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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 I^2 heterogeneity test (Higgins et al., 2003).

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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, $I^2 = 0\%$). 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., Khambat, 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 (Aquamin®, 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, $I^2 = 96\%$). 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,

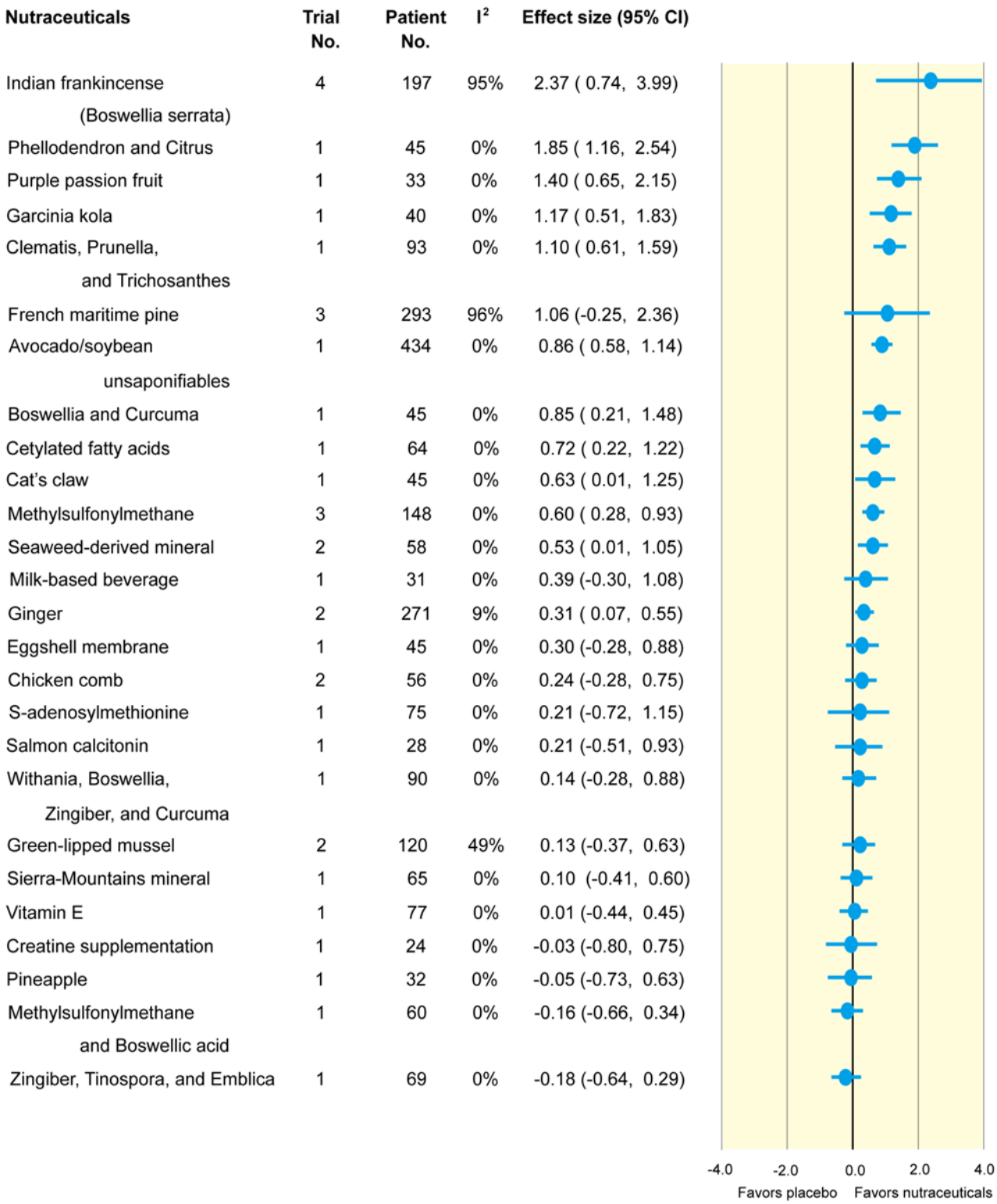

Figure 1. Short-term efficacy of nutraceuticals on pain alleviation

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.

Nutraceuticals	Trial No.	Patient No.	I^2	Effect size (95% CI)
Green-lipped mussel	2	120	0%	0.76 (0.39, 1.12)
Methylsulfonylmethane and Boswellic acid	1	60	0%	0.68 (0.17, 1.20)
Withania. Boswellia, Zingiber, and Curcuma	1	90	0%	0.45 (0.03, 0.86)
Vitamin E	1	77	0%	0.35 (-0.09, 0.80)
Collagen hydrolysate	2	403	0%	0.06 (-0.14, 0.25)

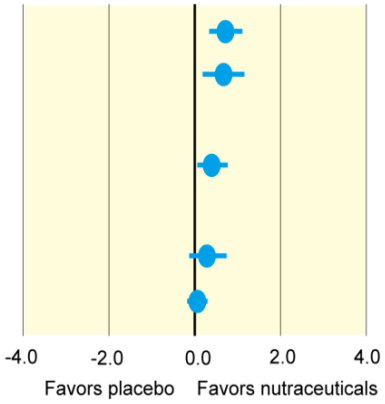

Figure 2. Long-term efficacy of nutraceuticals on pain alleviation.

Peel extract of *Passsiflora 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

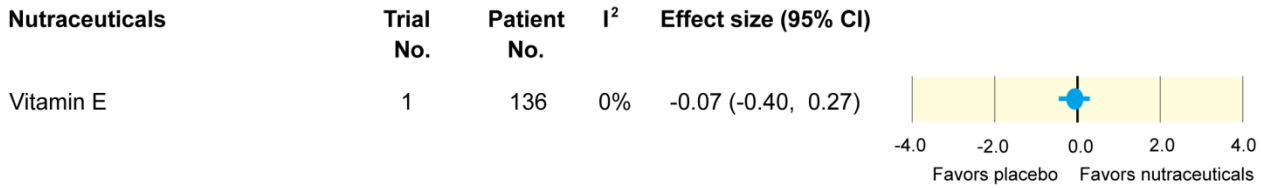

Figure 3. Efficacy of nutraceuticals on structural change.

AG, Eberbach, Germany) was administered (at an unknown dose). According to the current analyses, it was not more effective than placebo at the short- and long-term. However, the first trial reported that in further analysis, as categorized by country, patients from Germany gained more benefits than those from the USA and the UK.

Eggshell membrane

The short-term efficacy of eggshell membrane was investigated in one trial (Ruff et al., 2009). NEM® (Membrell LLC, Carthage, MO, USA), which is produced from eggshell membrane, was given to patients once daily in a dose of 500 mg. Current analysis reveals that NEM® was not more effective than placebo.

Salmon calcitonin

The short-term efficacy of oral salmon calcitonin was investigated in one trial (Manicourt et al., 2006). In this trial, oral salmon calcitonin was administered daily in the form of tablets at doses of 0.5 and 1 mg. Current analysis shows that oral salmon calcitonin was not more effective than placebo at either of these two doses.

Vitamin B5

The short-term efficacy of vitamin B5 was investigated in one trial (Haslock and Wright, 1971). Vitamin B5 was administered twice daily as an oral tablet with a dose of 50 mg. This trial reported that vitamin B5 did not provide any pain alleviation compared to placebo. Because it did not present enough data, we could not conduct the analysis.

Vitamin E

The efficacy of vitamin E was investigated in one trial (Brand et al., 2001). Vitamin E was administered once daily as an oral tablet with a dose of 500 IU. Current analyses for short- and long-term efficacy show that vitamin E did not provide any pain alleviation compared to placebo.

EFFICACY OF NEUTRACEUTICALS 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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