels of IL-1β, TNF-α, and IL-6 are associated with reduced levels of lubricants [33,99,100]. Lubricants furnish articular cartilage with anti-adhesive and protective properties, while decreased lubricants post-ACL injury heighten the risk of degradation. Inflammatory cells such as neutrophils and macrophages might congregate at the injured site, releasing inflammatory factors that exacerbate the inflammatory response [101]. ACL injury triggers oxidative stress, leading to the generation of free radicals, which may potentially damage joint tissues and cartilage, thus inducing inflammation and cellular damage. The prolonged existence of such inflammatory reactions can potentially propel the development of joint diseases [98]. The use of procyanidins has been demonstrated to mitigate inflammatory responses, thus indicating their potential to ameliorate the inflammatory aspect of ACL injuries [58,102,103].

3.2.1. Antimicrobial activity

Postoperative infection following ACL reconstruction is a severe and challenging complication. Delayed diagnosis and treatment of postoperative infections can aggravate cartilage damage [104,105]. To avert the catastrophic consequences of delayed intervention, early diagnosis and treatment are increasingly emphasized by orthopedic surgeons.

Bacteria play a role in promoting the progression of inflammation. Procyanidins possess certain antibacterial activity [106]. Abundant hydroxyl groups within procyanidins inhibit bacterial adhesion and coaggregation, reducing biofilm formation and inflammation [107]. Additionally, procyanidins exhibit antibacterial activity by inhibiting extracellular microbial enzymes, depriving microorganisms of essential substrates for growth, or directly affecting microbial metabolism through oxidative phosphorylation inhibition [108]. They have demonstrated antibacterial effects against Staphylococcus aureus, Escherichia coli, and Candida albicans strains [109]. The antibacterial properties of procyanidins may potentially inhibit or prevent infections, consequently reducing the likelihood of inflammation occurrence and progression.

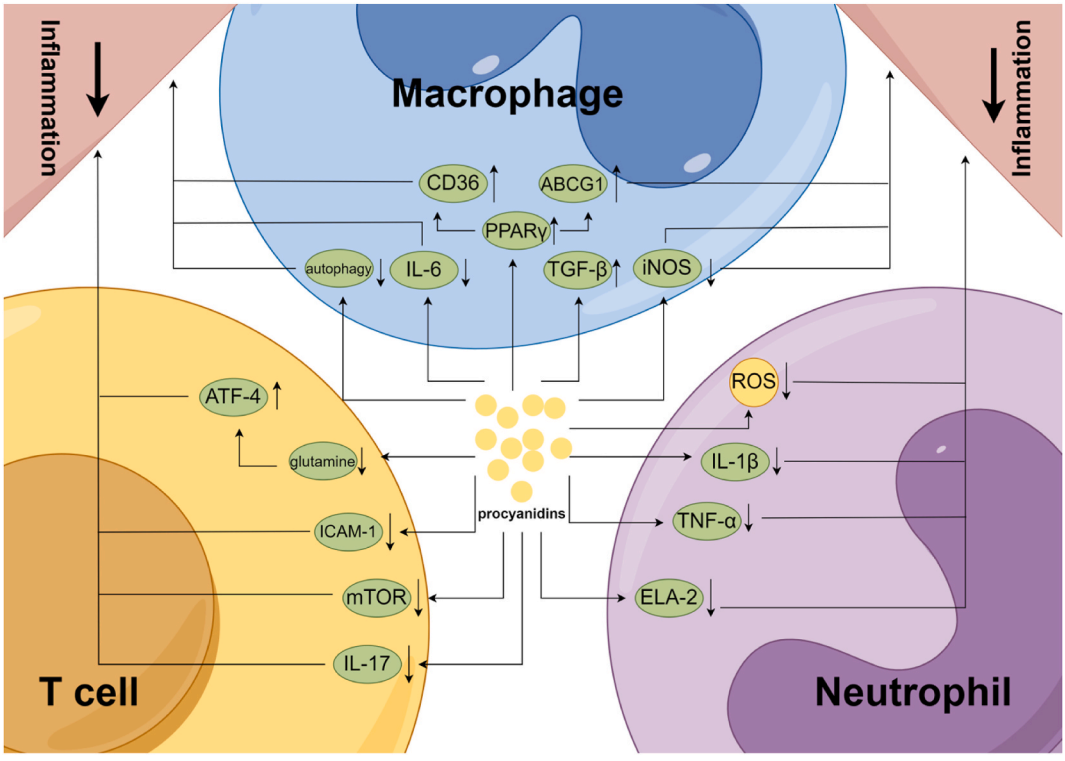

Fig. 3. Schematic diagram of the mechanism of procyanidins on macrophages. "↑" indicates upregulation, and "↓" indicates downregulation.

3.2.2. Suppression of inflammatory cells and factor release

Current research has revealed that procyanidins inhibit inflammatory cells such as macrophages, neutrophils, and T cells. In M2 macrophages, the expression of genes associated with inflammation, such as Found in Inflammatory Zone 1 (Fizz 1), arginase-1 (Arg 1), chitinase-3-like protein 3 (Ym1), and mannose receptor (CD206), plays a role in anti-inflammation and tissue repair. Procyanidin B2, by activating PPARγ, regulates M2 macrophage polarization and exerts beneficial anti-inflammatory effects [110]. Procyanidins inhibit macrophage autophagy and upregulate Slamf8 expression in macrophages. Slamf8 acts as a negative regulator of inflammatory responses, downregulating the JAK-STAT and inflammatory pathways [111]. Procyanidins, through activating the STAT3 and NF-κB pathways, can prevent the elevation of inflammatory cytokines and activation of pro-inflammatory macrophages induced by lipopolysaccharide (LPS) [112]. The mechanism by which procyanidins affect macrophages is depicted in Fig. 3.

Following infiltration into inflamed areas, neutrophils produce reactive oxygen species (ROS) and release proteases (elastase, matrix metalloproteinases - MMPs), chemokines, and cytokines (IL-8, IL-1β). In the context of chronic inflammation, neutrophils activated by various stimuli enhance their pro-inflammatory properties. Procyanidins are potent inhibitors of ROS production in neutrophils and reduce the release of MIP-1β and IL-8 [113]. Procyanidins also inhibit enzymes released by neutrophils, such as elastase-2 and MMP-9, thereby slowing down the progression of inflammation [114]. Additionally, procyanidins effectively intervene in the pro-oxidative and pro-inflammatory functions of neutrophils by downregulating the secretion of IL-1β and ELA-2 [115].

Excessive activation of T cells promotes inflammation. Procyanidins interact directly with alanine-serine-cysteine transporter 2 (ASCT2) to inhibit the influx of glutamine, thereby inhibiting the AAR pathway that mediates the inhibition of IFN-γ production in CD2 T cells [116]. Procyanidins inhibit the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 in T cells while stimulating the secretion of anti-inflammatory cytokines such as IL-4, IL-10, IL-13, and TGF-β1 [117].

3.2.3. Other inflammatory-related mechanisms

Studies have indicated that procyanidins can directly influence inflammation-related signaling pathways. They may potentially inhibit LPS-induced pro-inflammatory gene expression by blocking the NF-κB and MAPK pathways, thus reducing the intensity and duration of inflammatory responses [118]. ER function is associated with several potential pathways in inflammation signal transduction. ER stress leads to the activation of NF-κB and TNF-α receptor-associated factor 2 (TRAF2), which are involved in inflammation signal transduction [119]. ER stress could result in the phosphorylation of JNK and IKK, promoting signal transduction and inflammation [120]. Procyanidins intervene in ER stress through a PPARδ-mediated mechanism, thereby inhibiting inflammation [121]. Procyanidins can decrease ER stress-related expression of peIF2α, ATF6α, and CHOP proteins, reducing the generation of superoxide radicals and ONOO in ER stress. They exhibit significant ER decompression potential, showing substantial anti-inflammatory effects [122].

The inhibitory pathways of procyanidins against inflammation are diverse and complex. However, their complete mechanisms have not been fully elucidated, and the fundamental principles underlying their anti-inflammatory effects have yet to be uncovered. Further exploration of their mechanisms through more effective experimentation, especially human trials, is necessary to apply their effects to clinical treatment. The superior anti-inflammatory properties of procyanidins in various aspects can hinder the inflammatory mechanisms associated with cartilage injury and impede its progression.

3.3. Oxidative stress mechanism

Oxidative stress and inflammation are closely linked pathological processes, with one often easily inducing the other. Both processes are frequently observed concurrently under various pathological conditions [123]. Procyanidins, with their potent antioxidant activity, can scavenge free radicals and oxidative byproducts within the body, safeguarding cells from damage caused by oxidative stress. Moreover, the suppression of immune stress contributes to alleviating inflammatory responses [124].

Constituent cells of the ACL, once damaged, release detrimental molecules such as free radicals and reactive oxygen species. These molecules can trigger cellular inflammatory reactions, thereby exacerbating oxidative stress [125]. Free radicals and reactive oxygen species can interact with vital biomolecules such as proteins, lipids, and DNA, resulting in oxidative damage. This, in turn, may impair cellular structure and function, affecting the stability and repair capability of the ACL [126]. Furthermore, oxidative stress may prompt apoptosis in ACL cells, leading to diminished cell counts and consequently impacting the ligament's physiological function and repair process [32]. Research indicates that oxidative stress can influence the synthesis and degradation of the ACL extracellular matrix, thus altering the ligament's structural and mechanical characteristics. Ultimately, the damage inflicted by oxidative stress serves to propel the progression of PTOA [127].

Studies have shown that procyanidins possess robust antioxidant activity and are adept at neutralizing and eliminating free radicals [128,129]. Free radicals, being highly reactive molecules, readily engage with cellular components, culminating in oxidative damage. Procyanidins exhibit antioxidant attributes by quenching DPPH and ABTS radicals [130]. Advanced glycation end products (AGEs) trigger oxidative stress, and procyanidins' ability to inhibit AGEs can mitigate oxidative stress [131]. Procyanidins activate antioxidant enzymes, augment antioxidant enzyme expression via the MAPK pathway, regulate the NF-κB pathway [132], induce Nrf2 expression to activate HO-1 and NQO-1 and enhance the body's antioxidant capacity [133]. Procyanidins can reduce ROS levels and diminish the expression of pertinent cytokines, such as interleukin-1β (IL-1β), IL-8, and tumor necrosis factor-α (TNF-α) [134]. Certain oxidative reactions necessitate chelation of metal ions, such as iron [135] and copper [136]. During procyanidin metabolism, gallic acid can be generated, which can bind with these metal ions, curtailing their involvement in free radical generation and thereby restraining oxidative reactions. Additionally, these reaction products may also harbor antioxidative and xanthine oxidase inhibitory activities [137]. Mitochondria serves as the chief endogenous source of ROS, encompassing hydrogen peroxide and superoxide anions [138].

Hence, the inhibitory actions of procyanidins contribute to diminishing the extent of oxidative stress. Moreover, procyanidins elevate the expression of SIRT1 protein, thereby modulating mitochondrial function to lower ROS levels [139]. Procyanidins might increase the expression of proteins regulating mitochondrial biogenesis, such as PGC-1α and NRF1, to safeguard mitochondria and attenuate oxidative stress [140].

3.4. Neuro-muscular and vascular mechanisms

Studies indicate that following ACL tear, decreased joint stability could lead to imbalances in surrounding neuro-muscular function. Weakened muscle strength and control result in abnormal joint movement [141], imposing additional stress on joint structures and soft tissues, thereby accelerating the progression of cartilage injury. Sustained ligament laxity and impaired muscle function-induced changes in neuro-muscular feedback may contribute to progressive degradation of intra-articular structures [142,143]. Research suggests that procyanidins protect spinal motor neurons from apoptosis and maintain the integrity of neuro-muscular junctions, where a reduction in reactive astrocytes and microglia could be the primary mechanism by which procyanidins sustain motor neuron survival and overall motor function [144].

Peripheral vasculature may also suffer damage concomitant with ACL injury, involving responses such as inflammation and oxidative stress, resulting in vasoconstriction and impaired blood circulation, subsequently affecting the repair and recovery processes in the injured area. Jankovic et al. reported that procyanidins might promote vasodilation by activating soluble guanylate cyclase to enhance NO secretion [145]. Procyanidins can also mitigate inflammation, apoptosis, and oxidative stress in vascular endothelial cells to safeguard vascular function [146,147]. This suggests that procyanidins could be a promising therapeutic agent for post-ACL tear vascular damage, thus potentially reducing the incidence of cartilage injury.

In summary, cartilage injury following ACL tear represents a complex pathological process involving the interplay of multiple mechanisms. In addition to joint instability, inflammatory responses, oxidative stress, and alterations in knee joint biomechanics, factors such as neural and vascular damage, and neuro-muscular dysfunction, among others, also play significant roles. The application of procyanidins in the treatment of cartilage injury exerts varying degrees of influence across these mechanisms. Through synergistic interactions with diverse mechanisms, procyanidins effectively reduce and repair cartilage injury after ACL tear while concurrently providing multifaceted support and protection for joint repair and recovery.

4. Applications of Procyanidins in Cartilage injury after ACL tear

The applications of procyanidins are focused on delivery systems and delivery methods. Currently, there are various delivery systems for procyanidins, including emulsion gels, hydrogels, nanoparticles, microparticles, liposomes, etc.

Emulsion gels are usually prepared based on proteins, polysaccharides, or their mixtures, and the characteristics of oil droplets play a crucial role in the properties and functions of the system [148]. Emulsion gels, as colloidal solid materials, possess a unique three-dimensional network structure and strong mechanical properties, making them capable of providing excellent protection for bioactive substances [149]. Recently, a new method for preparing physically cross-linked starch-based emulsion gel beads using a water-in-oil emulsion gelation process was developed to effectively load procyanidins [150].

Microparticles with sizes ranging from 1 μm to 1000 μm have become advanced functional materials in the field of drug delivery, and their unique characteristics, such as carefully tailored size, complex morphology, and multiple compartments, have shown significant potential in drug delivery [151]. Using the multiple emulsion method, PAC-loaded lactic-co-glycolic acid (PLGA) microparticles containing procyanidins were prepared, and preliminary studies have confirmed that PLGA/proanthocyanidins (PAC) microparticles do not affect cell viability at the tested concentrations, indicating potential application prospects [152]. 2-methylacryloyloxyethyl phosphorylcholine phosphorylcholine (MPC) -modified methacrylate anhydride-hyaluronic acid (HAMA) particles can deliver drugs to treat OA [153]. This drug delivery system has good biocompatibility and has the potential to deliver procyanidins. Nanoparticles are defined as solid colloidal particles with sizes ranging from 10 to 1000 nm, and their applications have attracted increasing attention in recent years [154]. Nanoparticles loaded with procyanidins conjugated with folic acid-chitosan (PC-CS/FA-NPs) prepared using ion gelation technology have demonstrated good application potential [155].

Liposomes, with nanoscale size and a biomembrane-like structure, possess excellent biocompatibility and are becoming increasingly useful as delivery systems in drug development. Liposomes are relatively stable and can contain hydrophilic drugs in their aqueous core while accommodating lipophilic drugs within their lipid bilayers [156]. Experimental evidence has shown that liposomes are effective carriers for the stability and transport of procyanidins, enhancing their bioavailability [157].

Hydrogels have promising potential as carriers for procyanidins in repairing cartilage injury after ACL tear. Hydrogels are three-dimensional polymeric materials formed through the crosslinking of polymers, and they can be composed of both natural and synthetic polymers [158]. Hydrogel scaffolds for repairing or regenerating damaged biological tissues hold great potential in treating injuries and diseases [159]. Commonly used hydrogels for tissue repair are often composed of hyaluronic acid. When using hyaluronic acid (HA) as the main component, a hydrogel system composed of HA and EGCG showed advantages such as in situ gelation and resistance to hyaluronidase-mediated degradation, making it injectable and prolonging its residence time in vivo [160]. Research has demonstrated that the HA-EGCG hydrogel system exhibits excellent ROS scavenging activity without causing cellular toxicity [161]. Hydrogels have the potential to delay the progression of cartilage injury after ACL tear and even repair cartilage injury, but current research is still limited to animal experiments. For instance, a porous dual-crosslinked hydrogel containing sodium alginate (SA) and silk sericin (SS), whose porous structure and enhanced mechanical properties make the three-dimensional system closer to the cartilage damage repair microenvironment, was designed for in situ repair of cartilage damage, and it exhibited excellent

biocompatibility in both in vitro and in vivo experiments [162].

The delivery methods of procyanidins mainly include oral administration and injection. Oral administration involves loading EGCG into ion hydrogels made from gelatin and γ-polyglutamic acid to protect EGCG from the harsh gastrointestinal environment [163]. However, oral administration is less effective than injection, with injection delivery tending to utilize injectable hydrogels as carriers. Injectable hydrogels offer good biocompatibility and are poised to become genuine carriers for procyanidins in protecting cartilage.

5. Conclusions and perspectives

In conclusion, the research landscape and potential applications of procyanidins in the repair of cartilage injury following ACL tear present an intriguing avenue for further exploration. This review has highlighted the multifaceted mechanisms through which procyanidins exert their beneficial effects in mitigating the complex pathophysiological processes underlying cartilage injury. Notably, procyanidins have demonstrated anti-inflammatory, antioxidative, neuroprotective and vasculoprotective properties, collectively contributing to their potential in repairing cartilage injury.

Investigations into the therapeutic application of procyanidins have largely focused on their integration into delivery systems and methodologies. Emulsion gels, hydrogels, nanoparticles, microparticles, and liposomes have emerged as promising carriers for procyanidins, enhancing their stability, bioavailability, and targeted delivery. Notably, the development of injectable hydrogels presents exciting prospects for delivering procyanidins in a clinically feasible manner, holding potential for sustained efficacy and localized treatment.

While research into procyanidin application for repairing cartilage injury following ACL tear is still in its early stages, the outstanding anti-inflammatory properties of procyanidins cannot be overlooked. The evolving landscape of materials science and drug delivery systems further augments the outlook for successful clinical translation. Although challenges remain, such as the need for rigorous clinical trials to substantiate the findings from preclinical studies, promising preclinical evidence suggests that procyanidins could revolutionize the approach to repairing cartilage injury after ACL tear.

To conclude, the expanding knowledge of the multifaceted effects of procyanidins, coupled with advancements in delivery systems, propels the field toward harnessing the full potential of procyanidins for the repair of cartilage injury. Continued collaborative efforts between researchers from various disciplines, including pharmacology, materials science, and orthopedics, will be pivotal in driving this research frontier forward. Ultimately, the translational success of procyanidins in cartilage injury repair has the potential to revolutionize clinical practice, significantly enhancing the quality of life for individuals susceptible to this condition.

Data availability

Not applicable.

Ethics approval

Not applicable.

CRediT authorship contribution statement

Hanlin Chen: Writing – review & editing, Writing – original draft, Conceptualization. **Jingrui Li:** Writing – review & editing, Writing – original draft. **Shaofei Li:** Writing – original draft. **Xiaoqi Wang:** Writing – original draft. **Ge Xu:** Writing – original draft. **Molan Li:** Writing – original draft. **Guangjie Li:** Funding acquisition.

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.

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