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An analysis of the combination frequencies of constituent medicinal herbs in prescriptions for the treatment of bone and joint disorder in Korean medicine: determination of a group of candidate prescriptions for universal use

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ABSTRACT

Background: This study aimed to select prescriptions (mixtures of medicinal herbs) used in the treatment of bone and joint disorders in Korean medicine, and through the analysis of medicinal herb combination frequencies, select a high-frequency medicinal herb combination group for further experimental and clinical research.

Methods: We systematically searched for terms related to bone and joint disorder in the "*Dongeuibogam* (*Dong yibaojian*)", a seminal Korean medicine book. We reviewed the results of published papers regarding the effects in bone and joint disorders (especially in osteoporosis, osteomalacia, osteopenia, rheumatoid arthritis, and degenerative arthritis).

Results: In total, 34 candidates of a medicinal herb combination for the treatment of bone and joint disorders(CMHCTBJDs) and nine candidates of a medicinal herb for the treatment of bone and joint disorders(CMHTBJDs) were selected.

Conclusion: : The candidates of a medicinal herb combination for the treatment of bone and joint disorders (CMHCTBJDs) and candidates of a medicinal herb for the treatment of bone and joint disorders(CMHTBJDs) proposed in this study can be useful material for text mining to develop natural products with the effects in BJDs and also it has the potential to reduce the experimental and developmental time period.

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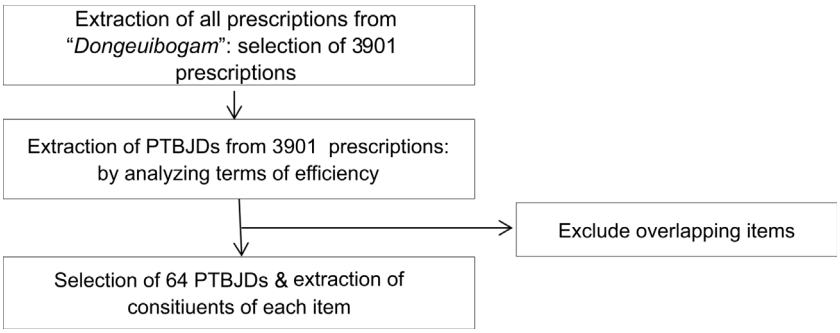

Fig. 1 – First research step; establishing a list of PTBJDs and constituents of each item in "*Dongeuibogam*". PTBJD, prescription for the treatment of bone and joint disorder.

1. Introduction

Natural products and their derivatives have historically been invaluable as a source of therapeutic agents.[1] Although their application is often viewed with skepticism by the Western medical establishment, they are used in ancient medical traditions such as Ayurveda and traditional Chinese medicine (TCM) which are a rich source of therapeutic leads for the pharmaceutical industry.[2] However, it is very difficult to get a 'discovery' from traditional medicine.[2]

This study is a kind of 'discovery', namely 'mining' from Korean medicine(KM) that is one of traditional medicine.

We aimed to sort candidates of medicinal herb combinations which have a high probability of treatment effect for more than one disorder among high morbidity rate disorders such as osteoporosis, osteomalacia, osteopenia, rheumatoid arthritis, and degenerative arthritis by analyzing constituent herbs from prescriptions (mixtures of medicinal herbs) which are widely used for various kinds of bone and joint disorders (BJD) in KM.

Furthermore, in this study, the frequency of medicinal herb combinations comprising each prescription for the treatment of bone and joint disorder (PTBJD) was analyzed after selecting all of the prescriptions recorded in "*Dongeuibogam* (*Dong yi bao gian*)", a principal piece of Korean medicine literature, for the treatment of BJDs.

Although commonly used prescriptions for specific symptoms are fixed in Western medicine, the prescription could be different for individuals in KM since the prescriptions are customized based on patient's age, gender, etc. Therefore, many prescriptions exist for specific symptoms in KM, and that is why we combined all individual medicinal herbs from PTBJDs when analyzing the frequency of individual medicinal herbs and combinations of medicinal herbs from PTBJD.

2. Methods

This methodology assumed that the higher the dose within a PTBJD, the stronger the effect, and that the more frequently used medicinal herbs are in PTBJDs, the more important it is.[3]

In this paper, we found frequency of individual medicinal herbs and combinations of less than seven medicinal herbs from PTBJD in "*Dongeuibogam*" and made a list of high-ranked combinations.

By assessing the efficacy of the medicinal herbs of the combinations via analysis of previous studies, we would like to suggest preliminary data for experimental and clinical researchers to develop new herbal formulae for osteoporosis, osteomalacia, osteopenia, rheumatoid arthritis, and degenerative arthritis.

Since it is practically hard to develop herbal formulae using more than six medicinal herbs, the number of medicinal herbs is limited from one to six.

This study is comprised of three steps. Each step was performed as described in the following section.

2.1. *Establishing a list of PTBJDs and constituents of each item in "Dongeuibogam"*

According to the medical information website produced by the National Library of Medicine (MedlinePlus; https://www.nlm.nih.gov/medlineplus/), definitions of osteoporosis, osteomalacia, osteopenia, rheumatoid arthritis, and degenerative arthritis are "a condition that affects especially older women and is characterized by decrease in bone mass with decreased density and enlargement of bone spaces producing porosity and brittleness", "a disease of adults that is characterized by softening of the bones and is analogous to rickets in the young", "reduction in bone volume to below normal levels especially due to inadequate replacement of bone lost to normal lysis", "a usually chronic disease that is considered an autoimmune disease and is characterized especially by pain, stiffness, inflammation, swelling, and sometimes destruction of joints", and "arthritis typically with onset during middle or old age that is characterized by degenerative and sometimes hypertrophic changes in the bone and cartilage of one or more joints and a progressive wearing down of apposing joint surfaces with consequent distortion of joint position and is marked symptomatically especially by pain, swelling, and stiffness" respectively.

However, as there is no correspondent definition in "*Dongeuibogam*", we tried to select specific indications which are the most similar to symptoms of Western medicine by analyzing terms describing effects and selected all prescriptions which have one of the specific indications.

To sum up, in the first step, after selecting all of the prescriptions recorded in "*Dongeuibogam*", their indications were analyzed and the medicinal herbs constituting each of the PTBJD were selected (Fig. 1). Data of "*Dongeuibogam*" was obtained from a state-run website, "Korean traditional knowledge portal" (http://www.koreantk.com/ktkp2014/).

2.2. *Selection of medicinal herb combinations from 64 PTBJDs in order of frequency*

In the second step, the combinations with the highest repeat frequencies were selected as candidates of a medicinal herb combination for the treatment of bone and joint disorders (CMHCTBJD), and all medicinal herbs which comprise these combinations were selected as candidates of a medicinal herb for the treatment of bone and joint disorders (CMHTBJD). Only the medicinal herbs with doses in the upper 80% cumulative proportion per prescription were included in the CMHCTBJD (Fig. 2). This ensured that only main therapeutic medicinal herbs were selected.

2.3. *Preliminary evaluation of the effects of CMHTBJDs via analysis of previous studies*

2.3.1. *Selection and analysis of previous studies regarding effects in BJDs*

We searched for CMHTBJDs in the previous studies, and identified relevant studies.

2.3.2. *Searching the database*

In addition to commonly used scientific databases (such as PubMed, Cochrane, and Scopus), Korean databases (Ndsl, Oasis, and Riss) were used since we were searching specifically for studies related to KM. The starting period for these study searches was not defined; however, June 30, 2015, was set as the final time point.

2.3.3. *Searching keywords*

The final goal of this study was selecting CMHTBJDs which have treatment effects on at least one of BJDs, especially osteoporosis, osteomalacia, osteopenia, rheumatoid arthritis, or degenerative arthritis among various BJDs (Fig. 3). We used the following terms for the searches: "scientific names of CMHTBJD (and names of herbal medicine of CMHTBJD) + osteoporosis, osteomalacia, osteopenia, rheumatoid arthritis, degenerative arthritis".

3. Results

3.1. *Sixty-four PTBJDs in "Dongeuibogam"*

In total, 64 PTBJDs were selected in "*Dongeuibogam*" and each PTBJD comprised an average of 7.9 medicinal herbs (Table 1).

3.2. *Selection of medicinal herb combinations from 64 PTBJDs by frequency order*

The following medicinal herb combinations were selected: 53 combinations of one medicinal herb; 141 combinations of two medicinal herbs; 209 combinations of three medicinal herbs; 246 combinations of four medicinal herbs; 232 combinations of five medicinal herbs; and 169 and combinations of six medicinal herbs. By focusing on the top five of each of these (plus ties) selection of the following occurred: five combinations comprising one medicinal herb, 13 combinations of two medicinal herbs, 10 combinations of three medicinal herbs, five combinations of four medicinal herbs, and one combination of five medicinal herbs. These comprise the CMHCTBJD with a highest probability of efficacy in the treatment of BJD. Also, it is noted that all CMHCTBJDs comprised only nine medicinal herbs (Table 2).

3.3. *Preliminary evaluation of the effects of nine CMHTBJDs via analysis of previous studies*

A total of 496 studies of nine CMHTSs were found; of these, 80 studies were concerned with effects in at least one of osteoporosis, osteomalacia, osteopenia, rheumatoid arthritis, and degenerative arthritis, resulting in an average of 8.9 publications per candidate herb (Fig. 4).

Studies were specifically divided into *in vitro* studies (VT), *in vivo* studies (VV), clinical studies (C), and reviews (R). A number of previous studies on each medicinal herbs are 13 for *Angelica gigas* Nakai., root (VT:6, VV:'4, R:3), five for *Atractylodes japonica* Koidz. ex Kitam., rhizome (VT:1, VV:3, R:1), two for *Poria cocos* (Schw.) Wolf., sclerotium (VV:1, R:1), 10 for *Paeonia lactiflora* Pall., root (VT:3, VV:6, R:1), nine for *Rehmannia glutinosa* (Gaertn.) DC., root (VT:5, VV:4), 10 for *Dioscorea polystachya Turcz.*, rhizome (VT:4, VV:6), one for Gypsum (VV:1), 28 for *Panax ginseng* Mey., root (VT:13, VV:13, R:1, C:1), and two for *Saposhnikovia divaricata* (Turcz.) Schischk., root (VT:2). According to these, nine CMHTBJDs have been subjects of research studies on osteoporosis, osteomalacia, osteopenia, rheumatoid arthritis, and degenerative arthritis (Table 3).

4. Discussion

In this paper, medicinal herbs which have high probability of treatment effect for more than one disorder among five BJDs in KM were selected from "*Dongeuibogam*" by analyzing frequency and effectiveness. Then, analysis of the previous studies was done.

According to Table 3, an average of 8.9 studies per CMHTS that described their effects in at least one of five BJDs was obtained. We found that more than 10 researches on four items such as *Angelica gigas* Nakai. (root), *Paeonia lactiflora* Pall. (root), *Dioscorea polystachya Turcz* .(rhizome), and *Panax ginseng* Mey. (root) have already been performed, although one or two studies on two CMHTS including gypsum and *Poria cocos* (Schw.) Wolf. (sclerotium) were done.

Looking at the possible mechanisms of nine CMHTSs in Table 3 the final results found were: (1) *Angelica gigas* Nakai, root: Angelica gigas Nakai prevents cartilage destruction and bone loss via inhibitory effect on osteoclast differentiation, also beneficial effect on inflammatory and arthritic diseases; (2) *Atractylodes japonica* Koidz. ex Kitam., rhizome: *Atractylodes japonica* Koidz is effective on osteoporosis by inhibiting differentiation and function of osteoclast; (3) *Poria cocos* (Schw.) Wolf., sclerotiu: *Poria cocos* (Schw.) Wolf. inhibits osteoclast

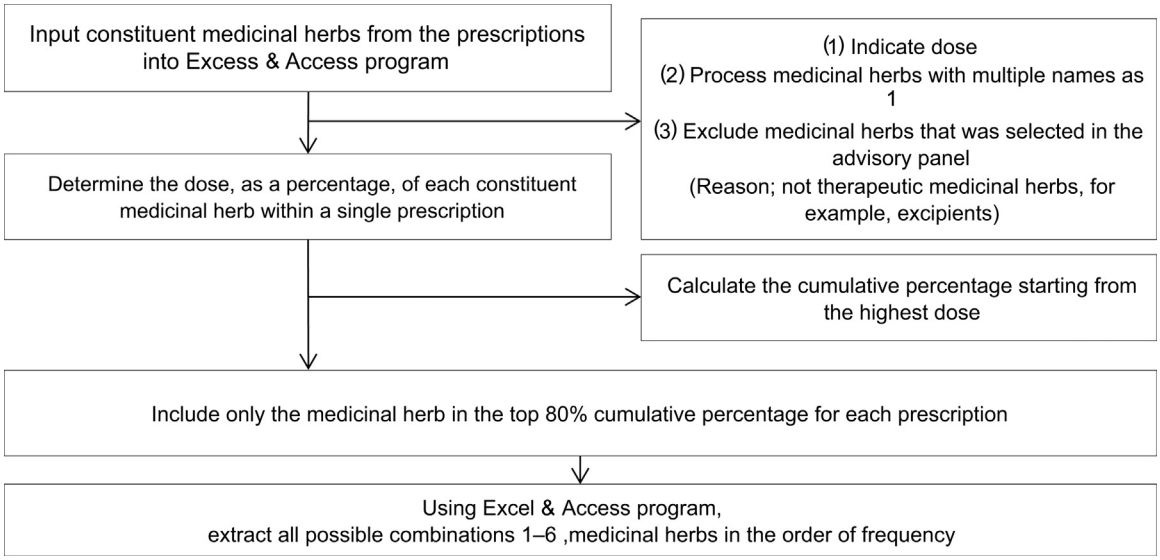

Fig. 2 – Second research step; selection of medicinal herb combinations from 64 PTBJDs in the order of frequency. PTBJD, prescription for the treatment of bone and joint disorder.

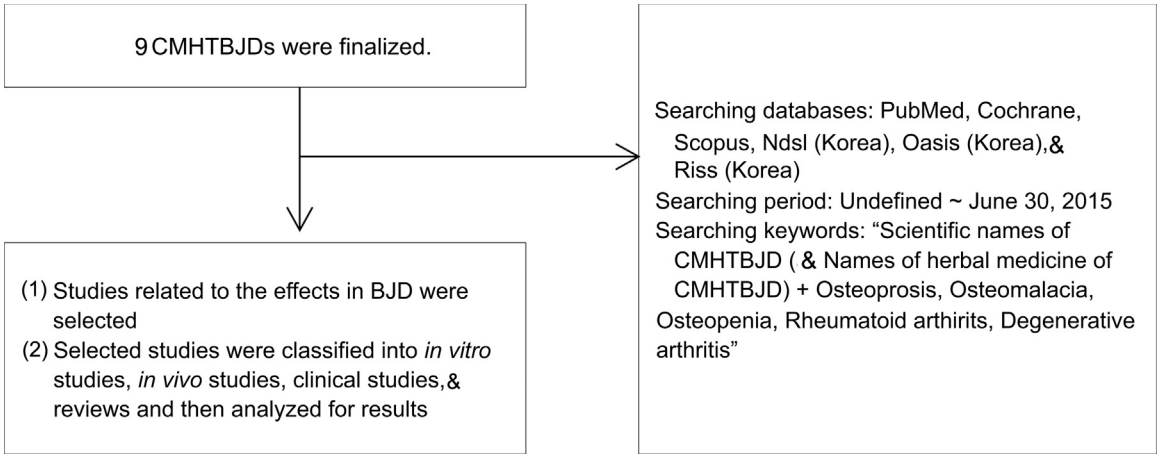

Fig. 3 – Third research step; preliminary evaluation of the effects of CMHTBJDs via analysis of previous studies. BJD, bone and joint disorder; CMHTBJD, candidates of a medicinal herb for the treatment of bone and joint disorder.

Table 1 – Sixty-four PTBJDs from "*Dongeuibogam*"

Name of PTBJDs (No. of constituents)
Baifuzisan (8)/Baihuguizhitang (5)/Baozhentang (20)/Busundangguisan (7)/Butianwan (1)/Cangzhufujiandang (9)/Cangzhugao (2)/Chaijianmeiliansan (4)/Dafangfengtang (13)/Dajupitang (4)/Dancangzhuwan (1)/Dangguigao (18)/Digupisan (9)/Dingtongsan (12)/Dixiansan (5)/Duhuojishengtang (15)/Ermiaocangbaisan (2)/Ermiaosan (2)/Ershenggao (3)/Fuzitang (8)/Guntanwan (4)/Hugusan (12)/Huoxuesan (1)/Jiangusan (2)/Jiaweilonghusan (5)/Jiaweiqianghuotang (9)/Jiegudan (10)/Jiegusan (7)/Jieguzijindan (9)/Liuweidihuangyuan (6)/Lurongsijinwan (9)/Maidousan (6)/Maijiansan (11)/Manjingsan (9)/Meiyaojiangshengdan (9)/Qianghuoxuduantang (15)/Qianghuoyufengtang (27)/Qianjinzhimiwan (4)/Qinggusan (9)/Qingshenganluwan (8)/Qizhixiangfuwan (1)/Quanshenghugusan (7)/Renshenqingjisan (9)/Ruxiangdingtongwan (7)/Ruxiangheihudan (9)/Shengxisan (6)/Shenxianjijidan (22)/Tianmawan (10)/Tietanyuan (5)/Tuanyusan (6)/Weishengtianhuayuan (12)/Wubishanyaoyuan (12)/Wuwutang (3)/Wuzhengtang (9)/Wuzhengwan (7)/Wuzhuwan (5)/Xialingwanshoudan (5)/Xianyiliangtang (8)/Yiziqingjinsan (10)/Yuhangao (4)/Yuzhenwan (4)/Zirantongsan (12)/Ziyindabuwan (13)
PTBJD, prescription for the treatment of bone and joint disorder.

differentiation, and triterpenoids, which are obtained from *Poria cocos*, are known to have crucial influence on rheumatoid arthritis; (4) *Paeonia lactiflora* Pall, root: *Paeonia lactiflora* Pall regulates osteoclast differentiation and formation, and

Table 2 – Medicinal herb combinations from 64 PTBJDs in the order of frequency (80%)*

No of constituents in each combination; name of constituents (frequency)
1; E(13)/A(6)/D(4)/F(4)/G(4)
2; A, D(4)/A, E(4)/C, D(3)/A, B(3)/A, C(3)/B, C(3)/B, D(3)/E, I (3)/B, E(3)/C, E(3)/E, G(3)/E, H(3)/D, E(3)
3; A, D, E(3)/A, B, C(3)/A, B, D(3)/A, B, E(3)/B, C, D(3)/A, C, D(3)/B, D, E(3)/E, D, C(3)/A, C, E(3)/B, C, E(3)
4; A, B, D, E(3)/A, B, C, D(3)/B, C, D, E(3)/A, C, D, E(3)/A, B, C, E(3)
5; A, B, C, D, E(3)
9 CMHTBJDs: *Angelica gigas* Nakai., root (A), *Atractylodes japonica* Koidz. ex Kitam., rhizome (B), *Poria cocos* (Schw.) Wolf., sclerotium (C), *Paeonia lactiflora* Pall., root (D), *Rehmannia glutinosa* (Gaertn.) DC., root (E), *Dioscorea polystachya Turcz.*, rhizome (F), Gypsum(G), *Panax ginseng* C.A.Mey., root (H), *Saposhnikovia divaricata* (Turcz.) Schischk., root (I)

*Selecting CMHCTBJDs as the top five on the basis of frequency, only including frequencies >3, and including ties for 5th place.
CMHTBJD, candidates of a medicinal herb for the treatment of bone and joint disorder; PTBJD, prescription for the treatment of bone and joint disorder.

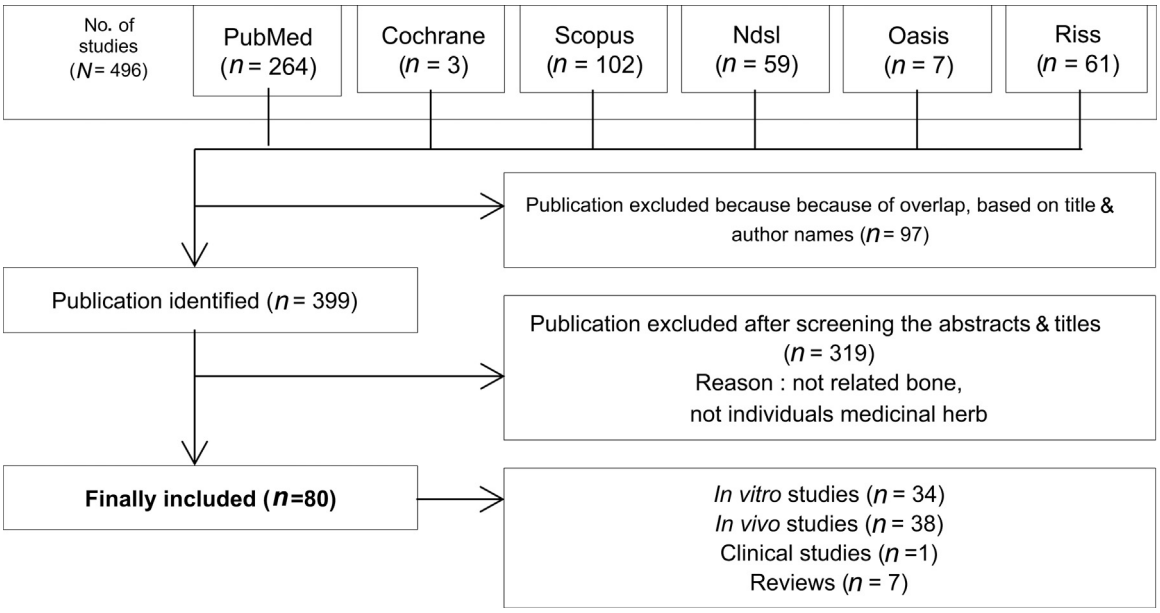

Fig. 4 – Number of previous studies on nine CMHTBJDs.
CMHTBJD, candidates of a medicinal herb for the treatment of bone and joint disorder.

suppresses inflammatory process, as its effect in curing rheumatoid arthritis is shown in other previous studies; (5) *Rehmannia glutinosa* (Gaertn.) DC., root: *Rehmannia glutinosa* (Gaertn.) DC. is capable of moderating inflammatory disease and ameliorating osteoporosis via osteoblast proliferation, as well as preventing obese and bone loss on postmenopausal women; (6) *Dioscorea polystachya Turcz.*, rhizome: *Dioscorea polystachya* Turcz. inhibits bone resorption and functions as an efficient treatment for osteoporosis; (7) gypsum (VV:1): gypsum improves amount, density, and biomechanical performance of bone trabeculae in osteoporotic vertebra; (8) *Panax ginseng* Mey., root: *Panax ginseng* Mey. promotes bone differentiation through improving osteogenic abilities and inhibiting osteoclastic functions, prevents bone loss and enhances bone density and strength, and protects the cell against cartilage degradation, consequently showing potential as highly effective therapeutic agent for osteoarthritis, osteoporosis, and rheumatoid arthritis; and (9) *Saposhnikovia divaricata* (Turcz.) Schischk., root: *Saposhnikovia divaricate* (Turcz.) Scischk. reduces inflammatory responses and osteoblast activity.

However, in spite of the explanations so far, there could be a few fundamental questions regarding methodology and results of this study since the research method we used was not general.

First of all, one may wonder if it is possible to match today's BJDs and BJDs written in the classical literature. Of course, the definition of BJDs in KM and Western medicine is different, nevertheless we tried to select specific indications which are the most similar to symptoms of today's BJDs by analyzing terms describing effects and selected all prescriptions which have one more of specific indications. As shown above, we tried to select information from classical literature that is the closest to today's theory but inconsistency of definition still remained. This has inevitable consequences because we select information from the classical literature which has a different theoretical system compared with today's system. Although carrying out follow up experiments or clinical research, we think we should solve problems that are derived from inconsistency of definition such as "the different terminology between ancient and modern disease" and "inclusion

Table 3 – Preliminary evaluation of the effects of nine CMHTBJDs in bone and joint disorder via analysis of the previous studies

Name of CMHTBJD/classification of the study (No.)/source database/main outcome		
Angelica gigas Nakai., root	VT (6)	(1) P/Prevents cartilage destruction in osteoarthritis & favor cartilage repair[4] (2) P, S/Demonstrates inhibitory effects on RANKL-mediated osteoclast differentiation in bone marrow macrophages *in vitro*[5] (3) P/Inhibits IL-1β-induced rheumatoid synovial fibroblast proliferation & COX-2, PGE2, & MMPs production[6] (4) P/Stimulates UDP-sugar synthase genes through promoting gene expression of IGF-1 & IGF1R in chondrocytes[7] (5) P/Decreases the hydrogen peroxide-induced IL-1beta, TNF-alpha, MMP-1 & MMP-13 & increases SOX9 gene expression[8] (6) R/Shows inhibitory effect on osteoclast differentiation & function[9]
	VV (4)	(1) P/Less trabecular bone loss & thick cortical areas were observed[10] (2) P/Prevents the OVX-induced bone loss in rats via estrogen-independent mechanism[11] (3) P/APS-3c can improve the proteoglycans synthesis of chondrocytes *in vivo* & IL-1 β-stimulated chondrocytes *in vitro*[12] (4) R, O/Has a suppressing inflammation effect on Freund's adjuvant arthritis in rats[13]
	RW (3)	(1) P, S/Has potent binding affinity with IL6R protein[14] (2) P, S/Has strong antiinflammatory & antiarthritic effects[15] (3) R/Turns out to be the most frequently used herb for the treatment of osteoporosis since 2000[16]
Atractylodes japonica Koidz. ex Kitam., rhizome	VT (1)	(1) N, O, R/Has beneficial effect on osteoporosis by inhibition of osteoclast differentiation & by inhibition of functioning osteoclast[17]
	VV (3)	(1) S/Increases the growth & differentiation of osteoblastic MC3T3-E1 cells[18] (2) S/Inhibits osteoclast differentiation from its precursors[19] (3) N, R/Decreases the arthritic scores & inhibits pathological changes of knee joint tissues in CIA mice[20]
	RW (1)	(1) P/Consists one of the most used herbal drugs prescription cluster for osteoporosis treatment[21]
Poria cocos (Schw.) Wolf., sclerotium	VV (1)	(1) N, R/Inhibits RANKL-induced osteoclast differentiation in bone marrow-derived macrophages[22]
	RW (1)	(1) P, S, N/Triterpenoids are known to have a pivotal influence on rheumatoid arthritis[23]
Paeonia lactiflora Pall., root	VT (3)	(1) N, S/Reduces or prevents osteoblast degeneration in osteoporosis[24] (2) S/Contributes to the prevention for osteoporosis[25] (3) R/May be useful as potential sources of therapeutic agents against postmenop- ausal osteoporosis[26]
	VV (6)	(1) P, N, S/Inhibits RANKL-induced osteoclastogenesis by inhibiting ERK, p38 & NF-κB pathway[27] (2) N/Negatively regulates osteoclast differentiation & formation[28] (3) N, S/Suppresses inflammatory process by reducing the production of prostaglandin E2, leukotriene B4, nitric oxide, reactive oxygen species, proinflammatory cytokines & chemokines[29] (4) N, R/Relieves arthrocele & arthralgia & elevates the contents of L-ENK, beta-END, IL-2 & degrades the contents of SP, IgG, IL-1beta, IL-6 & inhibits abnormal secretion accentuation of synovial cell like fiber[30] (5) S/Inhibits abnormal proliferation of synoviocytes & treats the rheumatoid arthritis[31] (6) S/Total glucosides of paeony treats rheumatoid arthritis[32]
	RW(1)	(1) P/The beneficial effects of total glucosides of peony in treating rheumatoid arthritis were verified by randomized controlled trials[33]
Rehmannia glutinosa (Gaertn.) DC., root	VT (5)	(1) N, R, S/Has potential as a therapeutic material to attenuate the inflammatory disease such as rheumatoid arthritis[34] (2) N/Contains active ingredients involved in bone tissue metabolism & may be effective in improving osteoporosis[35] (3) N, S/Improves the osteoporosis resulted from augmentation of osteoblast proliferation[36] (4) R/Shows remarkable inhibitive effect on RANKL-treated osteoclast differentiation without cytotoxicity[37] (5) P, N/Enhances the bone metabolism in osteoporosis[38]
	VV (4)	(1) N, R/Can be used for prevention & curing the postmenopausal obese[39] (2) N, C, S/Controls rapid reduction of bone turnover in postmenopausal women[40] (3) P, S/Prevention of bone loss[41] (4) N, R/Decreases the serum level of cholesterol & increases the serum level of ALP[42]
Dioscorea polystachya Turcz., rhizome	VT (4)	(1) P/Inhibits the IL-1β-induced expression of inflammatory mediators[43] (2) P, N, R/Reduces the proliferation of human fibroblast-like synovial cells[44] (3) P/Potents inhibitory activities on bone resorption[45] (4) P/Potents inhibition against bone resorption[46]
	VV (6)	(1) P/Might prevent bone loss during aging & provide beneficial effects in osteoporosis in elderly people[47] (2) P/Lies in the synchronous inhibitory effects on both the bone formation & the bone resorption[48] (3) N/Counteracts the progression of osteoporosis & augments bone mineral density[49] (4) P/Inhibits bone loss in bone mineral content[50] (5) P/Inhibits the decrease in cancellous bone mineral content, cancellous bone mineral density, & cortical bone mineral content[51]

– Table 3 (*Continued*)

		(6) N, O, R/Shows inhibitory effect on bone loss in osteoporetic condition, & reduces the increase of ALP activity & osteocalcin level in serum[52]
Gypsum	VV (1)	(1) P/Improves amount, density & biomechanical performance of bone trabeculae in osteoporotic vertebra[53]
Panax ginseng C.A.Mey., root	VT (13)	(1) P/Promotes the differentiation of bone marrow mesenchymal stem cells & mononuclear cells into osteoblasts & osteoclast[54] (2) P, S/Reduces receptor activator of nuclear factor kappa B ligand-induced tartrate-resistant acid phosphatase activity, pit formation (actin rings), & TRAP-positive multinucleated cells development in RAW264.7 cells[55] (3) P/Inhibits osteoclastogenesis by suppressing MAPK in LPS-activated RAW264.7 cells[56] (4) P, S/Plays an important therapeutic role in osteoporosis patients by improving osteogenic differentiation of Bone marrow stromal cells[57] (5) P/Has therapeutic potential for preventing cartilage collagen matrix breakdown in diseased tissues such as those found in patients with arthritic disorders[58] (6) P/Protects the cell against the development of chondrocyte senescence in osteoarthritis[59] (7) P/Exerts a protective effect against the cartilage degradation of osteoarthritis[60] (8) P/Can be a potential alternative to the current antiTNF-alpha therapeutics for rheumatoid arthritis[61] (9) P, S/Reduces cell infiltration & cartilage destruction in the arthritic joint[62] (10) N, R/Has osteogenic & antiosteoclastogenesis properties & regards as potential therapeutic agents for management of osteoporosis[63] (11) N, R/Has beneficial effects against arthritis without any adverse effects[64] (12) S/Inhibits dexamethasone-induced apoptosis through promotion of GPR120 induction in bone marrow-derived mesenchymal stem cells[65] (13) R/Can be applicable for the improvement of arthritic symptoms as a new diet-supplement[66]
	VV (13)	(1) P/Prevents loss of cell viability caused by Dex-induced apoptosis in MC3T3E1 cells[67] (2) P, S/The serum levels of TNF—a, IL—1β, & IL—6 were increased[68] (3) P/The bone-modulating effects of PNS may be due to the increased bone formation & decreased bone resorption[69] (4) P/Protects against bone loss in rat model by increasing the serum levels of TNF—α, IL—1β, & IL—6[68] (5) P/Enhances bone mineral density, bone strength, & prevents the deterioration of trabecular microarchitecture without hyperplastic effect on uterus[70] (6) P, S/Can ameliorate arthritis in mice with CIA by targeting pathogenic Th17 & osteoclast differentiation[71] (7) P/Alleviates autoimmune arthritis by suppressing T cell activation[72] (8) N, R/Alternative medicine for the relief & prevention of rheumatoid arthritis symptoms[73] (9) S/Prevents postmenopausal bone loss by inhibiting osteoclast differentiation, a process controlled by estrogen[74] (10) S/Inhibits osteoclastogenesis by modulating NF-κB & MAPKs pathways[75] (11) S/Inhibits differentiation & maturation of osteoclasts[76] (12) S/Reduces the carrageenan-induced paw edema & suppresses the production of serum IL-6[77] (13) P/The expression levels of chondrogenic genes, such as type II collagen & SOX9, were increased in the presence of ginsenoside Rb1[78]
	RW (1)	(1) P, N, R, S/Most important therapeutic agent for the treatment of osteoporosis[79]
	CS (1)	(1) P/Enhances the therapeutic effect in treating rheumatoid arthritis[80]
Saposhnikovia divaricata (Turcz.) Schischk., root	VT (2)	(1) P/Reduces the inflammatory responses in the joints of collagen-induced arthritis rats[81] (2) N, R/Reduce osteoblast activity[82]

CMHTBJD, candidates of a medicinal herb for the treatment of bone and joint disorder; CS, Clinical study; C, Cochrane; N, Ndsl; O, Oasis; P, PubMed(); (), RW, Review; R, Riss; S, Scopus, VT, *in vitro* study, VV, *in vivo* study.

and exclusion criteria". Therefore, even though inconsistency of definition is existed, it is worthwhile to try to select CMHCTBJDs and CMHTBJDs by matching today's BJDs and BJDs written in the classical literature.

Second of all, one may wonder why 80% of medicinal herbs in PTBJD are only included in CMHCTBJD in the second step of method. In Korean traditional prescription, a little amount of herbs, such as *Zingiber officinale* Roscoe so-called "Guide herb (shǐyào)" are added for balance of medicinal herbs or to improve digestive functions. These "Guide herb (shǐyào)" do not have major treatment effects but frequently added in prescriptions; which means just frequently used medicinal herbs in prescriptions does not mean that the herbs are principle ingredients. Therefore, the minor herbs were excluded from CMHCTBJD and only 80% of medicinal herbs in PTBJD were included in CMHCTBJD. The other doubt in the second step of the method is that instead of selecting the most frequently used medicinal herbs in 64 PTBJD as CMHTBJD, why CMHTBJD is selected after sorting CMHCTBJD out. The reason is that prescriptions are not simply a quantitative addition of the individual medicinal herbs, instead they produce a superior efficacy to single medicines.[83,84] Therefore, proposing medicinal herbs of possible combinations instead of single medicines to a clinical researcher could be more useful for follow-up experiments.

Third, since definitions are different as shown above, main clinical signs are different; and therefore you might want to know which steps of which disease among five BJDs medicinal herbs or medicinal herb combinations can be used, and how to distinguish five BJDs from similar other diseases and use medicinal herbs or medicinal herb combinations. Also one might wonder how optimum component ratio of medicinal herbs of the combination can be decided after selecting medicinal herb combinations. As the purpose of this study is a selection of information from classical literature, it seems that these kinds of problems are beyond research range and thus it is hard to answer in this paper. These problems should be solved during follow-up experiments or clinical research.

Fourth, because previous research is not done for all of nine CMHTBJDs and type and result of the previous research is a little different, you may think that there are some different results between ancient and modern literature analysis. But, the reason for doing modern literature analysis in this study is not to compare to ancient literature analysis. Instead it is because proposing candidates of medicinal herb to experimental and clinical researchers by discovering from the classical literature is also the final purpose of this study. By summarizing previous studies for experimental and clinical researchers, it is expected to motivate researchers to conduct follow-up study and help to establish research direction using candidates of medicinal herb selected from this research. Therefore, instead of comparing previous research and ancient literature analysis and discussing the difference, we think that it is a more productive way to refer to previous research and find a direction of follow up study of 34 CMHCTBJDs and nine CMHTBJDs.

The fundamental questions discussed above are not only key points but also characters of this paper. Therefore, if you do not agree with the authors' answers, you may criticize this paper as the paper lacks methodological structure. The answer regarding the criticism is as below. We have done "text mining and literature review" regarding "cognitive-enhancing herbal formulae" and "medicinal herbs in prescriptions for the treatment of stroke" using similar methodology that this research used.[85,86] Subsequently, we have done experimental research on efficacy of medicinal herbs using the result we gotobtained.[87,88] As a result, although it is hard to conclude since there are only two cases, we provisionally conclude that the methodology (text mining and literature review) is very useful for selection of medicinal herbs which had the specific efficacy we were looking for.

In the present study, we finally selected 34 CMHCTBJDs and 9 CMHTBJDs from "*Dongeuibogam*" and reviewed the results of previous studies regarding the effects in BJDs (especially in osteoporosis, osteomalacia, osteopenia, rheumatoid arthritis, and degenerative arthritis). In order to develop universally applicable PTBJDs, it will be necessary to conduct longer and more complex experiments and clinical trials. However, the methodology used in this study is regarded as a meaningful challenge to discover âŁœa hidden treasureâŁ? for BJDs from classical literature. The result of this study, 34 CMHCTBJDs and 9 CMHTBJDs, will be certainly valuable as fundamental data for experiment and clinical research.

Conflicts of interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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REFERENCES

1. Koehn FE, Carter GT. The evolving role of natural products in drug discovery. *Nat Rev Drug Discov* 2005;4:206–20.
2. Corson TW, Crews CM. Molecular understanding and modern application of traditional medicines: triumphs and trials. *Cell* 2007;130:769–74.
3. Oh YT, Kim SC, Lee BW. Estimation study of the herbal formula's effects by the compositional herbal effects (Guideline of the herbal effects intensity). *J Korean Medical Classics* 2008;21:49–57.
4. Magdalou J, Chen LB, Wang H, Qin J, Wen Y, Li XJ, et al. *Angelica sinensis* and osteoarthritis: a natural therapeutic link? *Biomed Mater Eng* 2015;25(Suppl):179–86.
5. Kong L, Zhao Q, Wang X, Zhu J, Hao D1, Yang C. *Angelica sinensis* extract inhibits RANKL-mediated osteoclastogenesis by downregulated the expression of NFATc1 in mouse bone marrow cells. *BMC Complement Altern Med* 2014;14:481.
6. Lee WS, Lim JH, Sung MS, Lee EG, Oh YJ, Yoo WH. Ethyl acetate fraction from *Angelica sinensis* inhibits IL-1β-induced rheumatoid synovial fibroblast proliferation and COX-2, PGE2, and MMPs production. *Biol Res* 2014;47:41.
7. Wen Y, Li J, Tan Y, Qin J, Xie X, Wang L, et al. *Angelica sinensis* polysaccharides stimulated UDP-sugar synthase genes through promoting gene expression of IGF-1 and IGF1R in chondrocytes: promoting antiosteoarthritic activity. *PLoS One* 2014;9:e107024.
8. Chen MP, Yang SH, Chou CH, Yang KC, Wu CC, Cheng YH, et al. 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* 2010;59:587–95.
9. Wang X. Plant-derived modulators of osteoclastogenesis as therapeutic agents for bone loss [MA thesis] Bibliography 2014, p. 79–95.
10. Choi KO, Lee I, Paik SY, Kim DE, Lim JD, Kang WS, et al. Ultrafine *Angelica gigas* powder normalizes ovarian hormone levels and has antiosteoporosis properties in ovariectomized rats: particle size effect. *J Med Food* 2012;15:863–72.
11. Lim DW, Kim YT. Antiosteoporotic effects of *Angelica sinensis* (Oliv.) diels extract on ovariectomized rats and its oral toxicity in rats. *Nutrients* 2014;6:4362–72.
12. Qin J, Liu YS, Liu J, Li J, Tan Y, Li XJ, et al. Effect of *Angelica sinensis* polysaccharides on osteoarthritis *in vivo* and *in vitro*: a possible mechanism to promote proteoglycans synthesis. *Evid Based Complement Alternat Med* 2013:794761.
13. Mi SR, Yeo CY, HK Jae. The effect of *Angelica gigas* NAKAI pharmacopuncture at ST(36) and BL(23) on Freund's adjuvant arthritis in rats. *The Acupuncture* 2010;27:25–34.
14. Lee WY, Chen HY, Chen KC, Chen CY. Treatment of rheumatoid arthritis with traditional Chinese medicine. *Biomed Res Int* 2014, 528018.

15. Yang CL, Or TC, Ho MH, Lau AS. Scientific basis of botanical medicine as alternative remedies for rheumatoid arthritis. *Clin Rev Allergy Immunol* 2013;44:284–300.
16. Min BK, Sung SK, HC Seok. A literature review of herbal medicines on osteoporosis studies – reviewing articles published after year 2000. *J Orien Rehabil Med* 2010;20.
17. Park S-T, Lee M-S, Jeon B-H, Park K-I, Oh J-M. Effect of atractylodis rhizoma alba on osteoclast formation. *Korean J Orient Physiol Pathol* 2011;25:109–14.
18. Chang K-M, Choi E-M, Kim G-H. Effects of medicinal plant *Atractylodes japonica* on MC3T3-E1 cells. *Food Sci Biotechnol* 2014;23:1173–6.
19. Ha H, An H, Shim K-S, Kim T, Lee KJ, Hwang YH. et al Ethanol extract of *Atractylodes macrocephala* protects bone loss by inhibiting osteoclast differentiation. *Molecules* 2013;18:7376–88.
20. Kim S-H, Park Y-K. Effects of *Atractylodis rhizoma* alba extract on collagen-induced arthritis in mice. *Korea J Herbol* 2012;27:1–6.
21. Gao Z, Lu Y, Halmurat U, Jing J, Xu D. Study of osteoporosis treatment principles used historically by ancient physicians in Chinese medicine. *Chin J Integr Med* 2013;19: 862–8.
22. Cheon Y-H, Kwack S-C, Oh J-M, Choi M-K, Kim J-J, Kwak H-B, et al. Effect of hoelen in RANKL-induced osteoclast differentiation. *Korean J Orient Physiol Pathol* 2012;26:320–4.
23. Ríos JL. Chemical constituents and pharmacological properties of *Poria cocos*. *Planta Med* 2011;77:681–91.
24. Kwang SS. Protective effect of albiflorin against oxidative-stress-mediated toxicity in osteoblast-like MC3T3-E1 cells. *Fitoterapia* 2013;89:33.
25. Yen PH. A new monoterpene glycoside from the roots of *Paeonia lactiflora* increases the differentiation of osteoblastic MC3T3-E1 cells. *Arch Pharm Res* 2007;30:1179–85.
26. Kim HJ. *Isolation of resveratrol and its derivatives from the seeds of Paeonia lactiflora Pall., and their biological activity [Doctorate thesis]*. Daegu: Department of Food and Nutrition Graduate School, Catholic University of Daegu; 2002.
27. Huei-Yann T. Paeonol inhibits RANKL-induced osteoclastogenesis by inhibiting ERK, p38, and NF-κB pathway. *Eur J Pharmacol* 2008;588:124–33.
28. Bo RP. Inhibitory effect of Paeoniae radix alba ethanol extract on osteoclast differentiation and formation. *Korean J Orient Physiol Pathol* 2015;29:51.
29. Wei Z. Mechanisms involved in the therapeutic effects of *Paeonia lactiflora* Pallas in rheumatoid arthritis. *Int Immunopharmacol* 2012;14:27.
30. Li J. Mechanism study of action on compatible using of total alkaloids of Radix Aconiti Praeparata and total glycosides or polysaccharides of Radix Paeoniae Alba therapy on rheumatoid arthritis in rats. *China journal of Chinese materia medica* 2009;34:2937.
31. Yong QZ. Effects and mechanism of paeoniflorin, a bioactive glucoside from paeony root, on adjuvant arthritis in rats. *Inflamm Res* 2007;56:182–8.
32. Wang B, Chen M-Z, Xu S-Y. Effect of total glucosides of paeony on synoviocyte function and splenocyte proliferation in adjuvant arthritis rats. *Chin J Pharmacol Toxicol* 1994;8:128–32.
33. Dong YH. Antiinflammatory and immunomodulatory effects of *Paeonia lactiflora* pall., a traditional Chinese herbal medicine. *Front Pharmacol* 2011;25.
34. Chang HJ. Antiinflammatory activities of ethylacetate extract of *Rehmannia glutinosa* in LPS-induced RAW 264.7 cells. *Food Sci Biotechnol* 2009;18:923–7.
35. Jung KK. OPB, a water extract from *Rehmannia glutinosa Libosch* and *Eleutherococcus senticosus* Max, inhibits osteoclast differentiation and function. *Int J Oral Biol* 2007;32:23–34.
36. Gyu JL. The effect of dried roots of *Rehmannia glutinosa* extract on osteoblast in rat fetus calvarial cells. *J Orient Obstet Gynecol* 2013;26(3):33–43.
37. Sung JK. Inhibitory effect of Sangbowhan on osteoclast differentiation and bone resorption, Doctorate Thesis, Wonkwang University, 2015;2.
38. Oh KO, Kim SW, Kim JY, Ko SY, Kim HM, Baek JH, et al. Effect of *Rehmannia glutinosa* Libosch extracts on bone metabolism. *Clin Chim Acta* 2003;334:185–95.
39. Soo IJ. Effects of the Rehmanniae Radix Preparat on ovariectomized rats. *Korea J Herbol* 2005;20:61.
40. Soo YO. Effects of *R. glutinosa* and *E. senticosus* on postmenopausal osteoporosis. *Korean J Physiol Pharmacol* 2007;11:121–7.
41. Dong WL. Dried root of *Rehmannia glutinosa* prevents bone loss in ovariectomized rats. *Molecules* 2013;18:5804–13.
42. Lee JA. *Effects of the rehmanniae radix preparat on osteoporotic rats induced by ovariectomy [Master's thesis]*. Dongshin: Graduate School of Dongshin University; 2004, p. 28.
43. Wang L, Ma T, Zheng Y, Lv S, Li Y, Liu S. Diosgenin inhibits IL-1β-induced expression of inflammatory mediators in human osteoarthritis chondrocytes. *Int J Clin Exp Pathol* 2015;8:4830–6.
44. Kim MJ, Kim HN, Kang KS, Baek NI, Kim DK, Kim YS, et al. Methanol extract of *Dioscoreae rhizoma* inhibits proinflammatory cytokines and mediators in the synoviocytes of rheumatoid arthritis. *Int Immunopharmacol* 2004;4:1489–97.
45. Yin J, Kouda K, Tezuka Y, Le Tran Q, Miyahara T, Chen Y, et al. New diarylheptanoids from the rhizomes of *Dioscorea spongiosa* and their antiosteoporotic activity. *Planta Med* 2004;70:54–8.
46. Yin J, Kouda K, Tezuka Y, Le Tran Q, Miyahara T, Chen Y, et al. Steroidal glycosides from the rhizomes of *Dioscorea spongiosa*. *J Nat Prod* 2003;66:646–50.
47. Hung YT, Tikhonova MA, Ding SJ, Kao PF, Lan HH, Liao JM, et al. Effects of chronic treatment with diosgenin on bone loss in a D-galactose-induced aging rat model. *Chin J Physiol* 2014;57:121–7.
48. Zhang Z, Xiang L, Bai D, Fu X, Wang W, Li Y, et al. Treatment with *Rhizoma dioscoreae* extract has protective effect on osteopenia in ovariectomized rats. *Scientific World J* 2014:645975.
49. Kam LW, Yau ML, Wan LK, Kai FL, Ng TB, Ho PC, et al. A novel, stable, estradiol-stimulating, osteogenic yam protein with potential for the treatment of menopausal syndrome. *Stephen Cho. Sci Rep* 2015;5:10179.
50. Yin J, Tezuka Y, Kouda K, Le Tran Q, Miyahara T, Chen Y, et al. *In vivo* antiosteoporotic activity of a fraction of *Dioscorea spongiosa* and its constituent, 22-O-methylprotodioscin. *Planta Med* 2004;70:220–6.
51. Yin J, Tezuka Y, Kouda K, Le Tran Q, Miyahara T, Chen Y, et al. Antiosteoporotic activity of the water extract of *Dioscorea spongiosa*. *Biol Pharm Bull* 2004;27:583–6.
52. Hwang GS, Lee DY. Effects of *Dioscorea batatas* on estrogen-deficient osteoporosis. *Kor J Oriental Preventive Medical Society* 2003;7:55–66, 1226–7066.
53. Liu D, Wu ZX, Zhang Y, Wang CR, Xie QY, Gong K, et al. Local treatment of osteoporotic sheep vertebral body with calcium sulfate for decreasing the potential fracture risk: microstructural and biomechanical evaluations. *J Spinal Disord Tech* 2016;(August (7)):E358–64, http://dx.doi.org/10.1097/BSD.0b013e3182a22a96.
54. Wenxi D, Shufang D, Xiaoling Y, Liming Y. *Panax notoginseng* saponins suppress radiation-induced osteoporosis by regulating bone formation and resorption. *Phytomedicine* 2015;22:813–9.

55. Siddiqi MH, Siddiqi MZ, Kang S, Noh HY, Ahn S, Simu SY, et al. Inhibition of osteoclast differentiation by ginsenoside Rg3 in RAW264.7 cells via RANKL, JNK, and p38 MAPK pathways through a modulation of cathepsin K: an *in silico* and *in vitro* study. *Phytother Res* 2015, http://dx.doi.org/10.1002/ptr.5374.
56. Jang YJ, Kim ME, Ko SY. *n*-Butanol extracts of *Panax notoginseng* suppress LPS-induced MMP-2 expression in periodontal ligament fibroblasts and inhibit osteoclastogenesis by suppressing MAPK in LPS-activated RAW264.7 cells. *Arch Oral Biol* 2011;56:1319–27.
57. Li XD, Wang JS, Chang B, Chen B, Guo C, Hou GQ, et al. *Panax notoginseng* saponins promotes proliferation and osteogenic differentiation of rat bone marrow stromal cells. *J Ethnopharmacol* 2011;134:268–74.
58. Lee JH, Lim H, Shehzad O, Kim YS, Kim HP. Ginsenosides from Korean Red Ginseng inhibit matrix metalloproteinase-13 expression in articular chondrocytes and prevent cartilage degradation. *Eur J Pharmacol* 2014;724:145–51.
59. So MW, Lee EJ, Lee HS, Koo BS, Kim YG, Lee CK, et al. Protective effects of ginsenoside Rg3 on human osteoarthritic chondrocytes. *Mod Rheumatol* 2013;23:104–11.
60. Shin JS, Park N, Ra J, Kim Y, Shin M, Hong M, et al. *Panax ginseng* C.A. Meyer modulates the levels of MMP3 in S12 murine articular cartilage cell line. *J Ethnopharmacol* 2009;124:397–403.
61. Chang SH, Choi Y, Park JA, Jung DS, Shin J, Yang JH, et al. Antiinflammatory effects of BT-201, an *n*-butanol extract of *Panax notoginseng*, observed *in vitro* and in a collagen-induced arthritis model. *Clin Nutr* 2007;26:785–91.
62. Kim HA, Kim S, Chang SH, Hwang HJ, Choi YN. Antiarthritic effect of ginsenoside Rb1 on collagen induced arthritis in mice. *Int Immunopharmacol* 2007;7:1286–91.
63. Muhammad HS. *Characterization of the molecular actions and efficacy of ginsenosides on bone with emphasis on osteoporosis [PhD thesis]*. Kyung Hee: Kyung Hee University; 2014.
64. Jeong T-Y. *Inhibitory effect of Korean ginseng extract on type II collagen-induced arthritis [PhD thesis]*. Yonsei: Yonsei University; 2009.
65. Gao B, Huang Q, Jie Q, Zhang H-Y, Wang L, Guo Y-S, et al. Ginsenoside-Rb2 inhibits dexamethasone-induced apoptosis through promotion of GPR120 induction in bone marrow-derived mesenchymal stem cells. *Stem Cells Dev* 2015;24:781–90.
66. Kang MH, Jung CS. Antiinflammatory and antirheumatoid action of *Panax ginseng* head butanol fraction. *J Pharml Sci* 2003;14.
67. Kim J, Lee H, Kang KS, Chun KH, Hwang GS. Protective effect of Korean Red Ginseng against glucocorticoid-induced osteoporosis *in vitro* and *in vivo*. *J Ginseng Res* 2015;39:46–53.
68. Avsar U, Karakus E, Halici Z, Bayir Y, Bilen H, Aydin A, et al. Prevention of bone loss by *Panax ginseng* in a rat model of inflammation-induced bone loss. *Cell Mol Biol* 2013;59:1835–41.
69. Shen Y, Li YQ, Li SP, Ma L, Ding LJ, Ji H. Alleviation of ovariectomy-induced osteoporosis in rats by *Panax notoginseng* saponins. *J Nat Med* 2010;64:336–45.
70. Shen Y, Li YQ, Li SP, Ma L, Ding LJ, Ji H. Alleviation of ovariectomy-induced osteoporosis in rats by *Panax notoginseng* saponins. *J Nat Med* 2010;64:336–45.
71. Jhun J, Lee J, Byun JK, Kim EK, Woo JW, Lee JH, et al. Red ginseng extract ameliorates autoimmune arthritis via regulation of STAT3 pathway, Th17/Treg balance, and osteoclastogenesis in mice and human. *Mediators Inflamm* 2014:351856.
72. Chen J, Wu H, Wang Q, Chang Y, Liu K, Song S, et al. Ginsenoside metabolite compound k alleviates adjuvant-induced arthritis by suppressing T cell activation. *Inflammation* 2014;37:1608–15.
73. Jeong C-S. Effects of the butanol extract of head of *Panax ginseng* on Type II collagen-induced arthritis in DBA/1J mice. *J Appl Pharmacol* 2007;15:235–9.
74. Lee H-Y, Park S-H, Chae S-W, Soung N-K, Oh M-J, Kim JS, et al. Aqueous ginseng extract has a preventive role in RANKL-induced osteoclast differentiation and estrogen deficiency-induced osteoporosis. *J Funct Foods* 2014;13:192–203.
75. Cheng B, Li J, Du J, Lv X, Weng L, Ling C. Ginsenoside Rb1 inhibits osteoclastogenesis by modulating NF-κB and MAPKs pathways. *Food Chem Toxicol* 2012;50:1610–5.
76. Gu Y, Fan W, Yin G. The study of mechanisms of protective effect of rg1 against arthritis by inhibiting osteoclast differentiation and maturation in cia mice. *Mediators Inflamm* 2014:305071.
77. Lee J-Ha, Lee J-Hb, Lee Y-M, Kim P-N, Jeong C-S. Potential analgesic and antiinflammatory activities of *Panax ginseng* head butanolic fraction in animals. *Food Chem Toxicol* 2008;46:3749–52.
78. Kim S, Na JY, Song KB, Choi DS, Kim JH, Kwon YB, et al. Protective effect of ginsenoside Rb1 on hydrogen peroxide-induced oxidative stress in rat articular chondrocytes. *J Ginseng Res* 2012;36:161–8.
79. Siddiqi MH, Siddiqi MZ, Ahn S, Kang S, Kim YJ, Sathishkumar N, et al. Ginseng saponins and the treatment of osteoporosis: mini literature review. *J Ginseng Res* 2013;37:261–8.
80. Zhang JH, Wang JP, Wang HJ. Clinical study on effect of total panax notoginseng saponins on immune related inner environment imbalance in rheumatoid arthritis patients. *Zhongguo Zhong Xi Yi Jie He Za Zhi* 2007;27:589–92.
81. Xiang Y. The suppressive effects of *Saposhnikovia divaricata* (Fangfeng) chromone extract on rheumatoid arthritis via inhibition of nuclear factor-κB and mitogen activated proteinkinases activation on collagen-induced arthritis model. *J Ethnopharmacol* 2013;148:842–50.
82. Jeon JM. *Effects of Ledebouriella seseloides extracts on lipid and bone formation in ovariectomized rats*. Department of Food and Nutrition Graduate School, Silla University; 2014.
83. Jia W, Gao WY, Yan YQ, Wang J, Xu ZH, Zheng WJ, et al. The rediscovery of ancient Chinese herbal formulas. *Phytother Res* 2004;18:681–6.
84. Scholey AB, Kennedy DO. Acute, dose-dependent cognitive effects of *Ginkgo biloba*, *Panax ginseng*, and their combination in healthy young volunteers: differential interactions with cognitive demand. *Human Psychopharmacology: Clinical and Experimental* 2002;17:35–44.
85. Pae SB, Yun BC, Han YK, Choi BT, Shin HK, Baek JU. Cognitive-enhancing herbal formulae in Korean medicine: identification of candidates by text mining and literature review. *J Altern Complem Med* 2016;22:413–8.
86. Yun BC, Pae SB, Han YK, Choi MJ, Choi BT, Shin HK, et al. An analysis of the combination frequencies of constituent medicinal herbs in prescriptions for the treatment of stroke in Korean medicine: determination of a group of candidate prescriptions for universal use. *Evid Based Complement Alternat Med* 2016:2674014.
87. Pak ME, Kim YR, Kim HN, Ahn SM, Shin HK, Baek JU, et al. Studies on medicinal herbs for cognitive enhancement based on the text mining of Dongeuibogam and preliminary evaluation of its effects. *J Ethnopharmacol* 2016;179:383–90.
88. Min JK. *Evaluation of neuroprotective effect of Shuanghe-tang based on Dongeuibogam analysis using ischemic stroke mice model [Master's thesis]*. Pusan: Pusan National University; 2017.