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Review Article

Medical treatment of osteoarthritis: botanical pharmacologic aspect

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Osteoarthritis (OA) is the most common form of arthritis, and its prevalence is expected to further increase as our society ages. Despite many approaches to cure OA, no drugs are currently proven to modulate the progression of OA. Nowadays, new OA treatment options are holistically developed and one of the approaches of treatment option is botanical drugs. Some botanical drugs for OA have shown both therapeutic effect comparable to refined drugs in small studies and fewer side effects. Hence, there are various health functional foods which are known to relieve symptoms of OA. However, since there are many botanical products, clinicians are not familiar to the efficacy of each botanical product, making it challenging to use them appropriately in clinical practice. Here, we summarize the botanical products available for treating OA, including prescription botanical drugs and health functional foods available in Korea. Further studies and the purification of effective molecules from botanical products will be necessary in future.

Keywords: Osteoarthritis, Botanical drug, Ethnopharmacology

INTRODUCTION

Osteoarthritis (OA) is a chronic degenerative disease of the joints. The latest OA management guidelines commonly suggest non-steroidal anti-inflammatory drugs (NSAIDs) as the first choice for OA treatment [1-3]. NSAIDs focus on controlling the inflammation and reducing the pain in affected joints caused by OA; however, it is known that they have minimal effect on the regeneration of damaged cartilage and joint structures. Furthermore, prescribing NSAIDS to OA patients sometimes burdensome to clinicians as they are known to occasionally accompany serious side effects (kidney injury, peptic ulcer disease, etc.).

There are currently no established disease modifying osteoarthritis drugs proven to slow or reverse the progression of OA. As our society gradually ages, the prevalence of OA is expected to increase, so there is a need to develop new drugs for OA that have fewer side effects and are effective for treating the disease.

Currently, new OA treatment options are being holistically developed in countries around the world, and one of the representative approaches is the use of botanical drugs. Botanical drugs refer to medicines containing plant-based ingredients that are used to treat, diagnose, and relieve symptoms of diseases. Chemicals purified from plants, such as paclitaxel, and highly purified products derived from industrial-based fermentation systems, such as biopharmaceuticals, are not considered botanical products based on plant sources. In Korea, both botanical drugs in the form of medicines that can be prescribed in hospitals and food-based products in the form of health functional foods and health supplement foods are consumed under the approval of the Ministry of Food and Drug Safety. These botanical

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drugs for OA have the advantage of having similar therapeutic effects and fewer side effects compared to highly refined drugs, so they are often prescribed in clinical practice.

However, since there are many types of botanical products, it is difficult to know the efficacy of each one, making it challenging to use them appropriately in actual clinical practice. Here, we conduct a general review of botanical products available for OA, including prescription botanical drugs and health functional foods available in Korea.

DEFINITION

As mentioned above, botanical drugs refer to medicines containing plant-based ingredients that are used to treat, diagnose, and relieve symptoms of diseases. On the other hand, health supplement foods, as the name suggests, are foods that support health and refer to all food products consumed for the promotion of health. It is difficult to accurately determine whether such products are actually effective because they become popular through word of mouth rather than direct evidence. Unlike health supplement foods, health functional foods are certified effective by the Ministry of Food and Drug Safety. The certification of such foods is based on the raw ingredients included in them; that is, if a certain amount of a certified individual functional ingredient is included, they are certified as health functional foods. Of course, however, the certification from the Ministry of Food and Drug Safety does not mean the health functional food is recognized as a standard treatment option through credible multiple randomized controlled clinical trials for a disease.

BOTANICAL DRUGS FOR OA IN KOREA

This part discusses botanical drugs that can be prescribed to treat OA patients in clinics and introduces laboratory experiments and clinical trials (Table 1). The drugs introduced in this section contain combinations of herbs that are not purified as a single molecule. Commercial drugs that are purified in the course of manufacturing and thus composed of a single molecule are excluded from this review because they should be classified as drugs containing purified molecules rather than botanical drugs.

Joins (SKI306X)

Joins is an extracted mixture of 3 medical herbs (dried root of *Clematis mandshurica*, dried root of *Trichosanthes kirilowii*, and dried flower and stem of *Prunella vulgaris*) [4]. It is the first Korea Food and Drug Administration-approved botanical drug developed in Korea.

In vitro and in vivo experiments on SKI306X showed that it inhibited the degradation of proteoglycan and reduced the effect of OA-like change in a rabbit OA model [4]. In a study comparing the treatment effect of SKI306X with that of diclofenac in patients with knee OA, SKI306X showed a similar level of reduction in visual analogue scale (VAS) global pain scores and significantly fewer heartburn symptoms compared to the diclofenac group [5]. A later study on the cartilage protective effect and anti-inflammatory effect of SKI306X revealed that it inhibits the production of prostaglandin E2 (PGE_2), tumor necrosis factor-α (TNF-α), and interleukin-1β (IL-1β) [6]; reduces glycosaminoglycan release from cartilage explants; and inhibits IL-1β-induced matrix metalloproteinase (MMP) gene expression in human osteoarthritic cartilage [7].

A recent retrospective cohort study reported that the use of SKI306X is associated with a higher risk of cardiovascular events than the use of naproxen when taken for 15–60 days [8]. However, the hazard ratio showed no difference when taken for less than 14 days or more than 61 days. Kim et al. [9] also showed that SKI306X reduced Th17 cytokine-induced TNF-α, IL-1β, and receptor activator of nuclear factor kappa-B ligand (RANKL) expression and osteoclast differentiation, presenting the possibility of rheumatoid arthritis therapy for regulating inflammation and joint destruction.

Layla (PG201)

Layla, approved by the Ministry of Food and Drug Safety in 2012, is a botanical drug developed in Korea. It is an ethanol extract of a mixture of 12 herbs including *Chaenomelis speciosa* Nakai (Rosaceae; *Chaenomelis fructus*), *Achyranthes bidentata* Blume (Amaranthaceae; *Achyranthis radix*), and *Acanthopanax senticosus* Maxim (Araliaceae; *Acanthopanacis cortex*) [10].

Studies have shown that PG201 reduces the matrix degradation enzymes MMP-1, MMP-3, and MMP-13 in rat and rabbit arthritis models and shows a reducing effect on IL-1β and PGE_2, which are related to cartilage damage, proving itself to be a useful OA treatment [11,12]. In a phase 3 clinical study targeting patients with symptomatic knee OA, both the PG201 600

Table 1. Summary of botanical drugs and health functional ingredients for treatment of OA

	Compositions	Experimental effects on OA pathogenesis	Clinical trials
Botanical drugs			
Joins (SKI306X) [5-7]	Mixture of 3 herbs - *Clematis mandshurica* - *Trichosanthes kirilowii* - *Prunella vulgaris*	Reduces production of PGE_2, TNF-α, and IL-1β Downregulation of MMP gene expression	Comparable reduction of VAS global pain score (vs. diclofenac)
Layla (PG201) [11-16]	Mixture of 12 herbs - *Chaenomelis speciosa* - *Achyranthes bibentata* - *Acanthopanax senticosus* - *Cinnamomum aromaticum* - *Gentiana macrophylla* - *Clematis Chinensis* - *Angelica Sinensis* - *Cnidium officinale* - *Gastrodia elata* - *Carthamus tinctorius* - *Phlomis umbrosa* - *Ledebouriella seseloides*	Downregulation of MMP gene expression Reduces production of IL-1β and PGE_2 Lowers production of nitrite by iNOS expression	Comparable reduction of VAS score (vs. celecoxib) Noninferiority of VAS score reduction (vs. SKI306X)
Shinbaro (GCSB-5) [19-21,23,25,26]	Mixture of 6 herbs - *Ledebouriellae Radix* - *Achyranthis Radix* - *Acanthopanacis Cortex* - *Cibotii Rhizoma* - *Glycine Semen* - *Eucommiae Cortex*	Inibition of nitric oxide production Suppression of proinflammatory cytokines (IL-1β and TNF-α)	Comparable reduction of WOMAC score and pain VAS score (vs. celecoxib) Reduction of AUSCAN pain score and better outcome of OMERACT-OARSI response (vs. placebo)
Avocado soybean unsaponifiable [31,32,34]	Unsaponifiable element of Avocado Soybean oils	Inhibition of IL-1 induced MMP-3 activity and PGE_2 synthesis Increase synthesis of glycosaminoglycan and collagen of chondrocyte	Reduction of pain VAS score (vs. placebo)
Functional Ingredients			
Boswellia [38,39]		Inhibitory effect on TNF-α production	Improvement of VAS score and WOMAC score (vs. placebo)
Green-lipped mussel [40,43]		Attenuated expression of mRNAs of MMP-3, MMP-13, and ADAMTS5 in human chondrocyte	Improvement of VAS pain score (vs. placebo)
Rosehip [45,47]		Reduced expression of MMP-1, MMP-3, and MMP-13 and ADAMTS-4	Improvement of WOMAC score (vs. placebo)
Curcuma [48,50,51]		Protection of IL-1β induced apoptotic chondrocytes Downregulation of cytoplasmic PLA2, COX-2	Improvement of VAS score & WOMAC score (vs. placebo) Comparable change of VAS score & WOMAC score (vs. NSAID)
Acanthopanax [54]		Decreased expression of iNOS, MMP-3, MMP-13 and increased expression of aggrecan and collagen II in human OA chondrocyte	
Achyranthes [57]		Decreased expression of MMP-2, MMP-9 Decreased production of IL-1β and TNF-α	

Table 1. Continued

Compositions	Experimental effects on OA pathogenesis	Clinical trials
Chrysanthemum [61,62]	Decreased expression of MMPs Enhanced expression of ECM synthetic gene COL2A1 and ACAN	Reduced K-WOMAC score (vs. placebo)
Fruit of *Litsea japonica* [64,65]	Decreased expression of MMPs Decreased production of IL-1β and TNF-α	Improved VAS score & WOMAC score (vs. placebo)
Panax ginseng [67,68,70]	Decreased expression of MMPs Increased expression of type II collagen and aggrecan	Improved DASH score (vs. placebo)
Panax notoginseng [69]	Decreased production of IL-1β and TNF-α	

OA: osteoarthritis, PGE_2: prostaglandin E2, TNF-α: tumor necrosis factor-α, IL-1β: interleukin-1β, MMP: matrix metalloproteinase, VAS: visual analogue scale, WOMAC: Western Ontario and McMaster Universities Osteoarthrtis Index, AUSCAN: Australian/Canadian Osteoarthritis Hand Index, OMERACT-OARSI: Outcomes Measures in Rheumatology-Osteoarthritis Research Society International, PLA2: phospholipase A2, COX-2: cyclooxygenase-2, NSAID: non-steroidal anti-inflammatory drug, DASH: disabilities of the arm, shoulder and hand.

mg group and the celecoxib 200 mg group showed a significant decrease in mean 100-mm pain VAS scores compared to the placebo group and no statistical difference was observed in VAS scores between the PG201 group and the celecoxib group [13]. In a phase IV clinical study versus SKI306X conducted after its approval for clinical use, PG201 showed non-inferiority in reduction of VAS scores and did not show significant differences in any of the secondary outcomes (pain VAS scores, Western Ontario and McMaster Universities Osteoarthrtis Index [WOMAC] scores, EuroQol- 5 Dimension scores, overall symptom self-assessment scores, rescue medication consumption) [14].

A study on the anti-inflammatory mechanism of PG201 after approval of the drug reported that PG201 inhibited the expression of inducible nitric oxide synthase (iNOS) through the activation of Nrf2 and heme oxygenase-1 (HO-1) by the PI3K signal transduction pathway, resulting in lowering nitrite production [15]. Another study also reported that PG201 inhibits the nitric oxide (NO) and PGE_2 production of macrophages [16]. Focusing on PG201's anti-inflammatory effect, PG201 has recently been reported to slow the progression of experimental autoimmune encephalomyelitis in mice and alleviate symptoms through a mechanism that inhibits effector T cell activation [17], indicating opportunities to treat other diseases such as multiple sclerosis in addition to OA.

Shinbaro (GCSB-5)

Shinbaro, another botanical drug used to treat OA developed in Korea, was approved by the Ministry of Food and Drug Safety in 2014. Shinbaro is a mixture of 6 crude herbs traditionally used to treat OA in Eastern Asia: *Ledebouriellae radix*, *Achyranthis radix*, *Acanthopanacis cortex*, *Cibotii rhizoma*, *Glycine semen*, and *Eucommiae cortex*. For the purification, the mixture is powdered and boiled in distilled water followed by ultrafiltration to remove components with molecular weights over 10,000 [18].

The pharmacological effects of GCSB-5 on osteoarthritic joints have been demonstrated to include the inhibition of NO production [19,20], suppression of the level of proinflammatory cytokines [21], and reduction of cyclooxygenase-2 (COX-2) enzymes in macrophages [22]. Chung et al. [23] reported that GCSB-5 suppressed the inflammation of acute and chronic arthritis in a mouse model, and the suppression of lipopolysaccharide-induced NO production was proposed as a mechanism.

In a study of the in vivo analgesic effect, GCSB-5 increased the threshold of pain via a peripheral mechanism [24]. In a prospective study on efficacy and safety comparing GCSB-5 with celecoxib in knee OA patients, GCSB-5 showed a comparable reduction in WOMAC scores, pain VAS scores, etc. and a comparable safety profile [25].

In a phase IV study on 756 patients, GCSB-5 again showed comparable gastrointestinal safety to celecoxib; notably, no gastroduodenal ulcers or bleeding/perforation were reported [26].

With the good clinical results on knee OA patients, another clinical study on hand OA patients was performed. In this study, the group treated with GCSB-5 showed greater reductions in Australian/Canadian Osteoarthritis Hand Index (AUSCAN) pain scores and better Outcomes Measures in Rheumatology-Osteoarthritis Research Society International (OMERACT-OARSI) responses than the placebo group [27]. No further GCSB-5 studies on hand OA have been performed.

GCSB-5 has been studied as a substitute for NSAIDs in not only OA but also other diseases. GCSB-5 has been shown to reduce mechanical allodynia and downregulate neuroglial activity in a rat model of lumbar disc herniation [28,29]. In a recent study, GCSB-5 exhibited an anti-inflammatory and anti-nociceptive effect on the collagen-induced arthritis of mice [30], showing its potential as a drug for types of autoimmune arthritis, such as rheumatoid arthritis.

Avocado-soybean unsaponifiable

Avocado-soybean unsaponifiable (ASU) is a nutraceutical composed of extracts from avocado and soybean oils developed in France. The major components of ASU are phytosterols, fat-soluble vitamins, and triterpene alcohols [31].

Like other approved botanical drugs, the effect of ASU on human articular chondrocytes and OA patients has been studied extensively. Previous studies have reported that ASU may exert its anti-inflammatory effect by decreasing the production of multiple inflammatory cytokines (IL-6, IL-8, and PGE_2) of human articular chondrocytes and by inhibiting IL-1-induced MMP-3 activity and PGE_2 synthesis [31,32]. It has also been shown to promote the synthesis of glycosaminoglycan and collagen of articular chondrocytes [32]. Another study showed that ASU may accelerate cartilage repair in OA by stimulating subchondral osteoblasts [33].

There have been a few observational and clinical studies on ASU for OA management. A recent systematic review and meta-analysis of randomized placebo-controlled trials reported that ASU administration significantly reduced pain VAS scores in OA patients [34]. However, the study also reported that in the subgroup analysis, ASU administration only improved the pain VAS scores of knee OA patients and produced no statistical change in the pain VAS scores of hip OA patients.

There was no significant adverse effect in the ASU administration group compared to the placebo group. In this context, the Ministry of Food and Drug Safety of Korea announced that ASU's approval would be limited to knee OA in 2021.

FUNCTIONAL INGREDIENTS OF HEALTH FUNCTIONAL FOODS FOR OA IN KOREA

This part introduces functional ingredients certified by the Ministry of Food and Drug Safety as health functional foods. Again, each ingredient is introduced based on laboratory experiments and clinical trials (Table 1). Although functional ingredients have certification, they currently cannot be prescribed in clinics for therapeutic purposes.

Boswellia

Boswellia serrata extract, or boswellic acid, is known to have an anti-inflammatory effect, and treatment attempts have been made for various inflammatory diseases (chronic bronchitis, asthma, chronic inflammatory bowel disease, etc.) [35].

The use of Boswellia/boswellic acid in the treatment of OA has been studied mainly in China and India. Those studies have shown that it not only has anti-inflammatory properties but also relieves pain and improves physical function [36,37].

A study reported that 3-O-Acetyl-11-keto-β-boswellic acid (AKBA), one of the extracts of Boswellia, has an inhibitory effect on TNF-α production and blocks MAPK/NFκB activation, providing a molecular background for the effect of Boswellia [38]. However, most of the studies on Boswellia have been small, poorly organized pilot studies. A recent meta-analysis on the effect of Boswellia on OA reported that only 7 of 497 studies were eligible for the meta-analysis [39].

Although the study showed that Boswellia and its extract is effective for alleviating pain and enhancing OA functional scores, higher-quality clinical studies are needed to prove its effect and ultimately enable its development as a highly recommended commercial drug. Currently, Boswellia is one of two herbal remedies recommended by the 2019 OARSI guideline for the management of OA (grade 3) [1].

Green-lipped mussel

Perna canaliculus, the green-lipped mussel, is endemic to New Zealand. It is grown for aquaculture only in New Zealand and trademarked as the greenshell™ mussel (GSM). Most of the studies of GSM have been clinical trials rather than evaluations of its anti-inflammatory effect at the cellular level. Jhun et al. [40] reported that the administration of GSM to chondrocytes

attenuated the expression of mRNAs of MMP-3, MMP-13, and ADAMTS5 in IL-1β-stimulated human OA chondrocytes.

Furthermore, recently, a New Zealand research group reported that the addition of oil from GSM to the diet of diet-induced metabolic OA rats resulted in both decreased plasma levels of the C telopeptide of type II collagen (CTX-II), which is known as a biomarker of cartilage degradation, and a cartilage protective effect in histology [41]. The same research group also reported that the use of GSM whole extract or lipid extract reduced the VAS pain scores of knee/hip OA patients in a systematic review [42]. They also reported that both VAS pain scores and plasma CTX-II levels decreased in postmenopausal women with obesity who received 3 g/day of whole GSM powder compared to those who received placebo [43].

However, another research group in New Zealand reported that GSM extract did not significantly lower WOMAC scores or VAS pain scores in moderate to severe hip OA patients [44]. In this study, only joint stiffness improved in patients with GSM treatment. Like other health functional foods, GSM is not yet available on prescription in Korea.

Rosehip

Rosehip or fruits of dog rose (*Rosa canina L.*) has long been known as a source of vitamin C in tea and other products. Traditionally, it has been used for gastritis, diarrhea, polydipsia, and vitamin C deficiency.

Winther et al. [45] conducted a study on the effect of rosehip powder on symptomatic early-stage OA. The results showed decreased WOMAC scores for pain in the group given a rosehip herbal remedy for 3 weeks compared to the placebo group; however, after 3 months, there was no statistical difference in WOMAC scores for pain between the groups. Warholm et al. [46] reported that the administration of rosehip powder improved hip joint mobility compared with placebo in advanced OA patients. Based on these positive data on patients, a few studies regarding the in vitro effect of rosehip have been reported.

Kharazmi [33] reported that the aqueous extract of rosehip inhibited the chemotaxis as well as chemiluminescence of human peripheral blood leukocytes in vitro. They also identified an active anti-inflammatory molecule, galactolipid(2S)-1,2-di-O[(oZ,12Z,15Z)-octadeca-9,12,15-trienol]-3-O-B-D-galactopyranosy glycol (GOPO), from the extract of rosehip. Rosehip powder was also reported to reduce the expression of MMP-1, MMP-3, MMP-13, and ADAMTS-4, which are closely related to inflammatory cartilage damage [47].

Curcuma

Curcuma longa, which belongs to the ginger family, has been used for its anti-inflammatory, digestive effect as an alternative medicine. Curcumin, the main ingredient of *Curcuma longa*, has been proven to be effective in treating arthritis pain and OA [48].

The proposed anti-inflammatory mechanisms of curcumin include protection of IL-1β-induced apoptotic chondrocytes, improvement of early degenerative changes of articular cartilage, and downregulation of cytoplasmic phospholipase A2, COX-2 [48-50].

Small clinical trials of curcumin have been more actively conducted compared to other herbal remedies for OA. However, the quality of those trials has been somewhat limited. A recent meta-analysis on the effect and safety of curcumin as a treatment for OA included 15 studies, and it reported that *Curcuma longa* extract and curcumin can not only relieve pain (decrease VAS pain scores and WOMAC pain scores) but also improve joint function (decrease WOMAC function scores) without increasing the risk of side effects [51]. The study also reported an additional benefit of *Curcuma longa* to pain and function when it was used along with NSAIDS [51]. With these benefits, curcumin is recommended by the 2019 OARSI guideline for OA management (grade 3) [1].

Acanthopanax

Acanthopanax senticosus, commonly known as Siberian ginseng or ciwujia in China, is also a functional ingredient for OA certified by the Korean Ministry of Food and Drug Safety. However, compared to other functional ingredients for OA, most studies about *Acanthopanax* extract are about its immunomodulatory effect rather than its direct effect on the pathogenesis of OA [52,53].

Isofraxidin, which is one of the main components of *Acanthopanax* extract, was reported to have an inhibitory effect on the expression of iNOS, MMP-3, and MMP-13 and to increase expression levels of aggrecan and collagen II in human OA chondrocytes [54]. With a similar mechanism, isofraxidin treatment prevented both erosion of cartilage and thickening of subchondral bone in a mouse OA model [54]. These results serve as an indirect rationale for *Acanthopanax* extract to be used for OA treatment.

Achyranthes

The genus *Achyranthes* contains approximately 21 species, and they are distributed in tropical and subtropical countries [55]. Among these various species, *A. bidentata* (or *A. japonica*) and *A. aspera* are the two species most commonly used for traditional medicinal purposes in India and China. *A. bidentata* is approved as a health functional food in Korea and has traditionally been used to treat OA. Diverse in vitro studies and in vivo animal OA model studies have been reported recently.

Like other botanical drug experiments, the studies have focused on changes in the expression of collagen, aggrecan, MMP-3, MMP-9, IL-1β, etc. and histological changes in the knee joints of rats and rabbits [56-58]. However, there has been no clinical trial on the effect of *Achyranthes* on OA.

Chrysanthemum

Chrysanthemum zawadskii var. *latilobum* is a perennial flowering plant widely distributed in Korea, Japan, and China. It has long been used as an herbal medicine to alleviate vertigo, hypertensive symptoms, and colitis [59]. *Chrysanthemum* flower extracts are known for their diverse beneficial effects including anti-allergic and anti-inflammatory effects [60].

A recent in vitro study using human chondrocytes reported that *Chrysanthemum* extract treatment lowered the expression of metalloproteinases (MMP-1, 3, 9, 13) and normalized or reduced the expression of extracellular matrix synthetic genes, COL2A1 and ACAN, and the transcription factor SOX9 [61].

We found one clinical study on the efficacy of *Chrysanthemum* in OA patients, and it reported that *Chrysanthemum* extract reduced the total K-WOMAC scores of a trial group compared to a placebo group [62]. However, the difference in K-WOMAC scores was mainly in the Physical Function category. The Pain and Stiffness category K-WOMAC scores of the trial group did not differ significantly from those of the placebo group.

Fruit of *Litsea japonica*

Litsea japonica is an endemic plant in the southern areas of Korea and Japan. It contains various kinds of essential oils, fatty acids, alkaloids, and other nutrients.

It has been reported that the plant and fruit of *Litsea* have anti-inflammatory and anti-oxidant effects [63]. When injected intraarticularly, ethanol extract of the fruit of *Litsea japonica* reportedly decreased the mRNA expression of multiple metalloproteinases (MMP-2, 3, 7, 9) and decreased the expression of inflammatory cytokines (IL-1β, IL-6, and TNF-α) in a rat OA model [64].

One small randomized clinical trial evaluated the efficacy of the fruit of *Litsea japonica*. Patients who were assigned to the *Litsea* group showed significant improvement in VAS scores, WOMAC total scores, and subscales including Pain, Stiffness, and Function [65].

Panax ginseng and *Panax notoginseng*

Ginseng, which belongs to the genus *Panax*, is probably the most popular traditional herbal medicine for dietary and medicinal uses. Notoginseng also belongs to the genus *Panax*, and both are certified as health functional ingredients for OA. The

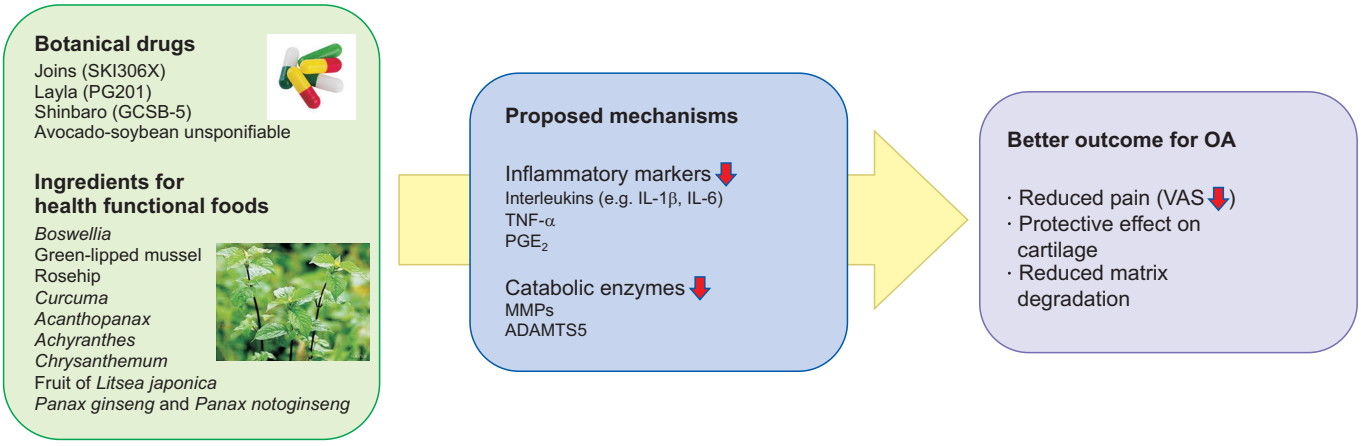

Figure 1. Schematic diagram for mechanism of botanical drugs and ingredients for health functional food for treatment of OA. OA: osteoarthritis, IL: interleukin, TNF-α: tumor necrosis factor-alpha, PGE_2: prostaglandin E2, MMP: matrix metalloproteinase, VAS: visual analogue scale.

bioactive components of ginseng and notoginseng are ginsenosides and notoginsenosides, respectively, and they are classified as steroidal saponins with a steroid-like configuration [66]. Ginsenosides (mainly Rb1, Rg1, Rg3, Rg5, and Ro) are well known for their anti-inflammatory effect. Numerous in vitro and in vivo studies on the activity of ginsenosides against OA have been reported [66-68].

The OA management effect of notoginsenosides has been relatively less studied than that of ginsenosides. Among the notoginsenosides, R1 exerts an anti-inflammatory effect for OA by inhibiting the IL-1β-induced activation of the NF-κB pathway via the Nrf2/HO-1 signaling pathway [69].

Although many studies have been conducted, clinical studies on the use of ginsenosides for OA are relatively scarce. A recent small clinical study reported that the DASH scores of hand OA patients were significantly reduced in patients administered red ginseng, while those of a placebo group remained unchanged [70]. To our knowledge, clinical trials of notoginseng for OA patients have not been reported.

CONCLUSION

Drugs and functional ingredients from botanical products have been highlighted and summarized in this review (Table 1, Figure 1). Although there have been many reports suggesting their effectiveness and low side effects as OA treatments, the lack of in vitro and in vivo experiments and randomized controlled trials prevent botanical drugs from being highly recommended OA treatment options. Thus, further studies and the purification of effective molecules from botanical products will be necessary in future.

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CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

AUTHOR CONTRIBUTIONS

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