ejpmr, 2020,7(1), 01-07

SJIF Impact Factor 6.222

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

LUBANRELIEF A NOVEL NATURAL TOPICAL FOR OSTEOARTHRITIS

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Article Received on 24/10/2019 **Article Revised on 14/11/2019** **Article Accepted on 04/12/2019**

ABSTRACT

Osteoarthritis (OA) is the most common type of arthritis. It is also known as degenerative arthritis or degenerative joint disease or "wear and tear" arthritis. It occurs when the cartilage or cushion between joints breaks down leading to pain, stiffness and swelling. The most common symptoms of osteoarthritis are stiffness, particularly first thing in the morning or after resting, and pain. Affected joints may get swollen after extended activity. OA is the major cause of disability in both the developed and developing countries. The worldwide estimate for symptomatic OA is 9.6% among men and 18% among women. In USA only OA affects approximately 27 million people. Osteoarthritis has no specific cause, however, there are several factors lead to the development of OA including excess weight, injury or overuse and genes, among others. As far as treatment of OA is concerned, this disease cannot be reversed, but treatment can reduce primary pain. There are several options that can help reduce pain and helps patients move better. It includes using oral non-steroidal anti-inflammatory drugs (NSAIDs) such as aspirin, ibuprofen, nabumetone and naproxen. It is sometimes possible to use NSAIDs temporarily and then discontinue them for periods of time without recurrent symptoms, thereby, decreasing the risk of side effects. Further, topical diclofenac topical gel (voltaren) is used to relieve osteoarthritis pain in the knees. It works by stopping the body's production of a substance that causes pain. Among other conventional treatment of OA is surgery, joint injection of glucocorticoids and hyaluronic acid. On the other hand, there are several non-conventional treatments used for OA including glucosamine and chondroitin sulfate, curcumin, Boswellia serrata extracts and others. In addition, acupuncture, electrostimulation and electromagnetic field and others are also used. We describe in this paper a new topical herbal remedy named LubanRelief with potent anti -inflammatory and analgesic properties that make it a promising treatment for osteoarthritis when taken alongside with OsteoLuban capsule.

KEYWORDS: OA including glucosamine and chondroitin sulfate, curcumin, Boswellia serrata extracts.

INTRODUCTION

Osteoarthritis (OA) is a type of joint disease that results from breakdown of joint cartilage and underlying bone.[1] OA is sometimes called degenerative joint disease or degenerative arthritis. OA is the most common chronic condition of the joints, progressive and debilitating. It can affect any joint, but it occurs most often in knees, hips, lower back and neck, small joints of the fingers and the bases of the thumb and big toe. It affects millions of people worldwide.[2] In normal joints, cartilage covers and protects the ending part of the bones, promoting friction and absorbing impacts. The progressive joint destruction leads to lameness, pain, mobility limitations and comprises the overall quality of life.[2] The most commonly involved joints are those near the ends of the fingers, at the base of the thumb, neck, lower back, knee, and hips.[3] Joints on one side of the body are often more affected than those on the other.[2] Causes of OA include previous joint injury, abnormal joint or limb development, and inherited factors.[3,4] Risk is greater in those who are overweight, have legs of different lengths, or have jobs that result in high levels of joint stress.[3,4,5] OA is believed to be caused by mechanical stress on the joint and low-grade inflammatory processes.[7] It develops as cartilage is lost and the underlying bone becomes affected[3] as pain may make it difficult to exercise, muscle loss may occur.[3,6]

Worldwide estimation reported over 100 million people globally suffer from OA, which is one of the most common causes of disability.[6,7] As per the WHO report on disability (2011), the prevalence of moderate and severe disability (in millions) due to OA in high-income countries was 1.9 and 8.1 in the age group of 0–59 and above 60 years, respectively. In the low- and middle-income countries, these figures were 14.1 and 19.4.[8] The worldwide prevalence estimate for symptomatic OA is 9.6% among men and almost double (18%) among women.[9]

Among the factors that can increase your risk of osteoarthritis include

- Older age. The risk of osteoarthritis increases with age.
- Sex. Women are more likely to develop osteoarthritis, though it isn't clear why.
- Obesity. Carrying extra body weight contributes to osteoarthritis in several ways, and the more you weigh, the greater your risk. Increased weight adds stress to weight-bearing joints, such as your hips and knees. Also, fat tissue produces proteins that can cause harmful inflammation in and around your joints.
- Joint injuries. Injuries, such as those that occur when playing sports or from an accident, can increase the risk of osteoarthritis. Even injuries that occurred many years ago and seemingly healed can increase your risk of osteoarthritis.
- Repeated stress on the joint. If your job or a sport you play places repetitive stress on a joint, that joint might eventually develop osteoarthritis.
- Genetics. Some people inherit a tendency to develop osteoarthritis.
- Bone deformities. Some people are born with malformed joints or defective cartilage.
- Certain metabolic diseases. These include diabetes and a condition in which your body has too much iron (hemochromatosis).

Diagnosis of OA is made with reasonable certainty based on history and clinical examination.[10,11] X-rays may confirm the diagnosis. The typical changes seen on X-ray include: joint space narrowing, subchondral sclerosis (increased bone formation around the joint). subchondral cyst formation, and osteophytes.[12] Usually other imaging techniques are not necessary to clinically diagnose osteoarthritis. In 1990, the American College of Rheumatology, using data from a multi-center study, developed a set of criteria for the diagnosis of hand osteoarthritis based on hard tissue enlargement and swelling of certain joints.[13] These criteria were found to be 92% sensitive and 98% specific for hand osteoarthritis versus other entities such as rheumatoid arthritis and spondyloarthropathies.[13] On the other hand, analyzing blood or joint fluid can help confirm the diagnosis.

Concerning treatment of OA, there are several options that can be categorized as follows

A. By mouth

The first line of treatment for OA by mouth is pain medication which is a NSAID drug represented by paracetamol (acetaminophen).[14,15] Pain relief does not differ according to dosage.[16] For mild to moderate symptoms effectiveness of acetaminophen is similar to NSAIDs such as naproxen, though for more severe symptoms NSAIDs may be more effective.[14] NSAIDs are associated with greater side effects such as gastrointestinal bleeding.[14] Another class of NSAIDs, COX-2 selective inhibitors (such as celecoxib) are equally effective when compared to nonselective NSAIDs.[17] Opioids by mouth, including both weak opioids such as tramadol and stronger opioids, are also often prescribed. Oral steroids are not recommended in the treatment of osteoarthritis.[15]

B. Topical

There are several NSAIDs available for topical use, including diclofenac. The use of topical capsaicin to treat osteoarthritis is controversial, as some reviews found benefit[18,19] while others did not.[20]

C. Joint injections

Joint injection of glucocorticoids (such as hydrocortisone) leads to short term pain relief that may last between a few weeks and a few months.[21] Injections of hyaluronic acid have not produced improvement compared to placebo for knee arthritis.[22,23]

D. Surgery

Includes joint replacement surgery or resurfacing.

E. Complimentary medicine

a. Glucosamine and chondroitin

The effectiveness of glucosamine is controversial.[24] Reviews have found it to be equal to[25,26] or slightly better than placebo.[27,28] A 2015 Cochrane review of clinical trials of chondroitin found that most were of low quality, but that there was some evidence of short-term improvement in pain and few side effects; it does not appear to improve or maintain the health of affected joints.[29]

b. Other remedies

Avocado–soybean unsaponifiable (ASU) is an extract made from avocado oil and soybean oil[30] that is sold under many brand names worldwide as a dietary supplement[31] and as a drug in France. A few high-quality studies of Boswellia serrata show consistent, but small, improvements in pain and function.[30] Curcumin[32], Phyto dolor[18], and s-adenosyl methionine (SAMe)[18] may be effective in improving pain .On the other hand, there is little evidence supporting benefits for some supplements, including: the Ayurvedic herbal preparations with brand names Articulin F and Eazmov; Duhuo Jisheng Wan, a Chinese herbal preparation; fish liver oil; ginger; Russian olive; the herbal preparation gitadyl; omega-3 fatty acids; the brand-name product Reumalax; stinging nettle; vitamins A, C, and E in combination; vitamin E alone; vitamin K; vitamin D; collagen; and willow bark. There is insufficient evidence to make a recommendation about the safety and efficacy of these treatments.[18,33]

c. Acupuncture and other interventions

While acupuncture leads to improvements in pain relief, this improvement is small and may be of questionable importance.[34] Waiting list–controlled trials for peripheral joint osteoarthritis do show clinically relevant benefits, but these may be due to placebo effects.[35,36]

Acupuncture does not seem to produce long-term benefits.

d. Electrostimulation techniques such as TENS have been used for twenty years to treat osteoarthritis in the knee, however there is no conclusive evidence to show that it reduces pain or disability. Further research is needed to determine if balneotherapy for osteoarthritis (mineral baths or spa treatments) improves a person's quality of life or ability to function.[37]

LubanRelief is a new class of herbal- based evidence remedy that contains monographic herbal ingredients (Boswellia sacra extract and sesame and peppermint oils) which is particularly designed for those suffering from OA. LubanRelief exhibited potential anti- inflammatory and analgesic properties both in vitro and in vivo and also in clinical studies. This OTC product is superior in its action compared to topical diclofenac topical gel (voltaren) and some other topical which are used to relieve osteoarthritis pain in the knees. The pharmacological action reported by this product indicated its action on the inflammatory response by blocking pro-inflammatory 5-lipoxygenease enzyme (5-LOX). Therefore, it is a class of products that can be used for OA and other related diseases such as rheumatism. This product is not only pain relief but also has potential effect in reducing "inflammation".

Description

LubanRelief is a very distinguished product that developed after careful preclinical and clinical studies. Several in vitro and in vivo studies were conducted to study the efficacy and safety of this product both in vitro and in vivo. For in vitro studies several human and murine cell lines were used including primary murine microglia, raw mouse macrophages, primary human monocytes and primary human fibroblasts to see its effect on prostaglandin E2, interleukin 1beta, tumor necrosis factor and interleukin6. These studies showed that the product possess significant anti- inflammatory properties.

For in vivo studies, the activity of the product was studied in albino rats using two different pharmacological screening tests, these are.

a. Inhibition of ascites using rats
b. Freund's adjuvant using rats

The results showed that LubanRelief exhibited a potential activity compared to phenylbutazone drug in causing a diminution of ascites fluid. Further, another confirmatory result from Freund's adjuvant test which clearly showed that LubanRelief is more active compared with the standard drugs used in this test represented by brufen and aspirin.

Further, the analgesic property of LubanRelief was evaluated using two pharmacological screening tests, these are:

a. Writhing induced by chemicals using mice
b. Hot plate test using mice

LubanRelief was more potent as analgesic in both pharmacological tests compared with the reference standard used in the two above tests represented by paracetamol.

On the other hand, the oral acute toxicity of LubanRelief was investigated in vivo utilizing healthy experimental mice as a model. A single dose was administered to the animals followed by monitoring for a period of 14 days after dosing and recording death and changes in animal behavior and any other physical variables. The results obtained indicated that the oral LD50 of LubanRelief is at least greater than 2000 mg/ kg in balb/c mice. In addition, LubanRelief neither induced any death nor caused any abnormal behavior when tested at a dose of 2000 mg/ kg. The skin sensitivity of LubanRelief was studied in guinea pigs. The animals were carefully observed for six weeks for the accumulation purposes. The followings scores were measured to see the effect of intradermal irritation of the LubanRelief.

1. Degree of erythema.
2. Presence of erythema.
3. Behavioral of the erythema.
4. Food and water intake.
5. Average body weight.

In addition, both gross and microscopic examinations were done on most of the important organs (liver, kidney, skin). Generally speaking, no changes in the color of the skin of the animals were recorded when compared with the untreated control and no edema was observed in the skin of the experimental animals. This indicate that LubanRelief has no irritation effect on the skin of guinea pigs. Further, no gross or pathological findings were observed in biopsies taken from the liver, kidney and skin in the experimental animals compared to the untreated controls. In order explain the healing effect of LubanRelief, it is evident from HPLC analysis of LubanRelief that Boswellic acids may contribute significantly in to the potency of this product.

LubanRelief (Figure1) is a very distinguished product that developed after careful preclinical and clinical studies. Several in vitro and in vivo studies were conducted to study the efficacy and safety of this product both in vitro and in vivo. For in vitro studies several human and murine cell lines were used including primary murine microglia, raw mouse macrophages, primary human monocytes and primary human fibroblasts to see its effect on prostaglandin E2, interleukin 1beta, tumor necrosis factor and interleukin6. These studies showed that the product possess significant anti-inflammatory properties.

For in vivo studies, the activity of the product was studied in albino rats using two different pharmacological screening tests, these are.

c. Inhibition of ascites using rats
d. Freund's adjuvant using rats

LubanRelief exhibited a potential activity compared to phenylbutazone drug in causing a diminution of ascites fluid. Further, another confirmatory result from Freund's adjuvant test which clearly showed that LubanRelief is more active compared with the standard drugs used in this test represented by Brufen and aspirin.

Further, the analgesic property of LubanRelief was evaluated using two pharmacological screening tests, these are:

c. Writhing induced by chemicals using mice.
d. Thermal stimulus using mice

LubanRelief was more potent as analgesic in both tests compared with the reference standard used in the two above tests represented by paracetamol.

Properties of LubanRelief:

* Helps in easing pain and reducing inflammation
*Helps in maintaining healthy joints, cartilages and tendons
*Helps to treat osteoarthritis
*Helps for short term relief of low back pain
*Helps for the relief of minor joint and articular pain
*Has antioxidant properties

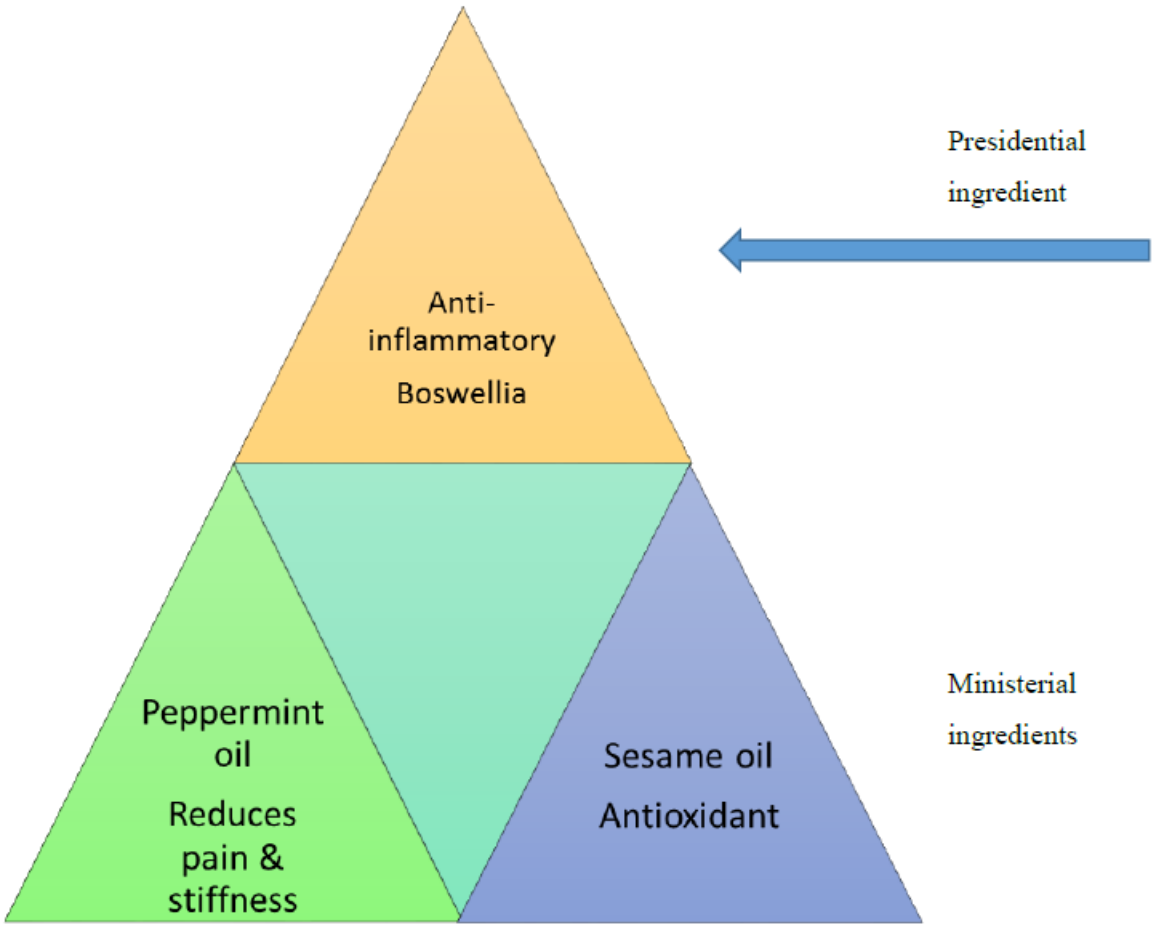

Figure 1.

Figure 2.

The healing paradigm of this product (figure2) is that its use encourages a person to use this product by patients suffering from osteoarthritis to suppress inflammation and ease pain.

- Frankincense contains alpha-keto boswellic acid (AKBA), Keto-boswellic acid (KBA), Beta-boswellic acid (β-BA) and other triterpenoid compounds. The pharmacological action documented for AKBA and KBA through leukotriene β-boswellic acid has enzyme cathepsin and microsomal prostaglandin E synthase as demulcent.
- Sesame oil contains fatty acids such as oleic, palmitic, stearic and linoleic acids. It's also very high in vitamins A&E and contains antioxidants and sesamol, which counteract free radicals (a primary cause of aging). Further, it improves oxidative stress-associated muscle dysfunction.
- Peppermint oil has a high menthol content. It also contains menthone, methyl acetate and others. It is effective as cooling and pain agent and relief from itching. In addition, it reduces pain and stiffness and has anesthetic effect.
- The medical and non-medical ingredients in LubanRelief work in an effective and synergistic way to support each of the claims, which on the other hand, support the healing paradigm.

RESULTS

LubanRelief is a product which consist of selected and unique blend of ingredients. The major ingredient is represented by the monographic and well- researched herb extract obtained from Omani oleogum resin which prove to have diversified actions. This extract includes six boswellic and two lupeolic acids, polyphenols, flavonoids, menthol, menthone, oleic and palmitic acids and other compounds. LubanRelief includes other unique combination of ingredients such as sesame oil, and peppermint oil which potentiate their effect on the body. According to feedback received from some clinicians who tested this product on patients suffering from osteoarthritis, the inflammation in patients with OA is reduced through the inhibition the release of pro-inflammatory mediators by boswellic acids. Further, with reduced "inflammation", nerve irritation will also decease which lead to reduced pain sensation. Being an antioxidant, LubanRelief facilitates removal of free radicals in the body that causes damage to the body structures including joints, cartilages, tendons, and synovial membrane. Finally, it seems that the medicinal ingredients in LubanRelief work in an effective and synergistic way to support each claim, which on the other hand, support the healing paradigm.

Properties of Luban Relief

LubanRelief is a unique natural health product composed of an optimized extract obtained from Boswellia sacra gum resin using special extraction procedure[38] and was characterized using HPLC/MS/MS method and contains 3.22 ug/mg 11-keto-beta boswellic acid(KBA); 50.400 ug/mg acetyl-11-keto-beta-boswellic acid (AKBA); 8.66 ug/mg lupeolic acid; 14.850 ug/mg alpha-boswellic acid (alpha –BA); 40.250 ug/mg beta-boswellic acid (Beta_BA); 42.550 ug/mg acetyl lupeolic acid; 49.900 ug/mg alpha-acetyl-boswellic acid and 86.200 ug/mg acetyl-beta-boswellic acid and other triterpenoid compounds. In addition, the product contains sesame oil and peppermint oil. The pharmacological action of this extract showed potential anti-inflammatory and analgesic effects. Further, it contains menthol oil which helps in reducing pain and stiffness as anti-inflammatory and anesthetic agent. Finally, it contains sesame oil which act as antioxidant and improve oxidative stress-associated muscle dysfunction. Therefore, the medicinal ingredients in LubanRelief work in an effective and synergistic way to support each of the claims, which on the other hand, support the healing paradigm.

Therapeutic values of LubanRelief Ointment

- May help as anti-inflammatory and analgesic.
- May improve oxidative stress-associated muscle dysfunction.
- Has antioxidant property and may improve oxidative stress-associated muscle dysfunction.
- May help as anaesthetic agent.

Recommended use of purpose

1. Boswellia extract have potential anti-inflammatory and analgesic effect
2. Sesame oil has antioxidant effect.
3. Peppermint oil have anesthetic and natural analgesic agent.

Side effects

1. No serious side effects were reported from using this product.
2. Contraindications:
3. No contraindications reported so far from using this product.

Direction for use

It is recommended to apply LubanRelief on the affected areas by massaging it circularly for few minutes 3-4 times daily.

REFERENCES

1. Arden N, Blanco F, Cooper C, Guermazi A, Hayashi D, Hunter D, Javaid MK, Rannou F, Roemer FW, Reginster JY (2015). Atlas of Osteoarthritis. Springer. p. 21. ISBN 978-1-910315-16-3. Archived from the original on 8 September 2017.
2. Martello E, Bigliati M, Bisanzio D, Biasibetti E, Dosio F, Pastorino D, De Nardi M, Bruni N (2019). Effects on pain mobility of a new diet supplement in dogs with osteoarthritis: A pilot Study. Annals of Clinical Laboratory Research.7 N (2): 304 (1-5) doi: 10.21767/2386-5180.100304.

3. "Osteoarthritis". National Institute of Arthritis and Musculoskeletal and Skin Diseases. April 2015. Archived from the original on 18 May 2015. Retrieved 13 May 2015.
4. Glyn-Jones S, Palmer AJ, Agricola R, Price AJ, Vincent TL, Weinans H, Carr AJ (July 2015). "Osteoarthritis". Lancet, 386(9991): 376–87.
5. Vingård E, Englund M, Järvholm B, Svensson O, Stenström K, Brolund A, Hall C, Kedebring T, Kirkeskov L, Nordin M (1 September 2016). Occupational Exposures and Osteoarthritis: A systematic review and assessment of medical, social and ethical aspects. SBU Assessments (Report). Graphic design by Anna Edling. Stockholm: Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU), 1. 253 (in Swedish). Retrieved 8 April 2018.
6. Conaghan P (2014). "Osteoarthritis – Care and management in adults" (PDF). Archived from the original on 22 December 2015.
7. Di Puccio F, Mattei L (January 2015). "Biotribology of artificial hip joints". World Journal of Orthopedics, 6(1): 77–94. doi:10.5312/wjo.v6.i1.77. PMC 4303792. PMID 25621213.
8. March L, Smith EU, Hoy DG, Cross MJ, Sanchez-Riera L, Blyth F, Buchbinder R, Vos T, Woolf AD (June 2014). "Burden of disability due to musculoskeletal (MSK) disorders". Best Practice & Research. Clinical Rheumatology, 28(3): 353–66. doi:10.1016/j.berh.2014.08.002. PMID 25481420.
9. Elsternwick (201 Zhang W, Doherty M, Peat G, Bierma-Zeinstra MA, Arden NK, Bresnihan B, Herrero-Beaumont G, Kirschner S, Leeb BF, Lohmander LS, Mazières B, Pavelka K, Punzi L, So AK, Tuncer T, Watt I, Bijlsma JW (March 2010).
10. Zhang W, Doherty M, Peat G, Bierma-Zeinstra MA, Arden NK, Bresnihan B, Herrero-Beaumont G, Kirschner S, Leeb BF, Lohmander LS, Mazières B, Pavelka K, Punzi L, So AK, Tuncer T, Watt I, Bijlsma JW (March 2010). "EULAR evidence-based recommendations for the diagnosis of knee osteoarthritis". Annals of the Rheumatic Diseases, 69(3): 483–9. doi:10.1136/ard.2009.113100. PMID 19762361.
11. Bierma-Zeinstra SM, Oster JD, Bernsen RM, Verhaar JA, Ginai AZ, Bohnen AM (August 2002). "Joint space narrowing and relationship with symptoms and signs in adults consulting for hip pain in primary care". The Journal of Rheumatology, 29(8): 1713–8. PMID 12180735.
12. Kalunian KC (2013). "Patient information: Osteoarthritis symptoms and diagnosis (Beyond the Basics)". UpToDate. Archived from the original on 22 September 2010. Retrieved 15 February 2013.
13. Altman R, Alarcón G, Appelrouth D, Bloch D, Borenstein D, Brandt K, Brown C, Cooke TD, Daniel W, Gray R (November 1990). "The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hand". Arthritis and Rheumatism, 33(11): 1601-10.
14. Flood J (March 2010). "The role of acetaminophen in the treatment of osteoarthritis". The American Journal of Managed Care. 16 Suppl Management (Suppl Management): S48–54. PMID 20297877. Archived from the original on 22 March 2015.
15. Zhang W, Moskowitz RW, Nuki G, Abramson S, Altman RD, Arden N, Bierma-Zeinstra S, Brandt KD, Croft P, Doherty M, Dougados M, Hochberg M, Hunter DJ, Kwoh K, Lohmander LS, Tugwell P (September 2007). "OARSI recommendations for the management of hip and knee osteoarthritis, part I: critical appraisal of existing treatment guidelines and systematic review of current research evidence". Osteoarthritis and Cartilage, 15(9): 981–1000. doi:10.1016/j.joca.2007.06.014. PMID 17719803.
16. Flood J (March 2010). "The role of acetaminophen in the treatment of osteoarthritis". The American Journal of Managed Care. 16 Suppl Management (Suppl Management): S48–54. PMID 20297877. Archived from the original on 22 March 2015.
17. Karabis A, Nikolakopoulos S, Pandhi S, Papadimitropoulou K, Nixon R, Chaves RL, Moore RA (March 2016). "High correlation of VAS pain scores after 2 and 6 weeks of treatment with VAS pain scores at 12 weeks in randomised controlled trials in rheumatoid arthritis and osteoarthritis: meta-analysis and implications". Arthritis Research & Therapy, 18: 73. doi:10.1186/s13075-016-0972-7. PMC 4818534. PMID 27036633.
18. De Silva V, El-Metwally A, Ernst E, Lewith G, Macfarlane GJ (May 2011). "Evidence for the efficacy of complementary and alternative medicines in the management of osteoarthritis: a systematic review". Rheumatology, 50(5): 911–20. doi:10.1093/rheumatology/keq379. PMID 21169345.
19. Cameron M, Gagnier JJ, Little CV, Parsons TJ, Blümle A, Chrubasik S (November 2009). "Evidence of effectiveness of herbal medicinal products in the treatment of arthritis. Part I: Osteoarthritis". Phytotherapy Research, 23(11): 1497-515. doi:10.1002/ptr.3007. hdl:2027.42/64567. PMID 19856319.
20. Altman R, Barkin RL (March 2009). "Topical therapy for osteoarthritis: clinical and pharmacologic perspectives". Postgraduate Medicine, 121(2): 139–47. doi:10.3810/pgm.2009.03.1986. PMID 19332972.
21. Arroll B, Goodyear-Smith F (April 2004). "Corticosteroid injections for osteoarthritis of the knee: meta-analysis". BMJ, 328(7444): 869. doi:10.1136/bmj.38039.573970.7C. PMC 387479. PMID 15039276.
22. Rutjes AW, Jüni P, da Costa BR, Trelle S, Nüesch E, Reichenbach S (August 2012). "Viscosupplementation for osteoarthritis of the knee: a systematic review and meta-analysis". Annals of Internal Medicine, 157(3): 180–91. doi:10.7326/0003-4819-157-3-201208070-00473. PMID 22868835.

23. Jevsevar D, Donnelly P, Brown GA, Cummins DS (December 2015). "Viscosupplementation for Osteoarthritis of the Knee: A Systematic Review of the Evidence". The Journal of Bone and Joint Surgery. American, 97(24): 2047–60. doi:10.2106/jbjs.n.00743. PMID 26677239.
24. Burdett N, McNeil JD (September 2012). "Difficulties with assessing the benefit of glucosamine sulphate as a treatment for osteoarthritis". International Journal of Evidence-Based Healthcare, 10(3): 222–6.
25. Wandel S, Jüni P, Tendal B, Nüesch E, Villiger PM, Welton NJ, Reichenbach S, Trelle S (September 2010). "Effects of glucosamine, chondroitin, or placebo in patients with osteoarthritis of hip or knee: network meta-analysis". BMJ, 341: c4675. doi:10.1136/bmj.c4675. PMC 2941572. PMID 20847017.
26. Wu D, Huang Y, Gu Y, Fan W (June 2013). "Efficacies of different preparations of glucosamine for the treatment of osteoarthritis: a meta-analysis of randomised, double-blind, placebo-controlled trials". International Journal of Clinical Practice, 67(6): 585-94. doi:10.1111/ijcp.12115. PMID 23679910.
27. Chou R, McDonagh MS, Nakamoto E, Griffin J (October 2011). "Analgesics for Osteoarthritis: An Update of the 2006 Comparative Effectiveness Review". Comparative Effectiveness Reviews. 38. Agency for Healthcare Research and Quality (AHRQ). PMID 22091473. Archived from the original on 10 March 2013.
28. Miller KL, Clegg DO (February 2011). "Glucosamine and chondroitin sulfate". Rheumatic Diseases Clinics of North America, 37(1): 103-18. doi:10.1016/j.rdc.2010.11.007. PMID 21220090. The best current evidence suggests that the effect of these supplements, alone or in combination, on OA pain, function, and radiographic change is marginal at best.
29. Singh JA, Noorbaloochi S, MacDonald R, Maxwell LJ (January 2015). "Chondroitin for osteoarthritis". The Cochrane Database of Systematic Reviews. 1: CD005614. doi:10.1002/14651858.CD005614.pub2. PMC 4881293. PMID 25629804.
30. Cameron M, Chrubasik S (May 2014). "Oral herbal therapies for treating osteoarthritis". The Cochrane Database of Systematic Reviews, 5(5): CD002947. doi:10.1002/14651858.CD002947. pub2. PMC 4494689. PMID 24848732.
31. Christiansen BA, Bhatti S, Goudarzi R, Emami S (January 2015). "Management of Osteoarthritis with Avocado/Soybean Unsaponifiables". Cartilage, 6(1): 30–44. doi:10.1177/1947603514554992. PMC 4303902. PMID 25621100.
32. Grover AK, Samson SE (January 2016). "Benefits of antioxidant supplements for knee osteoarthritis: rationale and reality". Nutrition Journal, 15: 1. doi:10.1186/s12937-015-0115-z. PMC 4700773. PMID 26728196.
33. Hussain S, Singh A, Akhtar M, Najmi AK (September 2017). "Vitamin D supplementation for the management of knee osteoarthritis: a systematic review of randomized controlled trials". Rheumatology International, 37(9): 1489–1498. doi:10.1007/s00296-017-3719-0. PMID 28421358.
34. Lin X, Manheimer E, Cheng K, Linde K, Lao L, Yoo J, Wieland S, et al. (January 2010). Manheimer E (ed.). "Acupuncture for peripheral joint osteoarthritis". The Cochrane Database of Systematic Reviews (1): CD001977. doi:10.1002/14651858.CD001977.pub2. PMC 3169099. PMID 20091527.
35. Huang K, Zhu G, Huang Z, Qin A, Fan S (September 2016). "The Effects of Acupuncture on Chronic Knee Pain Due to Osteoarthritis: A Meta-Analysis". The Journal of Bone and Joint Surgery. American Volume. 98 (18): 1578–85. doi:10.2106/jbjs.15.00620. PMID 27655986.
36. Manheimer E, Cheng K, Wieland LS, Shen X, Lao L, Guo M, Berman BM (May 2018). "Acupuncture for hip osteoarthritis". The Cochrane Database of Systematic Reviews. 5: CD013010. doi:10.1002/14651858.CD013010. PMC 5984198. PMID 29729027.
37. Verhagen AP, Bierma-Zeinstra SM, Boers M, Cardoso JR, Lambeck J, de Bie RA, de Vet HC (October 2007). "Balneotherapy for osteoarthritis". The Cochrane Database of Systematic Reviews (4): CD006864. doi:10.1002/14651858.CD006864. PMID 17943920.
38. Rashan L, Hasson,SSA, Simmet T, Mohammed SAA, Al-Jabri AAH (May 2019),: "Boswellic Acid Extraction".South African Patent Application No. 2019/02740,Filing Date 2 May 2019.
39. Schmiech M, Lang SJ, Werner K, Rashan LJ, Syrovets T, Simmet T (2019),: "Comparative analysis of pentacyclic triterpenic acid composition of oleaogum resins of different Boswellia species and their in vitro cytotoxicity against treatment-resistant human breast cancer cells". Molecules .24,2153; doi:10.3390/molecules24112153