Review

Effects of nutraceuticals on knee osteoarthritis: Systematic review

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Knee osteoarthritis is the most common form of joint disease and is a major cause of pain and physical disability among the elderly. Although, numerous treatments have been developed to treat osteoarthritis, no definitive treatments with high efficacy and low risk have been identified until now. In recent years, it has been reported that nutraceuticals may be good candidates for the management of knee osteoarthritis. This paper describes the efficacy of nutraceuticals for treating knee osteoarthritis in terms of pain and structural change. To accomplish this, this paper reports on the analysis of randomized, placebo-controlled, clinical trials that were published prior to December 2011.

Key words: Nutraceuticals, knee, osteoarthritis, pain.

INTRODUCTION

The knee is the most frequent site of pain in people over the age of 55 years. In a survey of elderly Chinese citizens, knee pain was the most common form of musculoskeletal disease (Woo et al., 1994). According to a recent community-based longitudinal study in Korea, the prevalence of knee pain was 46.2% (Kim et al., 2011). Moreover, among elderly people with knee pain, more than 50% showed radiographic evidence of osteoarthritis (McAlindon et al., 1992). Although, the diagnosis of osteoarthritis is often difficult and highly variable due to the slow onset of the condition (Woolf and Pfleger, 2003), the prevalence of symptomatic knee osteoarthritis has been reported to be 5 to 20% in elderly populations (Peat et al., 2001). Knee osteoarthritis is commonly associated with pain, joint stiffness, joint instability, synovial effusion, and pain-related psychological distress, all of which can impair quality of life and impose economic burdens on patients (Hunter et al., 2008; Altman, 2010).

Although, many efforts have been made to identify an optimal treatment for this disease, no definitive treatments with high efficacy and low risk have been reported until now. Recently, it was reported that nutraceuticals might be good treatment candidates that satisfy these requirements (Henrotin et al., 2011). To date, numerous papers have reviewed the results of trials that analyzed osteoarthritis of the hand, hip, and knee in the same study (Ameye and Chee, 2006; Henrotin et al., 2011; De Silva et al., 2011). However, analyzing different osteoarthritic sites in one study may produce misleading results because the anatomy, physiology, risk factors, and response to the same treatment regimens are often different for each site (Svensson et al., 2006; Zhang and Doherty, 2006).

This paper reviews the efficacy of nutraceuticals on knee osteoarthritis based on randomized, placebo-controlled and clinical trials. This paper excludes glucosamine and chondroitin, as these have been extensively studied and the results have been reported in recent papers (Black et al., 2009; Vangsness et al., 2009; Wandel et al., 2010). In our review of these clinical trials, we noted outcome measures of pain and structural change. We then calculated summary effect sizes (Hedge g effect) using a random effects model (DerSimonian and Laird, 1986). Data extraction methods can be available from our previous papers (Koog et al., 2010a, b). Inconsistencies between the results of trials were evaluated using the I² heterogeneity test (Higgins et al., 2003).
EFFICACY OF NEUTRACEUTICALS ON PAIN

Because osteoarthritis develops over many years and response times to treatments may be long (Altman et al., 1996), we specifically analyzed data that monitored nutraceuticals efficacy over terms closest to 3 (short-term) and 6 months (long-term). When trials reported more than one pain outcome measure, we extracted data according to the hierarchy of pain-related outcomes, as previously reported (Jüni et al., 2006). The effect sizes are presented in Figures 1 and 2.

S-Adenosylmethionine

The short-term efficacy of S-adenosylmethionine was tested in one trial (Bradley et al., 1994). S-Adenosylmethionine was administered daily as intravenous boluses of 400 mg for 5 days and then as oral tablets of 600 mg for 23 days. Current analysis reveals that S-adenosylmethionine did not alleviate knee pain. However, one review (De Silva et al., 2011) found that S-adenosylmethionine was effective in the management of osteoarthritis. Importantly, this paper analyzed trials that tested a dose of 1200 mg/day and did not incorporate a trial by Bradley et al. (1994). These results suggest that further investigation is needed to determine the efficacy of S-adenosylmethionine.

Methylsulfonylmethane

Three trials (Usha and Naidu, 2004; Kim et al., 2006; Debi et al., 2007) tested the short-term efficacy of methylsulfonylmethane. It was orally administered at doses of 1500, 3375, and 6000 mg/day. Our current analysis of these trials indicates that there is consistent evidence in support of methylsulfonylmethane as a treatment for knee pain (that is, I² = 0%). The summary effect size also indicates that methylsulfonylmethane was more effective at relieving knee pain than placebo.

Creatine supplementation

The short-term efficacy of creatine supplementation was investigated in one trial (Neves M Jr et al., 2011). Patients received 20 g•d⁻¹ of creatine monohydrate (Ethika®, São Paulo, Brazil) for 1 week and then 5 g for the next 11 weeks. Patients also received strengthening exercises as a co-intervention. Current analysis shows that creatine supplementation combined with strengthening exercises did not significantly alleviate knee pain more than placebo combined with strengthening exercises.

Extract of Boswellia serrata (Indian frankincense)

The short-term efficacy of Boswellia serrata extract was investigated in four trials from India. The first trial (Kimmatkar et al., 2003) tested WokvelTM Cap (Pharmanza Pvt Ltd., Khamarat, Gujarat, India) at a dose of 999 mg/day. The second trial (Sengupta et al., 2008) examined 5-Loxin® (PL Thomas & Co. Inc., Morristown, NJ, USA) at doses of 100 or 250 mg/day. The third trial (Sengupta et al., 2010) investigated 5-Loxin® at a dose of 100 mg/day and Aflapin® (Laila Nutraceuticals, Vijayawada, India) at a dose of 100 mg/day. The final trial (Vishal et al., 2011) examined Aflapin® at a dose of 100 mg/day. The second and third trials utilized a flare design, whereby only patients complaining of increased pain after stopping their usual treatment were included. It has been reported that the flare design produced larger treatment effects in non-steroidal anti-inflammatory drug trials (Trijau et al., 2010). Therefore, the severe heterogeneity (i.e., I² = 90%) in current analysis may be due to the use of the flare design. Current analysis presents that the extract of Boswellia serrata is efficacious for the treatment of knee pain.

Seaweed-derived minerals supplement

The short-term efficacy of a calcium- and magnesium-rich, seaweed-derived, mineral supplement (Aquamín®, Marigot Ltd., Cork, Ireland) was tested in two trials (Frestedt et al., 2008, 2009). The tested dose in both trials was 2400 mg/day. Although, the efficacy in each trial was not significant, current analysis combining data from both trials shows marginal significance. Therefore, further research is needed.

Sierra mountains-derived minerals supplement

SierraSil® (SierraSil Health Inc., Beaverton, OR, USA) is the brand name of the product derived from the mineral-rich clay found in the high Sierra Mountains in the USA. The short-term efficacy of SierraSil® was tested at doses of 2000 and 3000 mg/day in a single trial (Miller et al., 2005). In the current analysis, SierraSil® was not more effective than placebo at alleviating knee pain.

French maritime pine bark extract

The short-term efficacy of a French maritime pine bark extract (Pycnogenol®, Horphag Research, Ltd., Geneva, Switzerland) was investigated in three trials (Farid et al., 2007; Belcaro et al., 2008; Cisár et al., 2008). The tested doses were 150, 100, and 150 mg/day, respectively. Current analysis reveals severe heterogeneity among these three trials (that is, I² = 96%). Whereas one trial (Cisár et al., 2008) showed that Pycnogenol® was not more effective than placebo for alleviating knee pain, the other two trials (Farid et al., 2007; Belcaro et al., 2008) demonstrated significant pain improvement. Therefore,
Figure 1. Short-term efficacy of nutraceuticals on pain alleviation

2003), Zintona (Dalidar Pharma, Israel), which was extracted from *Zingiber officinale*, was administered orally at a dose of 1000 mg/day. However, this extract did not alleviate knee pain when compared to placebo. Current analysis combined over two trials shows significance for the short-term efficacy of ginger extract on knee pain.
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Figure 2. Long-term efficacy of nutraceuticals on pain alleviation.

### Peel extract of *Passiflora edulis* (purple passion fruit)

The short-term efficacy of purple passion fruit peel extract was investigated in one trial (Farid et al., 2010). Purple passion fruit peel extract was administered orally at a dose of 150 mg/day. Current analysis shows that it was much more effective than placebo.

### *Garcinia kola* seed

The short-term efficacy of *Garcinia kola* seed was investigated in one trial (Adegbehingbe et al., 2008). It was administered orally in a dose of 400 mg/day. *Garcinia kola* seed was more effective than placebo by a large margin.

### Pineapple extract

The short-term efficacy of bromelain (Lichtwer Pharm Ltd., Marlow, Buckinghamshire, UK), an aqueous extract of pineapple plant was investigated in one trial (Brien et al., 2006). Patients were instructed to take 800 mg/day orally. Current analysis shows that when compared to placebo, bromelain was not efficacious in the management of osteoarthritic knee pain.

### Extract of cat’s claw bark (*Uncaria guianensis*)

The short-term efficacy of cat’s claw bark extract was investigated in one trial (Piscoya et al., 2001). In this trial, patients received one tablet containing 100 mg of freeze-dried cat’s claw per day for 4 weeks. Current analysis shows that as compared to placebo, cat’s claw was only marginally more effective.

### Derivative of avocado/soybean unsaponifiables

The short-term efficacy of a derivative of avocado/soybean unsaponifiables (Piascledine, Pharmascience Inc., Montreal, Quebec, Canada) was tested in one trial (Appelboom et al., 2001). In this trial, Piascledine was administered orally at doses of 300 and 600 mg/day. At all doses, Piascledine was more effective than placebo.

### Extracts of *Boswellia carteri* and *Curcuma longa*

The short-term efficacy of extracts of *Boswellia carteri* and *Curcuma longa* was investigated in one trial (Badria et al., 2002). The extracts were prepared in 500 mg hard gelatin capsules. Patients received three capsules. Current analysis shows that the extracts were efficacious in improving knee pain compared to placebo.

### Combination of methylsulfonylmethane and *Boswellia sacra*

The short- and long-term efficacy of combination of two nutraceuticals, methylsulfonylmethane and *Boswellia sacra*, was investigated in one trial (Notarnicola et al., 2011). Patients received 5 g of methylsulfonylmethane (Lignisul®, Fine Neutraceuticals, Inc., Portland, ME, USA) and 7.2 mg of boswellic acids (Triterpenol®, Laborest Italia S.p.A., Milan, Italy) as one drug sachet a day for 2 months. Current analysis shows that although the combination was not more effective than placebo for the short-term effect, it was more effective for the long-term effect.

### Extracts of *Phellodendron amurense* bark and *Citrus sinensis* peel

NP 06-1 (Citrofen®, Next Pharmaceuticals Inc., Salinas,
CA, USA), a blend of extracts of *Phellodendron amurense* tree bark and *Citrus sinensis* peel, was examined in one trial (Oben et al., 2009). Patients were instructed to take NP 06-1 orally in a dose of 1480 mg/day. Current analysis for the short-term efficacy reveals that NP 06-1 was considerably more effective than placebo.

**Extracts of Zingiber officinale, Tinospora cordifolia, and Emblica officinalis**

One trial (Chopra et al., 2011) sponsored by Indian government investigated the 5 types of nutraceuticals. Among these types, extracts of Zingiber officinale, Tinospora cordifolia, and Emblica officinalis were reported to improve knee status and reduce analgesic consumption. Current analysis reveals that the extracts did not significantly alleviate knee pain.

**Extracts of Clematis mandshurica, Prunella vulgaris, and Trichosanthes kirilowii**

The short-term efficacy of SKI 306X (JOINS TAB., SK Chemicals, Seongnam, Korea), standardized extracts of 3 crude herbal components (*Clematis mandshurica* root, *Prunella vulgaris* flower and stem, and *Trichosanthes kirilowii* root = 1:1:2) was tested in one trial (Jung et al., 2001). SKI 306X tablets were administered at doses of 600, 1200, and 1800 mg/day. Current analysis shows that all doses were effective at alleviating knee pain when compared to placebo. Presently, SKI 306X is commonly prescribed by doctors in Korea.

**Extracts of Withania somnifera, Boswellia serrata, Zingiber officinale, and Curcuma longa**

The efficacy of RA-11 (ARTREX®, Bio-Ved Pharmaceuticals Inc., San Jose, CA, USA), standardized extract of 4 crude herbal components (*Withania somnifera, Boswellia serrata, Zingiber officinale, and Curcuma longa*) was investigated in one trial (Chopra et al., 2004). Patients took 2 capsules of RA-11 twice a day. Current analysis shows that whereas the short-term efficacy of RA-11 was not significant, the long-term efficacy was significant.

**Chicken comb extract**

While the efficacy of intra-articular injection of hyaluronic acid has been extensively evaluated in the past, the studies investigating oral administration of chicken comb extract are limited. The short-term efficacy of orally administered chicken comb extract was investigated in two trials. In the first trial (Kalman et al., 2008), chicken comb extract containing 60% hyaluronic acid (Hyal-Joint®, Bioiberica, Barcelona, Spain) was administered once in the morning at a dose of 80 mg/day. In the second trial (Nagaoka et al., 2010), 6 pills containing chicken comb extract were administered. The one-day dose of chicken comb extract was 630 mg. Current analysis shows that there was no statistical significance in favor of chicken comb extract.

**Milk-based beverage**

The short-term efficacy of a milk-based beverage was tested in one trial (Colker et al., 2002). In this trial, a beverage formulated with a milk protein concentrate (MicroLactin, Stolle Milk Biologics Inc., Cincinnati, OH, USA) was administered. Current analysis shows that the milk-based beverage was not more effective than placebo.

**Cetylated fatty acids**

The short-term efficacy of cetylated fatty acids was investigated in one trial (Hesslink et al., 2002). In this trial, patients received six capsules with each capsule containing 350 mg Celadrin™ (Imagenetix Inc., San Diego, CA, USA), 50 mg soy lecithin, and 75 mg fish oil. Current analysis shows that when compared to placebo, cetylated fatty acids were more efficacious at treating knee pain.

**Green-lipped mussel extract**

The efficacy of green-lipped mussel extract was investigated in two trials. In the first trial (Audeval and Bouchacourt, 1986), the freeze-dried extract of green-lipped mussel was orally administered (unknown dose).

In the second trial (Lau et al., 2004), Lyprinol® (Pharmalink International Ltd., Hongkong), a lipid extract of green-lipped mussel was administered in a dose of four capsules a day for 2 months and then 2 capsules a day. Current analyses show that although two types of green-lipped mussel extract were not efficacious in the short term, they were significantly efficacious in the long term.

**Collagen hydrolysate**

The long-term efficacy of collagen hydrolysate was tested in two trials. In the first trial (Moskowitz, 2000), a soluble powder obtained by hydrolysis of pharmaceutical gelatin was administered orally at a dose of 10000 mg/day. In the second trial (McAlindon et al., 2011), Fortigel® (Gelita
Efficacy of nutraceuticals on structural change.

Vitamin E

The 2-year efficacy of vitamin E was investigated in one trial (Wluka et al., 2002). This trial was an extension of the trial by Brand et al. (2001). Vitamin E, in a dose of 500 IU/day, was administered for 2 years. Current analysis indicates that vitamin E did not decrease cartilage loss compared to placebo (Figure 3).

CONCLUSION

We reviewed 41 trials for 27 nutraceuticals. Some nutraceuticals exhibited significant efficacy values for short-term reduction in knee pain: methylsulfonylmethane, Indian frankincense, seaweed-derived minerals, ginger, purple passion fruit, *Garcinia kola*, cat’s claw, SKI 306X, avocado/soybean unsaponifiables, cetylated fatty acids, *Boswellia carteri* and *Curcuma longa*, and *Phellodendron amurense* and *Citrus sinensis*. In contrast, no significant efficacy was noted for the following nutraceuticals: S-adenosylmethionine, Sierra Mountains-derived mineral, pineapple, RA-11, chicken comb, milk-based beverage, green-lipped mussel, eggshell membrane, salmon calcitonin, vitamin B5, and vitamin E. Inconsistent evidence was found for the French maritime pine treatment. Three nutraceuticals demonstrated long-term efficacy in significantly alleviating knee pain, including green-lipped mussel and RA-11. Inconsistent evidence was found for collagen hydrolysate. For the study that investigated the 2-year efficacy of vitamin E on structural change, it was found that vitamin E did not decrease the cartilage loss in the knee. However, because of the paucity of trials, there is a need for well-controlled trials to conclusively evaluate the efficacy of nutraceuticals in the management of knee osteoarthritis.

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REFERENCES

Adegbehingbe OO, Adesanya SA, Idowu TO, Okimi OC, Oyelami OA,
Iwalwela EO (2008). Clinical effects of Garcinia kola in knee osteoarthritis. J. Orthop. Surg. Res. 3: p. 34.

Altman R, Brandt K, Hochberg M, Moskowitz R, Bellamy N, Bloch DA, Buckwalter J, Dougados M, Ehrlich G, Lequesne M, Lohmander S, Murphy WA Jr, Rosario-Jansen T, Schwartz B, Triplett S (1996). Design and conduct of clinical trials in patients with osteoarthritis: recommendations from a task force of the Osteoarthritis Research Society. Results from a workshop. Osteoarthritis Cartilage. 4: 217-243.

Altman RD (2010). Early management of osteoarthritis. Am. J. Manag. Care. 16(Suppl Management): S41-47.

Altman RD, Marcussen KC (2001). Effects of a ginger extract on knee pain in patients with osteoarthritis. Arthritis Rheum. 44: 2531-2538.

Ameye LG, Chee WS (2006). Osteoarthritis and nutrition. From nutraceuticals to functional foods: a systematic review of the scientific evidence. Arthritis Res. Ther. 8: R127.

Appelboom T, Schuermans J, Verbruggen G, Henrotin Y, Reginster J (2001). Symptoms modifying effect of avocado/soybean unsaponifiables (ASU) in knee osteoarthritis. A double blind, prospective, placebo-controlled study. Scand. J. Rheumatol. 30: 242-247.

Audelet B, Bouchacourt P (1986). Etude controlee, en double aveugle contre placebo, de l’extrait de moule Perna canaliculus (mouleaux orles verts) dans la gonarthrose. Gaz. Med. 93: 111-116.

Badria FA, El-Farahaty H, Shabana AA, Hawas SA, El-Bataty M (2002). Boswellia serrata extract: a perspective treatment for knee osteoarthritis: a clinical evaluation. Altern. Complement. Ther. 8: 341-348.

Belcaro G, Cesaroni MR, Erichii L, Errich S, Gazzini G, Grippetto L, Ricci E, Zulli C, Errichi BM, Vinciguerra G, Badria FA, El F (2001). Effects of a natural extract of chicken combs with a high content of hyaluronic acid (Hyal Q) for knee osteoarthritis. Nutrition. 18: 388-392.

Belcaro G, Cesaroni MR, Erichii L, Errich S, Gazzini G, Grippetto L, Ricci E, Zulli C, Errichi BM, Vinciguerra G, Badria FA, El F (2001). Effects of a natural extract of chicken combs with a high content of hyaluronic acid (Hyal Q) for knee osteoarthritis. Nutrition. 18: 388-392.

Bennell KL, Cooper S (2007). Effectiveness of botulinum toxin A on calf muscles in patients with knee osteoarthritis. J. Rheumatol. 34: 363-643.

Boucart M, Cesarone MR, Errichi S, Zulli C, Errichi BM, Vinciguerra G, Badria FA, El F (2001). Effects of a natural extract of chicken combs with a high content of hyaluronic acid (Hyal Q) for knee osteoarthritis. Nutrition. 18: 388-392.

Boucart M, Cesarone MR, Errichi S, Zulli C, Errichi BM, Vinciguerra G, Badria FA, El F (2001). Effects of a natural extract of chicken combs with a high content of hyaluronic acid (Hyal Q) for knee osteoarthritis. Nutrition. 18: 388-392.

Brand C, Snaddon J, Bailey M, Cicuttini F (2001). Boswellia serrata extract: a perspective treatment for knee osteoarthritis: a clinical evaluation. Altern. Complement. Ther. 8: 341-348.

Brand C, Snaddon J, Bailey M, Cicuttini F (2001). Boswellia serrata extract: a perspective treatment for knee osteoarthritis: a clinical evaluation. Altern. Complement. Ther. 8: 341-348.

Brand C, Snaddon J, Bailey M, Cicuttini F (2001). Boswellia serrata extract: a perspective treatment for knee osteoarthritis: a clinical evaluation. Altern. Complement. Ther. 8: 341-348.

Brand C, Snaddon J, Bailey M, Cicuttini F (2001). Boswellia serrata extract: a perspective treatment for knee osteoarthritis: a clinical evaluation. Altern. Complement. Ther. 8: 341-348.

Brand C, Snaddon J, Bailey M, Cicuttini F (2001). Boswellia serrata extract: a perspective treatment for knee osteoarthritis: a clinical evaluation. Altern. Complement. Ther. 8: 341-348.

Brand C, Snaddon J, Bailey M, Cicuttini F (2001). Boswellia serrata extract: a perspective treatment for knee osteoarthritis: a clinical evaluation. Altern. Complement. Ther. 8: 341-348.

Brand C, Snaddon J, Bailey M, Cicuttini F (2001). Boswellia serrata extract: a perspective treatment for knee osteoarthritis: a clinical evaluation. Altern. Complement. Ther. 8: 341-348.

Brand C, Snaddon J, Bailey M, Cicuttini F (2001). Boswellia serrata extract: a perspective treatment for knee osteoarthritis: a clinical evaluation. Altern. Complement. Ther. 8: 341-348.

Brand C, Snaddon J, Bailey M, Cicuttini F (2001). Boswellia serrata extract: a perspective treatment for knee osteoarthritis: a clinical evaluation. Altern. Complement. Ther. 8: 341-348.

Brand C, Snaddon J, Bailey M, Cicuttini F (2001). Boswellia serrata extract: a perspective treatment for knee osteoarthritis: a clinical evaluation. Altern. Complement. Ther. 8: 341-348.

Brand C, Snaddon J, Bailey M, Cicuttini F (2001). Boswellia serrata extract: a perspective treatment for knee osteoarthritis: a clinical evaluation. Altern. Complement. Ther. 8: 341-348.

Brand C, Snaddon J, Bailey M, Cicuttini F (2001). Boswellia serrata extract: a perspective treatment for knee osteoarthritis: a clinical evaluation. Altern. Complement. Ther. 8: 341-348.
importance of the patellofemoral joint. Ann. Rheum. Dis. 51: 844-849.

Miller MJ, Mehta K, Kunte S, Raut V, Gaia J, Dhumale R, Shukla A, Tupali H, Parikh H, Bobrowski P, Chaudhary J (2005). Early relief of osteoarthritis symptoms with a natural mineral supplement and a herbomineral combination: a randomized controlled trial [ISRCTN38432711]. J. Inflamm. (Lond). 2: p. 11.

Moskowitz RW (2000). Role of collagen hydrolysate in bone and joint disease. Semin. Arthritis Rheum. 30: 87-99.

Nagaoka I, Nabeshima K, Murakami S, Yamamoto T, Watanabe K, Tomonaga A, Yamaguchi H (2010). Evaluation of the effects of a supplementary diet containing chicken extract on symptoms and cartilage metabolism in patients with knee osteoarthritis. Exp. Ther. Med. 1: 817-827.

Oben J, Enonchong E, Kothari S, Chambliss W, Garrison R, Dolnick D (2009). Phellodendron and Citrus extracts benefit joint health in osteoarthritis patients: a pilot, double-blind, placebo-controlled study. Nutr. J. 8: p. 38.

Peat G, McCarney R, Croft P (2001). Knee pain and osteoarthritis in older adults: a review of community burden and current use of primary health care. Ann. Rheum. Dis. 60: 91-97.

Piscoya J, Rodriguez Z, Bustamante SA, Okuhama NN, Miller MJ, Sandoval M (2001). Efficacy and safety of freeze-dried cat's claw in osteoarthritis of the knee: mechanisms of action of the species Uncaria guianensis. Inflamm. Res. 50: 442-448.

Ruff KJ, Devore DP, Leu MD, Robinson MA (2009). Eggshell membrane: a possible new natural therapeutic for joint and connective tissue disorders. Results from two open-label human clinical studies. Clin. Interv. Aging. 4: 235-240.

Sengupta K, Alluri KV, Satish AR, Mishra S, Golakoti T, Sarma KV, Dey D, Raychaudhuri SP (2008). A double blind, randomized, placebo controlled study of the efficacy and safety of 5-Loxin for treatment of osteoarthritis of the knee. Arthritis Res. Ther. 10: R85.

Svensson O, Malmenäs M, Fajutrao L, Roos EM, Lohmander LS (2006). Greater reduction of knee than hip pain in osteoarthritis treated with naproxen, as evaluated by WOMAC and SF-36. Ann. Rheum. Dis. 65: 781-784.

Trijau S, Avouac J, Escalas C, Gossec L, Dougados M (2010). Influence of flare design on symptomatic efficacy of non-steroidal anti-inflammatory drugs in osteoarthritis: a meta-analysis of randomized placebo-controlled trials. Osteoarthritis Cartilage, 18: 1012-1018.

Usha PR, Naidu MU (2004). Randomised, double-blind, parallel, placebo-controlled study of oral glucosamine, methylsulfonylmethane and their combination in osteoarthritis. Clin. Drug. Investig. 24: 353-363.

Vangnesson Jr. CT, Spiker W, Erickson J (2009). A review of evidence-based medicine for glucosamine and chondroitin sulfate use in knee osteoarthritis. Arthroscopy, 25: 86-94.

Wandel S, Jönin P, Tendal B, Niesch E, Villiger PM, Welton NJ, Reichenbach S, Trell S (2010). Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis. BMJ. 341: c4675.

Wigler I, Grotto I, Caspi D, Yaron M (2003). The effects of Zintona EC (a ginger extract) on symptomatic gonarthritis. Osteoarthritis Cartilage, 11: 783-789.

Wluka AE, Stuckey S, Brand C, Cicuttini FM (2002). Supplementary vitamin E does not affect the loss of cartilage volume in knee osteoarthritis: a 2 year double blind randomized placebo controlled study. J. Rheumatol. 29: 2585-2591.

Woo J, Ho KC, Lau J, Leung PC (1994). Musculoskeletal complaints and associated consequences in elderly Chinese aged 70 years and over. J. Rheumatol. 21: 1927-1931.

Woof AD, Pfleger B (2003). Burden of major musculoskeletal conditions. Bull. World Health Organ. 81: 646-656.

Zhang W, Doherty M (2006). EULAR recommendations for knee and hip osteoarthritis: a critique of the methodology. Br. J. Sports Med. 40: 664-669.