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Oxidative Stress and Inflammation in Osteoarthritis Pathogenesis: Role of Polyphenols

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Abstract

Osteoarthritis (OA) is the most prevalent joint degenerative disease leading to irreversible structural and functional changes in the joint and is a major cause of disability and reduced life expectancy in ageing population. Despite the high prevalence of OA, there is no disease modifying drug available for the management of OA. Oxidative stress, a result of an imbalance between the production of reactive oxygen species (ROS) and their clearance by antioxidant defense system, is high in OA cartilage and is a major cause of chronic inflammation. Inflammatory mediators, such as interleukin-1β (IL-1β), tumor necrosis factor-α (TNF-α) and interleukin-6 (IL-6) are highly upregulated in OA joints and induce ROS production and expression of matrix degrading proteases leading to matrix degradation and joint dysfunction. ROS and inflammation are interdependent, each being the target of other and represent ideal target/s for the treatment of OA. Plant polyphenols possess potent antioxidant and anti-inflammatory properties and can inhibit ROS production and inflammation in chondrocytes, cartilage explants and in animal models of OA. The aim of this review is to discuss the chondroprotective effects of polyphenols and modulation of different molecular pathways associated with OA pathogenesis and limitations and future prospects of polyphenols in OA treatment.

Graphical Abstract

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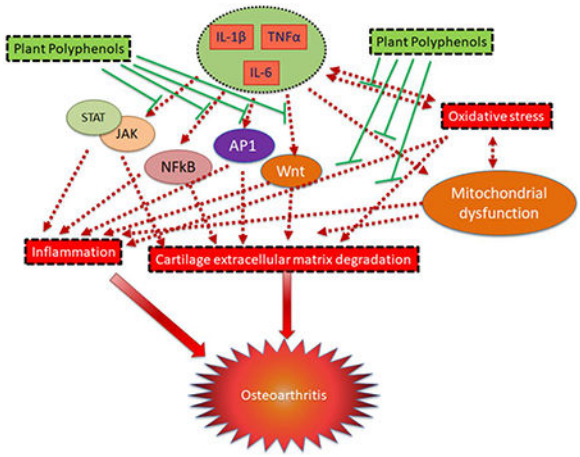

Keywords

Osteoarthritis; Polyphenols; Inflammation; Redox; Nrf2; Chondrocytes

1.0 Introduction

Osteoarthritis (OA) is the most common joint disease and a major cause of disability and reduced life expectancy in the ageing population [1, 2]. OA is a multifactorial disease with etiology ranging from normal ageing process, sex, genetic background and obesity to physical factors which include trauma and injury to the joints and a strong interplay between all these factors. OA pathogenesis is modulated by genetic and environmental factors in association with the activation of molecular and cellular pathways that participate in the advancement of joint injury. Thus, OA is not a single disease, rather it is the final stage of joint failure, the initial stage of which could be triggered and propagated by injury to cartilage, ligaments or other joint tissues (post-traumatic OA) or other causal factors. The diseased joint is characterized by synovial inflammation, oxidative stress, apoptosis in chondrocytes, cartilage extracellular matrix degradation, subchondral bone sclerosis and osteophyte formation leading to stiffness of the whole joint, pain and joint failure (Figure 1). To date, there is no disease-modifying therapy available for the treatment of OA due to poor understanding of the disease pathogenesis. Further understanding of the molecular and cellular pathways and their association with joint tissues is necessary to develop new therapeutic approaches for the prevention and treatment of OA. The currently available therapies for the management of OA include non-steroidal anti-inflammatory drugs (NSAIDs) which only provide temporary relief and neither prevents cartilage degradation nor have any effect on the reversal of cartilage degeneration. In addition, these agents have adverse side effects and toxicity [3, 4]. These limitations demand the development/ invention of new therapeutic approaches which have little to no side effects and in addition to anti-inflammatory and analgesic effects also improve the cartilage structure and reverse the cartilage destruction to improve overall joint health. Recent studies have shown that joint inflammation and oxidative stress is directly associated with OA progression [5, 6]. The

purpose of this review is to highlight the contribution of oxidative stress and inflammation in OA pathogenesis and summarize the therapeutic potential of polyphenols for OA.

2. Oxidative Stressing in Osteoarthritis

Reactive oxygen species (ROS) are oxygen containing free radicals including hydrogen peroxide (H_2O_2), hydroxy radical (OH^-), superoxide anion ($O2^-$) and nitric oxide (NO) and have unpaired electron which makes them unstable and highly reactive. ROS is normally produced in cells at low levels and is essential for the maintenance of cellular homeostasis and function [7]. However, the imbalance in this physiological mechanism leads to increased expression of inflammatory cytokines and chemokines, which causes oxidation of cellular macromolecules such as proteins, lipids and DNA altering their function. The major sites of ROS production include mitochondria, peroxisomes and other membranous structures containing NADPH oxidases (NOXs), Xanthine Oxidase (XO) and Nitric Oxide Synthase (NOS) [8]. It is estimated that approximately 2-3% of O_2 consumed in mitochondria during oxidative phosphorylation is converted to O_2^- rather than to water [9]. NOX complex is consist of 3 cytosolic (p40phox, p47phox and p67phox) and 2 membrane associated (p22phox and gp91phox) protein components. Under pathological conditions, cytosolic units translocate to inner surface of plasma membrane and form fully active enzyme complex leading to increased production of ROS. NOX components are expressed in chondrocytes, the only resident cell type of the cartilage, and are the major producers of ROS [10, 11]. XO produces H_2O_2 during oxidation of hypoxanthine to xanthine. The evidence of high levels of ROS production in OA cartilage comes from either chondrocytes isolated from end stage diseased cartilage or from the presence of lipid peroxidation and nitrosylation products in synovial fluids and in the cartilage [12, 13]. There are three isoforms of NOS, (1) the constitutive isoform mainly expressed in neuronal cell, neuronal NOS (nNOS), (2) endothelial NOS (eNOS) and (3) inducible NOS (iNOS). The nNOS and eNOS require calcium and calmodulin and produce a very low amounts of NO. The iNOS is the inducible form of NOS induced by inflammatory cytokines and produces relatively high amounts of NO and require low concentration of calcium for its activity. Reactive nitrogen species (RNS) are molecules derived from O_2^- and NO and cause damage to the cell by inducing nitrosative stress. iNOS expression is highly upregulated in chondrocytes in response to inflammatory cytokines stimulation such interleukin-1β (IL-1β), tumor necrosis factor α (TNFα), interferon-γ (IFN-γ) and IL-17 etc. [14–17]. Regardless of the source of production, NO may react with cellular proteins causing their nitrosylation which alter their normal function [18, 19]. NO has been reported to increase inflammation by activating nuclear factor kappa B (NFκB) pathway causing increased production of IL-1β and TNFα [20]. Under pathological conditions, excessive amounts of ROS function as secondary messengers and promote cartilage degradation by inducing the expression of matrix degrading proteases, reducing extracellular matrix (ECM) synthesis and inducing chondrocyte apoptosis.

Under conditions of increased ROS production, the cellular defense mechanism against oxidative stress gets activated and efficiently removes the ROS molecules from the cell. The cellular antioxidant defense system includes various enzymes, such as catalases, peroxiredoxins (Prxs), glutathione peroxidase (GPx), NADPH ubiquinone oxidoreductase

(NQO1) and superoxide dismutases (SODs) and nonenzymatic such as glutathione (GSH), ascorbic acid (vitamin C), α-tocopherol (vitamin E) etc. [9, 21]. SODs protect against oxidative stress by converting the O_2^- to H_2O_2, which is further eliminated by Prx, GPx and catalases. There are three isoforms of SODs, cytosolic SOD (SOD1 or Cu/Zn SOD), mitochondrial SOD (SOD2 or MnSOD) and extracellular SOD (SOD3 or EC-SOD) which is secreted outside the cell [22]. Prxs protect against H_2O_2 mediated oxidation of proteins by accepting the nascent oxygen at its thiol active site [23]. Catalases provide protection against oxidative stress by converting H_2O_2 to water and oxygen molecules. GPx protects membrane lipid oxidation by H_2O_2 by oxidizing GSH [24]. The expression of antioxidant defense system proteins including SOD, catalase and Gpx are downregulated in OA joints showing imbalance in redox in OA cartilage [25, 26]. Various *in vitro* and *in vivo* studies have shown that upregulation of cellular antioxidant defense system in chondrocytes suppresses the expression of catabolic genes and improves joint health. Nuclear factor (erythroid-derived 2)-like 2 (Nrf2), a master transcription factor regulator of the cellular antioxidant defense system, expression is dysregulated in OA and its deletion resulted in enhanced disease development in a mouse model of destabilization of medial meniscus (DMM) induced OA [27] which suggest a potential role of antioxidant defense system in the protection against OA. In a study, Prx3 (mitochondrial Prx) was reported to be hyperoxidized in aged and OA human cartilage indicating increased oxidative stress [28]. OA chondrocytes treated with Menadione showed high levels of oxidized Prx3 which was associated with decreased pro-survival signaling (Akt) and increased pro-death signaling (p38)[28]. Interestingly, mitochondria targeted expression of catalase (MCAT) suppressed the Menadione induced catabolic effects in chondrocytes and suppressed age-related progression of OA in a mouse model [28]. The scavenger of mitochondrial superoxide, SOD2 is downregulated in human and mouse OA cartilage [29]. Mitochondrial dysfunction or deregulation of SOD2 expression may lead to excessive ROS production which may cause irreversible damage to the chondrocytes and induce cell death by apoptosis or necrosis [9]. We have shown that autophagic clearance of dysfunctional mitochondria and suppression of ROS is essential for the survival of chondrocytes under pathological condition [30]. NO and its derivative have also been reported to increase the damage to cartilage during OA development [6, 20, 31] and targeting of NO was found to suppress the progression of OA in a mouse model of experimental OA [17]. NO is produced in chondrocytes in a two-step conversion process of L-Arginine to L-Citrulline which is catalyzed by iNOS whose expression is highly upregulated in OA cartilage and in chondrocytes under pathological conditions [32].

Oxidative stress is the result of excessive production of ROS, which is beyond the capacity of the cellular antioxidant defense system to effectively remove from the cells. Overproduction of ROS and induction of oxidative stress in chondrocytes are one of the major contributors to OA pathogenesis [6, 9, 33, 34]. Many studies have shown that the ROS levels are highly upregulated in the human OA cartilage and chondrocytes [30, 34–36]. We have shown earlier in an *in vitro* study that stimulation of primary human OA chondrocytes and mouse chondrocytes with IL-1β increases the production of cellular and mitochondrial ROS which promotes chondrocyte apoptosis [30] mimicking the *in vivo* condition observed in OA cartilage [37]. Exposure of chondrocytes with H_2O_2,

Menadione, 3-morpholinosydnonimine (SIN1), tert-butyl hydroperoxide (TBHP) or other pro-oxidants have been reported to increase inflammation and apoptosis [28, 38] showing that oxidative stress induces inflammation in chondrocytes. Increase in oxidative stress positively correlates with collagen degradation [34] suggesting a role of ROS in cartilage matrix catabolism. In addition, in different studies, NO and H_2O_2 have been reported to suppress proteoglycan synthesis showing the role of ROS in suppressing cartilage matrix anabolism [6]. Taken together these studies show that oxidative stress has a detrimental effect on joint health and function and targeting these pathways might be of therapeutic importance for the management of OA.

3. Inflammation in Osteoarthritis

Inflammation is a necessary cellular response in the fight against infection, however, chronic, unregulated inflammation is associated with the pathophysiology of several human diseases including neurological diseases, obesity, diabetes, autoimmune disease, cancer and rheumatoid arthritis [39, 40]. Recent studies show increased levels of proinflammatory cytokines and chemokines in the synovial fluids of end stage OA patients [41–43]. Several studies with animal models of OA also show high levels of inflammation in experimental OA joints and support the idea of anti-inflammatory approach of treatment of OA.

Chondrocytes are normally quiescent cells, however, during unfavorable conditions, get activated and produce a plethora of proinflammatory cytokines and chemokines that increase the expression of collagenases and aggrecanases leading to cartilage ECM degradation [44, 45]. Chondrocytes also express receptors for several of proinflammatory cytokines and chemokines. Thus, chondrocytes are the source as well as the target of proinflammatory cytokines in OA. TNFα, IL-1β and IL-6 represent the three highly expressed cytokines in OA joints and are actively produced by chondrocytes, synoviocytes, macrophages and osteoblast and play a critical role in the degeneration of articular cartilage matrix which makes them primary therapeutic target. Other than TNFα, IF-1β and IF-6, several other cytokines (such as IF-17, IF-18, MCP1, CXCF5, RANTES etc., see table 1), have also been reported to be associated with OA pathogenesis and may be targeted for therapeutic strategies [46–49] but the data is limited at this stage. Increase in the levels of the cytokines in joints play a central role in the pathogenesis of OA by modulating oxidative stress, cartilage ECM turnover and chondrocytes apoptosis [50].

Stimulation of primary chondrocytes and cartilage explants with IF-1β and TNFα mimic the *in vivo* pathological conditions by upregulating the expression of catabolic genes including IF-6, COX-2, iNOS, collagenases [matrix metalloprotease 13 (MMP-13)] and aggrecanases [a disintegrin and metalloproteinase with thrombospondin motif (ADAMTSs)] and by down regulating the expression of anabolic genes such as aggrecan and type II collagen [51–55]. Animal studies with ADAMTS4 [56] and ADAMTS5 [57] knockout mouse models show that ADAMTS5 is the major aggrecanase associated with OA pathogenesis and catalytically is multiple fold more active than ADAMTS4 [58]. IF-1β mediated activation of cells is through binding and activation of specific cell surface receptor, IF-1 receptor type I (IF-1RI). IF-1RI expression is highly upregulated in OA chondrocytes compared to normal chondrocytes [59]. Many cell types including chondrocytes express natural competitive

inhibitor of IF-1β, IF-1 receptor antagonist (IF-IRa) which binds to IF-1RI but does not transduce a signal and has anti-inflammatory properties [60]. TNFα functions as ligand for two specific receptors [TNF receptor I (TNFRI) and TNFRII] which are expressed on cell membrane on various cell types including chondrocytes. Compared to normal chondrocytes, OA chondrocytes express high levels of TNFRI which is the dominant receptor for TNFα [61]. Intraarticular injection of either of TNFα or IL-1β into rabbit knee joints triggered the progression of OA which was augmented upon combined injection [62]. In another study, deletion of IL-1β was reported to reduce the severity of DMM induced OA in a mouse model [63]. However, deletion of IL-1β or IL-1β converting enzyme the usual suspects in OA pathogenesis, accelerated the development of experimental OA in mouse model showing that complete deletion of IL-1β or IL-1β converting enzyme augments the pathogenesis of OA [64, 65]. These results show that the proinflammatory cytokines, which appear to play pathogenic role in the development of OA, are also important for the maintenance of chondrocyte homeostasis and joint health and a fine balance of these inflammatory mediators is required for normal functioning of the joint and knowledge in this area is far from complete.

IL-6 signaling involves many components including a multimeric receptor complex consist of membrane bound IL-6 receptor (IL-6R), soluble IL-6 receptor (sIL-6R) and gpl30. Normal chondrocytes express very low levels of IL-6, whose expression is highly upregulated upon treatment with proinflammatory cytokines such as TNFα or IL-1β [66–68]. Treatment of cartilage explants with IL-6 upregulated the expression of MMP-13 [69]. Expression of levels of IL-6 and sIL-6R is increased in the synovial fluid of OA patients [70]. We found increased expression of IL-6 in chondrocytes of the damaged area of human OA cartilage [66]. Suppression of IL-6 expression in Zcchc6 knockout mice reduced the severity of experimental OA in a mouse model of post-traumatic OA[67]. Antibody mediated neutralization of systemic levels of IL-6 or small molecule inhibitor of STAT3 signaling (downstream signaling pathway of IL-6 mediated receptor activation) was reported to ameliorate cartilage degradation in a DMM induced OA mouse model [71]. Intraarticular injection of IL-6 protein promoted cartilage destruction in a mouse model [72]. However, in a study using IL-6 knockout mouse, the severity of age-related OA in male mice was significantly increased, but not in female mice [73] suggesting that low levels of IL-6 may be required to maintain chondrocyte homeostasis and play a protective role at some stage, at least in age-related OA.

4. Major signaling pathways in OA pathogenesis

The expression of proinflammatory cytokines, cyclooxygenase, iNOS, MMPs and other proteinases in chondrocyte is tightly regulated by inflammatory pathways, including the three (ERK, JNK and p38) mitogen activated protein kinases (MAPK), NFκB, API, JAK/STAT and Wnt pathway. The pathological effects of ROS, IL-1β, TNFα and IF-6 in chondrocytes and in cartilage are due to the activation of various proinflammatory signaling pathways (Figure 2). Stimulation of chondrocytes with IF-1β initiates a cascade of events leading to the activation of p38-, JNK- and ERK-MAPK, PKC, increase in the intracellular Ca^{+2} and nuclear translocation of NFκB, API, STATs and ATFs [45, 51, 54, 74–76]. Activation of NFκB signaling pathway mediates the upregulation of several

inflammatory cytokine and chemokine genes, iNOS and COX-2 and increased expression of cartilage ECM degrading proteases such as MMP-1, MMP-9, MMP-13, ADAMTS4, and ADAMTS5 [77]. Recent studies have established a significant role of Wnt/β-catenin signaling in OA pathogenesis [78]. The expression of Wnt signaling mediators such as Wnt ligands and β-Catenin is upregulated in OA cartilage [79]. Activation of Wnt/β-Catenin signaling in chondrocytes augmented IF-1β induced expression of MMPs and ADAMTSs [80]. Intraarticular injection of a small molecule inhibitor of Wnt/β-Catenin signaling pathway reduced the severity of experimental OA in a mouse model [81]. ROS molecules function as intermediate signaling molecules in multiple signaling pathways. Stimulation of chondrocytes with IF-1β increases the production of ROS which induces mitochondrial dysfunction and may augment the IF-1β induced production of ROS [30, 45]. Increased ROS levels activate redox sensitive transcription factors such as AP1 and contribute to the proinflammatory phenotypic alterations in chondrocytes including the expression of IF-6, COX-2, iNOS and their products PGE2 and NO. In addition, increased prooxidant load can also suppress proteoglycan synthesis by inhibiting the PI3/Akt signaling and activating MEK/ERK signaling pathway [82]. TNFα increased the expression of cFos/AP1 via NADPH oxidase mediated production of ROS in bovine chondrocytes [83]. IF-1β induced expression of cFos and MMP-1 in chondrocytes depends on ROS production [84]. Treatment of chondrocytes with prooxidant TBHP activated the MEK/ERK pathway [82]. Activation of JNK in chondrocytes by IF-1β and TNFα is dependent on the production of ROS indicating a potential role of ROS in OA pathogenesis [85]. In a recent study we have shown that IL-1β induced the activation of cFos/AP1 and upregulated the expression of IL-6 and MMP-13 [68]. These findings suggest that ROS mediated inflammation is induced via activation cFos/AP1 pathway. In addition, direct stimulation of chondrocytes with H_2O_2 or NO activated JNK pathway indicating that JNK is the major target of ROS mediated inflammatory response [85]. Deletion of JNK prevented the increase in the expression of IL-1 and TNF, IL-6, IL-18 and ADAMTS4 in a DMM mouse model of OA [86].

5.0 Targeting oxidative stress and inflammation with plant polyphenols

Polyphenols are secondary metabolites produced by almost every part of plants, including fruits, flowers, leaves and bark. Many common fruits (such as grapes, cherries, apples, pomegranate, oranges), herbs and spices are very rich source of polyphenols. These compounds have potent anti-inflammatory and antioxidant properties. The antioxidants property of polyphenols depend on a polyphenol's ability to scavenge ROS molecules, inhibit the expression of prooxidant genes and increase the expression of antioxidant genes such as SODs, catalases [87–89]. The anti-inflammatory activity of polyphenols depends on their ability to suppress pro-inflammatory signaling pathways such as MAPK, API and NFκB. Several studies have demonstrated a potential OA suppressing activity of polyphenolic compounds which depend mainly on their antioxidant and anti-inflammatory properties [87, 89]. The anti-inflammatory and antioxidant effects of many polyphenols including pomegranate extract, Butein, green tea polyphenol, EGCG, Resveratrol, Wogonin, Quercetin, Harpagoside, Curcumin, Morin and several others have been tested in *in vitro* and *in vivo* models of OA.

We have shown earlier that Butein, a chalcone, rich extract of *Butea monosperma* flowers and purified Butein showed potent antioxidant property and suppressed the expression of IL-6 and metalloproteases by enhancing autophagy in chondrocytes via modulation of AMPK/mTOR signaling pathway [66, 90]. Butein activates AMPKα by inducing the phosphorylation of AMPKα$^{Thr\text{-}172}$and suppresses mTOR activity by reducing the phosphorylation of mTOR$^{Ser\text{-}2448}$ [66, 90]. We have also showed that an extract of *Scutellaria baicalensis* and purified Wogonin suppresses the IL-1β induced expression of IL-6, COX-2, iNOS and metalloproteases and reduces the production of PGE2 and NO [45, 91]. Wogonin increases the expression and activity of Nrf2, the master transcription regulator of antioxidant defense enzymes and increased the expression of HOI providing resistance against IL-1β induced oxidative stress in primary human chondrocytes [45, 91]. Harpagoside, an iridoid, suppressed IL-1β induced expression of MMP-13 and a plethora of proinflammatory cytokines and chemokines including IL-6 through the inhibition of cFos/AP-1 signaling pathway and independent of c-Jun and NFκB pathway in primary human OA chondrocytes [68]. Harpagoside when given in combination with glucosamine hydrochloride, chondroitin sulfate, methylsulfonyl methane and bromelain extract showed protective effect in formalin induced rat OA model by suppressing the expression of IL-1β and TNF-α [92].

Pomegranate *(Punicagranatum)* fruit extract (PFE) which is rich in gallic acid, ellagic acid and punicalagin polyphenols suppressed IL-1β induced expression of MMP-1, −3 and −13 and COX-2 expression in primary human chondrocytes through the inhibition of p38-MAPK and JNK-MAPK and their downstream transcription factors, cJun and ATF2 [93, 94]. PFE also suppressed NFκB activation by preventing the phosphorylation of IκBα [93, 94]. PFE was found to inhibit the activation of RUNX-2 transcription factor via the inhibition of MKK3/p38α-MAPK signaling pathway [75]. Delphinidin, an active constituent of pomegranate fruit, suppressed IL-1β induced expression of COX-2 and PGE2 production through the inhibition of NFκB-inducing kinase (NIK) and IL-1 receptor-associated kinase-1 (IRAKI) mediated activation of NFκB pathway in human OA chondrocytes [53].

Green tea polyphenol, Epigallocatechin 3-gallate (EGCG), a catechin, shows potent anti-inflammatory properties which depends on its ability to suppress the IL-1β induced expression of inflammatory mediators in primary human chondrocytes and cartilage explants [16, 54]. EGCG suppressed the expression of several proinflammatory cytokines and chemokines including IL-1β, IL-6, IL-7, TNFα, LIF, MCSF, Oncostatin M, MCP-1, MCP-2 and IL-8 in primary human chondrocytes through the inhibition of NFκB and MAPK signaling pathway [16, 54]. EGCG suppressed the advanced glycation end products induced expression of TNFα and MMP-13 in primary human chondrocytes via the inhibition of ρ38-, JNK- and ERK-MAPK [74, 95]. Intraarticular injection of EGCG in a collagenase-induced arthritis model in rats suppressed inflammation [96]. Intraperitoneal injection of EGCG in a DMM induced OA mouse model was shown to exert chondroprotective effects by reducing the expression levels of IL-1β, TNFα and metalloproteases [97]. In another *in vitro* study, EGCG was reported to suppress the expression of inflammatory mediators in human fibroblast-like synoviocytes [98].

Quercetin (3,3',4',5,7-pentahydroxy-flavone), a flavonoid found in many common fruits and vegetables such as onion, has strong antioxidant activity and reduced the levels of ROS by increasing the expression of glutathione and glutathione peroxidase in a rat model of OA [99]. An extract of *Ginkgo biloba* leaves enriched in Quercetin has anti-inflammatory activity and suppressed IL-1β and LPS induced expression of iNOS, COX-2 and NO and PGE2 production in human OA chondrocytes and in a rat model of OA [100]. Intraperitoneal injection of Quercetin suppressed the oxidative stress and reduced the severity of OA in a rat model through the activation of SIRT1/AMPK pathway [101]. Intraarticular injection of Quercetin mixed with thermosensitive hydrogel suppressed the cartilage degradation and slowed the progression of OA in a rat model [102]. In another study, intraarticular injection of Quercetin was shown to suppress inflammatory response in a rat model of OA by inhibiting Akt/NFκB signaling pathway [103].

Morin, a flavanol, found in members of Moraceae family, increased the expression of HO1 and suppressed the IL-1β induced oxidative stress in chondrocytes via activation of the transcription factor Nrf2 [104]. Morin also suppressed the IL-1β induced expression of MMP-13, iNOS and COX-2 and their product NO and PGE2 in chondrocytes through the inhibition of NFκB signaling pathway [104, 105]. In another study, Morin suppressed the IL-1β induced expression of MMP-3 and MMP-13 and upregulated the expression of TIMP-1 through the suppression of JNK-, p38- and ERK-MAPK signaling pathway [106]. Oral administration of Morin slowed the progression of ACLT induced OA in a rat model [106].

Curcumin, a phenylpropanoids and the major constituent of turmeric, is a common spice and has been widely shown to have potent anti-inflammatory properties. The chondroprotective effect of curcumin has been shown in several *in vitro* and *in vivo* studies using chondrocytes, cartilage explants and various animal models [107–109]. Oral administration of Curcumin and tetrahydrocurcumin suppressed the expression of IL-1β, IL-6 and metalloproteases and alleviated the pain and cartilage degeneration in a rat [107] and mouse [108] model of experimental OA. Another study showed that chemically modified curcumin suppressed inflammation and slowed the progression of OA in an ACLT induced OA model in rabbit [110]. Ferulic acid, a derivative of curcumin and a component of the cell walls of various plants including oats, rice and the seeds of orange and apples, possess strong anti-inflammatory and antioxidant properties and was reported to suppress H202 induced expression of TNFα and IL-1β [111].

Resveratrol (trans-3,4',5-trihydroxystilbene), a phytoalexin, found in the skin of red grapes has been shown to have potent antioxidant and anti-inflammatory activity [112]. Intra-articular injection of Resveratrol in ACLT induced OA in rabbit suppressed the expression of iNOS and production of NO [113]. Resveratrol also suppressed the IL-1β, TNF-α and IL-6 expression levels in rats with experimental OA [114]. In another study, Resveratrol reduced AGEs induced expression of iNOS, COX-2 and MMP-13 in chondrocytes via the inhibition of NFκB and API signaling pathways [115]. Resveratrol was found to activate SIRT1 in chondrocytes and blocked NFκB activation and suppressed IL-1β induced expression of iNOS in human chondrocytes [116]. Resveratrol activated SIRT1 and suppressed IL-1β induced expression of HIF-2α in human chondrocytes and intraarticular

injection of resveratrol slowed the progression of experimental OA in a mouse model of OA [117]. Resveratrol also protected rabbit chondrocytes against sodium nitroprusside induced apoptosis by scavenging the SNP induced ROS and NO [118]. Resveratrol induced the expression ofHO-1 via the activation ofNrf2 and suppressed oxidative stress in rat with OA [114]. Oral administration of Resveratrol suppressed inflammation via the inhibition of TLR4 signaling and ameliorated high fat diet induced OA [119].

Olive oil is a rich source of polyphenols and is extensively used in Mediterranean diet [120]. Several *in vitro* and *in vivo* studies using olive oil have been reported to improve joint health and function [121, 122]. Hydroxytyrosol, a polyphenol found in olive oil, activates autophagy and prevents chondrocyte's death [123]. Oral uptake of extra virgin olive oil rich diet has anti-inflammatory effects and suppressed IL-6 expression and upregulated the expression of lubricin in a rat model of ACLT induced OA [124, 125]. These and other studies provide support to the use of Olive oil containing diets as a possible approach to maintain healthy joint function.

In addition to the above mentioned plant-derived compounds, several other polyphenols were shown to suppress oxidative stress and inflammation in chondrocytes and alleviated OA pathogenesis. We showed recently that Imperatorin, a secondary metabolite found in the plants of Apiaceae and Rutaceae family members suppressed the expression of iNOS and NO production by suppressing ERKl/2-AP1(cFos/cJun) pathway [32]. We also showed that Imperatorin can bind to iNOS and suppress its enzymatic activity. In an *in vitro* study, Genistein, an isoflavone, suppressed the LPS and IL-1β induced expression of COX-2, iNOS and NO production in chondrocytes [126]. An aqueous extract of Java tea (*Orthsiphonstaminens)* suppressed inflammation in cartilage explant and reduced the severity of OA in monosodium iodoacetate (MIA) induced OA in rat [127]. Olive and grape seed extracts enriched in hydroxytyrosol and procyanidins (HT/PCy) suppressed the expression of iNOS, COX-2 and metalloproteases in chondrocytes stimulated with IL-1β and showed chondroprotective effects in post-traumatic models of OA in mice and rabbits [128]. In an *in vivo* study using guinea pig model of spontaneous OA, Oleuropein enriched diet significantly suppressed the synovial inflammation and serum levels of PGE2 [129]. Chlorogenic acid treatment inhibited IL-1β induced expression of iNOS and COX-2 and suppressed the production of PGE2 and NO in human chondrocytes [130]. Chlorogenic acid enriched butanol extract of WIN-34B inhibited the expression and production of inflammatory mediators TNFα, IL-1β, PGE2 and NO in human cartilage explant and chondrocytes through the inhibition of IL-1β induced JNK-, p38-MAPK signaling pathway [131]. Chlorogenic acid enriched aqueous extract of *Anthriscnssylvestris* leaves were shown to suppress the expression of inflammatory mediators, such as, iNOS and COX-2 and production of NO and PGE2 in rat primary chondrocytes via the inhibition of MAPK and NFKB pathway [132]. Oral uptake of Pycnogenol was reported to reduce joint pain and other symptoms of OA [133, 134]. Stachydrine prevented IL-1β induced expression of IL-6, COX-2 and iNOS in chondrocytes through the inhibition of NFκB pathway [135]. We have shown earlier that an extract from cat's claw *(Uncaria guianensis*) suppressed IL-1β induced production of NO through the upregulation of insulin like growth factor-1 [136]. Apigenin was reported to block the IL-1β induced NFκB and Smad2/3 pathway in SW1353 chondrosarcoma cells [137]. Ginger extract suppressed IL-1β induced expression of TNFa,

IL-6 and IL-8 through the inhibition of p38-MAPK, JNK-MAPK pathway using cartilage explants and primary human chondrocytes [138].

6.0 Conclusions and Future Studies

Oxidative stress and inflammation in chondrocytes and other joint tissues are associated with the progression and severity of the disease making them ideal targets for its management. Recent studies have provided new insights and have increased our understanding of the molecular pathways involved in the pathogenesis of OA. The studies discussed in this review show that polyphenolic compounds, such as EGCG, Butein, Wogonin, Resveratrol, Curcumin have strong anti-inflammatory and antioxidant properties and exert chondroprotective effects in chondrocytes and cartilage explants cultures and animal models of OA. These polyphenols have been shown to scavenge ROS and activate the antioxidant defense system in chondrocytes and suppressed inflammation by inhibiting pro-inflammatory signaling pathways. Future studies focused on the delivery of therapeutic amounts of polyphenolic compounds to the affected joints, which is a major limitation associated with OA treatment, are required to increase the treatment efficacy and improve joint health and function. In summary, the recent findings have shown that plant polyphenols have the potential to be developed as an effective therapy for the management of OA. Randomized clinical trial studies with polyphenols and with large number of volunteers are required to fully establish the chondroprotective role of polyphenols.

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Abbreviations

ADAMTS	A Disintegrin and Metalloproteinase with Thrombospondin Motifs
COX-2	Cyclooxygenase-2
DMM	Destabilization of Medial Meniscus
ECM	Extracellular Matrix
GPx	Glutathione peroxidase
GSH	Glutathione
H_2O_2	Hydrogen peroxide
IFN-γ	Interferon-γ
IL-1RI	IL-1 receptor type I
IL-IRa	IL-1 receptor antagonist
IL-1β	Interleukin-1β

IL-6	Interleukin 6
IL-6R	IL-6 receptor
MAPK	mitogen activated protein kinases
MMP	Matrix Metalloproteinase
NFκB	Nuclear Factor Kappa B
eNOS	endothelial Nitric Oxide Synthase
iNOS	inducible Nitric Oxide Synthase
nNOS	neuronal Nitric Oxide Synthase
NO	Nitric Oxide
NOS	Nitric Oxide Synthase
NOXs	NADPH oxidases
NQO1	NADPH ubiquinone oxidoreductase
Nrf2	Nuclear factor (erythroid-derived 2)-like 2
NSAIDs	Non-Steroidal Anti-inflammatory Drugs
OA	Osteoarthritis
PGE2	Prostaglandin E2
Prxs	Peroxiredoxins
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
SODs	superoxide dismutases
TNF-α	Tumor Necrosis Factor-α
XO	Xanthine Oxidase

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Highlights

- Here, we discussed the role of oxidative stress and inflammation in OA pathogenesis.
- Here, we discussed the antioxidant and anti-inflammatory activities of polyphenols.
- Polyphenolic compounds suppress oxidative stress and inflammation in OA joints.
- Polyphenols inhibit the activation of key signaling pathways in OA pathogenesis.
- We discuss here the possibility of development of polyphenol(s) for OA management.

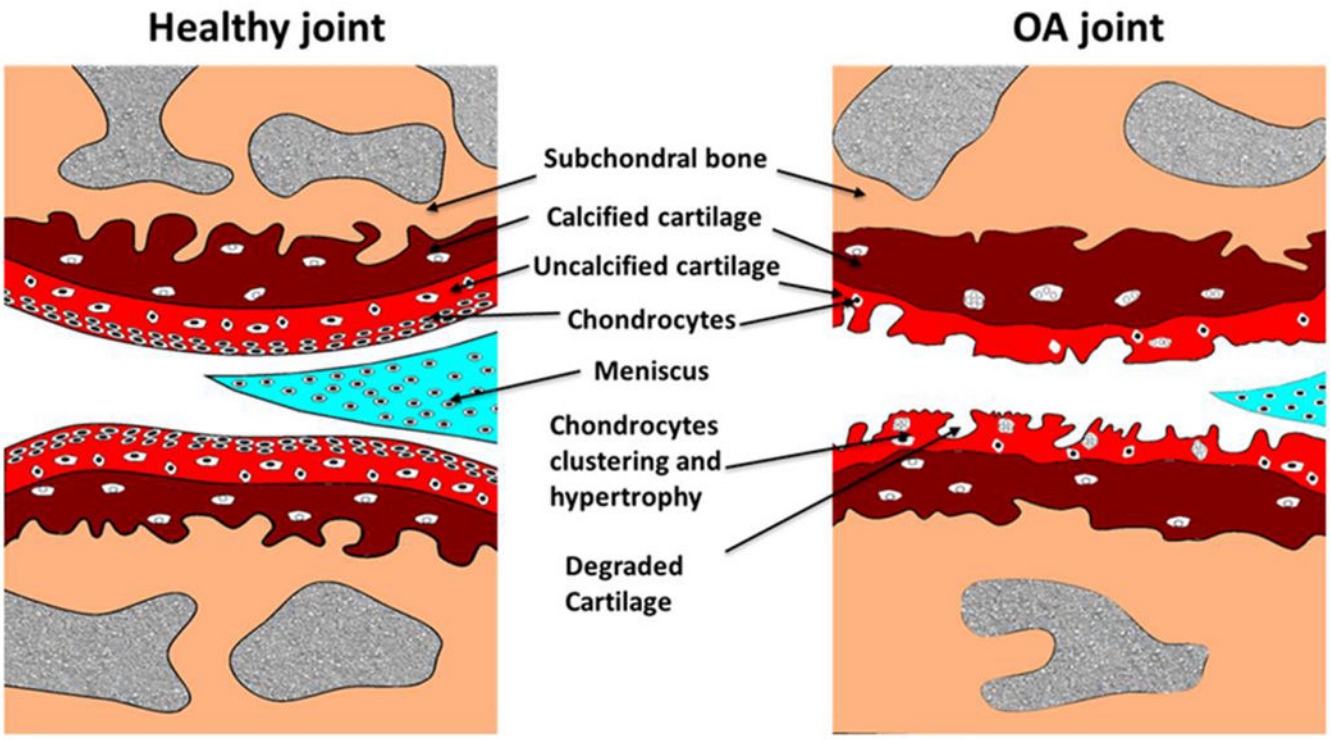

Figure 1:
Schematic representation of normal and OA knee joint. The healthy joint (on left) has smooth cartilage surface with normal chondrocyte distribution and OA joint shows cartilage degeneration and subchondral bone changes.

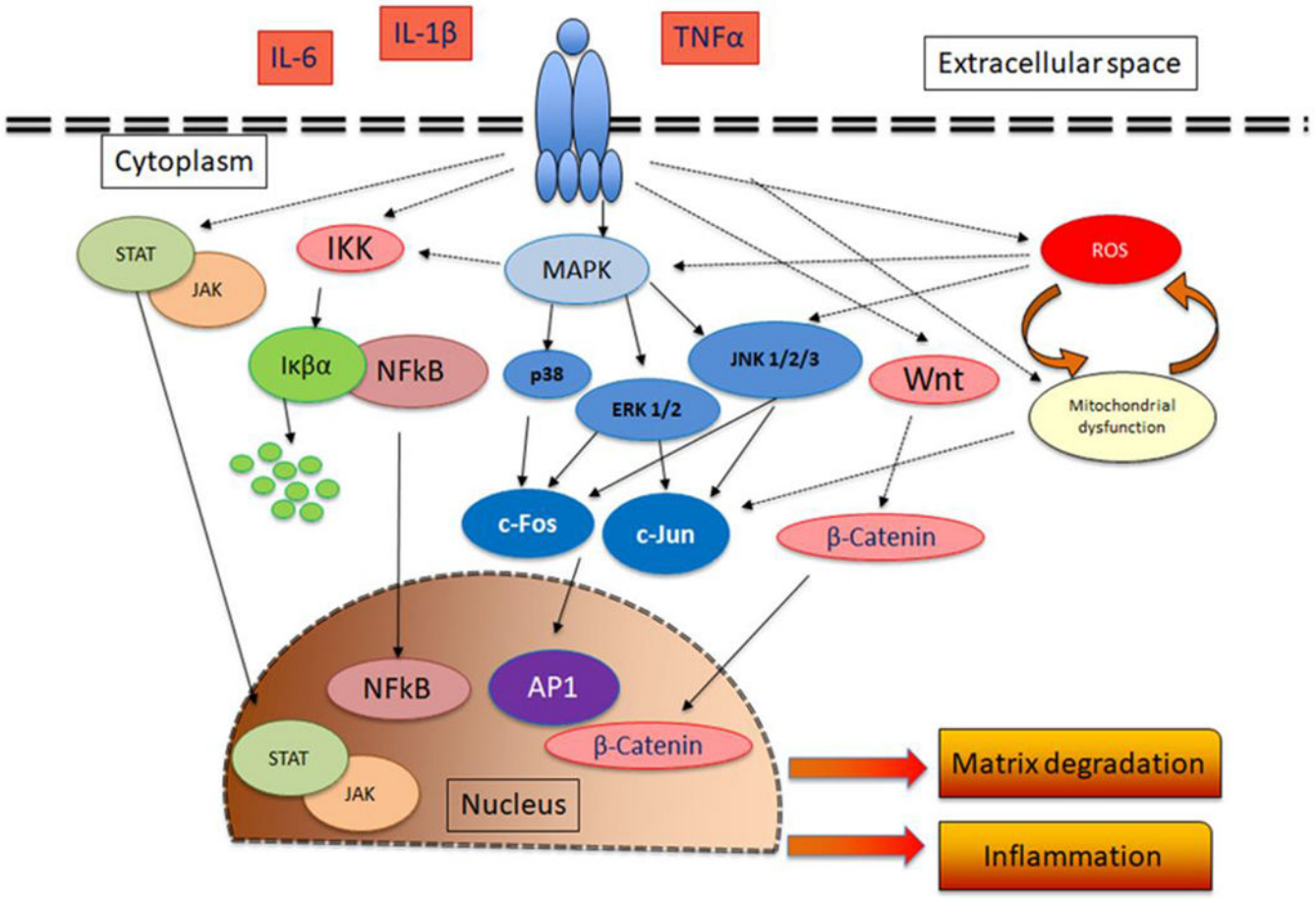

Figure 2:

Schematic representation of the major signaling pathways activated by proinflammatory cytokines (IL-1β, TNFα and IL-6) in chondrocytes and their downstream effects. Stimulation of chondrocytes with IL-1β, TNFα and IL-6 leads to the activation of JAK/STAT, MAPK, AP1, NFκB and Wnt signaling pathways These cytokines also modulate mitochondrial function and ROS production. The activation of these pathways lead to increased expression of inflammatory molecules, matrix degrading proteases in chondrocytes.

Table 1:

Cytokines and chemokines and their role in the pathogenesis of OA

Cytokine	Role in OA	Reference
IL-1β	Increased in OA joint synovial fluid, cartilage, synovial membrane and subchondral bone. It increases the production of iNOS, COX-2, IL-6, TNF-α IL-8, MCP1, RANTES and the levels of PGE2 and NO in chondrocytes and in cartilage explants. Increases the levels of matrix degrading proteases MMP-1, MMP-3, MMP-9, MMP-13, ADAMTS-4 and ADAMTS-5 and matrix degradation. Suppresses the synthesis of type II collagen and aggrecan and proteoglycan.	[52, 74, 86]
TNF-α	Increased in OA joint synovial fluid, cartilage, synovial membrane and subchondral bone. It increases the production of iNOS, COX-2, IL-6, IL-8, MCP1, RANTES and the levels of PGE2 and NO in chondrocytes and in cartilage explants. Increases the levels of matrix degrading proteases MMP-1, MMP-3, MMP-9, MMP-13, ADAMTS-4 and ADAMTS-5 and matrix degradation. Suppresses the synthesis of type II collagen and aggrecan.	[61]
IL-6	Increased in OA joint synovial fluid, cartilage, synovial membrane and serum of OA patients. Upregulates MMP-13 expression in chondrocytes. Downregulates the expression of type II collagen.	[66, 70]
IL-15	Increased in the synovial fluids of OA joints. Is associated with joint pain.	[48]
IL-17	Increased in the synovial fluids of OA joints. Induces IL-1β, TNF-α and IL-6 expression and suppresses proteoglycan synthesis.	[14, 46]
IL-18	Increased in the OA joints cartilage and synovial fluid. Increases the production of MMP-1, MMP-3, MMP-13.	[47]
LIF	Increased in the synovial fluids of OA joint. Enhances cartilage extracellular matrix degradation. Increases matrix degrading proteases expression and nitric oxide levels.	[49, 139]
MCP1	Increased in OA joint tissue and in chondrocytes under pathological conditions	[54]
RANTES	Increased in OA joint tissue and in chondrocytes under pathological conditions	[54]
IL-8	Increased in OA joint tissue and in chondrocytes under pathological conditions	[54, 70]
IL-4 and IL-10	Anti-inflammatory. Increase the expression of IL-IRa and TIMP and decrease IL-1β, TNF-α expression.	[46, 54]