Natural Products as Sources of Novel Drug Candidates for the Pharmacological Management of Osteoarthritis: A Narrative Review

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Abstract
Osteoarthritis is a chronic degenerative articular disorder. Formation of bone spurs, synovial inflammation, loss of cartilage, and underlying bone restructuring have been reported to be the main pathologic characteristics of osteoarthritis symptoms. The onset and progression of osteoarthritis are attributed to various inflammatory cytokines in joint tissues and fluids that are produced by chondrocytes and/or interact with chondrocytes, as well as to low-grade inflammation in intra-articular tissues. Disruption of the equilibrium between the synthesis and degradation of the cartilage of the joint is the major cause of osteoarthritis. Hence, developing a promising pharmacological tool to restore the equilibrium between the synthesis and degradation of osteoarthritic joint cartilage can be a useful strategy for effectively managing osteoarthritis. In this review, we provide an overview of the research results pertaining to the search for a novel candidate agent for osteoarthritis management via restoration of the equilibrium between cartilage synthesis and degradation. We especially focused on investigations of medicinal plants and natural products derived from them to shed light on the potential pharmacotherapy of osteoarthritis.

Key Words: Osteoarthritis, Pharmacotherapy, Natural products

INTRODUCTION

Osteoarthritis can be defined as a type of articular diseases resulting from the destruction of articular cartilage and subchondral bone. It is the most common degenerative joint disease, especially in elderly people. The joint stiffness and pain have been known to be the most common symptoms of osteoarthritis and inflammation in synovial tissues, the formation of bone spurs, joint cartilage degeneration, and changes in the underlying bone are its pathological characteristics (Mankin, 1982; Aigner and McKenna, 2002). Mechanical stress, injury of the articular structure, inflammation, oxidative stress, and older age were reported to be the etiological factors of osteoarthritis. However, an effective and definitive method for the cure or, at least, management of osteoarthritis has not yet been developed, since the molecular mechanism of the destruction of articular tissues has not been clearly elucidated (Lim et al., 2017; Min et al., 2018; Yoo et al., 2018). To date, the final goal in the management of osteoarthritis is to regulate symptoms including pain, improve the quality of life, and mitigate disability (Blagojevic et al., 2010). Currently, pharmacological management and non-pharmacological management are used for the regulation of osteoarthritis (Table 1). For the non-pharmacological management of osteoarthritis, body weight loss, exercise, and articular surgery are recommended (Anandacoomarasamy and March, 2010). The pharmacological interventions for osteoarthritis include the use of nonsteroidal anti-inflammatory drugs (NSAIDs), symptomatic slow-acting drugs for osteoarthritis, analgesics, putative disease-modifying agents, bone-acting agents, agents for intraart-
ticular injection such as corticosteroids and hyaluronic acid (Cho et al., 2018; Gregori et al., 2018; Hwang et al., 2018). However, these agents are ineffective against the root-cause of osteoarthritis, cause a multitude of severe side effects, and are inadequate for the long-term management of osteoarthritis (Shen and Gatti, 2013; Lee et al., 2017). The onset and progression of osteoarthritis are attributed to various inflammatory cytokines in joint tissues and fluids that are produced by chondrocytes and/or interact with chondrocytes, as well as to low-grade inflammation in intra-articular tissues (Aigner and McKenna, 2002). Disruption of the equilibrium between the synthesis and degradation of the cartilage of the joint is the major cause of osteoarthritis (Mankin, 1982). Thus, developing a promising pharmacological tool to restore the equilibrium between the synthesis and degradation of osteoarthritis joint cartilage can be a useful strategy for effective osteoarthritis management. In this review, we attempted to summarize the results of research for searching a novel candidate agent that could regulate osteoarthritis by restoring the equilibrium between cartilage synthesis and degradation. We particularly focused on studies of medicinal plants and natural products for the management of osteoarthritis.

CURRENT CONVENTIONAL PHARMACOTHERAPY FOR THE MANAGEMENT OF OSTEOARTHRITIS

Thus far, NSAIDs, symptomatic slow-acting drugs for osteoarthritis, analgesics, putative disease-modifying agents, bone-acting agents, and agents for intra-articular injection including corticosteroids and hyaluronic acid have been used as pharmacological agents for the management of osteoarthritis. However, it has been reported that these agents are not efficacious against the root-cause of osteoarthritis, cause many severe side effects, and are not adequate for the long-term management of osteoarthritis (Shen and Gatti, 2013; Lee et al., 2017).

NSAIDs

NSAIDs are the most frequently used agents for the management of osteoarthritis. They showed moderate activity against osteoarthritic pain; however, it is recommended that NSAIDs be used intermittently or for a short period. NSAIDs can be classified as cyclooxygenase-2 (COX-2)-selective agents and non-selective agents. COX-2-selective agents are celecoxib, meloxicam, rofecoxib, valdecoxib, pirmacoxib, and etoricoxib. Non-selective COX inhibitors are diclofenac, diflunisal, etodolac, flurbiprofen, ibuprofen, indomethacin, ketoprofen, nabumetone, naproxen, oxaprozin, piroxicam, sulindac, tolmetin, azapropanzone, carprofen, melcufenamate, tenoxicam, etofenamate, nimesulide, and tiaprofenic acid. Among these, diclofenac, naproxen, celecoxib, rofecoxib, and etoricoxib have been frequently used to manage osteoarthritic pain (Gore et al., 2012).

Symptomatic slow-acting drugs in osteoarthritis

Glucosamine hydrochloride, chondroitin sulfate, diacerein, and glucosamine sulfate are classified as symptomatic slow-acting drugs for osteoarthritis. Prescription-grade chondroitin sulfate and glucosamine sulfate are recommended as first-line agents for the pharmacological management of genicular osteoarthritis. These agents have been reported to show an improvement in physical function and pain in osteoarthritis (Bruyere et al., 2014).

Analgesics

Acetaminophen, tramadol, and opioids including oxycodone are used to control the pain in osteoarthritis during a short period, although these agents are not associated with an improvement in pain in the long term (Hochberg et al., 2012; McAlindon et al., 2014).

Putative disease-modifying agents

Sprifermin, doxycycline, PG-116800 (a matrix metalloproteinase inhibitor), and cindunstat can be classified as putative disease-modifying agents for osteoarthritis. While clinical trials to prove the efficacy of these agents are ongoing, thus far, these agents have not shown significant improvements in structural changes in the joint (Pavelka et al., 2003).

Bone-acting agents

Risedronate, zoledronic acid, strontium ranelate, calcitriol, and vitamin D are classified as bone-acting agents for the regulation of osteoarthritis. They are antiresorptive agents or bone-forming agents. Bone-acting agents showed some potential benefit in the turnover of subchondral bone, although these agents did not show a significant improvement in structural changes of the joint (Baker-LePain and Lane, 2012).

Agents for intra-articular injection

Corticosteroids including triamcinolone, betamethasone, and methylprednisolone and hyaluronic acid are classified as agents for intra-articular injection. Generally, to regulate the acute exacerbation of genicular osteoarthritis, intra-articular injection of corticosteroids is recommended. During the initial 2 to 3 weeks of intervention, intra-articular injection of corticosteroids showed a greater beneficial effect. Furthermore, dur-

| Table 1. The management of osteoarthritis |
|------------------------------------------|
| Pharmacological management              |
| Nonsteroidal anti-inflammatory drugs (NSAIDs) |
| Symptomatic slow-acting drugs in osteoarthritis Analgesics |
| Putative disease-modifying agents |
| Bone-acting agents |
| Agents for intra-articular injection including corticosteroids and hyaluronic acid |
| Non-pharmacological management          |
| Body weight loss |
| Taking exercises |
| Articular surgery |

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ing follow-up periods of 3 and 6 months, intra-articular injection of hyaluronic acid showed a greater beneficial effect. The combinational administration of corticosteroids and hyaluronic acid by intra-articular injection showed a moderate beneficial effect on the pathophysiology of osteoarthritis. However, for long-term pain, intra-articular injection of hyaluronic acid did not show a significant improvement (Bannuru et al., 2009).

**SEARCH FOR NOVEL CANDIDATE AGENTS FOR REGULATING OSTEOARTHRITIS FROM MEDICINAL PLANTS AND NATURAL PRODUCTS DERIVED FROM THEM**

Inflammation has been reported to be involved in the loss of articular cartilage in osteoarthritis and this mild inflammatory reaction leads to the development of the disease (Kulich et al., 2007). TNF-α and IL-1β, the main catabolic inflammatory cytokines, play a pivotal role in the process of articular cartilage degradation. These cytokines increase the expression and catabolic activity of matrix metalloproteinases (MMPs) on articular cartilage destruction via activation of the NF-κB signaling pathway. Further, the activated NF-κB signaling pathway and other intracellular signaling pathways in concert aggravate the cartilage degeneration (Dean et al., 1989; Birkedal-Hansen et al., 1993). The extracellular matrix present in the joint cartilage regulates the physiological function and metabolism of chondrocytes. Collagen type II and proteoglycans including hyaluronic acid, glycosaminoglycan, and chondroitin sulfate consist of the extracellular matrix. Chondrocyte death (apoptosis), the induction of extracellular matrix degradation, and compromised production of the extracellular matrix might provoke articular cartilage destruction in osteoarthritis (Garnero et al., 2000; Burrage et al., 2006). Based on this information (Table 2), in the present section of this review, we provide an overview of the results of many studies aimed at searching for novel candidate agents for regulating osteoarthritis through control of the equilibrium between the synthesis and degradation of cartilage, especially from medicinal plants and natural products derived from them (Table 3). The medicinal plants and natural products derived from them are listed according to alphabetical order hereon.

**Achyranthes bidentata**

Polysaccharides contained in Achyranthes bidentata induced the transition of the G1/S phases of the cell cycle and expression of collagen type II in chondrocytes. They stimulated the expression of CDK6, CDK4, and cyclin D1, promoting the cell cycle and proliferation of chondrocytes (Weng et al., 2014).

**Aconitum carmichaelii**

Aconitum carmichaelii showed preventive activity against the decrease in bone density and degeneration of cartilage. It stimulated the proliferation of chondrocytes (Tong et al., 2014).

**Arnica montana**

In a rat model of collagen-induced arthritis (CIA), the total extract of Arnica montana showed an anti-inflammatory effect, in which was reflected by decreased levels of IL-6, NO, IL-1β, TNF-α, and IL-12. The extract also showed an antioxidative effect (Sharma et al., 2016).

**Astaxanthin**

Astaxanthin, a carotenoid, showed anti-inflammatory and antioxidative effects on cartilage. It suppressed the expression of MMPs including MMP-13, MMP-3, and MMP-1. Astaxanthin also inhibited the phosphorylation of p38 mitogen-activated protein kinase (MAPK) and p44/42 MAPK, and the degradation of inhibitory kappa B (iκB) (IL-1β)-stimulated chondrocytes (Chen et al., 2014a).

**Apigenin**

Apigenin, an anti-inflammatory flavonoid compound, was reported to suppress the gene expression of MMPs including MMP-1, MMP-13, MMP-3, a disintegrin and metalloproteinase with thrombospondin motif-5 (ADAMTS-5), and ADAMTS-4, in primary cultured rabbit chondrocytes. It also decreased the proteolytic activity and secretion of MMP-3. Furthermore, intra-articular injection of apigenin inhibited the in vivo production of MMP-3 protein in the rat knee joint (Park et al., 2016).

**Apis mellifera**

Venom from the bee species, Apis mellifera, was reported to suppress the expression of MMP-8 and MMP-1 stimulated by TNF-α by affecting the NF-κB signaling pathway. Furthermore, bee venom blocked the TNF-α-induced phosphorylation of ERK1/2, Akt, and JNK (Jeong et al., 2016).

**Astragalin**

The antioxidative and anti-inflammatory flavonoid compound, kaempferol-3-O-glucopyranoside, also known as astragalin, was reported to inhibit the IL-1β-stimulated activation of NF-κB and MAPK in chondrocytes in patients with osteoarthritis. Astragalin also decreased the production of prostaglandin E2 (PGE2) and nitric oxide (NO) and the expression of cyclooxygenase-2 (COX-2) and inducible nitric oxide synthase (iNOS) (Ma et al., 2015).

**Aucubin**

Aucubin, a natural anti-inflammatory product derived from diverse medicinal plants including Eucommia ulmoides, suppressed the inflammatory response through blocking the phosphorylation and degradation of iκB and the translocation of NF-κB p65 in rat articular chondrocytes stimulated by IL-1β. Furthermore, the compound decreased the production of NO and expression of iNOS, COX-2, and MMPs (Wang et al., 2015).

**Baicalin**

Baicalin, a natural product derived from Scutellaria baicalensis, has been reported to inhibit the expression of MMP-13 and MMP-3 in human chondrocytes. It also stimulated the

**Table 2. The major drug targets of some natural products**

| Induction of extracellular matrix degradation by matrix metalloproteinases | Compromised production of the extracellular matrix | The apoptosis and proliferation of chondrocytes | Inflammation and oxidative stress generated in articular tissues |

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Table 3. The list of medicinal plants and natural products showing the effect on the pathophysiology of osteoarthritis

| Medicinal plants                          | Natural products                      |
|-------------------------------------------|---------------------------------------|
| *Achyranthes bidentata* (Weng et al., 2014) | Astaxanthin (Chen et al., 2014a)      |
| *Aconitum carmichaelii* (Tong et al., 2014) | Apigenin (Park et al., 2016)          |
| *Arnica Montana* ( Sharma et al., 2016)    | Astragalin (Ma et al., 2015)           |
| *Apis mellifera* (Jeong et al., 2016)      | Aucubin (Wang et al., 2015)            |
| *Bauhinia championi* (Li et al., 2013)     | Baicalein (Zhang et al., 2015)         |
| *Boswellia serrata* (Khajuria et al., 2008; Blain et al., 2009; Ammon, 2010; Sengupta et al., 2010; Vishal et al., 2011; Umar et al., 2014) | Bavachin (Cheng et al., 2014)          |
| *Clematis chinensis* (Wu et al., 2010)     | Baicalein (Zhang et al., 2014)         |
| *Eucommia ulmoides* (Lu et al., 2013; Xie et al., 2015) | Berberine (Wu et al., 2016)           |
| *Harpagophyti procumbenti* (Chantre et al., 2000; Chrubasik et al., 2002; Wegener and Lupke, 2003) | Betulin (Ra et al., 2015)              |
| *Panax notoginseng* (Chang et al., 2007)   | Betulin (Ra et al., 2015)              |
| *PG201* (Shin et al., 2003; Park et al., 2005; Ha et al., 2016) | Betulin, a natural anti-inflammatory compound isolated from *Betulae Cortex*, inhibited IL-1β-induced gene expression of MMP-13, MMP-3, and MMP-1 (Wu et al., 2013; Zhao et al., 2014; Liu et al., 2015; Zhou et al., 2015). |
| *Phellodendron amurense* (Kim et al., 2011; Kim et al., 2017) | Biocillin A (Wu et al., 2014)          |
| *Schisandrae Fructus* (Jeong et al., 2015) | Biochanin A (Wu et al., 2016)          |
| *SKI306X* (Jung et al., 2001; Kim et al., 2005; Kim et al., 2017) | Biocillin A (Wu et al., 2014)          |
| *Symphytum officinale* (Grube et al., 2007) | Biocillin A (Wu et al., 2014)          |
| *Whitania somnifera* (Sabina et al., 2008; Ganesan et al., 2011; Ramakanth et al., 2016) | Biocillin A (Wu et al., 2014)          |
| *Willow bark* (Schmid et al., 2001; Beer and Wegener, 2008; Uehleke et al., 2013) | Biocillin A (Wu et al., 2014)          |
| *Zingiber officinale* (Altman and Marcusson, 2001; Grzanna et al., 2005; van Breemen et al., 2007) | Biocillin A (Wu et al., 2014)          |
| *Arnica Montana* (Weng et al., 2013)       | Catechins (Leong et al., 2014)         |
| *Aconitum carmichaelii* (Tong et al., 2014) | Catechins (Leong et al., 2014)         |
| *Symphytum officinale* (Altman and Marcusson, 2001; Grzanna et al., 2005; van Breemen et al., 2007) | Catechins (Leong et al., 2014)         |
| *Sambucus nigra* (Weng et al., 2013)       | Celastrol (Ding et al., 2013)          |
| *Ginseng* (Park et al., 2015)              | Crocin (Ding et al., 2010)             |
| *Curcumin* (Funk et al., 2006; Nonose et al., 2014) | Delphinidin (Haseeb et al., 2013)      |
| *Gliadulin* (Haseeb et al., 2013)          | Delphinidin (Haseeb et al., 2013)      |
| *Delphinidin* (Haseeb et al., 2013)        | Delphinidin (Haseeb et al., 2013)      |
| *Ferulic acid* (Chen et al., 2010)         | Delphinidin (Haseeb et al., 2013)      |
| *Gentiopicroside* (Zhao et al., 2012)       | Delphinidin (Haseeb et al., 2013)      |

production of glycosaminoglycan (GAG) and collagen type II through by affecting the phosphorylation of ERK and p38 (Zhang et al., 2014).

**Bauhinia championii**

Polysaccharides present in *Bauhinia championii* were reported to stimulate the proliferation of chondrocytes and promote the transition of the G1/S phases of the cell cycle. These polysaccharides activated the intracellular signaling pathways pivotal in the maintenance of articular cartilage (Li et al., 2013).

**Bavachin**

Bavachin, a phytoestrogen present in a medicinal plant *Psoralea corylifolia*, was reported to protect against IL-1β-stimulated cartilage impairment via suppressing the degradation of IκBα and nuclear translocation of NF-κB (Cheng et al., 2010).

**Berberine**

Berberine, an anti-inflammatory natural product derived from *Rhizoma coptidis*, has been reported to block the degradation of cartilage and suppress NF-κB signaling pathways in a human chondrosarcoma cell line. Furthermore, it showed a potential chondroprotective effect through inhibiting the apoptosis of chondrocytes and the gene and protein expression of MMP-13, MMP-3, and MMP-1 (Wu et al., 2013; Zhao et al., 2014; Liu et al., 2015; Zhou et al., 2015).

**Betulin**

Betulin, a natural anti-inflammatory compound isolated from *Betulae Cortex*, inhibited IL-1β-induced gene expression of MMP-13, MMP-3, and MMP-3 although it stimulated type II collagen gene expression in primary cultured chondrocytes. Furthermore, intra-articular injection of betulin blocked in vivo MMP-3 production in knee joint chondrocytes (Ra et al., 2017).
Biochanin A
Biochanin A contained in red clover was reported to block IL-1β-induced expression of MMPs and restore the compromised expression of TIMP-1 via affecting the NF-κB signaling pathway in chondrocytes (Wu et al., 2014).

Boswellia serrata
A preparation of Boswellia serrata (BS) extract has been reported to inhibit the degeneration of cartilage by MMP-13, MMP-9, and MMP-13 and inflammation in arthritis by suppressing the functions of NO, COX-2, PGE2, and intercellular adhesion molecule-1 (ICAM-1) (Blain et al., 2009; Sengupta et al., 2010). In an animal model of CIA, BS extract showed antioxidative and anti-inflammatory effects (Umar et al., 2014). In a clinical trial, treatment with the extract decreased pain and increased functionality in patients with knee osteoarthritis (Vishal et al., 2011). Boswellic acids, which are natural products isolated from BS, were reported to block anti-inflammatory activity by inhibiting the NF-κB signaling pathway, in experimental models of arthritic inflammation (Khajuria et al., 2008; Ammon, 2010).

Catechins
Catechins, the main polyphenolic compounds present in tea, showed potential anti-arthritis effects, and epigallocatechin-3-gallate, a representative catechin, has been reported to exert chondroprotective activity by inhibiting IL-1β-stimulated expression of IL-8, PGE2, and COX-2, in human synovial fibroblasts (Huang et al., 2010). In an animal model, epigallocatechin-3-gallate decreased the levels of MMP-8, MMP-13, ADAMTS-5, MMP-1, and MMP-3 in articular cartilage (Leong et al., 2014).

Celastrol
In primary human osteoarthritic chondrocytes, celastrol, a natural product inhibiting heat shock protein (HSP) 90β, showed a suppressive effect on IL-1β-stimulated expression of MMP-13, MMP-3, MMP-1, COX-2, and iNOS-2 (Ding et al., 2013).

Clematis chinensis
In an animal model of osteoarthritis established by the intra-articular injection of monosodium iodoacetate, a saponin fraction isolated from Clematis chinensis, showed an inhibitory effect against cartilage damage and destruction of the joint by suppressing the decomposition of the extracellular matrix and chondrocyte injury (Wu et al., 2010).

Crocin
Crocin, a natural compound derived from Crocus sativus, was reported to block both the expression of MMP-13, MMP-3, and MMP-11 by inhibiting the NF-κB signaling pathway in articular chondrocytes and the degeneration of cartilage in vivo (Ding et al., 2010).

Curcumin
Curcumin, a natural compound isolated from Curcuma longa (CL), is a known anti-inflammatory agent and regulates diverse inflammatory statuses including osteoarthritis. The compound showed ameliorative effects on inflammation of the joint in an animal model of arthritis (Nonose et al., 2014). A preparation of CL total extract exerted an inhibitory effect against periarticular tissue damage and joint inflammation in an in vivo arthritis model via inhibiting the NF-κB signaling pathway (Funk et al., 2006).

Delphinidin
In osteoarthritic chondrocytes, delphinidin, an antioxidative anthocyanidin found in various vegetables and fruits, blocked the expression of COX-2 and PGE2. Delphinidin also suppressed IL-1β-induced NF-κB signaling by affecting IRAK-1 phosphorylation (Haseeb et al., 2013).

Eucommia ulmoides
An aqueous extract of Eucommia ulmoides showed anti-ostearthritic effects, based on histopathological examination of articular tissues and inhibitory regulation of serum and synovial fluid levels of MMP-13, MMP-3, and MMP-1 (Lu et al., 2013; Xie et al., 2015).

Ferulic acid
A natural product present in Angelica sinensis, ferulic acid, showed the potency of an anti-osteoarthritic agent by blocking the hydrogen peroxide (H2O2)-induced expression of MMP-13 and MMP-1 in chondrocytes (Chen et al., 2010).

GCSB-5
GCSB-5 is a standardized extract from a mixture of six herbs including Saposhnikovia divaricata, Acanthopanax japonica, Acanthopanax sessiliflorus, Cibotium barometz, Glycine max, and Eucommia ulmoides, developed in South Korea for the regulation of osteoarthritis in knee joint (Cho et al., 2016). In an animal model of osteoarthritis established using monosodium iodoacetate, intra-articular injection of GCSB-5 blocked the production of anti-type II collagen antibody and PGE2, regulating the balance of cytokines and inflammatory mediators (Kim et al., 2016). In a clinical trial, the safety and efficacy of GCSB-5 were comparable to those of celecoxib, a selective COX-2 inhibitor, in the treatment of knee joint osteoarthritis (Park et al., 2013).

Gentiopicroside
Gentiopicroside derived from Gentiana macrophylla suppressed the IL-1β-stimulated expression of MMPs and the phosphorylation of JNK, ERK, and p38, in murine articular chondrocytes. Furthermore, it promoted type II collagen production (Zhao et al., 2015).

Ginsenosides
Ginsenosides isolated from Panax ginseng showed various biological effects. Ginsenoside Rb1, a subtype of ginsenosides, suppressed the levels of MMP-13 and MMP-1, NO, iNOS, IL-1β, and TNF-α, and promoted the expression of type II collagen (Kim et al., 2012; Cheng et al., 2013). Ginsenosides Rg1, Rg3, Rg5, Rk1, Rf, Rd, Rc, and F4 were reported to exert chondroprotective effect (Huang et al., 2014; Lee et al., 2014).

Harpagophytyum procumbens
Harpagophytyum procumbens has been utilized as a folk medicine for managing musculoskeletal degenerative diseases including osteoarthritis. The total extract of Harpagophytyum procumbens exerted chondroprotective effects via blocking the activity of MMPs and elastase and the production of inflammation mediators including IL-1β and TNF-α (Fiebich et al., 2006).
et al., 2001). In a clinical trial, diverse HP extracts showed ameliorative effects on limited movement and pain in patients with osteoarthritis of the hip and knee (Chantre et al., 2000; Chrabasik et al., 2002; Wegener and Lupke, 2003).

**Honokiol**
Honokiol, a major natural compound isolated from *Magnolia officinalis*, blocked IL-1β-stimulated expression of MMP-13, IL-6, iNOS, NO, COX-2, and PGE2 via the NF-κB signaling pathway (Chen et al., 2014b).

**Icariin**
Icariin, a compound derived from *Epimedium pubescens*, was reported to inhibit the IL-1β-stimulated expression of MMP-13 in chondrocytes. Furthermore, it enhanced extracellular matrix synthesis and showed chondroprotective effects (Li et al., 2012).

**Luteolin**
Luteolin, a flavonoid compound derived from *Lonicerae flos*, blocked IL-1β-stimulated gene expression, secretion, and enzyme activity of MMP-3 in cultured articular chondrocytes. It inhibited the gene expression levels of ADAMTS-4, MMP-13, MMP-1, and ADAMTS-5, and affected the *in vivo* production of MMP-3 protein in the rat knee joint (Kang et al., 2014).

**Monotropein**
Monotropein, a compound present in *Morinda officinalis*, was reported to block IL-1β-stimulated expression of MMP-13 and MMP-3 in chondrocytes (Wang et al., 2014).

**Morin**
Morin, a flavonoid compound, has been reported to exert anti-inflammatory, antioxidative, and anticancer effects. Morin blocked IL-1β-stimulated expression of MMP-13 and MMP-3 and promoted the expression of TIMP-1 via suppression of the phosphorylation of ERK1/2 and p38 (Chen et al., 2012).

**Oleanolic acid**
Oleanolic acid, a triterpenoid compound present in various fruit and vegetables, promoted type II collagen gene expression and blocked the gene expression of ADAMTS-5, MMP-1, MMP-13, ADAMTS-4, and MMP-3. Furthermore, it decreased *in vitro* enzyme activity and *in vivo* production of MMP-3 (Kang et al., 2017).

**Panax notoginseng**
A preparation of *Panax notoginseng* (PN) extract suppressed the production of IL-1, iNOS, TNF-α, and MMP-13 *in vitro* (Chang et al., 2007).

**PG201**
PG201, a multi-component standardized extract of medicinal plants for managing the symptoms of osteoarthritis, showed a protective effect on the cartilage in an animal model of collagenase-induced arthritis (Shin et al., 2003; Park et al., 2005). It also showed a significant effect on osteoarthritis in a clinical trial (Ha et al., 2016).

**Phellodendron amurense**
*Phellodendron amurense*, a medicinal plant with immunostimulatory and anti-inflammatory properties, was reported to protect articular cartilage via blocking IL-1β-stimulated type II collagen degradation and proteoglycan release (Kim et al., 2011).

**Pinocembrin**
Pinocembrin contained in propolis showed a suppressive effect on MMP-13 and MMP-3 expression through affecting the NF-κB signaling pathway in human chondrocytes (Zhang et al., 2015).

**Piperine**
Piperine, a compoundpresent in *Piper nigrum*, has been reported to exert a suppressive effect on IL-1β-induced elevated levels of MMPs, COX-2, NO, PGE2, and iNOS through NF-κB signaling (Ying et al., 2013).

**Prunetin**
Prunetin, a natural product found in *Glycyrrhiza glabra*, inhibited the *in vivo* production of MMP-3 stimulated by IL-1β. It also blocked the gene expression, secretion, and enzyme activity of MMP-3 in primary cultured rabbit chondrocytes (Nam et al., 2016).

**Resveratrol**
Resveratrol, a well-known natural product derived from diverse plants including grapes, has been reported to suppress the expression of iNOS, COX-2, TNF-α, and IL-1β by blocking the NF-κB signaling pathway (Wang et al., 2012). It was reported that resveratrol blocked the gene expression and secretion of MMP-3 in rabbit chondrocytes. Furthermore, it suppressed IL-1β-stimulated gene expression of various MMPs via blocking of the phosphorylation of inhibitory kappa B kinase (IKK), phosphorylation and degradation of inhibitory kappa Bα (IκBα), and phosphorylation and nuclear translocation of NF-κB p65 in human chondrocytes (Kang et al., 2018).

**Schisandrae Fructus**
The ethanol extract of *Schisandrae Fructus* showed chondroprotective activity and inhibited the expression of COX-2, MMPs, and iNOS via suppressing the phosphorylation of JNK, p38, and ERK1/2, and NF-κB signaling, in human chondrocytes (Jeong et al., 2015).

**Sinomenine**
Sinomenine, a natural product derived from *Sinomenium acutum*, has been reported to decrease MMP-13 expression and glycosaminoglycan (GAG) release. It also increased TIMP-1 activity, thereby suppressing apoptosis of cells and fragmentation of DNA in chondrocytes (Ju et al., 2010a).

**SKI306X**
Kim et al. (2005) reported that SKI306X blocked the degradation of the matrix by suppressing the gene expression, secretion and enzyme activity of MMPs, in rabbit articular cartilage. In a double-blind, controlled clinical trial, SKI 306X, a standardized extract of a mixture of three medicinal plants including *Trichosanthes kirilowii*, *Prunella vulgaris*, and * Clematis mandshurica*, showed a pain-relieving effect without significant adverse effects, in knee osteoarthritis patients (Jung et al., 2001). In another clinical trial, SKI306X showed a protective effect on the cartilage in patients with knee osteoarthritis (Kim et al., 2017).
**Symphytum officinalis**
Topical administration of a preparation of *Symphytum officinalis* extract could regulate pain and articular mobility in knee osteoarthritis (Grube et al., 2007).

**Tetramethylpyrazine**
Tetramethylpyrazine present in *Ligusticum wallichii* has been reported to suppress the apoptosis of chondrocytes and the expression of iNOS, MMP-13, COX-2, and MMP-3 and promote the expression of collagen type II and TIMP-1 (Ju et al., 2010b; Liang et al., 2014).

**Tetrandrine**
Tetrandrine isolated from *Stephania tetrandra* has been reported to exert the chondroprotective activity via blocking IL-1β-stimulated expression of MMPs and β-catenin signaling and promoting the expression of TIMP-1, *in vitro* and *in vivo* (Zhou et al., 2013). It also blocks the expression of PGE2, IL-6, TNFα, IL-1β, and NO via blocking NF-κB signaling in articular inflammation (Gao et al., 2016).

**Withania somnifera**
A preparation of the total extract of *Withania somnifera*, a medicinal plant used as a folk remedy for alleviating osteoarthritis, exerted a potential protective effect on the degradation of articular tissues by inhibiting collagenase activity (Ganesan et al., 2011). In a clinical trial, *Withania somnifera* extract showed a significant pain-relieving effect on osteoarthritic knee joint (Ramakanth et al., 2016). Withaferin A, the major active natural compound in *Withania somnifera*, showed anti-inflammatory action by controlling TNF-α, the paw volume, lipid peroxidation, and lysosomal enzymes, in an animal model of arthritis (Sabina et al., 2008).

**Willow bark**
Willow bark has long been utilized as a folk remedy for managing pain. A preparation of willow bark extract showed an inhibitory effect on the development of oxidative stress and production of proinflammatory cytokines in an animal model of arthritis (Sharma et al., 2011). This effect may be dependent on the blocking of monocyte activation by suppressing the activity of COX-2 and TNF-α (Bonaterra et al., 2010). In a few clinical trials, willow bark extract decreased the pain in osteoarthritis patients (Schmid et al., 2001; Beer and Wegener, 2008; Uehleke et al., 2013).

**Wogonin**
Wogonin, a flavonoid compound showing anti-inflammatory activity, exerted chondroprotective effects *in vitro* and *in vivo*. In cultured articular chondrocytes, wogonin promoted the expression of collagen type II and suppressed MMP expression. Furthermore, intra-articular injection of wogonin blocked the gene expression, production, and activity of MMP-3, and *in vivo* production of MMP-3 (Park et al., 2015).

**Zingiber officinale**
Ginger, *Zingiber officinale*, has been reported to show anti-inflammatory effects by elevating the serum level of corticosterone and blocking COX and lipoxygenase (LOX) (Grzanna et al., 2005; van Breemen et al., 2011). A preparation of *Zingiber officinale* extract controlled pain in patients with osteoarthritis (Altman and Marcussen, 2001).

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**Fig. 1.** Overview of pathophysiology and management of osteoarthritis and strategy for the development of a promising pharmacological tool. The onset and progression of osteoarthritis, a chronic degenerative articular disorder, are attributed to various inflammatory cytokines in joint tissues and fluids that are produced by chondrocytes and/or interact with chondrocytes, as well as to low-grade inflammation in intraarticular tissues. Disruption of the equilibrium between synthesis and degradation of the cartilage of the joint is the major cause of osteoarthritis. Developing a promising pharmacological tool to restore the equilibrium between synthesis and degradation of osteoarthritic joint cartilage can be a useful strategy for the effective management of osteoarthritis.
CONCLUSION AND FUTURE DIRECTION FOR OSTEOARTHRITIS RESEARCH

As mentioned previously, the use of agents for the conventional pharmacological management of osteoarthritis alone cannot address the root-cause of osteoarthritis. Furthermore, these agents show diverse and severe side effects and are not adequate for long-term management of osteoarthritis. On the other hand, a majority of natural products have shown inhibitory effects on proinflammatory cytokine-induced expression and catabolic activity of MMPs in articular cartilage via activation of the NF-κB signaling pathway. They showed suppressive effects on the apoptosis of chondrocytes, induction of extracellular matrix degradation, and decrease in the production of the extracellular matrix, in articular cartilage. However, there is no front-line candidate natural product and/or medicinal plant to reverse or prevent the development of the signs and symptoms of osteoarthritis, despite the many experimental and clinical studies conducted thus far (Fig. 1). Therefore, it is timely to develop an optimal candidate through optimization of the chemical structures of natural products showing the strongest anti-inflammatory, anti-apoptotic, and anti-catabolic activities, to restore the equilibrium between the synthesis and degradation of articular cartilage. Additionally, after joint injury, fibrotic cartilage is generated instead of the normal hyaline cartilage. Thus, it is ideal to develop a novel anti-fibrotic and anti-inflammatory candidate molecule that would facilitate the synthesis of the normal hyaline cartilage in the process of regeneration of articular cartilage.

CONFLICT OF INTEREST

The authors have declared that there is no conflict of interest.

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