Systematic Review

Effectiveness of Ginger on Pain and Function in Knee Osteoarthritis: A PRISMA Systematic Review and Meta-Analysis

Felipe Araya-Quintanilla, MSc[1,2], Héctor Gutiérrez-Espinoza, PhD[1,3], María Jesús Muñoz-Yanez, MSc[1], Úrsula Sánchez- Montoya, MSc[4], and Juan López-Jeldes, MSc[4]

From: [1]Rehabilitation and Health Research Center (CIRES), Universidad de las Américas, Santiago, Chile; [2]Faculty of Health Sciences, Universidad SEK, Santiago, Chile; [2]Physical Therapy Department, Clinical Hospital San Borja Arriarán, Santiago, Chile; [3]Faculty of Health, School of Nutrition, Universidad de las Américas, Santiago, Chile

Address Correspondence:
Felipe Araya-Quintanilla
Rehabilitation and Health Research Center (CIRES), Universidad de las Américas
PO Box 7500972
Santiago, Chile
E-mail: fandres.kine@gmail.com

Disclaimer: There was no external funding in the preparation of this manuscript.
Conflict of interest: Each author certifies that he or she, or a member of his or her immediate family, has no commercial association (i.e., consultancies, stock ownership, equity interest, patent/licensing arrangements, etc.) that might pose a conflict of interest in connection with the submitted manuscript.

Manuscript received: 04-28-2019
Revised manuscript received: 08-03-2019
Accepted for publication: 09-12-2019

Free full manuscript:
www.painphysicianjournal.com

Background: Ginger has been proposed as a complementary treatment for musculoskeletal pain. However, efficacy, type, and safety remains unclear.

Objectives: To determine the effectiveness of consumption or topical application of ginger for pain relief and knee function improvement in patients with knee osteoarthritis.

Study Design: Systematic review with meta-analysis of randomized clinical trials.

Methods: An electronic search was performed on Medline, Central, CINAHL, PEDro, SPORTDiscus, and LILACS databases. The eligibility criteria for selecting studies included clinical trials that compared consumption and/or topical ginger with placebo or other interventions for the pain relief and knee function in patients with medical diagnosis of knee osteoarthritis.

Results: Seven clinical trials met the eligibility criteria, and for the quantitative synthesis, 4 studies were included. For the comparison capsules versus placebo, mean difference for pain was –7.88 mm; 95% confidence interval (CI), 11.92 to 3.85 ($P = 0.00$), and standard mean difference for knee function was –1.61 points; 95% CI, –4.30 to –1.09 ($P = 0.24$). For the comparison of topical ginger versus standard treatment, standard mean difference for pain was 0.79 mm; 95% CI, –1.97 to 0.39 ($P = 0.19$), and standard mean difference for knee function was –0.51 points; 95% CI, –1.15 to 0.13 ($P = 0.12$).

Limitations: The current evidence is heterogeneous and has a poor methodologic quality.

Conclusions: There is insufficient evidence to support the use of oral ginger compared with placebo in the pain relief and function improvement in patients with knee osteoarthritis. For other comparisons, no statistically significant differences were found.

Key words: Osteoarthritis, knee osteoarthritis, ginger, pain, randomized clinical trial, systematic review

Pain Physician 2020: 23:E151-E161

Knee osteoarthritis (OA) is the most common form of arthritis and one of the leading causes of disability in elderly. This degenerative and progressive joint disease affects approximately 250 million people worldwide (1). It is characterized by the deterioration of cartilage in joints, generating an inflammatory response continuously and creating stiffness, pain, and impaired movement (2). Today, there is still no definitive treatment, and the therapeutic management is focused on controlling symptoms and improving the functionality (3,4). According to the recommendations by the American College of

Rheumatology, pharmacologic treatment has been proposed as the first line of therapeutic management in these patients; acetaminophen, nonsteroidal antiinflammatory drugs, and intraarticular injection are the most used drugs (4). However, there have been reported gastrointestinal disorders, such as dyspepsia and gastritis, that are associated with the continued use of these medications (5,6). Moreover, the nonpharmacologic conventional treatment focused on patient education and weight control has not been effective enough. Therefore it is necessary to develop new therapeutic approaches for the treatment of OA (4,5).

The ginger rhizomes have been proposed as a complementary treatment for rheumatoid arthritis, musculoskeletal pain, and throat pain, being used for prophylaxis because of its antibacterial properties, antivirals, analgesic, and antipyretic properties (6,7). Ginger contains several hundred known compounds, among them are curcumin, beta-carotene, capsacine, caffeic acid, and gingerols. The latter being the metabolically active substance, which is supposed to have the properties mentioned; however, the effect depends on both the concentration and the method to obtain the compound (8,9).

Both in vitro studies and in vivo animal experiments have documented the antiinflammatory potential of ginger and its constituents (7). Experimental studies have shown that ginger constituents inhibit the inflammation process by inhibiting arachidonic acid metabolism, a key pathway. Moreover, both in vitro and in vivo animal models have shown that ginger and its constituents inhibit both cyclooxygenase (COX) and lipoxygenase (LOX), and also act as an inhibitor of leukotriene synthesis (6,9-12). Based on these findings, recent studies have supported the use of ginger for the treatment of pain in OA (6,9,12).

Despite the results of experimental studies, systematic reviews (SR) have remained controversial regarding the effectiveness of ginger in OA (13,14). Bartels et al (13) concluded that the consumption of ginger was moderately effective in patients with hip and knee OA, however, the low sample sizes and heterogeneity of populations make it difficult to extrapolate their results. Terry et al (14) concluded that the low quality of clinical trials and the evidence of the effectiveness of ginger to treat pain relief in patients with knee OA remained insufficient. Furthermore, it has not been possible to establish the effects of other modalities of ginger and generate a dose-response relationship.

Objective

The aim of this study was to determine the effectiveness of the intake and/or topical application of ginger in the pain relief and improved knee function in patients with knee OA.

Methods

Protocol and Registration

This systematic review was conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement and followed the recommendations of the Cochrane Collaboration Handbook (15-17). The register number in the International Prospective Register of Systematic Review (PROSPERO) is CRD42018093088.

Eligibility Criteria

Studies were regarded eligible for inclusion if the following criteria were fulfilled: (1) population: patients over 18 years with knee OA, without distinction of race and gender; (2) type of intervention: consumption and/or topical application of ginger; (3) comparison: placebo, standard treatment, or other therapeutic interventions; (4) outcome: studies have evaluated the clinical effectiveness of pain intensity and knee function; and (5) type of study: randomized clinical trials or controlled clinical trials published in English or Spanish until February 2019.

The criteria for excluding studies were as follows: (1) studies that involved patients with other pathologies of the knee-joint complex, such as unspecific knee pain, patellar tendinopathy, patellofemoral pain, iliotibial band syndrome, and meniscus injuries; (2) patients with a history of acute trauma, previous surgery in the affected knee; and (3) studies that did not assess clinical outcomes were not considered.

Electronic Search

We systematically searched Medline (via PubMed), the Cochrane Central Register of Controlled Trials (Central), the Latin American and the Caribbean Literature in Health Sciences (LILACS), the Cumulative Index to Nursing and Allied Health Literature (CINAHL), SPORTDiscus, and Physiotherapy Evidence Database (PEDro) databases from inception until February 2019.

The search strategy used included a combination of the following Medical Subjects Headings (MeSH) terms: "knee osteoarthritis," "osteoarthritis," "ginger,"

"Zingiber officinale," and "placebo." With the free-text terms, we used the following: "osteoarthrosis," "ginger," and "clinical trial." For the search in the Medline and Central databases, the Cochrane Highly Sensitive Search Strategies for identifying randomized trials was used (16). We also manually searched the references of selective articles to identify additional, potentially relevant studies. The literature search was independently conducted by 3 reviewers (FA-Q, HG-E, and MJ-M), and disagreements were solved by consensus or by involving a fourth researcher (US-M).

Study Selection

Three of the authors (FA-Q, HG-E, and MJ-M) independently screened the titles and abstracts of references retrieved from searches. We obtained the full text for references that any authors considered to be potentially relevant. Disagreements were resolved by consensus or by consultation with a fourth author (US-M).

Data Collection Process

Three authors (FA-Q, HG-E, and MJ-M) used a standardized form to independently extract data on outcomes for each trial. The following data were extracted from the original reports: (1) authors, year of publication, and country; (2) sample characteristics (sample size, age distribution, and gender); (3) characteristics of ginger; (4) characteristics of placebo or standard treatment; (5) length of follow-up and mail outcomes; and (6) main results.

Risk of Bias for Individual Studies

Assessment of risk of bias of individual studies was performed as recommended by the Cochrane Collaboration Handbook (16). This tool evaluates the risk of bias according to 7 domains: generation of the random sequence, concealment of the randomization sequence, blinding of patients and treatments, blinding of the evaluation of the results, incomplete results data, selective reporting of results, and other biases. Each domain could be considered as low risk of bias, unclear risk of bias, or high risk of bias. Data extraction and quality assessment were independently performed by 3 reviewers (FA-Q, HG-E, and JL-J), and inconsistencies were solved by consensus or by involving a fourth researcher (MJ-M). The agreement rate among reviewers was calculated using kappa statistics.

Statistical Methods

The DerSimonian and Laird random effects of the Mantel–Haenszel fixed effects methods were used (17,18), depending on the heterogeneity, to compute a pooled estimate of mean difference (MD) or standardized mean difference (SMD), and respective 95% confidence intervals (CI) for pain intensity and knee function. The heterogeneity of results across studies was evaluated using the I2 statistic, which is considered as might not be important (0%-40%), may represent moderate (30%-60%), may represent substantial (50%-90%), and considerable (75%-100%) heterogeneity (16). Additionally, the corresponding *P* values were considered. Meta-analyses were performed with the RevMan 5.3 program (The Nordic Cochrane Centre for The Cochrane Collaboration, Copenhagen, Denmark). Publication bias was evaluated by visual inspection of funnel plots, as well as by using the method proposed by Sterne et al (19).

Results

Study Selection

A total of 58 studies were found through the electronic search. Finally, 7 studies met eligibility criteria and were included in the systematic review (2,4,6,9,20-22). The detailed steps of the article selection process for the systematic review and the cause of exclusion of the other 3 studies are described in a flow diagram in Fig. 1.

Study Characteristics

Table 1 summarizes the characteristics of the included studies. The overall population included 371 patients. The mean of patients per study was 115, and the age range of the patients was between 52.7 and 65.2 years, with an average of 55.6 years.

Risk of Bias Within Studies

As evaluated by the Cochrane Collaboration's tool for assessing risk of bias for all clinical trials, 42.8% of the studies showed a high risk of bias (2,6,20), 31.6% a medium risk of bias (4,21,22), and 25.6% a low risk of bias (9). When studies were analyzed by individual domains, the random sequence generation was suitable in 25.3% of the studies. Adequate allocation concealment was observed as low risk of bias in 25% of the studies and unclear in 80%. Outcome assessors were blinded in 15% of the studies, whereas incomplete outcome data and selective reporting were observed in 80% as low risk of bias (Figs. 2 and 3).

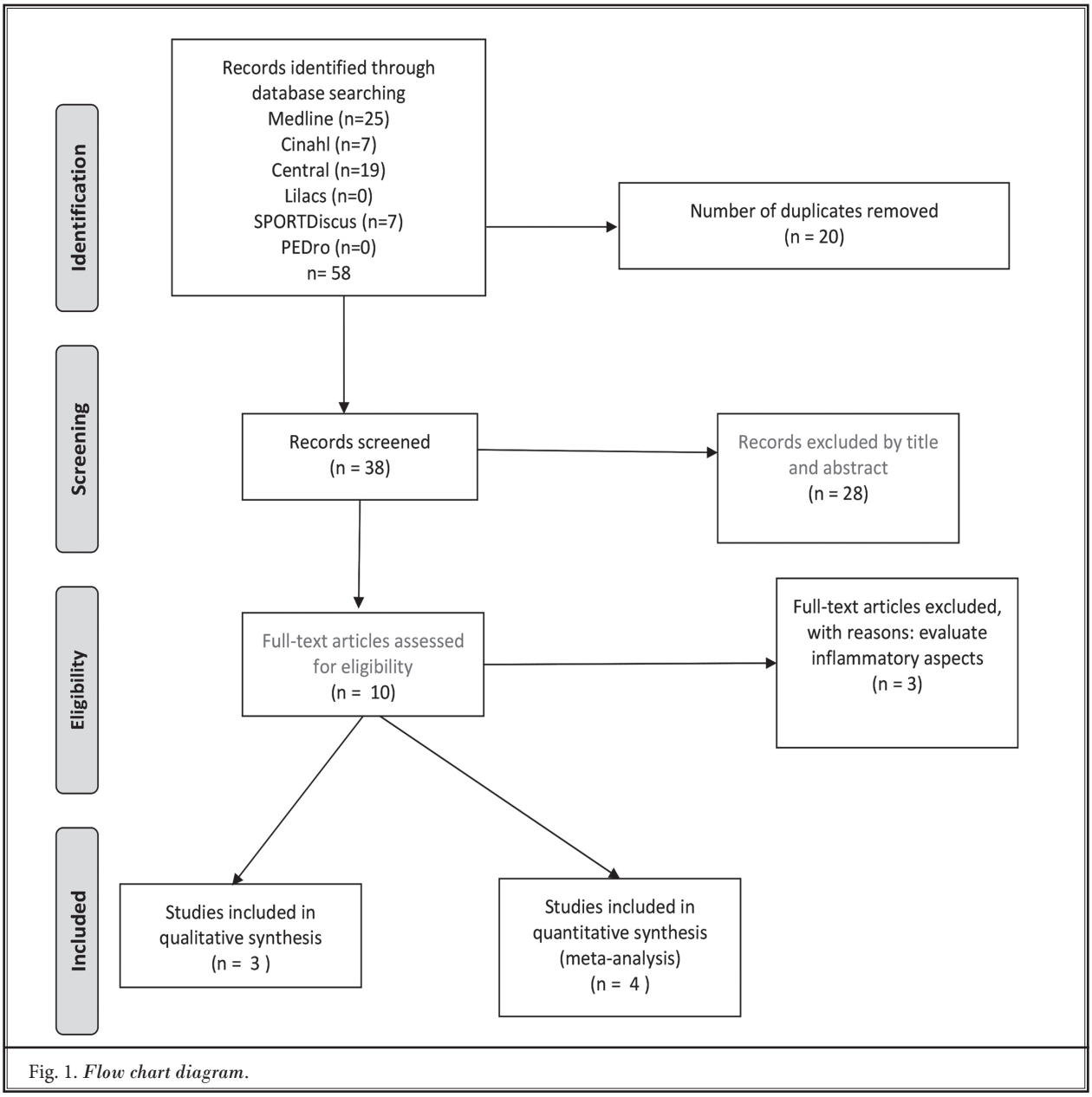

Fig. 1. *Flow chart diagram.*

Synthesis of Results

Pain

Four of the articles included in the quantitative synthesis evaluated the intensity of pain (4,9,20,22). The pooled MD estimate showed that significant difference was found in the level of pain in the consumption of ginger compared with placebo in the first month (MD, –7.88 mm; 95% CI, –11.92 to 3.85; P = 0.0001; Fig. 4) with low heterogeneity (I^2, 0%; P = 0.57). For the comparison of topical use of ginger compared with standard treatment in the first month, the pooled SMD estimate showed that no significant difference was found in the level of pain in the first month (SMD, –0.79 mm; 95% CI, –1.97 to 0.39; P = 0.19; Fig. 5) with considerable heterogeneity (I^2 = 92%; P = 0.57).

Knee Function

Four of the articles included the quantitative synthesis to evaluate the knee function with the

Table 1. *Characteristics of the studies included in the systematic review and meta-analyses of the effects of ginger in patients with knee osteoarthritis.*

Author/ Year/ Country	Patients Characteristics	Intervention	Follow-Up/ Outcome Measures	Results
Altman et al 2001 (9) (United States) (Quantitative synthesis)	Patients with knee OA grade 2, 3, and 4 according to Kellgren and Lawrence. MOR: block randomization generated by central computer. n = 247 patients EG: n = 124 Age: 64 years (SD = 11.5) CG: n = 123 Age: 66.3 years (SD = 11.6)	EG: 2 capsules daily, each containing 255 mg of extract of ginger (EV. EXT77) for 6 weeks. CG: placebo capsules with coconut oil at the same dose as the EG.	There was no follow-up. Outcome measures: - Pain: VAS–Function: WOMAC - Global State - Quality of life: SF-12 - Adverse effects	At the end of the treatment: -*VAS when standing ↓EG 8.1 mm (P = 0.005) compared with the CG. -*VAS walking ↓EG 6.4 mm (P = 0.016) compared with the CG. -*WOMAC pain ↓EG 4.4 pts (P = 0.112) compared with the CG. -*WOMAC stiffness ↓EG 6.8 pts (P = 0.018) compared with the CG. -*WOMAC function ↓EG 3 pts (P = 0.134) compared with the CG. -*WOMAC total ↓EG3.9 pts (P = 0.087) compared with the CG.
Zakeri et al 2011 (4) (Iran) (Quantitative synthesis)	Patients with knee OA based on clinical and radiologic criteria according to the ACR. MOR: does not mention method of randomization. n = 204 patients EG: n = 103 Age: 48.4 years (SD = 11.1) CG: n = 101 Age: 45.7 years (SD = 12.5)	EG: 2 capsules daily, each containing 250 mg of ginger (Zintoma) for 6 weeks. CG: 2 capsules daily of placebo for 6 weeks.	There was no follow-up. Outcome measures: - Pain: VAS -Function: WOMAC -Adverse effects	At the end of the treatment: -*VAS when standing ↓EG 5.3 mm (P = 0.008) compared with the CG. -*VAS walking ↓EG 5.7 mm (P = 0.012) compared with the CG. -*WOMAC pain ↓GE 0.2 pts (P = 0.066) compared with the CG. -*WOMAC stiffness ↓GE 0.2 pts (P = 0.003) compared with the CG. -*WOMAC function ↓GE 0.2 pts (P = 0.003) compared with the CG. -*For the adverse effects there were no differences between groups (P > 0.05).
Niempoog et al 2012 (22) (Thailand) (Quantitative synthesis)	Patients with knee OA based on criteria clinicians according to AAR. MOR: does not mention method of randomization. n = 99 patients EG: n = 49 Age: 57.9 years (SD = 9.7) CG: n = 50 Age: 58.3 years (SD = 9.07)	EG: the 4% gel Plygersic, applied 1 mL of solution 4 times a day for 6 weeks. CG: sodium diclofenac gel at 1%, applied 1 mL of solution 4 times a day for 6 weeks.	There was no follow-up. Outcome measures: -*Symptoms and function: KOOS -*Adverse effects	At the end of the treatment the difference between GE and the CG: -*KOOS symptoms (P = 0.551). -*KOOS pain (P = 0.459). -*KOOS ADL (P = 0.629). -*KOOS sports and recreation (P = 0.674). -*KOOS quality of life (P = 0.280). -*For the adverse effects there were no differences between groups (P > 0.05).
Niempoog et al 2012 (21) (Thailand) (Qualitative synthesis)	Patients with knee OA based on criteria clinicians according to AAR. MOR: does not mention method of randomization. n = 49 patients EG: n = 26 Age: 48.9 years (SD = 7.4) CG: n = 23 Age: 49.1 (SD = 8)	EG: 2 capsules daily, each containing 500 mg of ginger for 2 months. CG: 2 capsules daily of placebo for 2 months.	There was no follow-up. Outcome measures: -*Symptoms and function: KOOS -*Adverse effects -*VAS	At the end of the fourth and eighth week the difference between EG and the CG: -*KOOS symptoms (P > 0.05). -*VAS (P > 0.05). -*KOOS AVD (P > 0.05). -*KOOS sports and recreation (P > 0.05). -*KOOS quality of life (P > 0.05). -*For the adverse effects there were no differences between groups (P > 0.05).
Paramdeep 2013 (6) (India) (Qualitative synthesis)	Patients with knee OA based on clinical and radiologic criteria according to the ACR. MOR: does not mention method of randomization. n = 60 patients EG1: n = 20 Age: 52.9 years (SD = 8.1) EG2: n = 20 Age: 50.1 years (SD = 11.3) CG: n = 20 Age: 54.8 years (SD = 9.7)	EG1: 1 capsule of ginger (750 mg) plus 1 oral placebo capsule daily for 12 weeks. EG2: 1 capsule of ginger (750 mg) plus 1 pills of 50 mg diclofenac daily for 12 weeks. CG: 1 pill of diclofenac 50 mg plus 1 oral placebo capsule daily for 12 weeks.	There was no follow-up. Outcome measures: -Function: WOMAC -Pain: VAS - Adverse effects	At the end of the treatment to the 12th week: -*For total WOMAC > difference between CG compared with EG1 (P < 0.05). - For total WOMAC > difference between EG2 compared with the EG1 (P < 0.05). - For total WOMAC > difference between EG2 compared with the CG (P > 0.05). -*For VAS and adverse effects there were no differences between groups (P > 0.05).

Table 1 (cont.). *Characteristics of the studies included in the systematic review and meta-analyses of the effects of ginger in patients with knee osteoarthritis.*

Author/ Year/ Country	Patients Characteristics	Intervention	Follow-Up/ Outcome Measures	Results
Bolognesi et al 2016 (2) (Italy) (Quantitative synthesis)	Patients with knee OA based on clinical and radiologic criteria. MOR: block randomization generated by a computer program. n = 54 patients EG: n = 28 Age: 52.3 years (SD = 4.2) CG: n = 26 Age: 53.1 (SD = 2)	EG: Supplementation is Morvadol (ginger plus glucosamine), 3 capsules per day for 1 week, and then 2 capsules per day, added to the pharmacologic management standard. CG: Pharmacological Management Standard for the control of the joint pain.	Follow-up to the 1, 3, and 6 months. Outcome measures: Function: - KPSI - Walking distance WOMAC - Pain free on treadmill - Biomarkers of inflammation and oxidative stress.	At the end of the treatment in the GE (Movardol) fourth week: -*KPSI $P = 0.05$. -*WOMAC function $P = 0.05$. -*Pain (VAS) P = 0.05 for the CG of standard treatment at week 4. -*KPSI $P > 0.05$. -*WOMAC function $P > 0.05$. -*Pain (VAS) $P > 0.05$.
Tosun et al 2017 (20) (Turkey) (Quantitative synthesis)	Patients with knee OA based on clinical and radiological criteria. MOR: does not mention method of randomization. n=68 patients EG: n=34 Age: 64.9 years (SD=10) CG: n=34 Age: 63.2 years (SD=7.7)	EG: standard treatment plus massage on the knee with oil of ginger for 20 minutes 2 times a week for 5 weeks. CG: standard treatment with meloxicam 15 mg oral daily, massage on the knee with antiinflammatory gel 2 times a day, 15 minutes of cold compresses 3 times a day for 5 weeks.	There was no follow-up. Outcome measures: - Pain: VAS -Function: WOMAC - Adverse effects	At the end of the treatment to the fifth week: -*VAS ↓EG compared with the CG ($P = 0.00$). -*WOMAC pain ↓EG compared with the CG ($P = 0.00$). -*WOMAC stiffness ↓EG compared with the CG ($P = 0.24$). -*WOMAC ↓EG function compared with the CG ($P = 0.00$). -*WOMAC total ↓EG compared with the CG ($P = 0.00$).

Abbreviations: AAR: American Association of Rheumatologists; ACR: American College of Rheumatologists; ADL: activities of daily living; CG: control group; EG: experimental group; KOOS: Knee Injury and Osteoarthritis Outcome Score; KPSI: Karnofsky Performance Scale; MOR: method of randomization; SD: standard deviation; VAS: Visual Analog Scale.

Western Ontario and McMaster Universities Arthritis Index (WOMAC) scale (4,9,20,22). The pooled SMD estimate showed that no significant difference was found in the knee function from the consumption of ginger compared with placebo in the first month (SMD, –1.61 points; 95% CI, –4.30 to 1.09; $P = 0.24$; Fig. 6) with considerable heterogeneity (I^2, 99%; $P = 0.00001$). For the comparison of topical use of ginger compared with standard treatment in the first month, the pooled SMD estimate showed that no significant difference was found in the knee function in the first month (SMD, –0.51 points; 95% CI, –1.15 to 0.13; $P = 0.12$; Fig. 7) with considerable heterogeneity (I^2, 76%; $P = 0.04$).

Publication Bias

Publication bias was not performed because only 7 articles were included in the systematic review and meta-analysis (23).

Discussion

These systematic review and meta-analysis provide an overview of the clinical evidence supporting the use of short-term consumption of ginger to relieve pain compared with placebo. Additionally, our findings suggest that no clinical or statistically significant differences were observed between pain and knee function in the other comparisons.

For pain relief, our findings are consistent with the study conducted by Bartels et al (13), in which they showed that ginger intake produced a statistically significant pain reduction in patients with knee and hip OA. Despite the SR of Terry et al (14), they concluded that evidence remains insufficient; however, the available data provide tentative support for the antiinflammatory role of ginger, which may reduce the subjective experience of pain in some conditions, such as OA. For knee function, our findings are not statistically significant both in the oral intake and topical application and

are contradictory with the evidence showed in other SRs (13,14).

Knee OA causes a chronic deterioration of the articular cartilage, thereby generating an inflammatory response. During the inflammatory process, a series of mediators are released at the site of injury, such as bradykinin, serotonin, histamine, prostaglandins, interleukins, and neuropeptides, among others (24). When interacting with the nociceptors, these mediators are able to modify the action thresholds and even activate some of the silent nociceptors, which can be depolarized to a stimulus that previously did not cause pain (24). In vitro studies (25,26) have shown that ginger is able to inhibit both COX and LOX, which are key enzymes for the formation of prostaglandins from arachidonic acid at the cellular level. In this way, ginger would be able to inhibit the activation of nociceptive pathways of pain, thus avoiding the formation of inflammatory mediators that finally decreases the threshold of neuronal action (27,28).

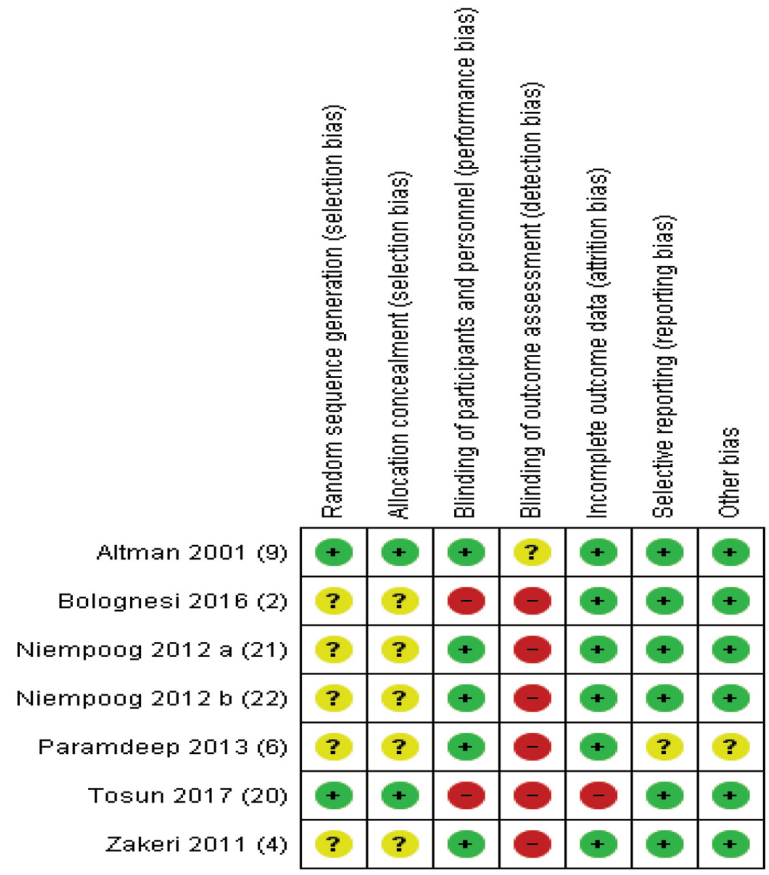

Fig. 2. *Summary of risk assessment of bias of included articles.*

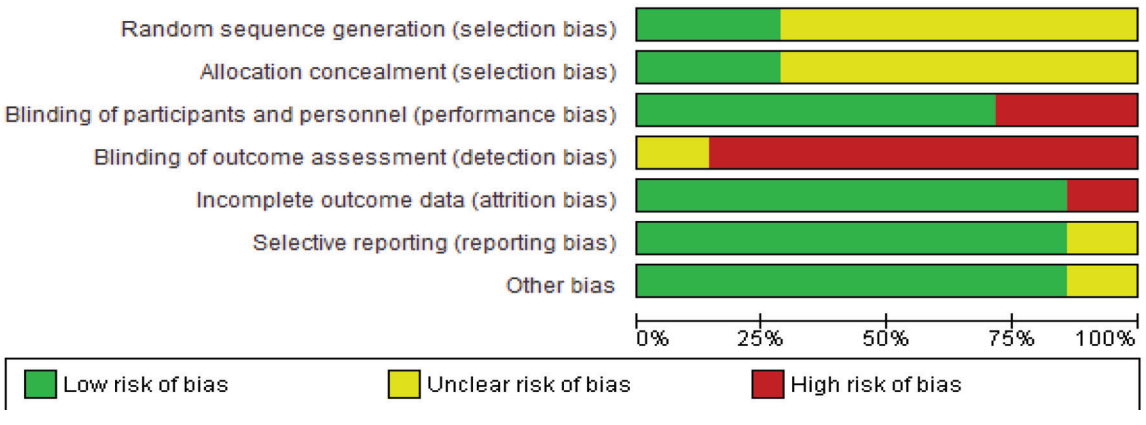

Fig. 3. *Bias risk graph presented as a percentage of all items included.*

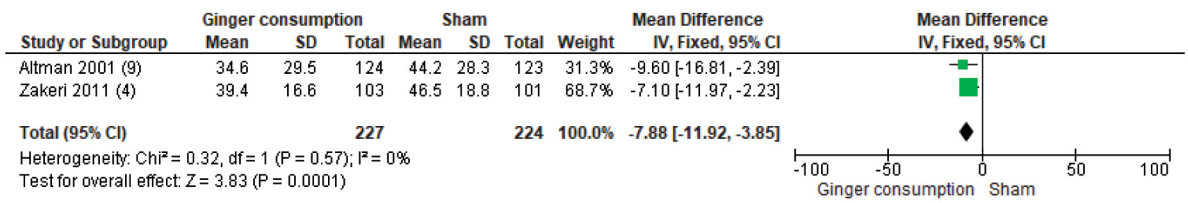

Fig. 4. *Comparison of ginger consumption in capsules versus placebo for pain.*

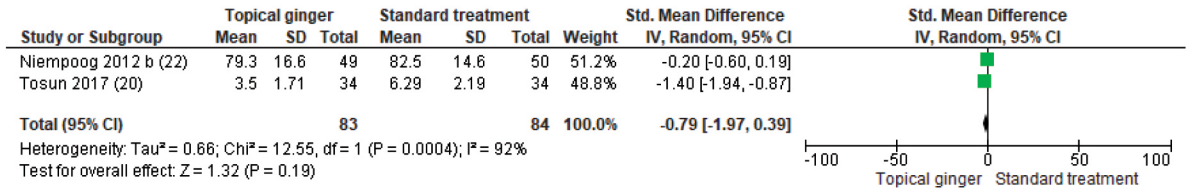

Fig. 5. *Comparison application with topical ginger versus standard treatment for pain intensity measured with the Visual Analog Scale at the first month.*

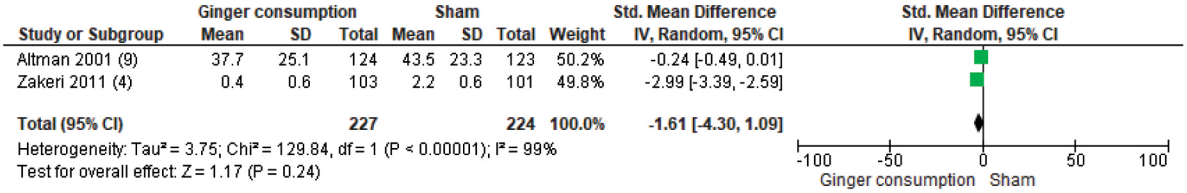

Fig. 6. *Comparison of consumption ginger in capsules versus placebo for the function measured with the WOMAC at the first month.*

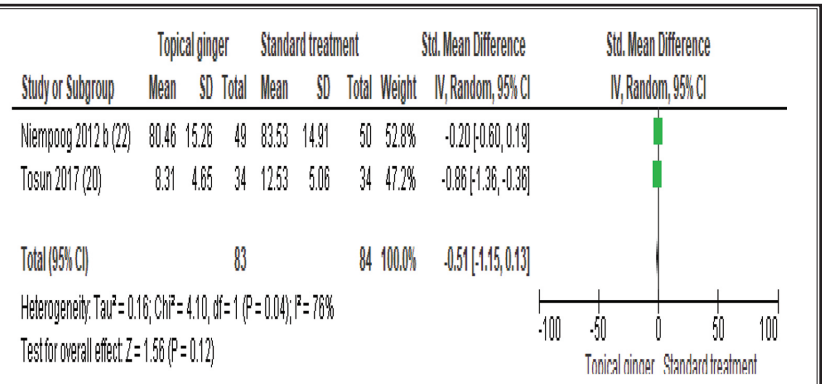

Fig. 7. *Comparison application with topical ginger versus standard treatment for function measured with the WOMAC questionnaire at the first month.*

Regarding the pharmacokinetics and bioavailability of the derivatives of the ginger rhizomes, in vitro studies showed that gingerol is rapidly absorbed when given orally, reaching maximum plasma concentration in 10 minutes and maximum tissue concentration in 30 minutes after intake (29,30). In topical application, the absorption of the active compounds is affected by factors, such as size of the particles, thickness of the skin, and vascularization. Chen et al (31) performed a study to evaluate the

transdermal permeability and cumulative amount of gingerol in the skin after the application of a dermal patch concentrate of gingerol. Their results showed that at 20 hours from the application, 42% of active substance are still found at the site of application in relation to the amount applied (30). The studies included in our review occupied both gel and oil forms of ginger, but due to gingerol as a natural compound, still more studies in respect to the topical absorption and bioavailability in humans are needed.

As pain that affects patients with OA is chronic and neurogenic, the fast plasma concentration reached by the ginger-derived compounds in oral intake enables local intervention of pain for the COX and LOX enzymes to occur more quickly, thus allowing pain relief (32). For the clinical applicability of oral ginger therapy for the treatment of pain in the studies included in our SR, the extraction of active substances and amount of gingerol given were different. This did not limit the effect of the intervention, but it is still unclear which are the most appropriate concentration and dose intervals to obtain the highest benefit from the oral therapy.

In all studies included in our SR, the knee function was assessed with the WOMAC questionnaire, originally created to evaluate the symptoms and physical disabilities perceived by the population with hip and knee OA, considering in its evaluation the pain, stiffness, activities of daily life, functional mobility, step, general function, and quality of life (33,34). The interventions studied in the present SR only have a minimal effect on pain, not in other domains of WOMAC. This can be explained by several factors. First, the ginger has inhibitory effects in arachidonic acid pathway and proinflammatory substances (35,36); therefore, just affect pain domain of WOMAC questionnaire. Second, knee OA is a progressive disease, and the severity of degenerative process may play role in the amount of improvement after treatment (4). In all studies included, there was moderate to advanced knee OA, making it difficult to find clinical effects in other domains of the WOMAC questionnaire. Finally, all studies included in our SR did not have other therapeutic treatments assigned, making difficult improvement of the stiffness, function mobility, and activities of daily diaries. These may interfere with the results of our study, therefore this explains the results of the WOMAC questionnaire, with small effects being not significant or clinically relevant (37). Regarding the adverse effects attributed to the use of ginger, the most commonly reported effects were related to the gastrointestinal tract, such as nausea, heartburn, and dyspepsia, with the majority being mild and without statistical significance.

The limitations of our study are as follows: (1) although we searched 6 databases and included articles in 3 different languages, we might have missed articles relevant to our search; (2) a high degree of statistical heterogeneity existed among the included studies. Potential sources of heterogeneity could be variations in the type and dose of the interventions occupied; (3) methodologic limitations, such as, unclear randomization, inadequately concealed allocation, and lack of blinding of the assessors, could overestimate the effect size of interventions studied; (4) because of the limited number of included studies, publication bias could not be assessed; and (5) in the planning stages, we intended to conduct subgroup analyses based on age, gender, and duration of the symptoms, although the results of stratified analysis in the individual trials were not available. Finally, the results of our study should be interpreted with caution because of the amount of studies included and to the different risks of bias that they presented.

Conclusions

This systematic review and meta-analysis demonstrates that there is insufficient evidence to support the use of oral ginger compared with placebo for the pain relief and function improvement in patients with knee OA. For other comparisons, no statistically significant differences were found. Future research is necessary with an adequate design and methodology to determine the effect of ginger in other comparisons.

References

1. Mora JC, Przkora R, Cruz-Almeida Y. Knee osteoarthritis: pathophysiology and current treatment modalities. *J Pain Res* 2018; 5:2189-2196.
2. Bolognesi G, Belcaro G, Feragalli B, et al. Movardol (N-acetylglucosamine, Boswellia serrata, ginger) supplementation in the management of knee osteoarthritis: Preliminary results from a 6-month registry study. *Eur Rev Med Pharmacol Sci* 2016; 20:5198-5204.
3. Argoff CE. Recent developments in the treatment of osteoarthritis with NSAIDs. *Curr Med Res Opin* 2011; 27:1315-1327.
4. Zakeri Z, Izadi S, Bari Z, Soltani F, Narouie B, Ghasemirad M. Evaluating the effects of ginger extract on knee pain, stiffness and difficulty in patients with knee osteoarthritis. *J Med Plant Res* 2011; 5:3375-3379.
5. Xu Q, Chen B, Wang Y, Wang X, Han D, Ding D. The effectiveness of manual therapy for relieving pain, stiffness, and dysfunction in knee osteoarthritis: A systematic review and meta-analysis. *Pain Physician* 2017; 20:229-243.
6. Paramdeep G. Efficacy and tolerability of ginger (Zingiber officinale) in patients of osteoarthritis of knee. *Indian J Physiol Pharmacol* 2013; 57:177-183.
7. Srinivasan K. Ginger rhizomes (Zingiber officinale): A spice with multiple health beneficial potentials. *Pharma Nutrition* 2017; 5:18-28.
8. Tjendraputra E, Tran VH, Liu-Brennan D, Roufogalis BD, Duke CC. Effect of ginger constituents and synthetic analogues on cyclooxygenase-2 enzyme in intact cells. *Bioorg Chem* 2001; 29:156-163.
9. Altman RD, Marcussen KC. Effects of a ginger extract on knee pain in patients with osteoarthritis. *Arthritis Rheum* 2001; 44:2531-2538.
10. Wang S, Zhang C, Yang G, Yang Y. Biological properties of 6-gingerol: A brief review. *Nat Prod Commun* 2014; 9:1027-1030.
11. Zhang M, Viennois E, Prasad M, et al. Edible ginger-derived nanoparticles: A novel therapeutic approach for the prevention and treatment of inflammatory bowel disease and colitis-associated cancer. *Biomaterials* 2016; 101:321-340.
12. Van Breemen RB, Tao Y, Li W. Cyclooxygenase-2 inhibitors in ginger (Zingiber officinale). *Fitoterapia* 2011; 82:38-43.
13. Bartels EM, Folmer VN, Bliddal H, et al. Efficacy and safety of ginger in osteoarthritis patients: A meta-analysis of randomized placebo-controlled trials. *Osteoarthritis Cartilage* 2015; 23:13-21.
14. Terry R, Posadzki P, Watson LK, Ernst E. The use of ginger (Zingiber officinale) for the treatment of pain: A systematic review of clinical trials. *Pain Med* 2011; 12:1808-1818.
15. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analysis: The PRISMA statement. *J Clin Epidemiol* 2009; 62:1006-1012.
16. Higgins JPT, Green S, editors. Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration, 2011. www.cochrane-handbook.org. Accessed April 10, 2018.
17. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analysis of studies that evaluate healthcare interventions: Explanation and elaboration. *BMJ* 2009; 339:b2700.
18. DerSimonian R, Kacker R. Random-effects model for meta-analysis of clinical trials: An update. *Contemp Clin Trials* 2007; 28:105-114.
19. Sterne JA, Egger M, Smith GD. Systematic reviews in health care: Investigating and dealing with publication and other biases in meta-analysis. *BMJ* 2001; 323:101-105.
20. Tosun B, Unal N, Yigit D, Can N, Aslan O, Tunay S. Effects of self-knee massage with ginger oil in patients with osteoarthritis: An experimental study. *Res Theory Nurs Pract* 2017; 31:379-392.
21. Niempoog S, Pawa KK, Amatyakul C. The efficacy of powdered ginger in osteoarthritis of the knee. *J Med Assoc Thai* 2012; 95:S59-S64.
22. Niempoog S, Siriarchavatana P, Kajsongkram T. The efficacy of Plygersic gel for use in the treatment of osteoarthritis of the knee. *J Med Assoc Thai* 2012; 95:S113-S119.
23. Sterne JA, Sutton AJ, Ioannidis JP, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011; 343:d4002.
24. Carlton M, Coggeshall R. Nociceptive integration: Does it have a peripheral component? *Pain Forum* 1998; 7:71-78.
25. Jana U, Chattopadhayay RN, Shaw BP. Preliminary studies on anti-inflammatory activity of Zingiber officinale Rosc., Vitex negundo Linn and Tinospora cordifolia (willid) Miers in albino rats. *Indian J Pharmacol* 1999; 31:232-233.
26. Mustafa T, Srivastava KC, Jensen KB. Drug development: Report, pharmacology of ginger, Zingiber officinale. *J Drug Dev* 1993; 6:25-89.{AU: Please confirm reference 26}
27. Phan PV, Sohrabi A, Polotsky A, Hungerford DS, Lindmark L, Frondoza CG. Ginger extract components suppress induction of chemokine expression in human synoviocytes. *J Altern Complement Med* 2005; 11:149-154.
28. Cortright DN, Krause JE, Broom DC. TRP channels and pain. *Biochim Biophys Acta* 2007; 1772:978-988.
29. Jiang SZ, Wang NS, Mi SQ. Plasma pharmacokinetics and tissue distribution of [6]-gingerol in rats. *Biopharm Drug Dispos* 2008; 29:529-537.
30. Zick SM, Djuric Z, Ruffin MT, Litzinger AJ, Normolle DP, Alrawi S. Pharmacokinetics of 6-gingerol, 8-gingerol, 10-gingerol, and 6-shogaol and conjugate metabolites in healthy human subjects. *Cancer Epidemiol Biomark Prev* 2008; 17:1930-1936.
31. Chen Y, Zhang C, Zhang M, Fu X. Assay of 6-gingerol in CO2 supercritical fluid extracts of ginger and evaluation of its sustained release from a transdermal delivery system across rat skin. *Pharmazie* 2014; 69:506-511.
32. Chainani-Wu N. Safety anti-inflammatory activity of curcumin: A component of tumeric (Curcuma longa). *J Altern Complement Med* 2003; 9:161-168.
33. López-Alonso S, Martínez-Sánchez C, Romero-Cañadillas A, Navarro–Casado F, Gonzalez–Rojo J. Metric properties of WOMAC questionnaires—original and reduced versions—to measure symptoms and Physical Functional Disability. *Atención Primaria* 2009; 9:613-620.
34. Gandek B. Measurement properties of the Western Ontario and McMaster Universities Osteoarthritis Index: A systematic review. *Arthritis Care Res (Hoboken)* 2015; 67:216-229.
35. Rondanelli M, Riva A, Morazzoni P,

et al. The effect and safety of highly standardized ginger (Zingiber officinale) and Echinacea (Echinacea angustifolia) extract supplementation on inflammation and chronic pain in NSAIDs poor responders. A pilot study in subjects with knee arthrosis. *Nat Prod Res* 2017; 31:1309-1313.

36. Fouda AM, Berika MY. Evaluation of the effect of hydroalcoholic extract of Zingiber officinale rhizomes in rat collagen-induced arthritis. *Basic Clin Pharmacol Toxicol* 2009; 104:262-271.
37. Devji T, Guyatt GH, Lytvyn L, et al. Application of minimal important differences in degenerative knee disease outcomes: A systematic review and case study to inform BMJ Rapid Recommendations. *BMJ Open* 2017; 7:e015587.