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Review

Efficacy and safety of ginger in osteoarthritis patients: a meta-analysis of randomized placebo-controlled trials

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SUMMARY

The aim of this study was to assess the clinical efficacy and safety of oral ginger for symptomatic treatment of osteoarthritis (OA) by carrying out a systematic literature search followed by meta-analyses on selected studies. Inclusion criteria were randomized controlled trials (RCTs) comparing oral ginger treatment with placebo in OA patients aged >18 years. Outcomes were reduction in pain and reduction in disability. Harm was assessed as withdrawals due to adverse events. The efficacy effect size was estimated using Hedges' standardized mean difference (SMD), and safety by risk ratio (RR). Standard random-effects meta-analysis was used, and inconsistency was evaluated by the I-squared index (I^2).

Out of 122 retrieved references, 117 were discarded, leaving five trials (593 patients) for meta-analyses. The majority reported relevant randomization procedures and blinding, but an inadequate intention-to-treat (ITT) analysis. Following ginger intake, a statistically significant pain reduction SMD = −0.30 ([95% CI: [(−0.50, −0.09)], $P = 0.005$]) with a low degree of inconsistency among trials ($I^2 = 27\%$), and a statistically significant reduction in disability SMD = −0.22 ([95% CI: ([−0.39, −0.04)]; $P = 0.01$; $I^2 = 0\%$]) were seen, both in favor of ginger. Patients given ginger were more than twice as likely to discontinue treatment compared to placebo ([RR = 2.33; 95% CI: (1.04, 5.22)]; $P = 0.04$; $I^2 = 0\%$]).

Ginger was modestly efficacious and reasonably safe for treatment of OA. We judged the evidence to be of moderate quality, based on the small number of participants and inadequate ITT populations.

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Introduction

Ginger has been an important ingredient in Asian medicine for centuries, particularly for pain relief in musculoskeletal diseases[1]. In Europe, ginger was listed in Galén's pharmacopoeia[2], and was mentioned by Plinius the Elder for medicinal use[3]. Since then, ginger has been part of the folk medicine and popular nutraceuticals. Ginger consists of a complex combination of biologically active constituents, of which the compounds gingerols, shogoals and paradols reportedly account for the majority of its anti-inflammatory properties[4]. However, there is variability in the compounding of ginger products. The relative composition in the extraction of ginger is determined by species of ginger, maturity of the rhizome, climate in which the plants are grown, when harvested, and preparation method of the extract[5].

Preclinical research has shown that ginger acts as an inhibitor of cyclooxygenase (COX), particularly the inducible form of COX (COX-2), rather than the constitutive form (COX-1)[6]. Ginger also inhibits lipo-oxygenase, resulting in suppression in the synthesis of the inflammatory leukotrienes[7]. Various ginger compounds and extracts have been tested as anti-inflammatory agents, where the length of the side chains determines the level of effectiveness. However, a combination of ginger extracts is more effective in decreasing inflammatory mediators than an individual compound[8]. Ginger extracts are, furthermore, found to inhibit the expression of tumor necrosis factor (TNF)-α in synoviocytes activated by either

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TNF-α or interleukin (IL)-1β[9,10], and in one study a ginger extract was shown to be as effective an anti-inflammatory agent as betamethasone[11].

Today the therapy for osteoarthritis (OA) is still directed towards symptoms, since no disease-modifying therapy has been established, and there is continued research into potential symptom-modifying drugs with minimal adverse reactions[12,13]. Apart from ginger, several other herbal medicines and nutraceuticals have been studied as alternatives to non-steroidal anti-inflammatory drugs (NSAIDs) in the treatment of OA. Among these are Boswella serrata, avocado–soybean unsaponifiables (ASU), rosehip, passion fruit peel extract, and curcuminoids[14–21]. Use of herbal medicine is, furthermore, mentioned in the latest OARSI guidelines for non-surgical management of knee OA[22], and a thorough evaluation of orally taken and topically applied complementary and alternative medicines in the treatment of OA is given in two systematic reviews by Long *et al.*[23], and by De Silva *et al.*[24].

With the growing interest in use of herbal and phytochemical products in the treatment of OA, the aim of this study was to assess the clinical evidence of efficacy and safety of oral ginger in the symptomatic treatment of OA, with an emphasis on the quality of the evidence (i.e., our confidence that the estimates of the effect are correct).

Methods

A systematic literature search, followed by study selection according to pre-specified eligibility criteria, data extraction, and statistical analyses, was performed based on a protocol following the standards of the Cochrane Collaboration (http://www.cochrane-handbook.org/), and reported according to the PRISMA statement[25]. After finalizing the protocol, it was made publicly available *via* PROSPERO (CRD42011001777): www.crd.york.ac.uk/PROSPERO/.

Retrieval of published literature

The following bibliographic databases were searched up to 24th April 2014: MEDLINE *via* PubMed from 1950, EMBASE *via* OVID from 1980, CINAHL *via* EBSCO from 1981, Web of Science from 1900, and Scifinder from 1907, as well as The Cochrane Central Register of Controlled Trials. The search strategy was: (Osteoarthritis OR osteoarthros*) AND (ginger OR zingiber OR gingifere OR ginginer OR zingiberis OR zinziber) AND (controlled OR placebo). All words were searched as free text and, where applicable, also as keywords. Reference lists from reviews were screened for further studies. In addition, we manually searched the *Osteoarthritis Research Society International* conference proceedings for the last 5 years.

Eligibility criteria

Inclusion criteria were: Randomized controlled trials (RCTs) comparing any oral ginger preparation (consisting only of extracts of ginger species) with placebo treatment. Participants were patients aged 18 or over with OA in any joint. Two reviewers (EMB, VNF) independently evaluated the studies for eligibility. Disagreements were resolved by discussion and/or a consensus meeting with other authors. No restrictions in language or publication year were applied.

Quality assessment: risk of bias

Two reviewers (VNF, RC) independently assessed (*i*) randomization including both sequence generation and the assessment of concealment of treatment allocation, (*ii*) blinding (incl., who were blinded), and (*iii*) adequacy of statistical analyses [i.e., proper intention-to-treat (ITT) analysis]. Randomization and concealment of allocation were considered adequate if the investigators responsible for patient selection and inclusion in a study were unable to predict which treatment was next. Blinding was considered adequate if participants and study personnel ensured complete lack of knowledge of treatment allocation, and that it was unlikely that the blinding had been broken during the trial period. Analyses were considered adequate if all randomized patients were analyzed in the group to which they were randomly allocated to regardless of the treatment received (ITT principle). We classified trials as violating the ITT principle if they explicitly reported exclusions from the analysis, if the number of patients analyzed was lower than the number of patients randomized, or if it was unclear whether exclusions from the analysis had occurred[26]. Any modified ITT population/analysis was categorized as unclear. Assessment of each entry involved answering a question, with answer 'Adequate' indicating low risk of bias (=adequate handling/reporting in the paper), 'Unclear' risk of bias (either lack of information or uncertainty concerning the potential for bias), whereas 'Inadequate' referred to an inadequate handling of the item (i.e., resulting in a high risk of bias *per se*). Disagreements were resolved by consensus (VNF, RC and EMB).

Data extraction and outcome measures

Data from the included trials were extracted by two reviewers (VNF and RC). A standard data-extraction form was developed for data collection. Being aware of the possible inclusion of trials with a cross-over design, which often will be subjected to carry-over bias[27], only data from the first period were included in those cases. The following information was systematically extracted as characteristics of the studies for each of the randomized trials and handled in a customized Microsoft Excel spread sheet: Study design, ITT population, numbers of patients included in the analysis, demographic characteristics, joints affected with OA, extraction technique and origin, study duration, dosage, and risk of bias.

The core-outcome data in each study consisted of the sample size of the ginger and the placebo group, the number of events in each group, or the values of continuous outcomes with the corresponding measure of dispersion converted into a feasible standard deviation in each group at the end of the study, or from change scores. Change scores were preferable. The co-primary outcome was change in pain and change in disability[28]. Safety was assessed using a pragmatic generic approach[29], extracting the number of withdrawals due to adverse events, serious adverse events, and the number of patients who discontinued for any reason.

Statistical analysis

Whenever possible we used results from the ITT population. For the continuous outcomes, pain and disability, we calculated the standardized mean difference (SMD) for each study[30] corresponding to Cohen's d-value[31]. In principle the unadjusted (Cohen's) SMD does not treat the variance as an estimate[32], thus we applied the Hedges' bias-correction by default to adjust for small-sample bias[33]. The SMDs were signed so that a negative value (SMD < 0) indicates benefit of ginger treatment. Risk Ratios (RRs) were calculated for the binary outcomes.

We used standard random-effects meta-analysis[34] as default option, whereas the fixed-effects model was applied for the purpose of sensitivity analysis. We calculated the I^2 statistic[35] which describes the percentage of total variation across trials due to heterogeneity rather than to chance[36]. For practical reasons we defined critical inconsistency thresholds as: I^2 values below 25%,

from 25% to 50%, and from 50% and above, corresponding to low, moderate, and high between-trial inconsistency, respectively. We estimated the Number Needed to Treat in order to Harm (NNH), with 95% confidence intervals (95% CI) on the basis of the combined RR value, applying the overall event rate in the placebo groups as a proxy for baseline risk. All results are given with 95% CIs.

A number of pre-specified stratified analyses were executed. Stratifying the available trial results according to clinically important factors and continuous variables at trial level were included in Restricted Maximum Likelihood (REML)-based (i.e., random-effects) meta-regression models[16]. Data were analyzed according to: Dose (mg/day), accumulated dose (protocolled intake mg during trial period), trial duration, and OA joint(s) affected. Analyses were performed using SAS software (version 9.2)[37,38].

Results

Study selection

Figure 1 shows the selection process among potentially eligible studies from the recovered references, following removal of duplicates. From the retrieved 122 references, 115 were discarded for the following reasons: Reviews or outreach papers like editorials, letters etc (72), *in vitro* studies (5), animal studies (8), not concerning OA (9), no placebo or not a controlled study (6), and finally not concerning oral ginger intake (15). Seven references were read in full-text, and two of those were discarded; one due to no oral ginger intake[39], and one due to no placebo[40]. Five studies were finally included in the meta-analysis[41–45].

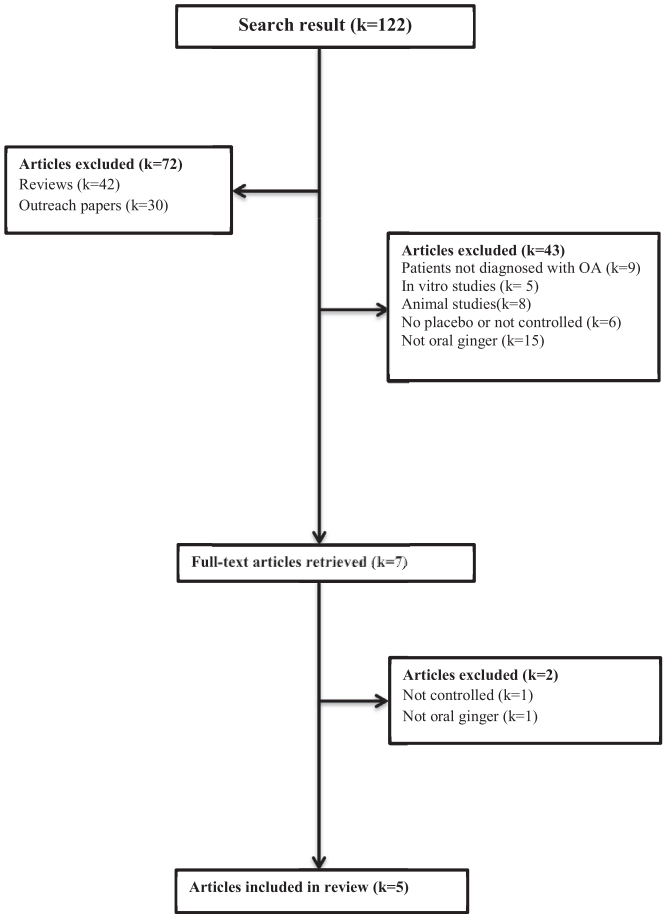

Fig. 1. Flow chart showing the selection of trials. RCTs: Randomized controlled trials.

Study characteristics

Table I shows the characteristics of the five selected trials. Two studies[42,43] had a study design with three arms, one of which was ibuprofen treatment. Two of the trials[42,44] used a cross-over design, thus only data from the first period of these trials was included in the statistical analyses. The number of patients in the ITT population, taking the mentioned study design into account, is displayed in Table I. In total, the five trials allocated 757 patients to ginger or a placebo-control group. Due to a large drop-out, only 593 patients from the five included studies were included in the primary analysis (i.e., pain). Thus the ITT populations available for the meta-analyses was characterized as inappropriate, since the influence of potential attrition bias is not included and cannot be adjusted for in the subsequent meta-analysis. Three trials[41,44,45] included patients with OA of the knee only, one trial[42] included patients with OA of the knee or the hip, and one trial[43] gave no information on type of OA joint.

The average age of the patients ranged from 47 years to 66 years, and the percentage of women included in the studies ranged from 26% to 80%. The daily dose of oral administration of ginger ranged from 500 mg/day to 1000 mg/day. Furthermore, the ginger products varied between studies. Even the two studies based on the same patent Eurovita extract 33 and extract 77 had a slightly different composition of the non-ginger content[41,42], although the extraction method was the same and the ginger composition should be the same, while the other products were produced by different extraction methods and ginger species compositions[43,44], and one study did not describe the extraction method[45]. Trial duration ranged from 3 to 12 weeks, resulting in a calculated accumulated dose ranging from 10,710 mg to 84,000 mg. The five trials had an adequate or unclear reporting of allocation concealment. The majority had an adequate quality of blinding, whereas all the studies applied an unclear or inadequate use of the ITT population (see Table I: 'Risk of Bias').

Efficacy

Figure 2(A) shows the SMD on pain reduction when comparing ginger with placebo. Combining the data from the five individual trials (593 patients in total), reporting pain as an outcome, produced a combined SMD of −0.30 (95% CI: −0.50 to −0.09, $P = 0.005$), supporting a statistically significant difference in the efficacy of ginger compared to placebo. The result is based on studies showing a modest degree of inconsistency ($I^2 = 27\%$). As expected from the reasonably consistent results, the corresponding analysis based on a Fixed Effects model revealed about the same clinical effect (SMD = −0.28 [95% CI: −0.47 to −0.08, $P = 0.0008$]). To ensure that this effect size would actually be statistically significant, and that the precision of the estimate was reasonable, we calculated the 'Optimal Information Size' (OIS)[46] as the number of patients required for an adequately powered individual trial with an SMD = 0.30. For a two-sample pooled *t*-test, with a statistical significance level of 5%, a total sample size of 352 patients in a balanced design (1:1) would be required to obtain a power of at least 80%. As the 'pain meta-analysis' meets the OIS criterion (data from 593 patients), there is no reason to downgrade the quality of evidence for imprecision.[47,48]

Figure 2(B) shows the SMD on disability reduction with ginger vs placebo. When combining the data from the four individual trials[41,42,44,45] (513 patients in total), self-reported disability showed a statistically significant combined SMD of −0.22 (95% CI: −0.39 to −0.04, $P = 0.01$). This supports efficacy of ginger compared to placebo. The result is based on studies with apparently no inconsistency ($I^2 = 0\%$), and the corresponding Fixed Effects

Table I
Characteristics of eligible trials

Study	Year	Design	*N* (Ginger)	*N* (Placebo)	Age (years)	Females (%)	Knee/hip	Extraction technique and origin	Trial duration (weeks)	Daily dose (mg/day)	Accumulated dose (mg total)	Risk of bias
Bliddal	2000	CO	19	19	66*	41 (73%)*	36/20*	Extract of Chinese ginger (Eurovita Extract 33) with a standardized content of hydroxyl-methoxy-phenyl compounds. Extraction method U.S. Patent Number: 6.638.525	3	510	10,710	A/A/C
Altman	2001	PG	124	123	65†	151 (61%)†	247/0†	Extract of dried ginger rhizomes and dried galanga rhizomes (Eurovita Extract 77) with a content of hydroxyl-methoxy-phenyl compounds. Extraction method U.S. Patent Number: 6.638.525.	6	510	21,420	A/A/B
Wigler	2003	CO	11	13	62‡	23 (79%)‡	29/0‡	Liquid carbon dioxide extraction of Zingiber officinale	12	1.000	84,000	B/A/C
Haghighi	2005	PG	40	40	59§	31 (26%)§	n.a./n.a	95 % ethanol extraction of Zingiber officinale Rosce	4	1.000	28,000	B/B/B
Zakeri	2011	PG	103	101	47†	164 (80%)†	204/0†	Extract of Zingiber officinale, Zingibraceae. Extraction method not described	6	500	21,000	B/A/C

CO: Cross-over design. PG: Parallel-group design. ITT Population: All randomized individuals. N (Ginger): Numbers of patients included in analysis of the experimental (ginger) group. N (Placebo): Numbers of patients included in analysis of the control (placebo) group.

* Numbers based on 56 patients reported evaluable.

† Numbers based on patients included in the analysis.

‡ Numbers based on ITT-population.

§ Numbers based on 120 patients randomized in three treatments groups of 40; ginger extract, placebo and ibuprofen. Knee/Hip: Numbers of joints affected with OA in either knee or hip. n.a.: Data not specified/available. Risk of bias was assessed as (*i*) randomization including both sequence generation and the assessment of concealment of treatment allocation, (*ii*) blinding (incl., who were blinded), and (*iii*) adequacy of statistical analyses (i.e., proper ITT analysis). A = adequate; B = unclear; C = inadequate.

model resulted in the exact same point estimate (SMD = −0.22, CI: −0.39 to −0.04, $P = 0.01$). In terms of the OIS criteria, the number of patients required for an adequately powered individual trial with an SMD = 0.22 would be a total sample size of 652 patients to obtain a power of at least 80%. As the 'disability meta-analysis' did not meet the OIS criterion (data from 513 patients), it is reasonable to downgrade the quality of the evidence for imprecision.

The results from the stratified and meta-regression analyses based on our primary outcome (pain reduction) with ginger vs placebo are presented in Table II: Estimates of SMDs varied to a large degree between the studies with an adequate blinding (SMD −0.21) and the study with an unclear blinding (SMD = −0.76), i.e., the clinical effect size could be more exaggerated in trials using an inappropriate masking technique warranting a downgrading for risk of bias. There was a statistically significant

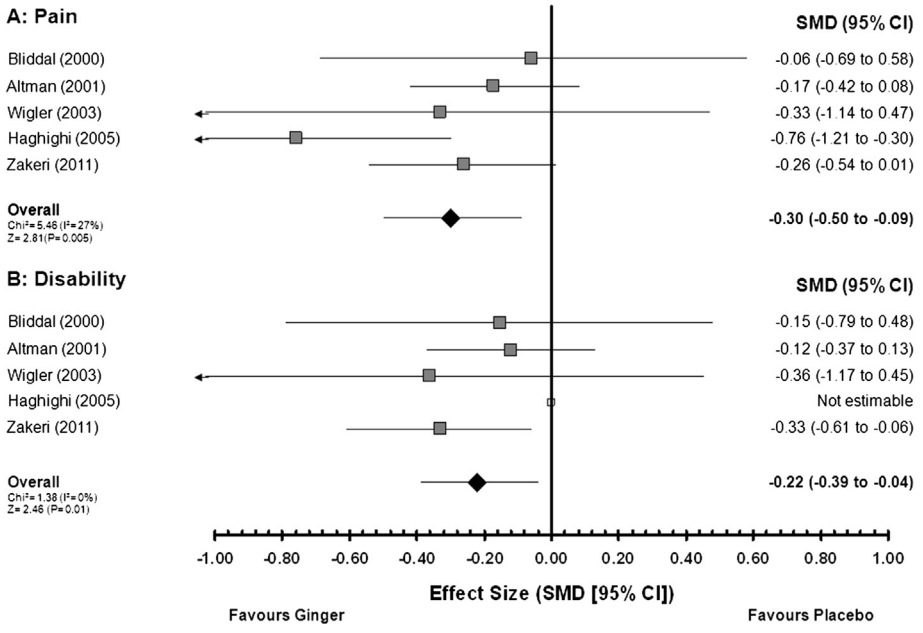

Fig. 2. Efficacy forest plots of trials comparing ginger with placebo in OA patients shown as SMD for (A) pain and (B) disability. The individual trial's effect measures are represented by a square, with 95% CIs indicated by horizontal lines. The total estimate and the corresponding 95% CI are represented by diamonds at the bottom of each forest plot.

Table II
Results of the stratified and meta-regression analyses.*

Variable	Total trials, *k*	ES, SMD	(95% CI)	τ^2	I^2	*P*-value for interaction
All studies	5	−0.30	(−0.51 to −0.08)	0.017	27%	n.a.
Study design				0.032	52%	0.60
Cross-Over	2	−0.17				
Parallel group	3	−0.34				
%Females				0.010	16%	0.11
Slope	n.a.	0.0088	(−0.002 to 0.019)			
Intercept	n.a	−0.85	(−1.56 to −0.15)			
Ginger extract				0.022	35%	0.23
Eurovita extract	2	−0.14	(−0.48 to 0.19)			
Other	3	−0.42	(−0.73 to −0.12)			
Trial duration (wks)				0.021	34%	0.75
Slope	n.a.	0.02	(−0.09 to 0.13)			
Intercept	n.a.	−0.40	(−1.08 to 0.28)			
Daily dose (mg/d)				0.000	0%	0.04
Slope	n.a.	−0.00092	(−0.0018 to −0.00004)			
Intercept	n.a	0.26	(−0.28 to 0.81)			
Accumulated dose (mg)				0.018	29%	0.61
Slope	n.a.	0.00	(−0.00002 to 0.00001)			
Intercept	n.a.	−0.21	(−0.61 to 0.20)			
Risk of bias:						
Allocation conc.				0.022	35%	0.23
Adequate	2	−0.14	(−0.48 to 0.19)			
Unclear	3	−0.42	(−0.73 to −0.12)			
Inadequate	0	–	–			
Blinding				0.000	0%	0.03
Adequate	4	−0.21	(−0.37 to −0.03)			
Unclear	1	−0.76	(−1.22 to −0.30)			
Inadequate	0	–	–			
ITT analysis				0.048	77%	0.53
Adequate	0	–	–			
Unclear	2	−0.40	(−0.78 to −0.01)			
Inadequate	3	−0.22	(−0.61 to 0.16)			

Data are based on the number of patients ($n = 593$) included in the primary analysis (i.e., pain). *k*: Numbers of sub-studies. ES: Effect size. SMD: Standardized mean difference. CI: Confidence interval. τ^2: Tau-squared (between-study variance). I^2: Inconsistency index (measuring heterogeneity). ITT: Intention to treat. n.a. not applicable.
* All analyses presented are based on REML (random effects) meta-analysis approach.

association between SMD and daily dose; i.e., daily dose seemed to be a relevant study-level covariate reducing the between study variation. The statistically significant slope supports upgrading of the quality of the evidence (more confidence in the estimates) with a biologically plausible dose–response association, providing us with more confidence in the estimate.

Safety

Of the five included trials, only three[41,42,44] reported usable data on safety (328 patients in total). Figure 3 shows a statistically significantly increased risk of withdrawals due to adverse events among patients allocated to ginger compared to placebo, with an RR = 2.33 (95% CI: 1.04–5.22; $P = 0.04$; $I^2 = 0\%$). The reported adverse events were though all related to bad taste or various forms of stomach upset, and none could be classified as 'serious' in terms of causing lasting harm, although they made the patients uncomfortable enough to decide to discontinue treatment. This combined estimate is based on (assumed) consistent findings ($I^2 = 0\%$). The NNH for ginger corresponds to 15 (95% CI: 5–500) patients. Forest plot and meta-analysis of all cause discontinuation (three trials and 610 patients; data not shown) presented a slightly increased risk among patients allocated to ginger compared to placebo, with an RR = 1.26; 95% CI: (0.83–1.93). This was though not statistically significant ($P = 0.11$; $I^2 = 54\%$). Only one trial[32] contributed to the analysis of serious adverse events (data not shown), with an RR of 0.33 (95% CI: [0.01–7.70]; $P = 0.49$; I^2 not applicable).

Discussion

Based on the empirical evidence, our data supports that oral ginger is able to reduce pain and disability in OA[46]. Our confidence in the clinical benefit and the optimal therapeutic dose is though moderate based on a double downgrading for Risk of Bias (i.e., serious limitations in the applicable ITT population estimates), and a subsequent upgrading due to the apparent dose–response relationship[49].

This review is based on the rigorous standards of the 'Methodological Expectations for Cochrane Intervention Reviews' (MECIR) and reported according to the PRISMA statement, and we believe this has minimized the potential for bias[25]. The presented quantitative analyses have been generated according to state of the art meta-analysis methodology[30], resulting in anticipated unbiased estimates.

The SMD of −0.30 for ginger compared with placebo corresponds to an effect size for pain which is only slightly above the critical threshold limit for a relevant SMD in OA[31], and it is comparable, although a little higher, to the SMD of −0.21 seen with intake of acetaminophen[50]. The observed pain reducing effect for ginger is in the same range as SMD previously reported for other

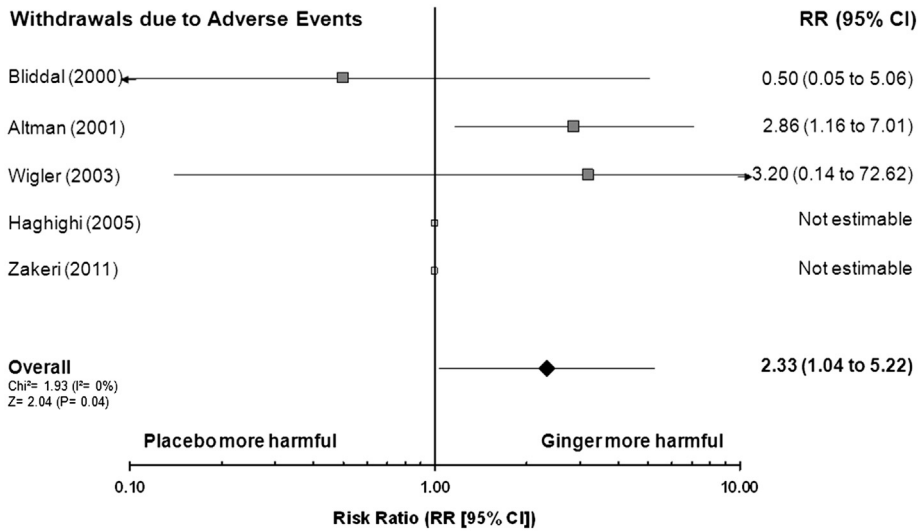

Fig. 3. Safety forest plot of trials comparing ginger with placebo in OA patients represented as RR for adverse events. The individual trial's effect measures are represented by a square, with 95% CIs indicated by horizontal lines. The total estimate and the corresponding 95% CI are represented by a diamond at the bottom of the forest plot.

nutraceuticals/herbal medicines like diacerein with an SMD of −0.24[51], ASUs with an SMD of −0.39[16], and rose hip powder of −0.37[17], all in comparison with placebo. Compared to the effect of NSAIDs, the SMD for ginger has an effect size in the middle of the NSAID range of −0.17 to −0.66, all when compared to placebo[52–54].

Since OA is a chronic disease with increasing need of treatment, it is important to find a right balance between benefit and harm with long term use of any applied treatment[55]. NSAIDs are commonly used in OA, but serious cardio-vascular and gastro-intestinal adverse effects of this group of drugs are well-known[13,56]. Ginger is, on the other hand, generally considered safe, and no serious adverse effects were seen when ginger extract was given to rats[57,58]. Main complaints with ginger intake are milder stomach upset, 'bad taste in the mouth', and similar[59,60], which also are the mentioned adverse effects which lead to withdrawal from treatment in the included studies in this meta-analysis. Ginger therefore seems a better treatment option than NSAIDs judged on possible adverse effects of the latter treatment. There could though be other concerns like allergy caused by the ginger preparations, and interactions with medication.

When looking at allergic reactions caused by ginger, a study demonstrated that ginger did not produce allergic reactions tested by prick-tests[61]. In contrast, extract from common ginger in an *in vitro* study showed a small, although insignificant, anti-allergenic effect[62].

It is well-documented that ginger is an anti-coagulant, and this will be of importance in connection with patients taking drugs like warfarin[59,63,64]. A particular important finding is the synergistic effect between ginger and nifedipine on anti-platelet aggregation[65]. Since OA patients in general are older subjects who are often overweight to obese, a subpopulation with a heart condition or high blood pressure can be expected. Recommendation on trying ginger as a therapy has therefore to take a possible interaction of ginger with the patients' other medication into account prior to recommending use of ginger.

Limitations

Even though we were comprehensive in our search strategy, the risk of publication bias is still present. Poor results or industrial influence tend to affect the probability of trials being published, and trials with positive findings are more likely to be published than trials with negative or null findings[66]. Our study is limited by the inadequate reporting in the included trials. Only two trials[41,42] reported adequate allocation of concealment, and three trials[43–45] were unclear in randomization and concealed allocation.

Four trials[41,42,44,45] reported adequate blinding, and one trial[43] was unclear. Trials with adequate allocation of concealment and adequate blinding tend to show a smaller treatment benefit than trials with unclear or inadequate allocation of concealment and blinding[67]. It is likely that our results overestimate the treatment benefit. This is especially due to unclear allocation of concealment[68]. Selective outcome-reporting bias is also likely in this field of research. Despite the use of a rigorous protocol for the selection of the outcomes included in the meta-analysis, this tends to lead to overestimation[28].

Ginger has a characteristic taste and flavor which questions the possibility of adequate blinding. Only one study describes the effort to minimize bias *via* instructions to the patients on how to swallow the capsules, and this study also reports a registration of the number of cases with bad taste[42]. The risk of bias due to taste and flavor cannot, however, be ruled out in any of the trials, since any patient experiencing 'bad taste in the mouth' may suspect being in the ginger group of the study, which in itself may cause a placebo effect. Another problem is the different ginger preparation in the included studies. Taste and content of active ginger components may vary, but there are no studies comparing these between the included products. In most trials on nutritional products, the lack of knowledge of the actual content of the active component, and, like for ginger, the lack of knowledge of the comparability between the different products used in the studies included in the meta-analysis, will therefore always put a question mark concerning a possible bias in the reported results.

All trials in our study applied an unclear/inadequate use of the ITT population, which possibly lead to attrition bias due to not including the per-protocol planned population. Empirical evidence shows that excluding randomized participants from the analysis affects the estimates of the treatment effect and increases the heterogeneity between trials[26]. Previous systematic reviews of the clinical effectiveness of ginger, one on OA patients[69], and one on trials using oral ginger for pain treatment[60], did not conduct meta-analyses. The first review[69] did not carry out a meta-analysis due to

limitations of reporting in the three eligible studies[42–44], and the exclusion of the Altman *et al.* study[42] due to use of a combined ginger preparation. In the second review[60], a meta-analysis was not conducted due to heterogeneity between studies. In the present study, original data was acquired from the authors[42], and a review of the registered extraction methods lead to an inclusion of the Altman *et al.* trial[41]. Thus, the total available data was adequate to conduct a meta-analysis.

In the studies included in our meta-analysis, all preparations are based on the same species of ginger, but the extraction methods, apart from the two Eurovita preparations with similar type of extraction, vary. The content of active components, especially gingerols, shogoals and paradols[4], are therefore likely to vary[70–73], and the composition of the different components in 1 g of 'ginger' is not necessarily well-defined. This will always be an issue with neutraceuticals of the same kind coming from different producers. The content of the active component may vary, and if one product has an optimal composition for effect on pain compared to the others, the results presented here may not give such a product full credit for effect.

Herbal remedies and other nutraceuticals are increasingly and extensively used by a substantial part of the population[74–78]. Unfortunately only few of the remedies have been tested for efficacy and safety in well-designed clinical trials.

Recent recommendations from the American College of Rheumatology (ACR) on therapies for OA of the hand, hip, and knee are based on consensus judgment of available evidence, and balancing the benefits and harms of both non-pharmacologic and pharmacologic modalities. The ACR provides a weak (conditional) recommendation for most pharmacologic modalities in the initial management of patients with knee OA. These include acetaminophen (paracetamol), oral and topical NSAIDs, tramadol, and intra-articular corticosteroid injections, intra-articular hyaluronate injections, duloxetine, and opioids[79].

The present meta-analysis on ginger for OA demonstrated that ginger has a superior effect on OA pain and disability to placebo, and apparently without serious adverse events. As a conclusion, ginger may be considered as part of the treatment of OA, where the patient is motivated for trying this nutraceutical. As with other complementary and alternative therapies, further studies from independent researchers would be able to show if the effects suggested by the present data will stand in the future. Also, as in all treatment of patients which may take other medication, known possible interaction between medicine and nutraceuticals must be considered.

Declaration of contributions

EMB: Conception and design; Analysis and interpretation of the data; Drafting of the article; Critical revision of the article for important intellectual content; Final approval of the article.

VF: Conception and design; Analysis and interpretation of the data; Critical revision of the article for important intellectual content; Final approval of the article.

HB: Conception and design; Interpretation of the data; Critical revision of the article for important intellectual content; Final approval of the article.

RA: Conception and design; Interpretation of the data; Critical revision of the article for important intellectual content; Final approval of the article.

CJ: Conception and design; Interpretation of the data; Critical revision of the article for important intellectual content; Final approval of the article.

ST: Conception and design; Interpretation of the data; Critical revision of the article for important intellectual content; Final approval of the article.

WZ: Conception and design; Interpretation of the data; Critical revision of the article for important intellectual content; Final approval of the article.

RC: Conception and design; Analysis and interpretation of the data; Critical revision of the article for important intellectual content; Final approval of the article.

Conflicts of interest

The Oak Foundation had no role in study design, data collection, data synthesis, data interpretation, writing the report, or the decision to submit the manuscript for publication. None of the authors are affiliated with, or funded by, any manufacturer of ginger. Both Professor Henning Bliddal and Professor Roy D. Altman disclose that they have previously performed trials with ginger in OA patients. RC declares that he is a statistical editor in the Cochrane Musculoskeletal Group and member of the GRADE Working Group.

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Original Article

COMPARING THE EFFECTS OF GINGER (*ZINGIBER OFFICINALE*) EXTRACT AND IBUPROFEN ON PATIENTS WITH OSTEOARTHRITIS

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Background: **Ginger (*Zingiber officinale*) extract supplementation has been shown to improve the severity of symptoms and decrease the nonsteroidal antiinflammatory drug (NSAID) requirements in patients with osteoarthritis (OA).**

Objective: **To assess the effects of ginger extract as an alternative to NSAIDs and as a supplement drug in the symptomatic treatment of OA.**

Methods: **Between April and October 2002, 120 outpatients with OA of moderate to severe pain, requiring only the use of NSAIDs, were enrolled into a double-blind, randomized, placebo-controlled clinical trial. These patients were randomized into three groups of 40, including the placebo (PL), ginger extract (GE), and ibuprofen (IBP) groups. After a washout period of one week (week 0), patients received either 30 mg ginger extract in two 500 mg capsules, placebo, or three 400 mg ibuprofen tablets daily for one month. Acetaminophen tablet was prescribed as a rescue analgesic during the study. The clinical assessments included a visual analog scale (VAS) for pain, gelling pain, joint swelling measurement, and joint motion slope measurement. Joint motion slope was measured by goniometry (normal = 130°, limited = 120°, and very limited = 110°).**

Results: **The improvement of symptoms (defined as reduction in the mean change) was superior in the ginger extract and ibuprofen groups than the placebo group. VAS scores and gelling or regressive pain after rising the scores were significantly higher in the PL group than both the GE and IBP groups, a month after the treatment ($P < 0.0001$). However, there was no significant difference in VAS and gelling pain scores between the ginger extract and the ibuprofen groups.**

Conclusion: **Ginger extract and ibuprofen were significantly more effective than the placebo in the symptomatic treatment of OA, while there was no significant difference between the ginger extract and ibuprofen groups in a test for multiple comparison.**

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Keywords: Ginger extracts • ibuprofen • inflammation • osteoarthritis • pain

Introduction

There is an increasing awareness, both in the medical community and among public, for the use of unconventional or alternative treatment modalities by patients.[1, 2] Patients with chronic painful disease often seek alternative therapy,[3] and currently ginger is one of the most popular herbal medications for rheumatic diseases. Ginger (*Zingiber officinale*) has been used for medicinal purposes since antiquity. In particular, it has been an important plant for the traditional Chinese and Indian medicines. Although one of its indications has been historically to treat rheumatic disorders, and although ginger extracts have shown the ability to inhibit arachidonic acid metabolism and have antiinflammatory action and/or anti-rheumatic properties,[4, 5] there are very limited published reports on the efficacy of this herb.[4, 6 – 8] The currently available treatment for osteoarthritis (OA) afford only palliative care. The prescription of simple analgesics, such as acetaminophen to

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reduce pain, generally precedes the treatment with nonsteroidal antiinflammatory drugs (NSAIDs). NSAIDs use is limited by the risk of adverse effects, particularly gastrointestinal and renal toxicity.

The purpose of this study was to assess the effects of ginger extract as an alternative to NSAIDs and as a supplement drug in the symptomatic treatment of OA.

Patients and Methods

Plant material and preparation of extract

Fresh rhizome of ginger (*Zingiber officinale* Rosce) was purchased from a local market in India and authenticated by a botanist (Institute of Medicinal Plants, Jahad-e-Daneshgahi). The plant was dried in the shade. The dried rhizome was powdered mechanically and extracted by cold percolation with 95% ethanol for 24 hr. The extract was recovered and 95% ethanol was further added to the plant material and the extraction continued. The process was repeated three times. The three extracts were pooled together and the combined extract was concentrated under reduced pressure (22 – 26 mm Hg) at 45 – 60˚C. Thirty gram of solvent-free extract was equivalent to one kilogram of the dried ginger (W/W) powder. The concentrate was weighed and combined with the necessary exipients, and then filled into 500-mg capsules, each containing 15 mg of the ginger extract. Lactose (placebo) was also capsulated similarly (all of the above-mentioned procedures were undertaken in the industrial pharmacy department of the Faculty of Pharmacy, Tehran University of Medical Sciences).

Patient selection and study design

This study was approved by the local committee for medical ethics and prior written informed consent was obtained from all patients. One hundred and twenty outpatients with OA (89 men, and 31 women), aged 52 to 64 years (mean: 58.5 years) were recruited for this study, which was carried out in the rheumatology clinic of Imam Khomeini Hospital. All the patients had complaints of clinical dysfunction and pain due to OA. Radiologically, it was verified that they had OA in the hip or knee with pain on movement of >30 mm on a 100-mm visual analog pain scale[9] (VAS, mean 69 mm) on their first visit for this study. The study was a double-blinded randomized placebo-controlled clinical trial. Exclusion criteria were rheumatoid arthritis, metabolic disorders (diabetes), gastrointestinal disorders (gastritis or duodenum ulcer), neurological disorders, and dementia. The patients were then randomized into three treatment groups of 40, receiving either 30 mg ginger extract in two 500 mg tablets; placebo daily, or three 400-mg ibuprofen capsules daily for one month. Acetaminophen was used as a rescue medication throughout the study (1 to 3 tablets daily). Treatment with analgesics and NSAIDs was discontinued during the one-week wash-out period.

The following measurements were taken from the above-mentioned agents:

- One hundred-mm VAS for assessing the severity of pain;
- Gelling pain;
- Joint swelling measurements; and
- Joint motion slope measurements.

Statistical analysis

The data expressed as mean±SEM were statistically analyzed by the analysis of variance (ANOVA) followed by the Kruskal-Wallis non-parametric test for between-group differences and Dunn's correction of the significance level for multiple comparison. The level of significance adopted was $P < 0.05$. Calculations were performed on a personal computer, using the Instat program, before breaking the code.

Results

Characteristics

A total of 120 patients with OA were enrolled in three treatment groups: ginger extract, placebo, and ibuprofen group. Table 1 shows a brief characteristical comparison of the study groups before the start of the treatment (baseline). There was no significant difference between the groups for mean age, pain, joint swelling measurement, joint motion slope measurement (one-way ANOVA), and sex (Chi-square).

Efficacy

During the treatment period, no patient was excluded from this study. At the end of one month of treatment, VAS and gelling or regressive pain after rising changed in comparison to the baseline

Table 1. Baseline characteristics of patients evaluated at the end of the washout period.

Characteristic	Treatment groups			*P* Value
	Ginger extract *n* = 40	Placebo *n* = 40	Ibuprofen *n* = 40	
Mean age (years)	58.3 ± 0.33	58.4 ± 0.36	58.8 ± 0.35	$P > 0.05$
Range	(55 – 64)	(52 – 62)		
Sex (man : woman)	29 : 11	28 : 12	32 : 8	$P > 0.05$
VAS	71.7 ± 3.5	64.2 ± 2.8	71.2 ± 2.4	$P > 0.05$
Gelling or regressive pain after rising score	3.65 ± 0.18	3.22 ± 0.27	3 ± 0.20	$P > 0.05$
Joint swelling scores	1.25 ± 0.06	1.07 ± 0.04	1.15 ± 0.05	$P > 0.05$
Joint motion slope scores	1.62 ± 0.07	1.37 ± 0.07	1.45 ± 0.07	$P > 0.05$

values (before treatment), but not in the remaining outcome parameters, including joint swelling measurement and joint motion slope measurement (Table 2). There was no significant difference between the three groups in terms of the pain level at study entry ($P > 0.05$), as examined by the Kruskal-Wallis nonparametric test. VAS changed from the entry median value of 64.2 ± 2.8 mm to 56.5 ± 3.6 mm in the placebo group, 71.7 ± 3.5 mm to 30 ± 3.7 mm in the ginger extract group, and 71.2 ± 2.48 mm to 28 ± 3 mm in the ibuprofen group (Figure 1). There was a significant difference between the three groups in VAS at the end of one month treatment ($P < 0.0001$), as examined by the Kruskal-Wallis nonparametric test. The Dunn's test for multiple comparisons showed a significant difference in these tests between the ginger extract and placebo ($P < 0.001$), as well as ibuprofen and placebo ($P < 0.001$), but not between the ginger extract and ibuprofen ($P > 0.05$) at the end of one month of treatment (Figure 1). Also gelling or regressive pain after rising the scores changed from the entry median values of 3.22 ± 0.27 to 1.77 ± 0.11 in the placebo group, to 3.65 ± 0.18 to 1.3 ± 0.13 in the ginger extract group, and 3.0 ± 0.2 to 0.97 ± 0.1 in the ibuprofen group (Figure 2). There was a significant difference between the three groups in the gelling pain at the end of one month treatment ($P < 0.0001$), as examined by the Kruskal-Wallis nonparametric test. The Dunn's test for multiple comparison showed a significant difference in these tests, between the ginger extract and placebo ($P < 0.05$) as well as the ibuprofen and placebo ($P < 0.001$), but not between the ginger extract and ibuprofen ($P > 0.05$) at the end of one month of treatment (Figure 2).

These results also showed a significant difference between both the ginger extract and ibuprofen groups with the placebo group, but not between the ginger extract and ibuprofen group.

The number of acetaminophen used in these treatment groups could not be assessed, because the majority of the patients did not fill in this form correctly.

Discussion

The findings of this study demonstrate a ranking of efficacy in pain level in patients with osteoarthritis, with ginger extract and ibuprofen being more effective than placebo. Nonetheless, there is an identical efficacy between the ginger extract and ibuprofen.

Although the use of NSAIDs in osteoarthritis is highly controversial,[10] the fact is that many physicians and patients favor these agents for short- and long-term use. However, the therapeutic utility of these agents is frequently limited by the development of side effects, especially gastrointestinal ulceration and ulcer complications. Ulcer complications, such as bleeding and perforation, associated with NSAID therapy often occur without warning and could be life threatening.

The active components of ginger are not known with certainty, but studies of the lipophilic rhizome extracts have yielded the potentially active

Table 2. The change in outcome parameters after a month of treatment.

Parameters	Treatment groups			*P* Value
	Ginger extract *n* = 40	Placebo *n* = 40	Ibuprofen *n* = 40	
VAS	30 ± 3.7	56.5 ± 3.6	28 ± 3.4	$P < 0.0001$
Gelling pain score	1.30 ± 0.13	1.77 ± 0.11	0.97 ± 0.11	$P < 0.0001$
Joint swelling scores	1.12 ± 0.52	1.02 ± 0.02	1.10 ± 0.04	$P > 0.05$
Joint motion slope scores	1.55 ± 0.07	1.30 ± 0.07	1.40 ± 0.07	$P > 0.05$

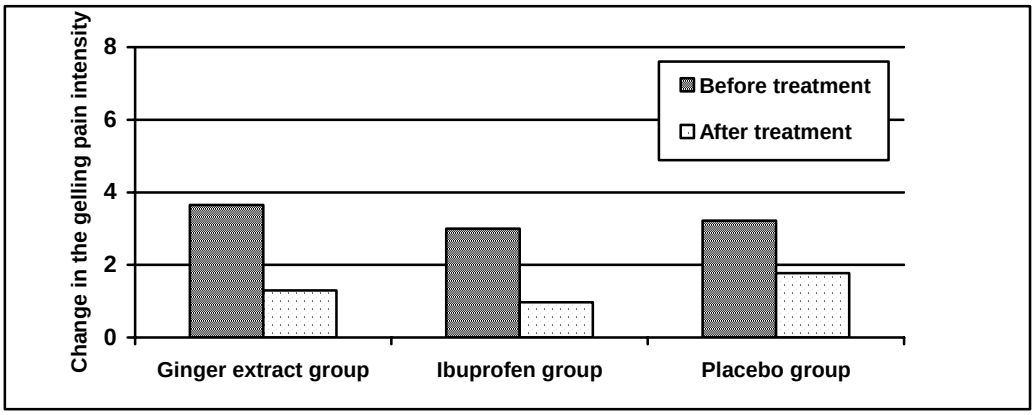

Figure 1. The effects of ginger extract, ibuprofen, and placebo on the change in the mechanical pain intensity. There was no significant difference between the groups before treatment ($P > 0.05$). There was a significant difference between the ginger extract and placebo groups ($P < 0.001$) and also, between the ibuprofen and placebo groups ($P < 0.001$) after treatment. There was no significant difference between the ginger extract and ibuprofen groups ($P > 0.05$).
Before treatment:
Ginger extract group = 3.65 ± 0.18; ibuprofen group = 3 ± 0.2; placebo group = 3.22 ± 0.27.
After treatment:
Ginger extract group = 1.3 ± 0.13; ibuprofen group = 0.97 ± 0.1; placebo group = 1.77 ± 0.11.

components, gingerols and shogaols.[11]

One of the mechanisms of inflammation is the increased oxygenation of arachidonic acid, which is metabolized by cyclooxygenase and 5-lipoxygenase, leading to prostaglandin E_2 and leukotriene B_4, two potent mediators of inflammation.[4] Ginger contains chemical substances with an antiinflammatory potential, and the effect might be attributed to the actions of gingerols, shogaols, diarylheptanoids, and dialdehyd diterpens, which may inhibit inflammatory prostaglandins.[12 – 14] These agents are dual inhibitors of eicosanoid synthesis, which makes the substances even more interesting in the field of rheumatology.[15 – 17] Thus, antiinflammatory effect of ginger may be due to a decrease in the formation of prostaglandins and leukotrienes.[18] A suppressive effect of ginger compounds in arthritic rats has been reported.[19, 20] A retrospective case series was reported on the use of ginger in 56 patients with rheumatoid arthritis, osteoarthritis, and muscle discomfort.[4] The patients subjectively described symptom relief, with many reporting that they were able to reduce their use of other

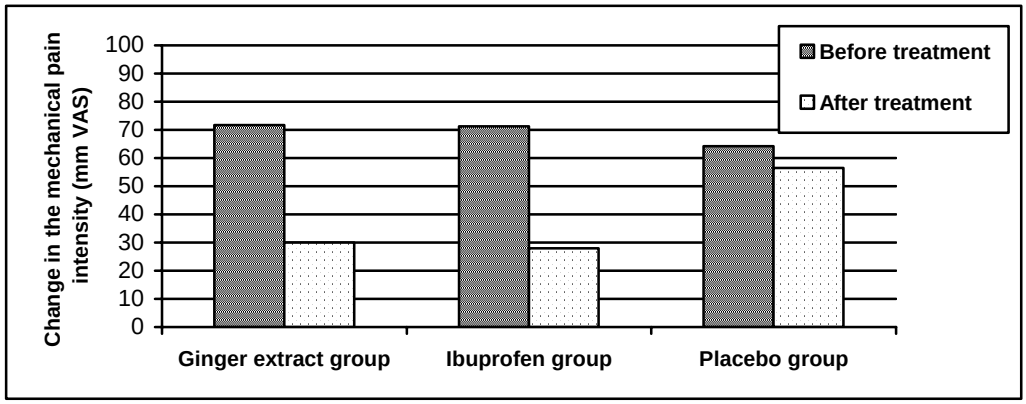

Figure 2. The effect of ginger extract, ibuprofen, and placebo on the change in gelling pain intensity. There was no significant differences between the groups before treatment ($P > 0.05$). There was a significant difference between the ginger extract and placebo groups ($P < 0.05$) and also, between the ibuprofen and placebo groups ($P < 0.001$) after treatment. There was no significant difference between the ginger extract and ibuprofen groups ($P > 0.05$).
Before treatment:
Ginger extract group = 71.7 ± 3.50; ibuprofen group = 71.2 ± 2.48; placebo group = 64.2 ± 2.8.
After treatment:
Ginger extract group = 30 ± 3.7; ibuprofen group = 28 ± 3; placebo group = 56.5 ± 3.6.

antiarthritis drugs. Not long ago, in various randomized, double-blind, placebo-controlled trials ginger was shown to reduce symptoms of osteoarthritis.[7, 8]

A one-month period of therapy with only one dose of ginger extract applied in this study might not have been adequate for all the effects of ginger extract to be detected. Future studies might look into the dose-response and duration of therapy of a standardized and highly concentrated ginger extract in patients with osteoarthritis.

In conclusion, the results of our study indicated that ginger extract could be used as an alternative to the NSAID and as a supplement drug in patients with osteoarthritis.

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Effects of a Ginger Extract on Knee Pain in Patients With Osteoarthritis

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Objective. **To evaluate the efficacy and safety of a standardized and highly concentrated extract of 2 ginger species, *Zingiber officinale* and *Alpinia galanga* (EV.EXT 77), in patients with osteoarthritis (OA) of the knee.**

Methods. **Two hundred sixty-one patients with OA of the knee and moderate-to-severe pain were enrolled in a randomized, double-blind, placebo-controlled, multicenter, parallel-group, 6-week study. After washout, patients received ginger extract or placebo twice daily, with acetaminophen allowed as rescue medication. The primary efficacy variable was the proportion of responders experiencing a reduction in "knee pain on standing," using an intent-to-treat analysis. A responder was defined by a reduction in pain of ≥15 mm on a visual analog scale.**

Results. **In the 247 evaluable patients, the percentage of responders experiencing a reduction in knee pain on standing was superior in the ginger extract group compared with the control group (63% versus 50%; $P = 0.048$). Analysis of the secondary efficacy variables revealed a consistently greater response in the ginger extract group compared with the control group, when analyzing mean values: reduction in knee pain on standing (24.5 mm versus 16.4 mm; $P = 0.005$), reduction in knee pain after walking 50 feet (15.1 mm versus 8.7 mm; $P = 0.016$), and reduction in the Western Ontario and McMaster Universities osteoarthritis composite index (12.9 mm versus 9.0 mm; $P = 0.087$). Change in global status and reduction in intake of rescue medication were numerically greater in the ginger extract group. Change in quality of life was equal in the 2 groups. Patients receiving ginger extract experienced more gastrointestinal (GI) adverse events than did the placebo group (59 patients versus 21 patients). GI adverse events were mostly mild.**

Conclusion. **A highly purified and standardized ginger extract had a statistically significant effect on reducing symptoms of OA of the knee. This effect was moderate. There was a good safety profile, with mostly mild GI adverse events in the ginger extract group.**

Present-day therapy for osteoarthritis (OA) of the knee is directed at symptoms, since there is no established disease-modifying therapy. Treatment programs involve a combination of nonpharmacologic and pharmacologic measures, utilizing a combination of analgesia, antiinflammatory, and intraarticular programs (1–3). If these are unsuccessful, a variety of surgical interventions are appropriate. Since none of the medicinal programs consistently provides adequate relief of pain, yet has attendant risk, the search continues for agents that might provide improvement in symptoms with minimal risk. While scientists have turned to the investigation of newly discovered pharmaceuticals, many patients have turned to herbal and other remedies that have not been adequately studied.

The purpose of the present study was to test an extract of *Zingiber officinale* Roscoe and *Alpinia galanga Linnaeus Willdenow* (both are of the Zingiberaceae family, commonly called "gingers"). The Zingiberaceae family consists of 49 genera and 1,300 species, of which there are 80–90 species of *Zingiber* and 250 species of *Alpinia* (4). The subspecies used in the tested extract were selected after analysis and testing of >100 varieties (species and subspecies) of Zingiberaceae for antiinflammatory effects, by in vivo assays and using animal models. The species selected by this process were grown and harvested under controlled conditions.

Ginger is a very popular spice and the world production is estimated at 100,000 tons annually, of

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which 80% is grown in China (5). Ginger also has a long tradition of medicinal use and has been used as an antiinflammatory agent for musculoskeletal diseases, including rheumatism, in Ayurvedic and Chinese medicine for more than 2,500 years (6,7). The German Commission E Monographs contains reviews of drugs, including herbal drugs, for quality, safety, and effectiveness. As a result of this review of more than 300 herbs by an expert committee under the German Federal Institute for Drugs and Medical Devices, many herbs have been excluded from sales in Germany. The Monographs lists ginger for use in dyspepsia and prevention of motion sickness (8). In the standard German text, *Hager's Handbuch der Pharmazeutischen Praxis*, ginger is listed as being used against nervousness, chronic inflammation of the intestine, coughing, conditions of the urinary tract and lower abdomen, rheumatism, and a sore throat (9).

Pharmacologically, ginger, similar to other plants, is a very complex mixture of compounds. *Zingiber officinale* contains several hundred known constituents (10), among them gingeroles, beta-carotene, capsaicin, caffeic acid, and curcumin. In addition, salicylate has been found in ginger in amounts of 4.5 mg/100 gm fresh root (11). This would correspond to <1 mg salicylate in 1 capsule of the presently tested ginger extract. The actions and especially the interactions of these ingredients have not been (and probably can not be easily) evaluated. Various powders, formulations, and extracts have, however, been commercially used and tested, both in vitro and in vivo, in animal models. In these models, ginger has been shown to act as a dual inhibitor of both cyclooxygenase (COX) and lipooxygenase (12), to inhibit leukotriene synthesis (13), and to reduce caregeenan-induced rat-paw edema (14,15), an animal model of inflammation.

Another related plant, galanga, commonly called greater galanga, is also widely used as a spice in the East and as a remedy for various ailments. It has an antiinflammatory action through inhibition of prostaglandin synthesis (16), and has traditionally been used for rheumatic conditions in South East Asian medicine (17). The volatile oil of *Alpinia galanga* L., which can be obtained by steam distillation of the rhizome, is a complex mixture containing 1,8-cineol and 1′-acetoxychavicol acetate which has antifungal (18) and antitumor (19) activity. The German Commission E Monographs lists the use of *Alpinia officinarum*, which is closely related to *Alpinia galanga*, for dyspepsia and loss of appetite. The US Food and Drug Administration lists ginger and *Alpinia officinarum* as "generally regarded as safe" (20). New research based on the traditional use of the gingers has led to the development of a patented ginger extract (EV.EXT 77). In vitro experiments have shown that the combined extract also inhibits the production of tumor necrosis factor α (TNFα) through inhibition of gene expression in human OA synoviocytes and chondrocytes (21).

In this study, we have evaluated the safety and efficacy of the extract in a double-blind, placebo-controlled study with intent-to-treat (ITT) analysis.

PATIENTS AND METHODS

Study design. The study was a 6-week, double-blind, placebo-controlled, parallel-group trial performed at 10 clinical centers in the US. It was designed according to guidelines on conduct of clinical trials as reported by the Osteoarthritis Research Society International (22) and as outlined in the International Conference on Harmonisation clinical practice guidelines (23). The protocol followed the 1975 Declaration of Helsinki as revised in 1983, with institutional review board approval, and all patients provided their oral and written informed consent. Patients were centrally randomized to receive treatment by a computer-generated allocation schedule, balanced by center, and both the investigators and the patients were blinded to treatment assignment.

Patients. Patients had OA of the knee by the American College of Rheumatology classification criteria using the decision tree format that includes radiographs (24). The radiographic changes had to include at least osteophytes and correspond to OA grades 2, 3, or 4 by the Kellgren and Lawrence criteria (25).

Admission criteria included the presence of knee pain on standing that had to be between 40 mm and 90 mm on a 100-mm visual analog scale (VAS) during the preceding 24 hours. This was assessed after a 1-week washout period. Both men and women $\geq$18 years old were included. Pain had to be of a degree so that it could be tolerated with alleviation using acetaminophen as an escape medication for 6 weeks. Prior treatment for OA was not a requirement. Patients with any of the following were excluded: rheumatoid arthritis, fibromyalgia, gout, recurrent or active pseudogout, cancer or other serious disease, signs or history of liver or kidney failure, asthma requiring treatment with steroids, treatment with oral corticosteroids within the prior 4 weeks, intraarticular knee depo-corticosteroids within the previous 3 months, intraarticular hyaluronate within the previous 6 months, prior treatment with immunosuppressive drugs such as gold or penicillamine, arthroscopy of the target joint within the previous year, significant injury to the target joint within the previous 6 months, other investigational drugs within the previous 1 month, fever $>$38°C at screening, and allergy to acetaminophen or ginger.

After screening, patients entered a 1-week "washout" for antiinflammatory and analgesic medications, during which they were allowed to take acetaminophen as needed up to 4 gm/day. Aspirin for anticoagulation up to 325 mg daily was allowed throughout the study.

If patients were determined to be eligible for the study, a baseline assessment of pain was performed after washout of medications that would affect the arthritis and prior to randomization. Each center was block-randomized with 130 patients receiving ginger extract and 131 patients receiving placebo.

Treatment. During the 6-week treatment period, patients ingested 1 capsule twice daily, morning and evening. Each capsule contained 255 mg of EV.EXT 77, extracted from 2,500–4,000 mg of dried ginger rhizomes and 500–1,500 mg of dried galanga rhizomes and produced according to good manufacturing practice (Eurovita Holding, Karlslunde, Denmark). Matching placebo capsules contained coconut oil. To minimize a possible pungent sensation, patients were instructed to swallow the whole (intact) capsule with a glassful of water at the time of a meal.

Acetaminophen was permitted as a rescue medication. Patients were instructed to take the rescue medication only when needed, to a maximum dosage of 2 tablets 4 times daily, i.e., 4 gm/day.

Drug accountability was calculated by pill count for both the study treatment and the rescue medication.

Assessments. The OA knee deemed to be more symptomatic was defined as the target joint by the investigator, and the knee-specific pain was assessed for this joint. The primary efficacy parameter was the proportion of responders experiencing at least a 15-mm reduction in pain between baseline and the final visit for knee pain on standing during the preceding 12 hours, as measured by a 100-mm VAS. Pain on standing is a validated measure of pain and coincides with question 5 of the Western Ontario and McMaster Universities (WOMAC) OA composite index (26). At the time of the design of this study, the full WOMAC index was not generally accepted as a primary efficacy variable in clinical trials of OA of the knee.

Secondary efficacy measures that were used to compare the 2 study groups were as follows: 1) average improvement in pain on standing, as measured by a 100-mm VAS; 2) consumption of rescue medication; 3) WOMAC index as measured by VAS, with one end of the scale being "no pain/stiffness/difficulty" and the other end, "extreme pain/stiffness/difficulty" (the total score was calculated as the mean response); 4) patient assessment of global status, in which the question, "Given all the ways your osteoarthritis affects you, how have you been doing the last 24 hours?" was evaluated on a 5-point Likert scale (1 = very poor, 2 = poor, 3 = average, 4 = good, 5 = very good); 5) quality of life assessment using the Short Form 12 (SF-12), which asks questions regarding the patient's condition during the preceding 4 weeks (27); and 6) pain in the knee after walking 50 feet, recorded immediately after walking and measured by a 100-mm VAS.

Efficacy and safety assessments were performed at baseline and after 2 and 6 weeks of treatment. The SF-12 was administered at screening and after 6 weeks of treatment only. Safety was assessed via open-ended questions concerning changes in the patients' health at each visit, supported by patients' responses on diary cards. For all adverse events, the onset, duration, and intensity (mild, moderate, or severe) of the event, as well as the action taken and outcome, were recorded. The relationship between an adverse event and the study medication was assessed, by the investigator, as none, remote, possible, probable, or definite. Adverse events were coded according to World Health Organization adverse reaction terminology (28). The adverse events were analyzed by preferred terms and by system organ classes.

Statistical analysis. Blinding was maintained until the final database was cleaned and locked. However, there was an interim analysis of 116 patients that was performed at a significance level of 0.01% by an independent statistician. The results were disclosed to the sponsor only. Neither the investigators nor the clinical research organization monitoring the study were aware of the results.

Sample-size calculation was based on results of an unpublished clinical trial using a ginger extract. Statistical evaluation was performed using SAS (SAS Institute, Cary, NC). The statistical analysis was performed using analysis of covariance for analysis of means, with baseline scores, center, sex, treatment-by-center interaction, and age as the covariates. Chi-square tests were used for analysis of responders, Student's *t*-test to analyze intake of rescue medication, and Fisher's exact test for comparing incidence of adverse events between groups. Except for the analysis of intake of rescue medication, the ITT last observation carried forward method was used. All analyses were performed 2-sided, with a minimum significance level of 5%.

RESULTS

Patients. There was no clinically relevant difference in the demographics between the 2 treatment groups (Table 1). The patients were predominantly women and predominantly white. Patients in both study groups were generally overweight, since the average body mass index was >30 kg/m^2 (range 18–65 kg/m^2).

All patients with at least 1 visit after the baseline evaluation were included in the ITT analysis. Fourteen patients, 8 receiving placebo and 6 receiving ginger extract, discontinued the trial before completing any evaluation of efficacy. Among the patients in the placebo group who discontinued, 3 dropped out due to adverse events, 4 were lost to followup, and 1 withdrew consent. Among the patients receiving ginger extract who discontinued, 3 dropped out due to adverse events and 3 were lost to followup. Thus, the modified ITT analysis included the 247 patients (95% of the total enrolled) who completed any postbaseline efficacy evaluation. A total of 194 patients (74%) completed the study without protocol violations. Fifty-seven patients discontinued prematurely (22% of the randomized population) (Table 2). The overall withdrawal rate was 28% in the ginger extract group and 16% among those receiving placebo. The withdrawal rate due to adverse events was 13% in the ginger extract group and 5% in the placebo group. There were no followup data available for the patients who withdrew from the study prematurely.

Table 1. Demographic characteristics of study population*

Variable	Randomized (n = 261)	Per protocol (n = 194)	Intent-to-treat	
			Ginger extract (n = 124)	Placebo (n = 123)
Age, mean ± SD years	65.2 ± 11.4	65.3 ± 11.3	64.0 ± 11.5	66.3 ± 11.6
Sex, %				
Men	37.5	36.1	40.3	36.6
Women	62.5	63.9	59.7	63.4
Race, %				
White	93.5	93.3	94.4	93.5
Nonwhite	6.5	6.7	5.6	6.5
Body mass index, mean ± SD kg/m^2	30.4 ± 6.6	30.3 ± 6.6	30.6 ± 6.8	30.1 ± 6.6
Diagnosed OA, mean ± SD years	7.3 ± 8.0	7.2 ± 7.5	7.0 ± 7.1	7.0 ± 7.5
Radiographic classification of knee OA, %†				
Stage 2	40.2	40.2	37.9	43.1
Stage 3	54.0	54.6	54.8	52.0
Stage 4	5.4	5.2	7.3	4.1

* OA = osteoarthritis.
† By the Kellgren and Lawrence criteria (25).

Compliance. Compliance was calculated from the amount of study medication (number of capsules) returned and the number of empty slots in the blister cards. Compliance was 98 ± 12% (mean ± SD) for the ginger extract group and 98 ± 18% for the placebo group.

Primary efficacy variable: pain on standing. Pain on standing after 6 weeks of treatment showed improvement in both treatment groups. However, as the primary efficacy parameter, there was a higher percentage of responders (improvement ≥15 mm on the VAS pain scale) in the ginger extract group (n = 78 [63%]) than in the placebo group (n = 62 [50%]; $P = 0.048$). An ITT analysis of all patients enrolled, regardless of whether they underwent any postbaseline efficacy evaluation, also showed a higher rate of responders in the ginger extract group (78 of 130, or 60%) than in the placebo group (62 of 131, or 47%) ($P = 0.040$). The analysis of means for pain on standing showed that the ginger extract group improved an average 8.1 mm more than did the placebo group ($P = 0.005$) (Figure 1).

A subset analysis was performed for increased responder levels. For ≥20-mm improvement in pain on standing, the ginger extract group showed a response superior to that of the placebo group (n = 73 [59%] versus n = 56 [46%]; $P = 0.036$). For a ≥25-mm improvement, the ginger extract group again displayed a

Table 2. Discontinuations among the randomized population*

Primary reason for early termination	Ginger extract (n = 130)	Placebo (n = 131)
Adverse event	17†	6
Withdrew consent	2	1
Perceived lack of efficacy	9	7
Noncompliance	1	2
Lost to followup	6	5
Intercurrent illness	0	0
Death	0	0
Other	1	0
Total	36	21

* Values are the number of patients.
† $P = 0.025$ versus placebo.

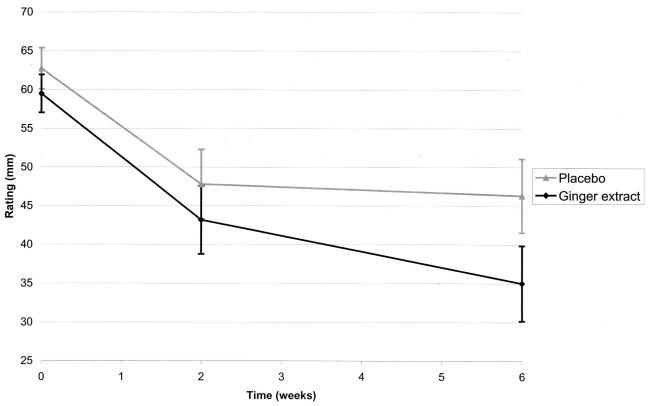

Figure 1. Knee pain on standing as measured by 100-mm visual analog scale after 2 and 6 weeks in patients with osteoarthritis receiving placebo (n = 123) or ginger extract (n = 124), in the intent-to-treat analysis. Bars show the mean pain rating (in mm) and 95% confidence intervals.

Table 3. Results of secondary parameters in the intent-to-treat analysis

Parameter, time point	Placebo (n = 123)*			Ginger extract (n = 124)*			Between-group difference	*P*
	Mean	SD	Change	Mean	SD	Change		
Pain after walking 50 feet								
Baseline	53.1	25.1		49.9	24.3			
Visit 4	44.2	28.3	−8.7	34.6	29.5	−15.1	6.4	0.016
WOMAC†								
Pain								
Baseline	49.9	19.1		49.6	19.4			
Visit 4	40.8	24.4	−9.1	36.1	26.2	−13.5	4.4	0.112
Stiffness								
Baseline	60.4	23.4		59.2	21.6			
Visit 4	49.1	26.3	−11.6	40.8	28.1	−18.4	6.8	0.018
Function								
Baseline	52.1	19.4		49.5	20.4			
Visit 4	43.4	23.7	−8.8	37.7	25.3	−11.8	3.0	0.134
Total								
Baseline	52.3	18.4		50.2	19.0			
Visit 4	43.5	23.3	−9.0	37.3	25.1	−12.9	3.9	0.087
Global status								
Baseline	2.8	0.8		3.0	0.8			
Visit 4	3.2	0.9	0.4	3.5	1.0	0.5	0.1	0.100
QOL (SF-12)‡								
Physical summary								
Baseline	32.0	7.4		32.9	8.9			
Visit 4	35.3	9.5	3.4	36.9	9.7	4.1	0.7	0.300
Mental summary								
Baseline	53.1	10.9		52.6	10.8			
Visit 4	53.0	10.5	0.0	53.4	10.9	0.5	0.5	0.700

* Numbers of patients vary between 121 and 124 at the single visits, and for quality of life (QOL), between 111 and 114.
† Western Ontario and McMaster Universities osteoarthritis index (WOMAC) consists of 24 questions, assessed on 100-mm visual analog scale, analyzed in 3 subscales as the average score for 5 questions on pain, 2 questions on stiffness, and 17 questions on function. The total score is calculated as the mean score for all 24 questions.
‡ The Short Form 12 (SF-12) consists of 12 questions that are combined into 8 scales, which are summarized in the physical and mental component summaries shown here.

superior response compared with that of the placebo group (n = 65 [52%] versus n = 48 [39%]; $P = 0.035$).

In an analysis of the patients who completed the study per protocol and experienced ≥15-mm improvement in pain on standing, results were similar to those of the ITT analysis, although the difference between the 2 treatment groups was smaller. The ginger extract group showed a response that was numerically superior (60 of 92, or 65%) to that of the placebo group (54 of 102, or 53%) ($P = 0.083$). In other parameters, significant improvements comparable with those in the ITT analysis were seen.

Secondary efficacy variables. The results of the secondary parameters were consistent with the findings with the primary parameter (Table 3). Pain after walking also demonstrated a significant improvement in the ginger extract group compared with the placebo group. The change in total WOMAC score was numerically superior in the ginger extract group versus the placebo group, with the greatest improvement seen in stiffness. Figure 2 shows the response on the individual questions of the WOMAC questionnaire, with responses to questions 6, 7, 11, 14, and 15 showing a significant improvement among patients receiving the ginger extract. Improvement in patient global status was numerically better in the ginger extract group and was statistically superior in a per protocol analysis ($P = 0.042$). There was no difference in the SF-12 score, since there was little change from baseline in either group. Acetaminophen use was equal in the 2 study groups (mean ± SD number of tablets daily 2.0 ± 1.9 in the ginger extract group and 2.2 ± 2.0 in the placebo group).

Analysis of individual variables showed no effect of age (>65 years versus <65 years), sex, center, or treatment-per-center interaction on the efficacy parameters. This analysis did show a difference in the baseline scores, especially in global status, with the placebo group having the worse scores. This difference cannot be explained, but it was adjusted for through the analysis of covariance.

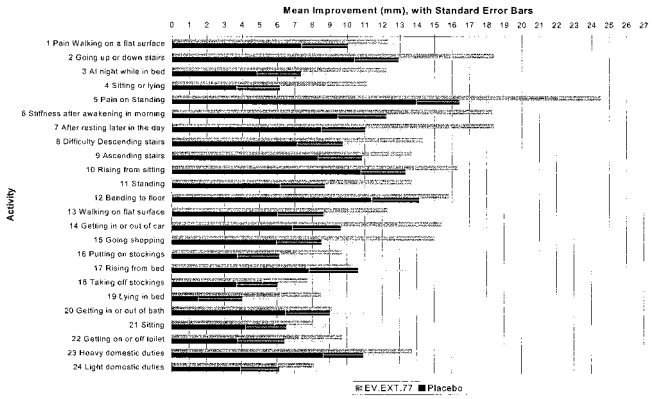

Figure 2. Mean change from baseline to the fourth visit in each functional measure of the Western Ontario and McMaster Universities osteoarthritis index for the 2 treatment groups, in the intent-to-treat analysis. Bars show the mean and standard error.

Adverse events. There were 314 adverse events reported on diary cards and by questioning. Seventy-six patients (59%) receiving ginger extract experienced 202 adverse events. Forty-nine patients (37%) receiving placebo experienced 112 adverse events. Only 1 group of adverse events showed a significant difference between the treatment groups: gastrointestinal (GI) adverse events were more common in the ginger extract group (116 events in 59 patients [45%]) compared with the placebo group (28 events in 21 patients [16%]).

None of the GI adverse events were considered serious by the investigators; 70% were reported as mild, 24% moderate, and 6% severe. When analyzing the events by preferred terms, the only events seen significantly more often in the ginger extract group were eructation, dyspepsia, and nausea. Words used by the patients included burping, belching, bad taste in the mouth, stomach upset, heartburn, and a burning sensation in the stomach. To examine whether preexisting conditions had any influence on this response, the patients' medical history was related to the adverse events. Thirty-six patients in each treatment group had a previous diagnosis of reflux disease, dyspepsia, ulcer, heartburn, gastritis, or hiatus hernia. Of these, 4 patients (11%) in the placebo group and 10 (28%) receiving ginger extract had at least 1 of the adverse events, including dyspepsia, eructation, or nausea; it was concluded that there was no connection to previous conditions.

There was no statistically significant difference between the number of severe adverse events in the 2 treatment groups. One serious adverse event occurred in the study, a myocardial infarction in a patient receiving placebo.

There was concern that the adverse events might affect the blinding of treatment status. Therefore, we examined the percentage of responders for pain on standing in the ginger extract group in the presence or absence of GI adverse events. There were 65% responders in the presence of dyspepsia, eructation, or nausea, and 62% responders in the absence of these adverse GI events ($P = 0.85$). Through this analysis, the adverse events were not found to significantly affect the outcome of the study.

Patients were informed about the possible pungency upon entering the study. Experience of the pungent taste was captured as adverse events to an extent, which may explain the incidence of these events. Still, the possibility exists that some subjects were not truly blinded due to the pungency of the ginger extract.

DISCUSSION

In a 1999 Gallup questionnaire among Americans with arthritis, 28% thought that herbals have a role in the treatment of arthritis, and 17% believed that herbals have a preventative role (29). In a 1997 US survey among 2,055 people, 27% of those with arthritis had used an alternative treatment for the disease within the last year (30). Herbal remedies and other nutraceuticals or botanicals are thus increasingly used by both the healthy and the sick. Unfortunately, few of the remedies have been tested for efficacy and safety in well-designed clinical trials.

In order to address this issue, in a 6-week, randomized clinical trial using ITT analysis in patients with OA of the knee, treatment with a ginger and galanga extract (EV.EXT 77) demonstrated a reduction in knee pain on standing when compared with patients receiving placebo. Additional analyses of the primary efficacy variable as well as changes in the WOMAC index and global status were consistent with the results of the primary efficacy variable. In this short-term study, there was no essential difference in the ginger and placebo groups for quality of life (measured by the SF-12) or consumption of rescue analgesia (acetaminophen). The treatment group also had an increase in GI adverse events.

The benefits found in this trial are consistent with the results described in the few existing reports in the literature. Three published studies on the use of ginger in arthritis have been identified. Two were collections of anecdotal reports (31,32). In the larger cohort, involving 56 patients with rheumatic disorders, more than 75% experienced relief of pain and swelling after an average

dosage of 3 gm raw ginger per day for periods varying between 3 months and 2 years (32). A randomized clinical trial included 67 patients, of whom 56 were able to be evaluated (33). This was a 3-way, crossover study comparing ibuprofen, ginger extract, and placebo. The ranking of efficacy was ibuprofen > ginger extract > placebo for VAS scores on pain and the Lequesne index, but no significant difference was seen when comparing ginger extract and placebo directly. Exploratory testing of the first period of treatment (before crossover) was performed and this showed a better effect of both ibuprofen and ginger extract compared with that of placebo ($P < 0.05$ by chi-square test).

In the WOMAC subgroups in the present study, the greatest improvement was seen in stiffness. The WOMAC index is described as being more sensitive to change in pain, followed by stiffness and function (34). Further investigation into the effects of ginger on stiffness appears warranted, since this may indicate a different mechanism of action than most other OA remedies.

This was a short-term study. At 6 weeks, the placebo effect appeared to fade, whereas the group treated with ginger extract continued to improve. Longer-term studies are needed.

Although the COX-2–specific inhibitors have less GI adverse effects than do nonselective nonsteroidal antiinflammatory drugs (NSAIDs), their overall safety versus placebo is not entirely known, and there are no studies comparing COX-2–specific inhibitors with the ginger extract. Both nonselective NSAIDs and COX-2–specific inhibitors have potential renal adverse effects (35) not described with the ginger extracts.

Some of the patients reported mild GI side effects in the form of dyspepsia, eructation, and nausea. These may be caused by the pungent taste of the ginger extract. Adverse events for NSAIDs can be classified into 3 categories (36): 1) "nuisance" symptoms, such as heartburn, nausea, dyspepsia, and abdominal pain; 2) mucosal lesions; and 3) serious GI complications, such as bleeding and perforation. On average, 10–12% of patients will experience dyspepsia while taking a nonselective NSAID, sometimes leading to death (36,37). Because ginger inhibits prostaglandin synthesis, there is the potential for GI ulceration. However, the effect of NSAIDs on the inflammatory process is mainly caused by inhibition of prostaglandin synthesis. Contrary to this, the ginger extract is a complex mixture that reduces inflammation through inhibition of prostaglandin synthesis, inhibition of lipooxygenase (13), and reduced production of TNFα (21).

We could find no data indicating mucosal lesions or bleeding after intake of ginger despite widespread use of ginger throughout the world. Surprisingly, both ginger (38) and galanga (39) have been shown to protect against ulcers in animal studies. The lack of severe GI adverse events seen in this study is consistent with the observations in the above-mentioned studies as well as in studies on other uses of ginger: seasickness (40), postoperative antiemetic (41,42), and vertigo (43).

A warning has been reported on the possible effect of ginger on bleeding time (44). In vitro studies have shown that ginger inhibits thromboxane synthesis and thereby platelet aggregation (45). In humans, an ex vivo study tested a single dose of 2 gm dried ginger (46). Another 3-way crossover study compared the oral intake of 15 gm raw ginger/day, 40 gm cooked stem ginger/day, and placebo for 2 weeks in 18 healthy volunteers (47). None of the tested ginger preparations produced any significant change in thromboxane synthesis. We could find no published data on adverse events connected with coagulation with ginger.

The average body mass index for this study population was high. Patients were enrolled without weight restrictions and may constitute a typical OA population in the US. The dosing of the ginger extract given was empirically based on the 1–2 capsules per day that is typically consumed in Europe. In retrospect, there may be concern that the US patients may have been underdosed. Without a dose-finding study, it is uncertain if a higher dose would have a better effect.

In conclusion, this study showed that a highly purified ginger extract has demonstrated a statistical effect of reducing pain in patients with OA of the knee. There was a good safety profile with mostly mild GI side effects. Long-term effects bear further investigation.

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