The Use of Ginger (Zingiber officinale) for the Treatment of Pain: A Systematic Review of Clinical Trials

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Conflict of Interest: None declared.

Perspective: This systematic review critically appraises the use of Zingiber officinale—or ginger—to treat pain. The findings of eight clinical trials provide tentative indications that it may be valuable in the treatment of pain and inflammation but highlight the need for further methodologically robust investigation.

Abstract

Background. Zingiber officinale (Z. officinale), commonly known as ginger, has been widely used traditionally for a variety of medicinal purposes, one of which is for the treatment of pain. The aim of this systematic review was to evaluate the evidence from all human participant clinical trials that have assessed the efficacy of ginger for the treatment of any type of pain.

Methods. Following a protocol, multiple databases were sought using comprehensive search strategies for Z. officinale and pain together with a trial filter for randomized or controlled clinical trials. Trials testing the efficacy of Z. officinale, used as a sole oral treatment against a comparison condition in human adults suffering from any pain condition, were included.

Results. Seven published articles, reporting a total of eight trials (481 participants), were included in the review. Six trials (two for osteoarthritis, one for dysmenorrhea, and three for experimentally induced acute muscle pain) found that the use of Z. officinale reduced subjective pain reports. The methodological quality of the included articles was variable. When assessed using the Jadad scale, which allows a score of between 0 and 5 to be given, included articles obtained Jadad ratings ranging from 2 to 5.

Conclusion. Due to a paucity of well-conducted trials, evidence of the efficacy of Z. officinale to treat pain remains insufficient. However, the available data provide tentative support for the anti-inflammatory role of Z. officinale constituents, which may reduce the subjective experience of pain in some conditions such as osteoarthritis. Further rigorous trials therefore seem to be warranted.

Key Words. Pain; Zingiber officinale; Systematic Review

Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) are generally considered to be the most effective treatment for inflammation and pain. However, the adverse effects associated with their use may outweigh the benefits for many patients, especially those suffering from long-term chronic conditions such as osteoarthritis [1]. Considering the potentially significant gastrointestinal and cardiovascular risks of NSAID use, increasing numbers of patients are searching for alternative forms of pain management, which meet their needs in terms of pain amelioration and minimal adverse effects. Zingiber officinale, commonly known as ginger, has a long tradition of medicinal use as an anti-inflammatory agent for musculoskeletal diseases in Ayurvedic and Chinese medicine [2,3]. Z. officinale is a member of the Zingiberaceae plant family, native to southern Asia, consisting of 49 genera and 1,300 species, 80–90 of which are Zingiber. It is a complex mixture of pharmacological compounds containing several hundred known constituents, including gingerols, beta-carotene, capsacin, caffeic acid, curcumin, and salicylate [4]. Previous investigations—of varying quality—have suggested that Z. officinale possesses anti-emetic, positive inotropic, and carminative properties to promote secretion of saliva and gastric juices and to inhibit platelet aggregation [4,5]. Several of its chemical constituents, including gingerols, shogaols, paradols, and zingerone, have demonstrated anti-inflammatory actions in vitro, inhibiting leukotriene synthesis, the activity of cyclooxygenase enzymes (COX-1 and COX-2), production of interleukins (Il-1 and Il-12), and tumor necrosis factor alpha in activated macrophages [6–9]. In addition, it has been suggested that Z. officinale and its constituents—particularly shogaols—have agonize
vallinoid (capsaicin) receptors TRPV1, which are involved in the central and peripheral processing of noxious stimuli [6,10].

There is a growing literature that has focused on assessing the value of the analgesic and anti-inflammatory properties of Z. officinale in human participants, including a recent review that evaluated the effectiveness of Z. officinale in the management of osteoarthritis [11]. As only three highly heterogeneous trials met their inclusion criteria, the authors concluded that the current evidence for the use of Z. officinale to treat osteoarthritis is weak. To the best of our knowledge, the value of Z. officinale to treat or manage other types of pain has not been systematically reviewed. The aim of the current review is to systematically summarize and critically evaluate the evidence from all human participant clinical trials of Z. officinale for the treatment of any type of chronic or acute pain in order to elucidate the role of Z. officinale in the management of pain.

Methods

A protocol was developed and adhered to. The protocol included a description of the inclusion criteria, search strategy, description of the proposed search process, outcomes to be assessed, and the responsibilities of each authors. The recent Preferred Reporting Items for Systematic Reviews & Meta Analyses (PRISMA) statement [12] was used to lend a framework for the reporting structure of the systematic review.

Eligibility Criteria

As outlined in the protocol, completed randomized controlled trials (RCTs) or controlled clinical trials (CCTs) testing the efficacy of products described as Z. officinale, used as a sole oral treatment against a comparison or placebo condition in human adults suffering from any type of pain, were included. The trials must have reported a pain-related outcome (visual analog scale [VAS], numeric rating scale [NRS], McGill Pain Questionnaire [MPQ], or any other self-reported pain rating). Trials of Z. officinale combined with other substances were excluded. No language or date restrictions were imposed.

Information Sources and Search Strategy

Electronic databases AMED and CINAHL (via the EBSCO interface), the Cochrane Library (via Wiley), EMBASE and Medline (via the OVID interface), and Web of Knowledge (via Thompson Reuters) were searched from their inception to September 2010. Websites of clinical trial registers were also considered for unpublished trial data. The search strategy included “ginger,” “pain,” and “RCT”-related search terms (detailed in Appendix 1 for Medline and modified for use in the other databases). Articles were located through a scoping search in major electronic databases and through scanning our own files. Reference lists of all retrieved articles were hand-searched for relevant studies. Contact was made with authors of recent trials yet to be published.
participants were analyzed. Participant group sizes were relatively small, ranging from 14 to 56. Three studies assessed the efficacy of *Z. officinale* for osteoarthritis, one for dysmenorrhea, and four (two of which were reported in the same article) for experimentally induced acute muscle pain. Pain intensity was assessed and reported by all studies. Studies assessing the use of *Z. officinale* for osteoarthritis and exercise-induced muscle pain used a 100-mm visual analog scale (VAS), with one study [21] using the 0–100 pain scale incorporated into a Hebrew validated version of Western Ontario and McMaster Universities Arthritis Index (WOMAC) [20]. The pain of dysmenorrhea was assessed using a 4-point scale (none, mild, moderate, and severe). A summary of the included trials and primary between-group analyses of pain outcomes is detailed in Table 1.

Table 2 summarizes the methodological details relating to each of the included trials. In terms of methodological quality, three of the trials (two reported in one publication) scored 5 on the Jadad scale [10,16], one scored 4 [21], two scored a Jadad rating of 3 [17,18], and two scored a Jadad rating of 2 [15,19]. None of the included trials reported more than 10 items (out of a total of 15) in the herbal-specific CONSORT statement, fully or partially. Two studies reported no dropouts during the trial period [15,18,19], and therefore, reported results were ostensibly based on intention-to-treat (ITT) principles. One trial specifically reported ITT analyses [21]. Five trials reported dropout rates: Black and O’Conner [15], 3.5%; Black and O’Conner [16]: Study 1, 5.5%; Study 2, 4.8%; Bliddal et al. [17], 25.3%; and Wigler et al. [21], 27.5%. Wigler et al. reported that eight participants dropped out due to perceived treatment inefficacy; three from group 1 (ginger extract first) and five from group 2 (placebo first). Two participants dropped out because of heartburn when using *Z. officinale*. In Bliddal et al.’s trial, 8 (out of 75) patients dropped out after the initial washout period, 4 due

Figure 1 Flowchart of eligibility assessment and inclusion. *One article reported two studies, taking the total number of studies to 8.*
## Table 1: Summary of included trials

<table>
<thead>
<tr>
<th>Author, Date (Ref.)</th>
<th>Design duration</th>
<th>Condition</th>
<th>No. of participants randomized (age)</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Outcome measure for pain</th>
<th>Main results between groups</th>
<th>Adverse events</th>
<th>Authors conclusion</th>
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</thead>
<tbody>
<tr>
<td>Black and O’Conner, 2008 [15]</td>
<td>3 days (1 day of preliminary testing, 2 days of experimental testing), DS, placebo-controlled, crossover trial</td>
<td>Acute eccentric exercise</td>
<td>25 (23.2 ± 4.2)</td>
<td>Z. officinale (2 g) × 6 tablets 0.4% gingerol, taken once prior to exercise condition</td>
<td>Placebo (2 g flour)</td>
<td>Muscle pain intensity (MPI) (100 mm VAS)</td>
<td>N/S difference in MPI between Z. officinale and placebo (P &gt; 0.05)</td>
<td>None reported</td>
<td>Compared with placebo, consumption of Z. officinale had no clinical or significant effect on pain or any other outcome measure</td>
</tr>
<tr>
<td>Black et al., 2010, Study 1 [10]</td>
<td>11-day DB placebo controlled</td>
<td>Acute eccentric exercise</td>
<td>36 (34 in analysis) 17 P’s in each condition (21.2 ± 0.7 Z. officinale (20.9 ± 0.6 placebo))</td>
<td>Raw Z. officinale (2 g) × 6 tablets taken within 2-minute period 6-gingerol:1.4 mg/g 8-gingerol:1.3 mg/g 10-gingerol:1.9 mg/g 6-shogaol:2.2 mg/g 11 days (eccentric exercise practiced on day 8)</td>
<td>Placebo (2 g of yellow cornflower)</td>
<td>Muscle pain intensity (MPI) 24, 48, and 72 hours after exercise (100 mm VAS)</td>
<td>MPI significantly lower in Z. officinale group 48 hours after exercise: Glass’ Δ = 0.78 SD, 25.3%, U = 85, P = 0.041. N/S difference at 48 and 72 hours</td>
<td>None reported</td>
<td>Daily consumption of raw and heat-treated Z. officinale resulted in moderate-to-large reductions in muscle pain</td>
</tr>
<tr>
<td>Black et al., 2010, Study 2 [10]</td>
<td>11-day DB placebo controlled</td>
<td>Acute eccentric exercise</td>
<td>42 (40 analyzed; 20 in each condition) (20.6 ± 0.6 Z. officinale (21.4 ± 0.8 placebo))</td>
<td>Heated Z. officinale, 2 g × 6 tablets taken within 2-minute period 6-gingerol:2.8 mg/g 8-gingerol:1.3 mg/g 10-gingerol:1.9 mg/g 6-shogaol:2.6 mg/g 11 days (eccentric exercise practiced on day 8)</td>
<td>Placebo (brown sugar)</td>
<td>MPI 24, 48, and 72 hours after exercise (100 mm VAS)</td>
<td>Pain intensity significantly lower in Z. officinale group 24 hours after exercise: Glass’ Δ = 0.57 SD, 22%, U = 127, P = 0.049. N/S difference at 48 and 72 hours (P &gt; 0.05)</td>
<td>None reported</td>
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<tr>
<td>Black and O’Conner, 2010 [16]</td>
<td>2-day DB, placebo-controlled crossover trial</td>
<td>Acute eccentric exercise</td>
<td>27 (24.0 ± 4.9 years F) (21.8 ± 2.7 years M)</td>
<td>Z. officinale, 2 g 6-gingerol:1.4 mg/g 8-gingerol:1.0 mg/g 10-gingerol:1.9 mg/g 6-shogaol:2.2 mg/g 24/48 hours after exercise</td>
<td>Placebo (2 g flour)</td>
<td>MPI (100 mm VAS)</td>
<td>N/S difference in change in ratings of muscle pain in both groups (less than 1 mm on 100 VAS, P = 0.82) 45 minutes after consumption After 24 hours, MPI decreased in intervention group 5.8 mm (14%), but 0% in placebo group. Cohen’s d = -0.48, n/s (P = 0.21)</td>
<td>None reported</td>
<td>2 g of Z. officinale does not attenuate muscle pain, inflammation or dysfunction 45 min after ingestion but may attenuate day-to-day progression of muscle pain</td>
</tr>
<tr>
<td>Author, Date (Ref.)</td>
<td>Design duration</td>
<td>Condition</td>
<td>No. of participants randomized (age)</td>
<td>Intervention</td>
<td>Comparison</td>
<td>Outcome measure for pain</td>
<td>Main results between groups</td>
<td>Adverse events</td>
<td>Authors conclusion</td>
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<tr>
<td>Bliddal et al., 2000 [17]</td>
<td>DB, placebo-controlled crossover trial. 3 weeks for each (no washout between interventions)</td>
<td>Osteoarthritis</td>
<td>56 (66 years, range 24–87)</td>
<td>Z. officinale extract 170 mg (Eurovita Extract 33) Three times a day</td>
<td>Ibuprofen 400 mg or placebo three times a day</td>
<td>Pain intensity (100 mm VAS)</td>
<td>After wash-out median VAS 51 mm. MPI changed by -15, -2, and +1 mm in ibuprofen, Z. officinale and placebo period, respectively</td>
<td>11 withdrawals (1 AE in Z. officinale due to “bad taste” in mouth)</td>
<td>Statistical difference between placebo, Z. officinale and ibuprofen. No significant difference between placebo and Z. officinale</td>
</tr>
<tr>
<td>Haghighi et al., 2005 [18]</td>
<td>1-month DB, comparative parallel trial</td>
<td>Osteoarthritis</td>
<td>120; 40 per group (58.5 years, range 52–64)</td>
<td>Z. officinale extract (30 g extract was equivalent to 1 kg of dried Z. officinale) 15 mg of extract two times a day, 500 mg tablets</td>
<td>Ibuprofen 400 mg three times a day</td>
<td>Pain intensity (100 mm VAS) Gelling pain Joint swelling Joint motion slope measurements</td>
<td>Significant difference between Z. officinale and placebo, ibuprofen and placebo (P &lt; 0.05), N/S difference between ibuprofen and Z. officinale (P &gt; 0.05)</td>
<td>None reported</td>
<td>Z. officinale extract and ibuprofen significantly more effective than placebo</td>
</tr>
<tr>
<td>Ozgoli et al., 2009 [19]</td>
<td>6-month DB, comparative trial; three parallel groups</td>
<td>Dysmenorrhea</td>
<td>150; 50 per group</td>
<td>Z. officinale (dried rhizome powder) 250 mg Four times a day 3 days from the start of menstrual period</td>
<td>1) Mefenamic acid 2) Ibuprofen Four times a day</td>
<td>Pain severity (0–3) Change in pain severity Satisfaction No. of capsules used</td>
<td>N/S diff between groups in pain severity, pain change (relief), stability or aggravation of symptoms, P &gt; 0.05</td>
<td>Four women in each group reported a slight increase in bleeding</td>
<td>Z. officinale was as effective as mefenamic acid and ibuprofen in relieving menstrual pain. No significant difference between placebo and Z. officinale</td>
</tr>
<tr>
<td>Wigler et al., 2003 [20]</td>
<td>24-week DB, placebo-controlled crossover trial</td>
<td>Gonarthritis</td>
<td>29; Z. officinale first 15, placebo first, 14 (42–85 years)</td>
<td>Z. officinale (250 mg) four times a day</td>
<td>Placebo (maltodextrin) Four times a day</td>
<td>Pain on movement (POM) (100 mm VAS) handicap</td>
<td>At 12 weeks, VAS POM reduced in both groups (P &gt; 0.05) at 24 weeks post crossover placebo-Zintona significantly lower (P &lt; 0.01)</td>
<td>Heartburn (2 P’s while using Zintona) Dropouts in weeks 1 (1) and 48 (1)</td>
<td>No significant difference between placebo and Zintona EC during the first 3 months of study, but 3 months after crossover, ginger extract group showed sign improvements over the placebo group</td>
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</table>

N/S = nonsignificant.
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<tr>
<td>Was similarity between groups compared at baseline?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Not reported</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Was trial described as randomized?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Was randomization procedure described and was it appropriate?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
<td>Not described</td>
<td>No randomization</td>
<td>Unclear</td>
</tr>
<tr>
<td>Was the treatment allocation concealed?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Unclear</td>
<td>Yes</td>
<td>No</td>
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<tr>
<td>Was the trial described as double blind?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Was the number of withdrawals/drop-outs in each group mentioned?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No dropouts</td>
<td>Partially</td>
<td>No dropouts</td>
<td>No dropouts</td>
<td>Yes</td>
</tr>
<tr>
<td>Was an analysis conducted on the intention-to-treat sample?</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>Was power calculation reported?</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Were eligibility criteria specified?</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>No. of items in section 4 of herbal-specific CONSORT statement described fully (F) and partly (P) (total 15 items)</td>
<td>6 fully</td>
<td>6 fully</td>
<td>4 fully</td>
<td>4 fully</td>
<td>1 fully</td>
<td>5 fully</td>
<td>5 fully</td>
<td>5 fully</td>
</tr>
<tr>
<td>Jadad score</td>
<td>5</td>
<td>5</td>
<td>5</td>
<td>2</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>4</td>
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</table>
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to pain after NSAID withdrawal and 4 due to withdrawal of consent. Thus, 67 participants were randomized; a further 11 participants were excluded or withdrew due to adverse events; intestinal strangulation (N = 1), restless legs (N = 1) (both placebo period), bad taste (Z. officinale period, N = 1) nausea (ibuprofen period, N = 1), unsatisfying therapeutic effect (N = 3), lithium treatment (N = 1), and others (e.g., non-compliance, N = 3).

Osteoarthritis

The duration of the intervention and control (placebo) periods ranged from 3 to 12 weeks. All trials included a placebo condition and two compared the use of Z. officinale with a placebo condition and with ibuprofen. Two trials [17,21] were crossover designs and of moderate methodological quality. One [21] compared 12 weeks of Zintona EC (based on standardized ethanol extract Z. officinale; 1 g/day) with 12 weeks of placebo prior to crossover (Zintona EC followed by placebo, then placebo followed by Zintona). Over the first 12 weeks, pain decreased significantly in both groups and no significant differences were observed between the active medication and the placebo condition at week 12. However, 12 weeks after crossover (week 24 of the trial), the pain in the Zintona-placebo group had increased, while for those in the placebo followed by ginger group, pain had decreased significantly further. At this point, highly significant differences were found between placebo–ginger group and ginger–placebo group (P < 0.01) for pain on movement (POM) (VAS) and handicap scores (WOMAC). In the placebo–Zintona EC group, POM had decreased by a mean of 67.57 points on a 100-point VAS for POM and 63.47 for handicap, while in the Zintona–placebo group, mean pain ratings began to rise, with a mean VAS of POM at 24 weeks increased from baseline scores to 82.1 for VAS pain and 80.8 for handicap. At 24 weeks, blinding was broken and both groups offered Zintona EC treatment for a further 24 weeks. At 48 weeks, the placebo group first reported VAS of POM of around 15.63 and treatment group of a mean of 9.00 and handicap ratings of 15.00 (placebo first) and 8.78 (Zintona first), with no significant differences between groups (P > 0.4). Rescue medication of up to four tablets of paracetamol (acetaminophen) per day (dose not specified) was permitted throughout the study period, except during the 12 hours preceding every point of clinical evaluation.

In a comparative parallel trial, Haghighi et al. [18] reported highly significant differences in pain and gelling pain VAS ratings between Z. officinale and placebo and between ibuprofen and placebo groups but no significant differences between ibuprofen and Z. officinale. Mean VAS pain ratings in the Z. officinale extract group fell by 27.7 points, while in the ibuprofen group, mean ratings fell by 29.2 points and were significantly greater than the observed change of 1.9 mm in mean VAS ratings in the placebo group. The authors concluded that the degree of efficacy between Z. officinale extract and ibuprofen was comparable. Although NSAIDs and other analgesic treatments were discontinued during a 1-week wash-out period, up to three tablets (exact dose not stated) of acetaminophen per day was permitted as rescue medication. Unfortunately, the amount of rescue medication taken by each of the treatment groups was not assessed due to errors made by patients when reporting the information.

Blidell et al. [17] provided 56 osteoarthritis patients with either 520 mg/day of Z. officinale extract (Eurovita Extract 33, EV.ext-33) ibuprofen or placebo for 3 weeks. VAS pain ratings after 3 weeks of ibuprofen use were significantly different from those obtained following the Z. officinale and the placebo conditions. Friedman tests for multiple comparisons found a highly significant difference between the ibuprofen condition and the Z. officinale or placebo condition (Friedman 24.65, P < 0.0001) and the same trend was found for acetaminophen use (rescue medication: Friedman 11.7, P < 0.01). However, the authors also carried out post hoc exploratory analysis of the first period of treatment, prior to crossover, and found a significantly better effect during this period in both ibuprofen and Z. officinale groups compared with the placebo group (chi-square test, P < 0.05).

Dysmenorrhea

One double-bind comparative trial [19] compared the use of Z. officinale (1 g/day) with mefenamic acid or ibuprofen to treat primary dysmenorrhea. Women (N = 150) were alternately allocated to each of the interventions for 3 days from the start of their menstrual period. Participants were sequentially allocated to intervention groups, and both patients and health care providers were blinded. Pain severity and change in pain severity (on 4-point scales) was compared between groups. The authors reported no significant differences between the groups before and after treatments, and participant compliance to treatment regime was comparable between groups. The authors suggested that Z. officinale may have anti-prostaglandin effects similar to those of mefenamic acid and ibuprofen; the principal active ingredient for these effects being gingerols.

Experimentally Induced Acute Pain

Black and colleagues carried out a series of studies assessing the effect of Z. officinale on experimentally induced acute pain [10,15,16]. In the first study [15], a double-blind, placebo-controlled crossover design was used to investigate whether a 2-g dose of Z. officinale would reduce quadriceps muscle pain during moderate intensity cycling exercise (VO2peak) when consumed 30 minutes before. In comparison with participants taking placebo, Z. officinale had no clinically meaningful or statistically significant effect on perceptions of muscle pain or any other outcome measures (oxygen consumption, heart rate, and ratings of perceived exertion). The authors suggest that these findings may be explained by the fact that prostaglandins, implicated in inflammatory pain conditions, do not play a significant role in this type of experimentally induced pain.
In a similar study [16], acute pain was experimentally induced in a controlled eccentric exercise condition. Participants ingested a 2-g dose of *Z. officinale* or placebo 24 and 48 hours after the exercise. Participants rated their pain 45 minutes after ingestion. No significant differences in pain, arm volume (inflammation), or range of movement were found. However, participants who had taken *Z. officinale* 24-hour post-exercise experienced less pain 1 day later, 48 hours after exercise than those assigned to the placebo condition. While not significant, the authors reported a moderately large difference between placebo and *Z. officinale* conditions (Cohen’s $d = 0.48$ standard deviation [SD]) and a 14% reduction in pain ratings in *Z. officinale* group, compared with a 0% change in the placebo group. They suggested that while a single dose of *Z. officinale* had no short-term effects on exercise-induced muscle pain (i.e., 45 minutes after ingestion), it may have a delayed effect.

In two further trials carried out by Black et al. [10], participants consumed either 2 g of raw or heated *Z. officinale* or placebo. Apart from the differences in the *Z. officinale* preparation (raw ginger containing 2.2 mg/g 6-shogaol, heated *Z. officinale* containing 2.6 mg/g 6-shogaol), the methodology for the two studies was identical. After 7 days of *Z. officinale* consumption, participants performed 18 eccentric actions for the elbow flexors, thus inducing acute pain and inflammation. Consumption of both raw and heat-treated *Z. officinale* resulted in significantly lower levels of pain (25% and 23%, respectively) 24 hours after exercise compared with the placebo group ($P = 0.049$). At 48 and 72 hours, this difference was not significant.

### Adverse Events and Cost Issues

In the present review, only two out of the eight included trials reported adverse events arising in those taking *Z. officinale*. These were infrequent and mild. In one study [21], two of the 29 participants experienced heartburn, while in another [15], adverse events were reported in all treatment conditions; those in the *Z. officinale* group reporting a bad taste in the mouth (5 out of 67) following *Z. officinale* consumption. Routine blood counts, liver, and renal function tests carried out during the longest of the included trials did not provide any evidence of toxicity after 48 weeks of *Z. officinale* use [21]. No study included cost of intervention as an outcome measure.

### Discussion

Five trials of *Z. officinale* for the treatment of osteoarthritis pain and experimentally induced muscle pain [10,16,18,21] reported improved pain ratings by participants using *Z. officinale* compared with those using a placebo. One study [19] reported no significant difference between the use of *Z. officinale*, ibuprofen, and mefenamic acid to treat the pain of dysmenorrhea. Two high-quality studies [15,17] reported finding no effects over and above nonspecific or placebo effects. One of these assessed the use of *Z. officinale* to attenuate experimentally induced acute muscle pain, while in the other, *Z. officinale* was taken over a 3-week period for chronic osteoarthritis. In both studies, the authors explored possible reasons for this lack of effect, for example, suggesting that the findings could be due to inappropriate dosing or timing of outcome assessment. Experimental research offers the opportunity to obtain data that are less susceptible to the noise inherent in clinical settings, and Black et al. [15] was able to provide some evidence to support the proposed hypoalgesic mechanisms of *Z. officinale* and/or its constituents, which is thought to be via the inhibition of prostaglandin and leukotriene release. They suggested that as prostaglandins do not play a pivotal role in exercise-induced muscle pain, and given that one of the proposed hypoalgesic mechanisms of *Z. officinale* and/or its constituents is thought to be via the inhibition of prostaglandin and leukotriene release, the observed lack of effect might be as expected. Currently available data indicate that *Z. officinale* appears to have a delayed therapeutic action [10,16] and there is therefore no evidence of short-term efficacy of *Z. officinale* in the treatment of very acute pain conditions.

Issues relating to appropriate therapeutic dosing and the length of treatment period were raised by Bliddal et al. [17], who suggested that these, in combination with the possibility of crossover effects, make the interpretation of the findings problematic. In response to a reviewer, Bliddal et al. suggested that carry-over effects, combined with the short duration of the intervention periods, may have confounded their data. Issues relating to heterogeneity and the lack of information reported in the included trials somewhat hinder attempts to quantify the potential value of *Z. officinale* for the treatment of pain. The efficacy of *Z. officinale* to ameliorate pain was reported in the studies where ostensibly higher doses of “ginger extract” were provided (1 g or more per day), whereas a study reporting nonsignificant differences provided a dosage of only 510 mg/day [17]. However, details relating to the quantity or percentage of active/marker constituents (gingerols, shogaols, etc.) and extraction methods were sparse. *Z. officinale* can be prepared into several forms (e.g., dried root powder, crude aqueous root extract) and the lack of clearly reported information relating to the constituents of herbal interventions makes meaningful between-study comparisons difficult.

The methodological quality of RCTs was variable (see Table 2). For example, compromises to blinding procedures (for example, differences in the numbers of tablets provided in each intervention condition) [18], a lack of placebo control groups [18,19], and adherence to ITT principles in half of the included trials may have jeopardized internal validity. In addition, information relating to the extent to which permitted rescue medication use differed between treatment and control groups makes it difficult to quantify the potential benefits of *Z. officinale*. Two studies [18,21] permitted acetaminophen as rescue medication for osteoarthritis use but failed to report data relating to its use. Moreover, although no studies indicated a conflict of

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In spite of these issues, the current synthesis of available data does provide some encouraging (albeit tentative) indications that the use of *Z. officinale* to treat some kinds of pain may produce specific positive effects. Similar findings were observed in a previous systematic review of *Z. officinale* [11], although this review was unable to draw any firm conclusions or recommend *Z. officinale* for osteoarthritic pain because the data were obtained from a very small number of trials of varying methodological quality. Correspondingly, the findings of the current review provide preliminary indications of efficacy in a larger number of clinical trials, including different kinds of pain, and highlight the need for further trials to be carried out which address the methodological shortcomings of previous investigations. Justification for further research also stems from pharmacological data which have suggested that *Z. officinale* can reduce the direct activation of type 3 and 4 afferent nerve fibers by substances such as bradykinin and sensitization of afferent fibers by prostaglandins and cytokines. As gingerols, shogaols, and zingerone are known as TRPV1 receptor agonists, located in dorsal root ganglion and central neural tissues, central involvement has also been implicated [22].

**Safety Issues**

The included clinical studies suggest that *Z. officinale* is relatively safe, with reported adverse effects being mild and the numbers of adverse events similar for intervention and placebo groups. However, adverse events—or the absence of these—still need to be systematically assessed and documented. Only two of the trials included in this review reported adverse events, although preclinical safety data do not rule out potential toxicity, particularly in relation to *Z. officinale* consumption over longer periods [22]. Further investigations are warranted to ensure that *Z. officinale* is taken in doses that are both safe and clinically effective.

**Limitations**

Our review has several limitations. Even though we believe our search strategy to be comprehensive, we cannot be sure that our efforts were successful as publication bias is a problem in all medical research [23] and this problem may be exacerbated in alternative medicine literature [5]. It has also been argued that a narrative summary is susceptible to bias, subjectivity, and limited by the absence of an effect size [24]. In order to minimize this possibility, three of the four reviewers (RT, LW, and PP) discussed the study findings and quality indicators in depth, as well as the potential impact of methodological shortcomings, resolving discrepancies with the fourth reviewer (EE) if necessary.

**Recommendations and Future Directions**

Any future trials should aim at testing the efficacy and safety of *Z. officinale* by addressing the significant methodological problems faced in the currently available data. In particular, trials should be comprehensively reported and test medication reported as fully as possible, conforming to the CONSORT guidelines and taking the recommendations outlined by the Initiative on Methods, Measurement and Pain Assessment in Clinical Trials (IMMPACT) document [25] into account. Future assessments of the value of *Z. officinale* to manage pain should also consider more formally numbers needed to treat—and numbers needed to harm—and compare these directly with conventional NSAID therapy. However, as Moore et al. [26] pointed out, comparisons of efficacy with other alternative interventions is not possible if the standards of quality, validity, and size are not met by the respective comparators. Recent guidelines suggest that it would be prudent to measure the effect of an intervention over relevant time frame. Regulatory authorities typically require 12-week trials and trials involving fewer than 50 patients per treatment arm are potentially more biased than larger trials.

Finally, the efficacy of *Z. officinale* in combination with other herbs requires examination. Two studies [4,27], which, because they did not assess solely *Z. officinale*, were excluded from the current review, as well as from a previous review of *Z. officinale* for osteoarthritis [11], used combinations of herbal interventions (*Z. officinale* and *Alpinia galanga*). Both of these were randomized, double-blind, and placebo-controlled trials and one was a multicenter trial, and although one did not describe some important methodological details, both reported decreases in pain reports in the active intervention group. The possibility that *Z. officinale* may provide more potent effects if used in combination with other herbal interventions therefore requires systematic investigation.

**Conclusion**

Conventional treatments for chronic pain are less effective than many patients hope for and are often associated with unacceptable adverse effects. The experience of pain incorporates affective and emotional aspects as well as intensity and patients who are unwilling to accept adverse effects of conventional pain medication or perceive these as lacking efficacy, often embark on their own search for alternatives. However, although *Z. officinale* is used traditionally throughout the world as an alternative treatment for pain and inflammatory conditions, empirical evidence of its efficacy remains inadequate due to a paucity of well-conducted trials. Therefore, the use of *Z. officinale* for the treatment of pain cannot be recommended at present. On the other hand, the converging evidence from clinical trials and from *in vitro* studies suggests that large, methodologically robust trials are warranted. Recent recommendations [14] provide an excellent framework for the development of future trials that focus on providing satisfactory answers to issues relating to the efficacy of
Z. officinale to ameliorate different types of pain, as well as dosing strategies, treatment duration, safety, and cost-effectiveness.

Acknowledgments

No external funding was received for this project. Paul Posadzki’s post as Associate Research Fellow was funded by Pilkington Family Trusts.

References


Appendix 1: Summary Search Strategy (Full Search Strategy Available from the Authors Upon Request)

Search Strategy for Medline

All ginger terms searched in title and abstract fields, and searched as a medical subject heading:
Aadrak; Alay; Ardraka; Bordia; curcumin gan jiang; Engeber; Ganjiang; gigibe; gingembre; ginger; gingerall; Gingerophilus; Gingerforce; gingifere; ginginer; gyn; Hashi Shunti; Imber; Immerwurzel; Inber; Inbwer; Inber$; ingwer$; kankyo; Schnapswurzel; sheng jiang; Shokyo; Singabera; sinjibil; Sunthi; Vishwabhesaj; Z$ officinal$; zanjabil; zerzero; Zinaxin; Zingerone; Zingiber; Zingiberaceae; Zingiberis; Zinopin; Zintona

All pain terms searched in title and abstract fields, and more general terms searched as a medical subject heading:
Ache$; Cramp$; discomfort; uncomfort$; Nocicept$; Sore$; Spasm$; Pain$; Analges$; alges$; algiatr$; Anaesthet$; Anesthet$; anodyn$; hyperalges$; hypoalges$; hyperesthes$; hyperaesthes$; hypoesthes$; hypoaesthes$; Anti-inflam$; inflam$; Angina; arthralgi$; arthrit$; osteoarthrit$; metatarsalg$; causalg$; reflex dystroph$; Sudeck$ atroph$; algoneurodystroph$; Dyesthes$; paraesthes$; Alldynia; neuritis; noxious; Dysmenorrh$; earache$; ear-ache$; colic$; fibromyalgi$; fibrositis; myalg$; glossalg$; toothache$; tooth-ache$; odontalg$; headache$; cephalalg$; cephalaea$; cerebralg$; encephalalg$; cephalodyn$; mastalgia; mastodynia; mammalg$; migrant$; hemicran$; neuropath$; neuralgi$; sciatic$; Lumbago; Carpel Tunnel Syndrome; Sprain$; bruise$; fracture$; strain$; osteopor$; Surg$; operat$; Tendinopath$; Synoviopath$; Bursopath$; Ligamentopath$; Enthesopath$; Enthesit$; arthropath$; parturition; parodynia; childbirth; Labo$r

All “clinical trials” terms searched in publication type fields:
All “clinical trials” terms searched in title and abstract fields:
clin$ trial$; singl$ blind$; doubl$ blind$; tripl$ blind$; trebl$ blind$; singl$ mask$; doubl$ mask$; tripl$ mask$; trebl$ mask$; placebo$; random$; Control$; prospectiv$

Terms were checked to spelling variations and opportunities for truncation ($).