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Network meta-analysis of some herbal medicines for osteoarthritis pain control: a methodology for the efficacy assurance of new pharmaceutical products

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Abstract

Background: Osteoarthritis is the most common cause of arthritis worldwide and one of the most debilitating physical ailments these days. Numerous studies have been conducted on the use of complementary medicine and herbal remedies in the control and reduction of symptoms of osteoarthritis. In this network meta-analysis and systematic review, we aimed to rank some of the herbal medications based on their efficiency in randomized-controlled trials. **Methods:** Online databases of Scopus, Google Scholar, PubMed and etc. have been searched for randomized controlled trials (RCTs) of herbal medications for treating osteoarthritis. Treatment response rates were interpreted as patients with satisfaction, reduced pain (based on a visual analog scale and McMaster Universities Osteoarthritis Index), and reduced use of conventional analgesics. Data were collected employing Odds Ratios (ORs) and analyzed. In WinBUGS and NetMetaXL a Bayesian network meta-analysis was carried out via the Monte Carlo Markov chain approach. **Results:** In total, 2328 patients were analyzed in 12 studies with 4 different herbal regimens including avocado/soybean, rosa canina, curcumin and ginger versus placebo. Method of comparison showed best probability of SUCRA followed by Curcuma longa (87.8%), Zingiber officinale (48.2%), Avocado soybean (48.02%), Rosa canina (47.82%), placebo (18.09%). efficacy of Curcuma longa was significantly higher from other herbal regimens and placebo. **Conclusion:** Our network meta-analysis ranked various herbal regimens used for osteoarthritis relief; this kind of methodology could be used to appropriately select herbals going to be used in new pharmaceutical preparations.

Keywords: network meta-analysis, curcuma longa, zingiber officinale, avocado/soybean, rosa canina, osteoarthritis

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INTRODUCTION

Osteoarthritis is the most common cause of arthritis worldwide, having severe economic and social burdens on the health system, cause severe pain and disability in patients (Glyn-Jones et al. 1991). Almost everyone is exposed to the disease but, it is the most common disease in the elderly (Arden and Nevitt 2006). Of the large joints in the body, the knee is one of the most common sites and knee osteoarthritis is one of the four major causes of physical disability in the elderly (Glyn-Jones et al. 1991). The disease is a silent process and

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usually presents with clinical symptoms when the severity of the disease has reached to irreversible stages. The basis of treatment in osteoarthritis is to relieve pain and minimize loss of physical function (Van den Berg 2011). Non-steroidal anti-inflammatory drugs are the best known drugs for the treatment of osteoarthritis pain that have some important and common side effects (Sinusas 2012). Conventional medical treatments may have a little impact on the course of the disease, and finding effective treatment to preserve and improve the function and quality of life of patients is of paramount importance (Jüni et al. 2006). Most treatments for osteoarthritis are expensive and have many side effects. The main purpose of osteoarthritis treatment is pain relief. Due to the increasing prevalence of osteoarthritis, there is a need for healthy and uncomplicated treatments in this regard (Richardson et al. 2007). Various studies point to the increasing tendency for complementary and traditional medicine treatments in the world. Herb is a plant or part of a plant that has medicinal, aromatic and edible value. Herbal remedies refer to the use of herbal products for their medicinal and therapeutic properties (Kamboj 2000; Meuss 2000; Vickers and Zollman 1999; Firenzuoli and Gori 2007). Plants form a major part of nature and have long been a human interest in food consumption and disease treatment. With the introduction of synthetic drugs into human life for ease of consumption, human attention to plants has declined, but today due to the side effects of synthetic drugs, the use of plants as medicines and beneficial foods has expanded both in world (7–10). Clinical trials are the most reliable method of preparing documentation for the clinical use of plants (Firenzuoli and Gori 2007). Clinical trials are needed to determine the efficacy of the studied plants for their use as herbal medicinal products. But at the same time, as clinical trials, unlike other types of studies, deliberately intervene on subjects, this method of research requires more consideration than other types and methods (Flower et al. 2012). In this study Bayesian network meta-analysis is used to rank some medicinal plants used in various clinical trials. The results of such studies can be used to determine the most proper formulation of herbs used in herbal product patents.

METHODS

Published literature in MEDLINE, EMBASE, BIOSIS Previews, Scopus, Google Scholar, and PubMed to identify were searched for English language articles published between 1950 and 2020 about herbal medications used for osteoarthritis pain treatment. The review included the following treatments: Curcuma longa, Zingiber officinale, Rosa canina, Avocado soybean. Active and placebo-controlled randomized controlled trials (RCTs) were selected for inclusion if published in English. The database search and systematic review was done based on Statement of Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA).

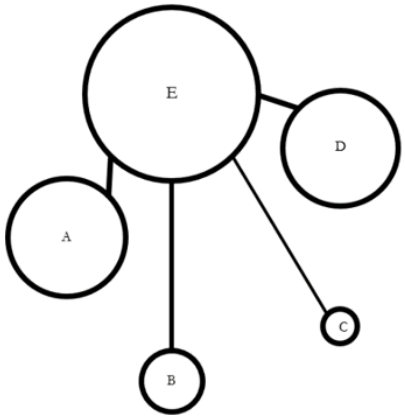
In this systematic and meta-analysis study, studies were enrolled based on inclusion and exclusion criteria. Inclusion criteria were studies that had reported a response rate to treatment and exclusion criteria included: irrelevant studies, inadequate data in the study, and inaccessibility to the full text of the articles. Of course, the papers whose abstracts provided the data were not completely excluded. According to the inclusion and exclusion criteria, the abstracts of the articles were studied by the researcher and the unrelated articles were excluded and the relevant articles were identified to extract the full text. During the search 99 articles were identified, of which 26 were completely unrelated after reviewing their abstracts. Out of 73 possible related abstracts, 2 abstracts were deleted due to unavailability of the full text and 71 full papers were reviewed. In the next step, 31 articles due to insufficient data, 12 articles due to the use of herbs mixed with other plants and 16 duplicate articles were excluded from the study; finally, 12 articles were enrolled in meta-analysis. A checklist was prepared for data extraction including variables: age, country of study, number of samples, type of studies, and response rate to treatment. Data were extracted from all studies. There were 2328 participants in the study. Response to treatment was determined by a variety of variables, such as patient reported satisfaction, decreased visual analog scale (VAS), reduced Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and decreased use of analgesic drugs.

To evaluate the quality of the papers, the full text of the articles was extracted from the bases by two evaluators using the Jadad scoring for trial studies. This tool has 5 main items, each of which deals with the reporting of an important part of a clinical trial. After a separate review by the two evaluators, the differences in the scoring were discussed and a final consensus was commented. Studies with minimum score of 3 were included in our review. Publication bias was evaluated with Egger's test.

A meta-analysis of the Bayesian network was carried out using WinBUGS software. Because the data sets given were dichotomous outcomes and included multi-arm trials, a binomial probability model that accounts for the use of multi-arm trials was used for the analyses. Trials with zero cells in both arms and nodes with no events were removed from the networks of proof because they do not contribute information or require interpretable information. Both fixed and random network effects meta-analyses were performed, although the model of fixed effects was selected as the reference analysis. Using Markov Chain Monte Carlo techniques, we modeled point estimates and 95%

Table 1. Enrolled studies

Study Id	country	Herbal regimen	dosage	Placebo regimen	outcome	Mean age	Treatment duration
Alipour, 2017	Iran	Ginger	500mg twice a day	conventional	VAS	≥50	12 weeks
Altman, 2001	US	Ginger	1 cap twice a day	coconut oil	VAS , WOMAC	≥ 18	6 weeks
Warholm, 2003	Norway	Rose-hip	500 mg twice a day	identical in appearance, taste, and smell to the rose-hip powder capsules	NA	65.2	16 weeks
Winther, 2005	Denmark	Rose-hip	500 mg twice a day	An inactive powder of similar taste, smell, and colour were produced for placebo.	WOMAC	≥ 35	12 weeks
Rein, 2004	Denmark	Rose-hip	500 mg twice a day	Identical placebo	Pain, Rescue medication, stiffness	≥33	12 weeks
Appleboom, 2001	Belgium	avocado/soybean	300 mg / 600 mg	Identical placebo	VAS	45≤age≥80	12 weeks
Lequesne, 2002	France	avocado/soybean	300 mg daily	NA	VAS	50≤age≥80	24 months
Maheu, 2014	France	avocado/soybean	300 mg daily	NA	VAS, WOMAC	35≤age≥82	36 months
Blotman, 1997	France	avocado/soybean	NA	NA	NA	62.9	12 weeks
Panahi, 2014	Iran	Curcumin	500 mg three times a day	NA	VAS, WOMAC	< 80	12 weeks
Nakagawa, 2014	Japan	Curcumin	180 mg twice a day	Made of starch, dextrin, and maltose.	VAS	≥40	8 weeks



Drug	Abbreviation
ginger	A
Rosa canina	B
Curcumin	C
Avocado soybean	D
placebo	E

Fig. 1. Network Diagram for herbal medications of osteoarthritis

credible intervals for odds ratios (OR). NetMetaXL also plots the posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model to identify any loops in the treatment network where inconsistency is present.

RESULTS

Finally, 12 studies (Alipour et al. 2017; Altman and Marcussen 2001; Appleboom et al. 2001; Blotman et al. 1997; Lequesne et al. 2002; Maheu et al. 2014; Naderi et al. 2016; Nakagawa et al. 2014; Panahi et al. 2014; Rein et al. 2004; Warholm et al. 2003; Winther et al. 2005) with 4 different herbal regimens including Avocado soybean, Rosa canina, curcumin, and ginger vs. placebo were analyzed. Totally 2328 patients were entered the study. **Table 1** shows the characteristics of studies. **Fig. 1** shows Network Diagram for herbal medications of osteoarthritis. There was no publication bias as Egger's test p-value was 0.361.

Table 2. SUCRA of each treatment regimen

Treatment	SUCRA
curcumin	0.8782
ginger	0.4825
Avocado soybean	0.4802
Rosa canina	0.4782
placebo	0.1809

In each group the number of patients is proportional to the circle size. The number of direct comparisons is reflected by the linking line width.

Fig. 2 displays the Forest plot of the outcomes of a meta-analysis of the enrolled studies to the Bayesian network. The relative effectiveness is plotted as an OR with a credible interval of 95 per cent. Based on these findings, the surface under the cumulative ranking curve (SUCRA) was calculated, since that is the most strongest effectiveness converted value according the ranking of each agent (Firenzuoli and Gori 2007). **Table 2** displays every treatment scheme's SUCRA. A higher SUCRA level implies better treatment outcomes based on the indirect comparison method. Curcumin displayed highest likelihood of SUCRA (87.8%), followed by ginger (48.2%), avocado soybean (48.02%),

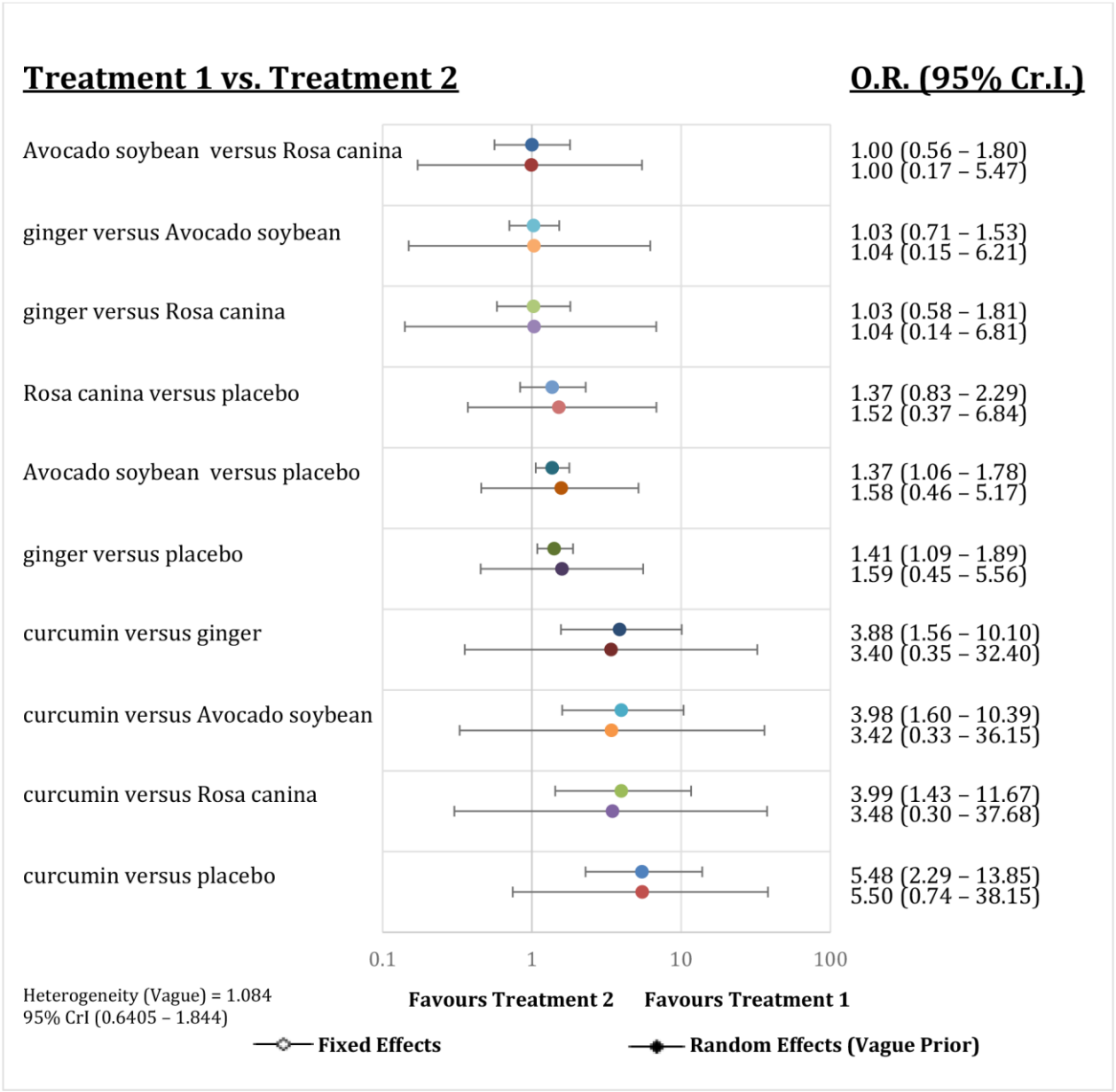


Fig. 2.

Table 3. League table of each regimen

curcumin				
3.88 (1.56 – 10.10)	**ginger**			
3.98 (1.60 – 10.39)	1.03 (0.71 – 1.53)	**Avocado soybean**		
3.99 (1.43 – 11.67)	1.03 (0.58 – 1.81)	1.00 (0.56 – 1.80)	**Rosa canina**	
5.48 (2.29 – 13.85)	1.41 (1.09 – 1.89)	1.37 (1.06 – 1.78)	1.37 (0.83 – 2.29)	**placebo**

OR >1 Means the Treatment in Top Left is Better

rosa canina (47.82%), placebo (18.09%). Heterogeneity (OR: 1.084 %, 95 percent CrI (0.6405 – 1.844) was not significant SUCRA, surface under the cumulative ranking curve.

Forest plot shows relative effect of each agent. Diamond is the summary estimate from the pooled studies with 95% Cr. Cr: credible interval Curcumin's therapy effectiveness was considerably higher than that of ginger (OR: 3.88, 95 percent CI: 1.56 – 10.10), avocado soybean (OR: 3.98, 95 percent CI: 1.60 – 10.39), and rosa canina (OR: 3.99, 95 percent CI: 1.43 – 11.67) in the league table, showing relative efficacy using OR and a 95 percent credible interval (**Table 3**).

Fig. 3 demonstrates the enrolled studies Inconsistency plot. The plot indicates each study's posterior mean deviance for the consistency model (horizontal axis), and the unrelated mean-effects model (vertical axis), together with the equality line.

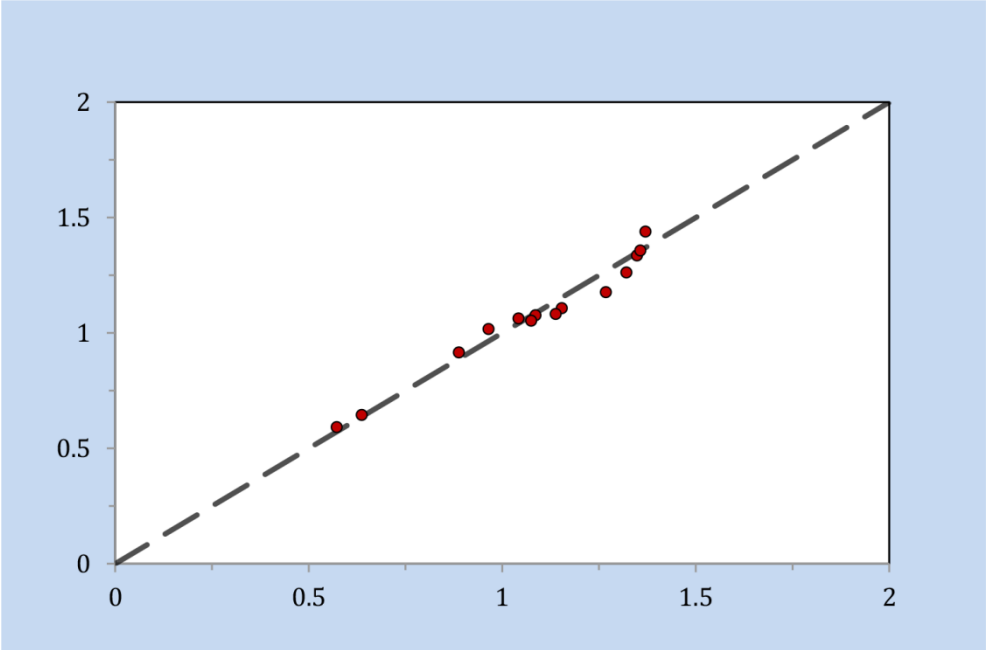


Fig. 3. Inconsistency plot from NetMetaXL

DISCUSSION

The importance of the use of medicinal plants and their products, including herbal remedies and processed foods, has increased in particular in the developing and developed countries in recent decades. Treatment with herbal remedies is one of the major components of complementary and alternative medicine that is growing in popularity. Therefore, attention to the quality, safety and efficacy of herbal products requires extensive research in this field. Medicinal herbs that are effective in treating osteoarthritis diseases, if used in combination with synthetic drugs, can reduce the required dose for synthetic analgesic drugs, thereby reducing the side effects of synthetic drugs (Herman et al. 2004). For example, non-steroidal anti-inflammatory drugs (NSAID), are one of the mainstays of osteoarthritis pain control; however, NSAID's usage is limited due to gastrointestinal and cardiovascular complications (McMahon et al. 2008). Therefore, medicinal plants that, while having optimal safety, can reduce the dose or need for non-steroidal anti-inflammatory drugs, as our study was looking for it as one of the study outcomes (Rovati et al. 2016). The use of herbal medicines by patients with osteoarthritis has been increasing. According to a US statics, approximately 90% of patients with arthritis use complementary therapies such as herbal remedies (Herman et al. 2004). Many patients try several alternative therapies. As more patients start using alternative medicine, physicians and pharmacists increasingly feel the need to become familiar with herbal remedies (Morelli et al. 2003). So, the prescribed herbal medicines need to follow some standards in quality and safety which herbal manufacturers are responsible for it. While the efficiency of herbal products is one of the most determining factors in its market, having the best efficient herbal formula would be in interest of pharmaceutical companies (Calixto 2000). Our main study strength is the key point that Network meta-analysis could help selecting most efficient Ingredients used in formula.

Curcuma longa, as the most efficient herb in our study, is from the Zingiberaceae family and is thought to have some roles in lipoxygenase, cyclooxygenase and κB-NF inhibition, and decreased production of inflammatory cytokines such as tumor necrosis factor alpha and some interleukins (Maheshwari et al. 2006; Kuptniratsaikul et al. 2009; Park and Conteas 2010). Curcumin also decrease the production of joint degrading enzymes, including collagenase, elastase and hyaluronidase (Kertia et al. 2011). Rosa canina is shown to have effect on reducing the level of reactive protein in human body (Mihaylova et al. 2015). It is an anti-inflammatory and immune system modifier (Mihaylova et al. 2015). The powder has been available as a medicine in Scandinavian countries since the past decade. Preliminary studies have shown that the drug produced from this powder may significantly relieve pain in osteoarthritis (Winther et al. 2005). Avocado/soy, another studied herbal preparation may repair osteoarthritis in the joint. They also inhibit COX-2 expression and PGE2 production in chondrocytes (Lippiello et al. 2008). A meta-analysis was performed to evaluate the efficacy of avocado and soybean products on four randomized controlled trials involving 664 patients with hip (41.4%) or knee (58.6%) osteoarthritis. The drug was significantly better than placebo in

reducing pain. Based on the results of this meta-analysis, patients may be advised to take the drug for a period of 3 months (Christensen et al. 2008).

CONCLUSION

In this study Curcuma longa was shown to have more efficiency than Zingiber officinale, Avocado/soybean, and Rosa canina. While the efficacy of herbal medicine may be due to the synergistic action of several compounds or the balance of synergistic and antagonistic actions, so that testing of individual compounds may not be a reasonable way to evaluate the efficacy of crude extracts used by patients. Therefore, various factors may contribute to the lack of efficacy of herbal therapies and the plants used in these products must be further studied.

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