BIOMOLECULES & THERAPEUTICS

Review
Biomol Ther 27(6), 503-513 (2019)

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

Young-Hoon Kang[1,†], Hyun Jae Lee[2,†], Choong Jae Lee[3,*] and Jin-Sung Park[4,*]

[1]Department of Oral Maxillofacial Surgery, Gyeongsang National University School of Medicine and Changwon Gyeongsang National University Hospital, Institute of Health Science, Gyeongsang National University, Jinju 52727,
[2]Smith Liberal Arts College and Department of Addiction Science, Graduate School, Sahmyook University, Seoul 01795,
[3]Department of Pharmacology, School of Medicine, Chungnam National University, Daejeon 35015,
[4]Department of Orthopaedic Surgery and Institute of Health Science, Gyeongsang National University School of Medicine and Gyeongsang National University Hospital, Jinju 52727, Republic of Korea

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 intraar-

Open Access **https://doi.org/10.4062/biomolther.2019.139**

Received Aug 28, 2019 **Revised** Sep 16, 2019 **Accepted** Sep 25, 2019
Published Online Oct 24, 2019

***Corresponding Authors**
E-mail: LCJ123@cnu.ac.kr (Lee CJ), jsparkler@naver.com (Park JS)
Tel: +82-42-580-8255 (Lee CJ), +82-55-750-8858 (Park JS)
Fax: +82-42-585-6627 (Lee CJ), +82-55-750-8104 (Park JS)
[†]The first two authors contributed equally to this work.

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 intraarticular injection including corticosteroids and hyaluronic acid
Non-pharmacological management	Body weight loss
	Taking exercises
	Articular surgery

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 osteoarthritic 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 derived from them, in order to shed light on the potential pharmacotherapy 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, polmacoxib, and etoricoxib. Non-selective COX inhibitors are diclofenac, diflunisal, etodolac, flurbiprofen, ibuprofen, indomethacin, ketoprofen, nabumetone, naproxen, oxaprozin, piroxicam, sulindac, tolmetin, azapropazone, carprofen, meclofenamate, 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 cindunistat 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, calcitonin, 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-

ing follow-up periods of 3 and 6 months, intra-articular injection of hyaluronic acid showed a greater beneficial effect. The combinatorial 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 (Kullich *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).

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

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 Bα (IκBα) in interleukin-1β (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 E_2 (PGE_2) 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).

Baicalein

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

Medicinal plants	*Achyranthes bidentata* (Weng *et al*., 2014)
	Aconitum carmichaeli (Tong *et al*., 2014)
	Arnica Montana (Sharma *et al*., 2016)
	Apis mellifera (Jeong *et al*., 2016)
	Bauhinia championi (Li *et al*., 2013)
	Boswellia serrata (Khajuria *et al*., 2008; Blain *et al*., 2009; Ammon, 2010; Sengupta *et al*., 2010; Vishal *et al*., 2011; Umar *et al*., 2014)
	Clematis chinensis (Wu *et al*., 2010)
	Eucommia ulmoides (Lu *et al*., 2013; Xie *et al*., 2015)
	GCSB-5 (Park *et al*., 2013; Cho *et al*., 2016; Kim *et al*., 2016)
	Harpagophytum procumbens (Chantre *et al*., 2000; Chrubasik *et al*., 2002; Wegener and Lupke, 2003)
	Panax notoginseng (Chang *et al*., 2007)
	PG201 (Shin *et al*., 2003; Park *et al*., 2005; Ha *et al*., 2016)
	Phellodendron amurense (Kim *et al*., 2011)
	Schisandrae Fructus (Jeong *et al*., 2015)
	SKI306X (Jung *et al*., 2001; Kim *et al*., 2005; Kim *et al*., 2017)
	Symphytum officinalis (Grube *et al*., 2007)
	Whitania somnifera (Sabina *et al*., 2008; Ganesan *et al*., 2011; Ramakanth *et al*., 2016)
	Willow bark (Schmid *et al*., 2001; Beer and Wegener, 2008; Uehleke *et al*., 2013)
	Zingiber officinalis (Altman and Marcussen, 2001; Grzanna *et al*., 2005; van Breemen *et al*., 2011)
Natural products (single compounds)	Astaxanthin (Chen *et al*., 2014a)
	Apigenin (Park *et al*., 2016)
	Astragalin (Ma *et al*., 2015)
	Aucubin (Wang *et al*., 2015)
	Baicalein (Zhang *et al*., 2014)
	Bavachin (Cheng *et al*., 2010)
	Berberine (Wu *et al*., 2013; Zhao *et al*., 2014; Liu *et al*., 2015; Zhou *et al*., 2015)
	Betulin (Ra *et al*., 2017)
	Biochanin A (Wu *et al*., 2014)
	Catechins (Leong *et al*., 2014)
	Celastrol (Ding *et al*., 2013)
	Crocin (Ding *et al*., 2010)
	Curcumin (Funk *et al*., 2006; Nonose *et al*., 2014).
	Delphinidin (Haseeb *et al*., 2013)
	Ferulic acid (Chen *et al*., 2010)
	Gentiopicroside (Zhao *et al*., 2015)
	Ginsenosides (Kim *et al*., 2012; Cheng *et al*., 2013; Huang *et al*., 2014; Lee *et al*., 2014)
	Honokiol (Chen *et al*., 2014b)
	Icariin (Li *et al*., 2012)
	Luteolin (Kang *et al*., 2014)
	Monotropein (Wang *et al*., 2014)
	Morin (Chen *et al*., 2012)
	Oleanolic acid (Kang *et al*., 2017)
	Pinocembrin (Zhang *et al*., 2015)
	Piperine (Ying *et al*., 2013)
	Prunetin (Nam *et al*., 2016)
	Resveratrol (Kang *et al*., 2018)
	Sinomenine (Ju *et al*., 2010a)
	Tetramethylpyrazine (Ju *et al*., 2010b; Liang *et al*., 2014)
	Tetrandrine (Zhou *et al*., 2013; Gao *et al*., 2016)
	Wogonin (Park *et al*., 2015)

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-1, 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, PGE_2, 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-arthritic 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-osteoarthritic 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 (H_2O_2)-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*, *Achyranthes 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).

Harpagophytum procumbens

Harpagophytum procumbens has been utilized as a folk medicine for managing musculoskeletal degenerative diseases including osteoarthritis. The total extract of *Harpagophytum 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., 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; Chrubasik *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 natural compound present in black pepper (*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 PGE_2, IL-6, TNF-α, 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).

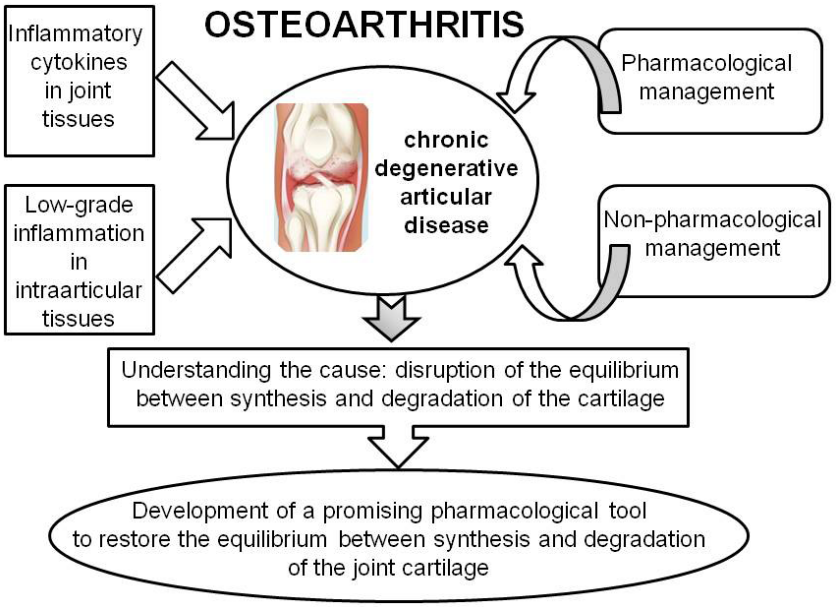

Fig. 1. Overview of pathophysiology and management of osteoarthritis and strategy for the development of a promising pharmacological tool. The onset and progression of osteoarthritis, a chronic degenerative articular disorder, are attributed to various inflammatory cytokines in joint tissues and fluids 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.

ACKNOWLEDGMENTS

This research was supported by NRF-2014R1A6A1029617 and NRF-2017R1C1B1005126, Basic Science Research Program through the National Research Foundation of Korea (NRF) funded by the Ministry of Education.

REFERENCES

Aigner, T. and McKenna, L. (2002) Molecular pathology and pathobiology of osteoarthritic cartilage. *Cell Mol. Life Sci.* **59**, 5-18.

Altman, R. D. and Marcussen, K. C. (2001) Effects of a ginger extract on knee pain in patients with osteoarthritis. *Arthritis Rheum.* **44**, 2531-2538.

Ammon, H. P. T. (2010) Modulation of the immune system by Boswellia serrata extracts and boswellic acids. *Phytomedicine* **17**, 862-867.

Anandacoomarasamy, A. and March, L. (2010) Current evidence for osteoarthritis treatments. *Ther. Adv. Musculoskelet. Dis.* **2**, 17-28.

Baker-LePain, J. C. and Lane, N. E. (2012) Role of bone architecture and anatomy in osteoarthritis. *Bone* **51**, 197-203.

Bannuru, R. R., Natov, N. S., Obadan, I. E., Price, L. L., Schmid, C. H. and McAlindon, T. E. (2009) Therapeutic trajectory of hyaluronic acid versus corticosteroids in the treatment of knee osteoarthritis: a systematic review and meta-analysis. *Arthritis Rheum.* **61**, 1704-1711.

Beer, A. M. and Wegener, T. (2008) Willow bark extract (Salicis cortex) for gonarthrosis and coxarthrosis—results of a cohort study with a control group. *Phytomedicine* **15**, 907-913.

Birkedal-Hansen, H., Moore, W. G. and Bodden, M. K. (1993) Matrix metalloproteinases: a review. *Crit. Rev. Oral Biol. Med.* **4**, 197-250.

Blagojevic, M., Jinks, C., Jeffery, A. and Jordan, K. P. (2010) Risk factors for onset of osteoarthritis of the knee in older adults: a systematic review and meta-analysis. *Osteoarthr. Cartil.* **18**, 24-33.

Blain, E. J., Ali, A. Y. and Duance, V. C. (2009) Boswellia frereana (frankincense) suppresses cytokine-induced matrix metalloproteinase expression and production of pro-inflammatory molecules in articular cartilage. *Phyther. Res.* **24**, 905-912.

Bonaterra, G. A., Heinrich, E. U., Kelber, O., Weiser, D., Metz, J. and Kinscherf, R. (2010) Anti-inflammatory effects of the willow bark extract STW 33-I (Proaktiv®) in LPS-activated human monocytes and differentiated macrophages. *Phytomedicine* **17**, 1106-1113.

Bruyere, O., Cooper, C., Pelletier, J. P., Branco, J., Luisa Brandi, M., Guillemin, F., Hochberg, M. C., Kanis, J. A., Kvien, T. K., Martel-Pelletier, J., Rizzoli, R., Silverman, S. and Reginster, J. Y. (2014) An algorithm recommendation for the management of knee osteoarthritis in Europe and internationally: a report from a task force of the European Society for Clinical and Economic Aspects of Osteoporosis and Osteoarthritis (ESCEO). *Semin. Arthritis Rheum.* **44**, 253-263.

Burrage, P. S., Mix, K. S. and Brinckerhoff, C. E. (2006) Matrix metalloproteinases: role in arthritis. *Front. Biosci.* **11**, 529-543.

Chang, S. H., Choi, Y., Park, J. A., Jung, D. S., Shin, J., Yang, J. H., Ko, S. Y., Kim, S. W. and Kim, J. K. (2007) Anti-inflammatory effects of BT-201, an n-butanol extract of Panax notoginseng, observed *in vitro* and in a collagen-induced arthritis model. *Clin. Nutr.* **26**, 785-791.

Chantre, P., Cappelaere, A., Leblan, D. and Al, E. (2000) Efficacy and tolerance of Harpagophytum procumbens versus diacerhein in treatment of osteoarthritis. *Phytomedicine* **7**, 177-183.

Chen, M. P., Yang, S. H., Chou, C. H., Yang, K. C., Wu, C. C., Cheng, Y. H. and Lin, F. H. (2010) The chondroprotective effects of ferulic acid on hydrogen peroxide-stimulated chondrocytes: inhibition of hydrogen peroxide-induced proinflammatory cytokines and metalloproteinase gene expression at the mRNA level. *Inflamm. Res.* **59**, 587-595.

Chen, W. P., Hu, P. F., Bao, J. P. and Wu, L. D. (2012) Morin exerts antiosteoarthritic properties: an *in vitro* and *in vivo* study. *Exp. Biol. Med.* **237**, 380-386.

Chen, W. P., Xiong, Y., Shi, Y. X., Hu, P. F., Bao, J. P. and Wu, L. D. (2014a) Astaxanthin reduces matrix metalloproteinase expression in human chondrocytes. *Int. Immunopharmacol.* **19**, 174-177.

Chen, Y. J., Tsai, K. S, Chan, D. C., Lan, K. C., Chen, C. F., Yang, R. S. and Liu, S. H. (2014b) Honokiol, a low molecularweight natural product, prevents inflammatory response and cartilage matrix degradation in human osteoarthritis chondrocytes. *J. Orthop. Res.* **32**, 573-580.

Cheng, C. C., Chen, Y. H., Chang, W. L., Yang, S. P., Chang, D. M., Lai, J. H. and Ho, L. J. (2010) Phytoestrogen bavachin mediates anti-inflammation targeting IκB kinase-IκBα-NF-κB signaling pathway in chondrocytes *in vitro*. *Eur. J. Pharmacol.* **636**, 181-188.

Cheng, W., Wu, D., Zuo, Q., Wang, Z. and Fan, W. (2013) Ginsenoside Rb1 prevents interleukin-1 beta induced inflammation and apoptosis in human articular chondrocytes. *Int. Orthop.* **37**, 2065-2070.

Cho, H. K., Kim, S. Y., Choi, M. J., Baek, S. O., Kwak, S. G. and Ahn, S. H. (2016) The effect of GCSB-5, a new herbal medicine, on changes in pain behavior and neuroglial activation in a rat model of lumbar disc herniation. *J. Korean Neurosurg. Soc.* **59**, 98-105.

Cho, J. Y., Gupta, S., Cho, H. S., Park, M. S., Mok, S. J., Han, I. and Kim, H. S. (2018) Role of nonsteroidal anti-inflammatory drug in treatment of extra-abdominal desmoid tumors. *Clin. Orthop. Surg.* **10**, 225-233.

Chrubasik, S., Thanner, J., Kunzel, O., Conradt, C., Black, A. and Pollak, S. (2002) Comparison of outcome measures during treatment with the proprietary Harpagophytum extract Doloteffin in patients with pain in the lower back, knee or hip. *Phytomedicine* **9**, 181-194.

Dean, D. D., Martel-Pelletier, J., Pelletier, J. P., Howell, D. S. and Woessner, J. F., Jr. (1989) Evidence for metalloproteinase and metalloproteinase inhibitor imbalance in human osteoarthritic carti-

lage. *J. Clin. Invest.* **84**, 678-685.
Ding, Q. H., Cheng, Y., Chen, W. P., Zhong, H. M. and Wang, X. H. (2013) Celastrol, an inhibitor of heat shock protein 90β potently suppresses the expression of matrix metalloproteinases, inducible nitric oxide synthase and cyclooxygenase-2 in primary human osteoarthritic chondrocytes. *Eur. J. Pharmacol.* **708**, 1-7.
Ding, Q., Zhong, H., Qi, Y., Cheng, Y., Li, W., Yan, S. and Wang, X. (2010) Anti-arthritic effects of crocin in interleukin-1β-treated articular chondrocytes and cartilage in a rabbit osteoarthritic model. *Inflamm. Res.* **62**, 17-25.
Fiebich, B., Heinrich, M., Hiller, K. and Kammerer, N. (2001) Inhibition of TNF-α synthesis in LPS-stimulated primary human monocytes by Harpagophytum extract SteiHap 69. *Phytomedicine* **8**, 28-30.
Funk, J. L., Frye, J. B., Oyarzo, J. N., Kuscuoglu, N., Wilson, J., McCaffrey, G., Stafford, G., Chen, G., Lantz, R. C., Jolad, S. D., Sólyom, A. M., Kiela, P. R. and Timmermann, B. N. (2006) Efficacy and mechanism of action of turmeric supplements in the treatment of experimental arthritis. *Arthritis Rheum.* **54**, 3452-3464.
Ganesan, K., Sehgal, P. K., Mandal, A. B. and Sayeed, S. (2011) Protective effect of Withania somnifera and Cardiospermum halicacabum extracts against collagenolytic degradation of collagen. *Appl. Biochem. Biotechnol.* **165**, 1075-1091.
Gao, L. N., Feng, Q. S., Zhang, X. F., Wang, Q. S. and Cui, Y. L. (2016) Tetrandrine suppresses articular inflammatory response by inhibiting pro-inflammatory factors via NF-κB inactivation. *J. Orthop. Res.* **34**, 1557-1568.
Garnero, P., Rousseau, J. C. and Delmas, P. D. (2000) Molecular basis and clinical use of biochemical markers of bone, cartilage, and synovium in joint diseases. *Arthritis Rheum.* **43**, 953-968.
Gore, M., Tai, K. S., Sadosky, A., Leslie, D. and Stacey, B. R. (2012) Use and costs of prescription medications and alternative treatments in patients with osteoarthritis and chronic low back pain in community-based settings. *Pain Pract.* **12**, 550-560.
Gregori, D., Giacovelli, G., Minto, C., Barbetta, B., Gualtieri, F., Azzolina, D., Vaghi, P. and Rovati, L. C. (2018) Association of pharmacological treatments with long-term pain control in patients with knee osteoarthritis: a systematic review and meta-analysis. *JAMA* **320**, 2564-2579.
Grube, B., Grünwald, J., Krug, L. and Staiger, C. (2007) Efficacy of a comfrey root (Symphyti offic. radix) extract ointment in the treatment of patients with painful osteoarthritis of the knee: results of a double-blind, randomised, bicenter, placebo-controlled trial. *Phytomedicine* **14**, 2-10.
Grzanna, R., Lindmark, L. and Frondoza, C. G. (2005) Ginger--an herbal medicinal product with broad anti-inflammatory actions. *J. Med. Food* **8**, 125-132.
Ha, C. W., Park, Y. B., Min, B. W., Han, S. B., Lee, J. H., Won, Y. Y. and Park, Y. S. (2016) Prospective, randomized, double-blinded, double-dummy and multicenter phase IV clinical study comparing the efficacy and safety of PG201 (Layla) and SKI306X in patients with osteoarthritis. *J. Ethnopharmacol.* **181**, 1-7.
Haseeb, A., Chen, D. and Haqqi, T. M. (2013) Delphinidin inhibits IL-1β-induced activation of NF-κB by modulating the phosphorylation of IRAK-1Ser376 in human articular chondrocytes. *Rheumatology* **52**, 998-1008.
Hochberg, M. C., Altman, R. D., April, K.T., Benkhalti, M., Guyatt, G., McGowan, J., Towheed, T., Welch, V., Wells, G. and Tugwell, P. (2012) American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. *Arthritis Care Res.* **64**, 465-474.
Huang, G. S., Tseng, C. Y., Lee, C. H., Su, S. L. and Lee, H. S. (2010) Effects of (−)-epigallocatechin-3-gallate on cyclooxygenase **2**, PGE2, and IL-8 expression induced by IL-1β in human synovial fibroblast. *Rheumatol. Int.* **30**, 1197-1203.
Huang, Y., Wu, D. and Fan, W. (2014) Protection of ginsenoside Rg1 on chondrocyte from IL-1β-induced mitochondria-activated apoptosis through PI3K/Akt signaling. *Mol. Cell. Biochem.* **392**, 249-257.
Hwang, C. J., Chung, S. S., Lee, K.Y., Lee, J. H., Moon, S. H., Kim, J. H., Cho, K. J., Ahn, J. S., Kim, D. S., Park, Y. S. and Park, H. J. (2018) Analgesic efficacy and safety of prolonged-release oxycodone/naloxone in Korean patients with chronic pain from spinal disorders. *Clin. Orthop. Surg.* **10**, 33-40.
Jeong, J. W., Lee, H. H., Choi, E. O., Lee, K. W., Kim, K. Y., Kim, S. G., Hong, S. H., Kim, G. Y., Park, C., Kim, H. K., Choi, Y. W. and Choi, Y. H. (2015) Schisandrae Fructus inhibits IL-1β-induced matrix metalloproteinases and inflammatory mediators production in SW1353 human chondrocytes by suppressing NF-κB and MAPK activation. *Drug Dev. Res.* **76**, 474-483.
Jeong, Y. J., Shin, J. M., Bae, Y. S., Cho, H. J., Park, K. K., Choe, J. Y., Han, S. M., Moon, S. K., Kim, W.J., Choi, Y.H., Kim, C. H., Chang, H. W. and Chang, Y. C. (2016) Melittin has a chondroprotective effect by inhibiting MMP-1 and MMP-8 expressions via blocking NF-κB and AP-1 signaling pathway in chondrocytes. *Int. Immunopharmacol.* **25**, 400-405.
Ju, X. D., Deng, M., Ao, Y. F., Yu, C. L., Wang, J. Q., Yu, J. K., Cui, G. Q. and Hu, Y. L. (2010a) Protective effect of sinomenine on cartilage degradation and chondrocytes apoptosis. *Yakugaku Zasshi* **130**, 1053-1060.
Ju, X. D., Deng, M., Ao, Y. F., Yu, C. L., Wang, J. Q., Yu, J. K., Cui, G.Q. and Hu, Y. L. (2010b) The protective effect of tetramethylpyrazine on cartilage explants and chondrocytes. *J. Ethnopharmacol.* **132**, 414-420.
Jung, Y. B., Roh, K. J., Jung, J. A., Jung, K., Yoo, H., Cho, Y. B., Kwak, W. J., Kim, D. K., Kim, K. H. and Han, C. K. (2001) Effect of SKI 306X, a new herbal anti-arthritic agent, in patients with osteoarthritis of the knee: a double-blind placebo controlled study. *Am. J. Chin. Med.* **29**, 485-491.
Kang, B. J., Ryu, J., Lee, C. J. and Hwang, S. C. (2014) Luteolin inhibits the activity, secretion and gene expression of MMP-3 in cultured articular chondrocytes and production of MMP-3 in the rat knee. *Biomol. Ther. (Seoul)* **22**, 239-245.
Kang, D. G., Lee, H. J., Kim, K. T., Hwang, S. C., Lee, C. J. and Park, J. S. (2017) Effect of oleanolic acid on the activity, secretion and gene expression of matrix metalloproteinase-3 in articular chondrocytes *in vitro* and the production of matrix metalloproteinase-3 *in vivo*. *Korean J. Physiol. Pharmacol.* **21**, 197-204.
Kang, D. G., Lee, H. J., Lee, C. J. and Park, J. S. (2018) Inhibition of the expression of matrix metalloproteinases in articular chondrocytes by resveratrol through affecting nuclear factor-kappa B signaling pathway. *Biomol. Ther. (Seoul)* **26**, 560-567.
Khajuria, A., Gupta, A., Suden, P., Singh, S., Malik, F., Singh, J., Gupta, B. D., Suri, K. A., Srinivas, V. K., Ella, K. and Qazi, G. N. (2008) Immunomodulatory activity of biopolymeric fraction BOS 2000 from Boswellia serrata. *Phyther. Res.* **22**, 340-348.
Kim, J. H., Huh, J. E., Baek, Y. H., Lee, J. D., Choi, D. Y. and Park, D. S. (2011) Effect of Phellodendron amurense in protecting human osteoarthritic cartilage and chondrocytes. *J. Ethnopharmacol.* **134**, 234-242.
Kim, J. H., Ryu, K. H., Jung, K. W., Han, C. K., Kwak, W. J. and Cho, Y. B. (2005) SKI306X suppresses cartilage destruction and inhibits the production of matrix metalloproteinase in rabbit joint cartilage explant culture. *J. Pharmacol. Sci.* **98**, 298-306.
Kim, J. I., Choi, J. Y., Kim, K. G. and Lee, M. C. (2017) Efficacy of JOINS on cartilage protection in knee osteoarthritis: prospective randomized controlled trial. *Knee Surg. Relat. Res.* **29**, 217-224.
Kim, S., Na, J. Y., Song, K. B., Choi, D. S., Kim, J. H., Kwon, Y. B. and Kwon, J. (2012) Protective effect of ginsenoside Rb1 on hydrogen peroxide-induced oxidative stress in rat articular chondrocytes. *J. Ginseng Res.* **36**, 161-168.
Kim, W. K., Chung, H. J., Pyee, Y., Choi, T. J., Park, H. J., Hong, J. Y., Shin, J. S., Lee, J. H., Ha, I. H. and Lee, S. K. (2016) Effects of intra-articular SHINBARO treatment on monosodium iodoacetate-induced osteoarthritis in rats. *Chin. Med.* **11**, 17.
Kullich, W., Fagerer, N. and Schwann, H. (2007) Effect of the NSAID nimesulide on the radical scavenger glutathione S-transferase in patients with osteoarthritis of the knee. *Curr. Med. Res Opin.* **23**, 1981-1986.
Lee, J. H., Lim, H., Shehzad, O., Kim, Y. S. and Kim, H. P. (2014) Ginsenosides from Korean red ginseng inhibit matrix metalloproteinase-13 expression in articular chondrocytes and prevent cartilage degradation. *Eur. J. Pharmacol.* **724**, 145-151.
Lee, M., Yoo, J., Kim, J. G., Kyung, H. S., Bin, S. I., Kang, S. B., Choi, C. H., Moon, Y. W., Kim, Y. M., Han, S. B., In, Y., Choi, C. H., Kim,

J., Lee, B. K. and Cho, S. (2017) A randomized, multicenter, phase III trial to evaluate the efficacy and safety of polmacoxib compared with celecoxib and placebo for patients with osteoarthritis. *Clin. Orthop. Surg.* **9**, 439-457.

Leong, D. J., Choudhury, M., Hanstein, R., Hirsh, D. M., Kim, S. J., Majeska, R. J., Schaffler, M. B., Hardin, J. A., Spray, D. C., Goldring, M. B., Cobelli, N. J. and Sun, H. B. (2014) Green tea polyphenol treatment is chondroprotective, anti-inflammatory and palliative in a mouse posttraumatic osteoarthritis model. *Arthritis Res. Ther.* **16**, 508.

Li, D., Yuan, T., Zhang, X., Xiao, Y., Wang, R., Fan, Y. and Zhang, X. (2012) Icariin: a potential promoting compound for cartilage tissue engineering. *Osteoarthr. Cartil.* **20**, 1647-1656.

Li, H., Li, X., Liu, G, Chen, J., Weng, X., Liu, F., Xu, H., Liu, X. and Ye, H. (2013) Bauhinia championi (Benth.) Benth. polysaccharides upregulate Wnt/β-catenin signaling in chondrocytes. *Int. J. Mol. Med.* **32**, 1329-1336.

Liang, Q. Q., Ding, D. F., Xi, Z. J., Chen, Y., Li, C. G., Liu, S. F., Lu, S., Zhao, Y. J., Shi, Q. and Wang, Y. J. (2014) Protective effect of ligustrazine on lumbar intervertebral disc degeneration of rats induced by prolonged upright posture. *Evid Based Complement. Alternat. Med.* **2014**, 508461.

Lim, H. A., Song, E. K., Seon, J. K., Park, K. S., Shin, Y. J. and Yang, H. Y. (2017) Causes of aseptic persistent pain after total knee arthroplasty. *Clin. Orthop. Surg.* **9**, 50-56.

Liu, S. C., Lee, H. P., Hung, C. Y., Tsai, C. H., Li, T. M. and Tang, C. H. (2015) Berberine attenuates CCN2-induced IL-1β expression and prevents cartilage degradation in a rat model of osteoarthritis. *Toxicol. Appl. Pharmacol.* **289**, 20-29.

Lu, H., Jiang, J., Xie, G., Liu, W. and Yan, G. (2013) Effects of an aqueous extract of Eucommia on articular cartilage in a rat model of osteoarthritis of the knee. *Exp. Ther. Med.* **6**, 684-688.

Ma, Z., Piao, T., Wang, Y. and Liu, J. (2015) Astragalin inhibits IL-1β-induced inflammatory mediators production in human osteoarthritis chondrocyte by inhibiting NF-κB and MAPK activation. *Int. Immunopharmacol.* **25**, 83-87.

Mankin, H. J. (1982) The response for articular cartilage to mechanical injury. *J. Bone Joint Surg. Am.* **64**, 460-466.

McAlindon, T. E., Bannuru, R. R., Sullivan, M. C., Arden, N. K., Berenbaum, F., Bierma-Zeinstra, S. M., Hawker, G. A., Henrotin, Y., Hunter, D. J., Kawaguchi, H., Kwoh, K., Lohmander, S., Rannou, F., Roos, E. M. and Underwood, M. (2014) OARSI guidelines for the non-surgical management of knee osteoarthritis. *Osteoarthr. Cartil.* **22**, 363-388.

Min, B. W., Kang., C. S., Lee, K. J., Bae, K. C., Cho, C. H., Choi, J. H., Sohn, H. J. and Sin, H. K. (2018) Radiographic progression of osteoarthritis after rotational acetabular osteotomy: minimum 10-year follow-up outcome according to the Tönnis grade. *Clin. Orthop. Surg.* **10**, 299-306.

Nam, D. C., Kim, B. K., Lee, H. J., Shin, H. D., Lee, C. J. and Hwang, S. C. (2016) Effects of prunetin on the proteolytic activity, secretion and gene expression of MMP-3 *in vitro* and production of MMP-3 *in vivo*. *Korean J. Physiol. Pharmacol.* **20**, 221-228.

Nonose, N., Pereira, J. A., Machado, P. R. M., Rodrigues, M. R., Sato, D. T. and Martinez, C. A. R. (2014) Oral administration of curcumin (Curcuma longa) can attenuate the neutrophil inflammatory response in zymosan-induced arthritis in rats. *Acta Cir. Bras.* **9**, 727-734.

Park, J. S., Lee, H. J., Lee, D. Y., Jo, H. S., Jeong, J. H., Kim, D. H., Nam, D. C., Lee, C. J. and Hwang, S. C. (2015) Chondroprotective effects of wogonin in experimental models of osteoarthritis *in vitro* and *in vivo*. *Biomol. Ther. (Seoul)* **23**, 442-448.

Park, J. S., Kim, D. K., Shin, H. D., Lee, H. J., Jo, H. S., Jeong, J. H., Choi, Y. L., Lee, C. J. and Hwang, S. C. (2016) Apigenin regulates interleukin-1β-induced production of matrix metalloproteinase both in the knee joint of rat and in primary cultured articular chondrocytes. *Biomol. Ther. (Seoul)* **24**, 163-170.

Park, K. C., Park, E. J., Kim, E. R., Kim, Y., Chung, S. H., Cho, B. W., Kim, S. and Jin, M. (2005) Therapeutic effects of PG201, an ethanol extract from herbs, through cartilage protection on collagenase-induced arthritis in rabbits. *Biochem. Biophys. Res. Commun.* **331**, 1469-1477.

Park, Y. G., Ha, C. W., Han, C. D., Bin, S. I., Kim, H. C., Jung, Y. B. and Lim, H. C. (2013) A prospective, randomized, double-blind, multicenter comparative study on the safety and efficacy of Celecoxib and GCSB-5, dried extracts of six herbs, for the treatment of osteoarthritis of knee joint. *J. Ethnopharmacol.* **149**, 816-824.

Pavelka, K., Bruyere, O., Rovati, L. C., Olejarova, M., Giacovelli, G. and Reginster, J. Y. (2003) Relief in mild-to-moderate pain is not a confounder in joint space narrowing assessment of full extension knee radiographs in recent osteoarthritis structure-modifying drug trials. *Osteoarthr. Cartil.* **11**, 730-737.

Ra, H. J., Lee, H. J., Jo, H. S., Nam, D. C., Lee, Y. B., Kang, B. H., Moon, D. K., Kim, D. H., Lee, C. J. and Hwang, S. C. (2017) Betulin suppressed interleukin-1β-induced gene expression, secretion and proteolytic activity of matrix metalloproteinase in cultured articular chondrocytes and production of matrix metalloproteinase in the knee joint of rat. *Korean J. Physiol. Pharmacol.* **21**, 19-26.

Ramakanth, G. S., Uday Kumar, C., Kishan, P. V. and Usharani, P. (2016) A randomized, double blind placebo controlled study of efficacy and tolerability of Withaina somnifera extracts in knee joint pain. *J. Ayurveda Integr. Med.* **7**, 151-157.

Sabina, E. P., Chandal, S. and Rasool, M. K. (2008) Inhibition of monosodium urate crystal-induced inflammation by withaferin A. *J. Pharm. Pharm. Sci.* **11**, 46-55.

Schmid, B., Lüdtke, R., Selbmann, H. K., Kötter, I., Tschirdewahn, B., Schaffner, W. and Heide, L. (2001) Efficacy and tolerability of a standardized willow bark extract in patients with osteoarthritis: Randomized placebo-controlled, double blind clinical trial. *Phytother. Res.* **15**, 344-350.

Sengupta, K., Krishnaraju, A. V., Vishal, A. A., Mishra, A., Trimurtulu, G., Sarma, K. V. S., Raychaudhuri, S. K. and Raychaudhuri, S. P. (2010) Comparative efficacy and tolerability of 5-Loxin and Aflapin against osteoarthritis of the knee: a double blind, randomized, placebo controlled clinical study. *Int. J. Med. Sci.* **7**, 366-377.

Sharma, S., Arif, M., Nirala, R. K., Gupta, R. and Thakur, S. C. (2016) Cumulative therapeutic effects of phytochemicals in Arnica montana flower extract alleviated collagen-induced arthritis: inhibition of both pro-inflammatory mediators and oxidative stress. *J. Sci. Food Agric.* **96**, 1500-1510.

Sharma, S., Sahu, D., Das, H. R. and Sharma, D. (2011) Amelioration of collagen-induced arthritis by Salix nigra bark extract via suppression of pro-inflammatory cytokines and oxidative stress. *Food Chem. Toxicol.* **49**, 3395-3406.

Shen, X. and Gatti, R. (2013) The safety and efficacy of intra-articular dual molecular weighted hyaluronic acid in the treatment of knee osteoarthritis: the I.D.E.H.A. study. *Orthop. Rev. (Pavia)* **5**, e33.

Shin, S. S., Jin, M., Jung, H. J., Kim, B., Jeon, H., Choi, J. J., Kim, J. M., Cho, B. W., Chung, S. H., Lee, Y. W., Song, Y. W. and Kim, S. (2003) Suppressive effects of PG201, an ethanol extract from herbs, on collagen-induced arthritis in mice. *Rheumatology (Oxford)* **42**, 665-672.

Tong, P., Xu, S., Cao, G., Jin, W., Guo, Y., Cheng, Y., Jin, H., Shan, L. and Xiao, L. (2014) Chondroprotective activity of a detoxicated traditional Chinese medicine (Fuzi) of Aconitum carmichaeli Debx against severe-stage osteoarthritis model induced by mono-iodoacetate. *J. Ethnopharmacol.* **151**, 740-744.

Uehleke, B., Müller, J., Stange, R., Kelber, O. and Melzer, J. (2013) Willow bark extract STW 33-I in the long-term treatment of outpatients with rheumatic pain mainly osteoarthritis or back pain. *Phytomedicine* **20**, 980-984.

Umar, S., Umar, K., Sarwar, A. H. M. G., Khan, A., Ahmad, N., Ahmad, S., Katiyar, C. K., Husain, S. A. and Khan, H. A. (2014) Boswellia serrata extract attenuates inflammatory mediators and oxidative stress in collagen induced arthritis. *Phytomedicine* **21**, 847-856.

van Breemen, R. B., Tao, Y. and Li, W. (2011) Cyclooxygenase-2 inhibitors in ginger (Zingiber officinale). *Fitoterapia* **82**, 38-43.

Vishal, A. A., Mishra, A. and Raychaudhuri, S. P. (2011) A double blind, randomized, placebo controlled clinical study evaluates the early efficacy of aflapin in subjects with osteoarthritis of knee. *Int. J. Med. Sci.* **8**, 615-622.

Wang, F., Wu, L., Li, L. and Chen, S. (2014) Monotropein exerts protective effects against IL-1β-induced apoptosis and catabolic responses on osteoarthritis chondrocytes. *Int. Immunopharmacol.*

23, 575-580.

Wang, J., Gao, J. S., Chen, J. W., Li, F. and Tian, J. (2012) Effect of resveratrol on cartilage protection and apoptosis inhibition in experimental osteoarthritis of rabbit. *Rheumatol. Int.* **32**, 1541-1548.

Wang, S. N., Xie, G. P., Qin, C. H., Chen, Y. R., Zhang, K. R., Li, X., Wu, Q., Dong, W. Q., Yang, J. and Yu, B. (2015) Aucubin prevents interleukin-1 beta induced inflammation and cartilage matri degradation via inhibition of NF-κB signaling pathway in rat articular chondrocytes. *Int. Immunopharmacol.* **24**, 408-415.

Wegener, T. and Lupke, N. (2003) Treatment of patients with arthrosis of hip or knee with an aqueous extract of devil's claw (Harpagophytum procumbens DC.). *Phytother. Res.* **17**, 1165-1172.

Weng, X., Lin, P., Liu, F., Chen, J., Li, H., Huang, L., Zhen, C., Xu, H., Liu, X., Ye, H. and Li, X. (2014) Achyranthes bidentata polysaccharides activate the Wnt/β-catenin signaling pathway to promote chondrocyte proliferation. *Int. J. Mol. Med.* **34**, 1045-1050.

Wu, C. M., Li, T. M., Tan, T. W., Fong, Y. C. and Tang, C. H. (2013) Berberine reduces the metastasis of chondrosarcoma by modulating the α v β 3 integrin and the PKC δ , c-Src, and AP-1 signaling pathways. *Evid. Based Complement. Alternat. Med.* **2013**, 423164.

Wu, D. Q., Zhong, H. M., Ding, Q. H. and Ba, L. (2014) Protective effects of biochanin A on articular cartilage: *in vitro* and *in vivo* studies. *BMC Complement. Altern. Med.* **14**, 444.

Wu, W., Xu, X., Dai, Y. and Xia, L. (2010) Therapeutic effect of the saponin fraction from Clematis chinensis osbeck roots on osteoarthritis induced by monosodium iodoacetate through protecting articular cartilage. *Phyther. Res.* **24**, 538-546.

Xie, G. P., Jiang, N., Wang, S. N., Qi, R. Z., Wang, L., Zhao, P. R., Liang, L. and Yu, B. (2015) Eucommia ulmoides Oliv. bark aqueous extract inhibits osteoarthritis in a rat model of osteoarthritis. *J. Ethnopharmacol.* **162**, 148-154.

Ying, X., Chen, X., Cheng, S., Shen, Y., Peng, L. and Xu, H. (2013) Piperine inhibits IL-1β-induced expression of inflammatory mediators in human osteoarthritis chondrocyte. *Int. Immunopharmacol.* **17**, 293-299.

Yoo, J. H., Oh, H. C., Park, S., H, Kim, J. K. and Kim, S. H. (2018) Does obesity affect clinical and radiological outcomes in minimally invasive total knee arthroplasty? Minimum 5-year follow-up of minimally invasive tka in obese patients. *Clin. Orthop. Surg.* **10**, 315-321.

Zhang, D., Huang, B., Xiong, C. and Yue, Z. (2015) Pinocembrin inhibits matrix metalloproteinase expression in chondrocytes. *IUBMB Life* **67**, 36-41.

Zhang, X., Zhu, Y., Chen, X., Zhang, Y., Zhang, Y., Jia, Y., Wang, H., Liu, Y. and Xiao, L. (2014) Baicalein ameliorates inflammatory-related apoptotic and catabolic phenotypes in human chondrocytes. *Int. Immunopharmacol.* **21**, 301-308.

Zhao, H., Zhang, T., Xia, C., Shi, L., Wang, S., Zheng, X., Hu, T. and Zhang, B. (2014) Berberine ameliorates cartilage degeneration in interleukin-1β-stimulated rat chondrocytes and in a rat model of osteoarthritis via Akt signaling. *J. Cell. Mol. Med.* **18**, 283-292.

Zhao, L., Ye, J., Wu, G. T., Peng, X. J., Xia, P. F. and Ren, Y. (2015) Gentiopicroside prevents interleukin-1 beta induced inflammation response in rat articular chondrocyte. *J. Ethnopharmacol.* **172**, 100-107.

Zhou, X., Li, W., Jiang, L., Bao, J., Tao, L., Li, J. and Wu, L. (2013) Tetrandrine inhibits the Wnt/β-catenin signalling pathway and alleviates osteoarthritis: an *in vitro* and *in vivo* study. *Evid. Based Complement. Alternat. Med.* **2013**, 809579.

Zhou, Y., Liu, S. Q., Yu, L., He, B., Wu, S. H., Zhao, Q., Xia, S. Q. and Mei, H. J. (2015) Berberine prevents nitric oxide-induced rat chondrocyte apoptosis and cartilage degeneration in a rat osteoarthritis model via AMPK and p38 MAPK signaling. *Apoptosis* **20**, 1187-1199.