Osteoarthritis and Cartilage 23 (2015) 13–21

Osteoarthritis and Cartilage

Review

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

E.M. Bartels † *, V.N. Folmer †, H. Bliddal †, R.D. Altman ‡, C. Juhl §, S. Tarp †, W. Zhang ‖, R. Christensen † §

† *The Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Denmark*
‡ *David Geffen School of Medicine, University of California, Los Angeles, CA 90024, USA*
§ *Institute of Sports Science and Clinical Biomechanics, University of Southern Denmark, Odense, Denmark*
‖ *Division of Rheumatology, Orthopedics and Dermatology University of Nottingham, Clinical Sciences Building, City Hospital, Nottingham, UK*

ARTICLE INFO

Article history:
Received 14 May 2014
Accepted 30 September 2014

Keywords:
Ginger
Osteoarthritis
Knee
Hip
Meta-analysis
Pain

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.

Prospero: CRD42011001777.

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

* Address correspondence and reprint requests to: E.M. Bartels, The Parker Institute, Department of Rheumatology, Copenhagen University Hospital, Bispebjerg and Frederiksberg, Nordre Fasanvej 57, DK-2000 Copenhagen F, Denmark. Tel: 45-38164168; Fax: 45-38164159.
E-mail address: Else.Marie.Bartels@regionh.dk (E.M. Bartels).

http://dx.doi.org/10.1016/j.joca.2014.09.024
1063-4584/

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].

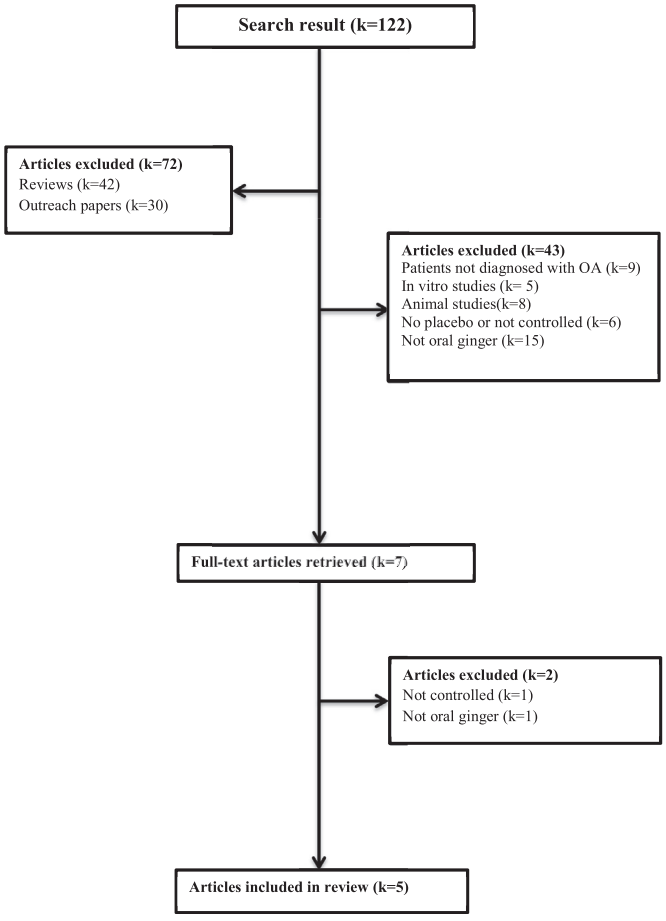

Fig. 1. Flow chart showing the selection of trials. RCTs: Randomized controlled trials.

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

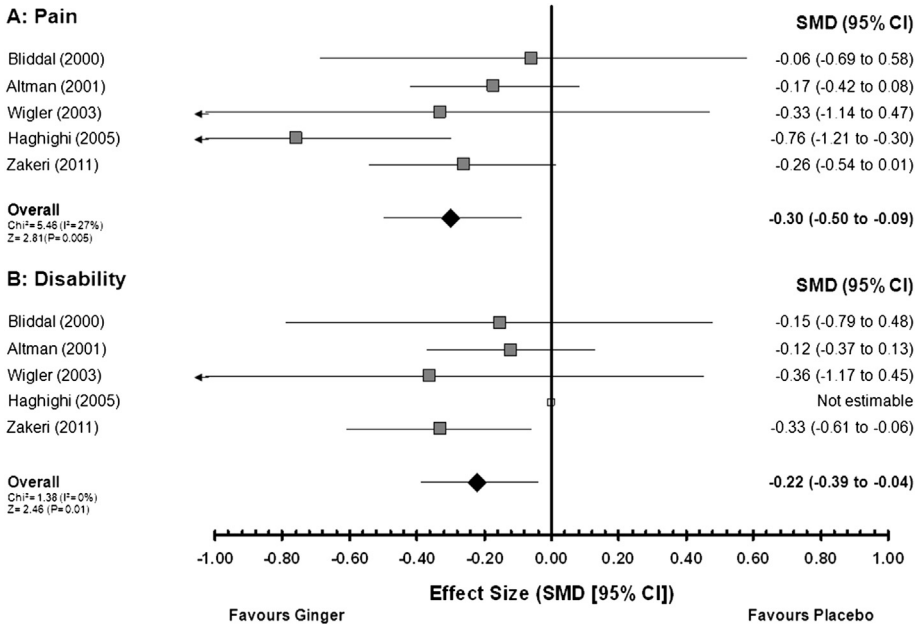

Fig. 2. Efficacy forest plots of trials comparing ginger with placebo in OA patients shown as SMD for (A) pain and (B) disability. The individual trial's effect measures are represented by a square, with 95% CIs indicated by horizontal lines. The total estimate and the corresponding 95% CI are represented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

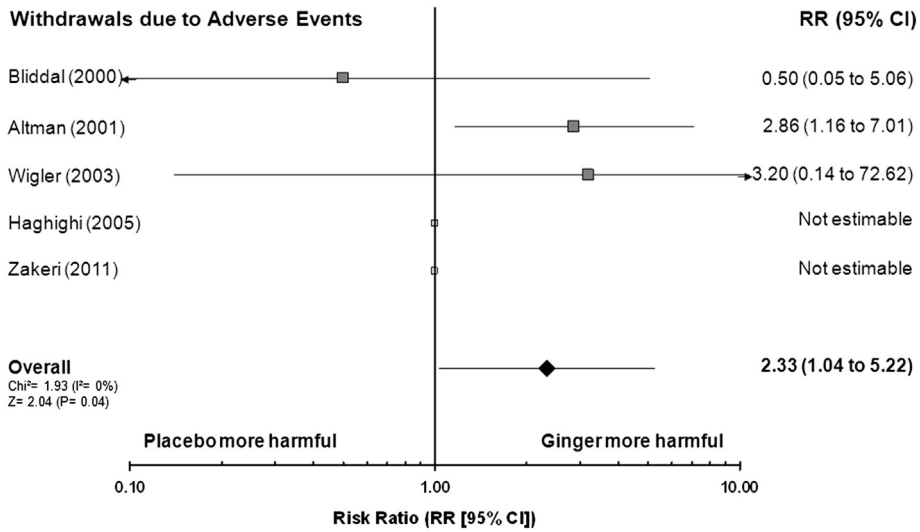

Fig. 3. Safety forest plot of trials comparing ginger with placebo in OA patients represented as RR for adverse events. The individual trial's effect measures are represented by a square, with 95% CIs indicated by horizontal lines. The total estimate and the corresponding 95% CI are represented by a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

Acknowledgments

This study was supported by grants from The Oak Foundation (OCAY-07-264) and from Frederiksberg Hospital. We wish to acknowledge both the scientific and personal support provided by Professor Bente Danneskiold-Samsøe MD, DMSc.

References

1. Ali BH, Blunden G, Tanira MO, Nemmar A. Some phytochemical, pharmacological and toxicological properties of ginger (Zingiber officinale Roscoe): a review of recent research. Food Chem Toxicol 2008;46(2):409–20.
2. Galenus C. De compositione pharmacorum. Lyon: Rollett, Philibert; 1547.
3. Plinius Secondus G. Historia Naturalis. Paris: Curacteribus Nicolai de Pratis ac impendio Francisci Regnault ac Johannis Frelon; 1511.
4. Tjendraputra E, Tran VH, Liu-Brennan D, Roufogalis BD, Duke CC. Effect of ginger constituents and synthetic analogues on cyclooxygenase-2 enzyme in intact cells. Bioorg Chem 2001;29(3):156–63.
5. Grzanna R, Lindmark L, Frondoza CG. Ginger – an herbal medicinal product with broad anti-inflammatory actions. J Med Food 2005;8(2):125–32.
6. Van Breemen RB, Tao Y, Li W. Cyclooxygenase-2 inhibitors in ginger (Zingiber officinale). Fitoterapia 2011;82(1):38–43.
7. Kiuchi F, Iwakami S, Shibuya M, Hanaoka F, Sankawa U. Inhibition of prostaglandin and leukotriene biosynthesis by gingerols and diarylheptanoids. Chem Pharm Bull (Tokyo) 1992;40(2):387–91.
8. Lantz RC, Chen GJ, Sarihan M, Solyom AM, Jolad SD, Timmermann BN. The effect of extracts from ginger rhizome on inflammatory mediator production. Phytomedicine 2007;14(2–3):123–8.
9. Frondoza CG, Sohrabi A, Polotsky A, Phan PV, Hungerford DS, Lindmark L. An in vitro screening assay for inhibitors of proinflammatory mediators in herbal extracts using human synoviocyte cultures. In Vitro Cell Dev Biol Anim 2004;40(3–4):95–101.
10. Phan PV, Sohrabi A, Polotsky A, Hungerford DS, Lindmark L, Frondoza CG. Ginger extract components suppress induction of chemokine expression in human synoviocytes. JAltern Complement Med 2005;11(1):149–54.
11. Ribel-Madsen S, Bartels EM, Stockmarr A, Borgwardt A, Cornett C, Danneskiold-Samsoe B, *et al.* A Synoviocyte model for osteoarthritis and rheumatoid arthritis: response to

ibuprofen, betamethasone, and ginger extract – a cross-sectional in vitro study. Arthritis 2012;1(1):505842.
12. Stannus O, Jones G, Cicuttini F, Parameswaran V, Quinn S, Burgess J, *et al*. Circulating levels of IL-6 and TNF-alpha are associated with knee radiographic osteoarthritis and knee cartilage loss in older adults. Osteoarthritis Cartilage 2010;18(11):1441–7.
13. Argoff CE. Recent developments in the treatment of osteoarthritis with NSAIDs. Curr Med Res Opin 2011;27(7):1315–27.
14. Cameron M, Chrubasik S. Oral herbal therapies for treating osteoarthrits. Cochrane Database Syst Rev 2014;5:CD002947.
15. Ernst E. Avocado-soybean unsaponifiables (ASU) for osteoarthritis – a systematic review. Clin Rheumatol 2003;22:285–8.
16. Christensen R, Bartels EM, Astrup A, Bliddal H. Symptomatic efficacy of avocado-soybean unsaponifiables (ASU) in osteoarthritis (OA) patients: a meta-analysis of randomized controlled trials. Osteoarthritis Cartilage 2008;16(4):399–408.
17. Christensen R, Bartels EM, Altman RD, Astrup A, Bliddal H. Does the rose hip powder of Rosa canina (rosehip) reduce pain in osteoarthritis patients? – a meta-analysis of randomized controlled trials. Osteoarthritis Cartilage 2008;16(9):965–72.
18. Farid R, Rezaieyazdi Z, Mirfeizi Z, Hatef MR, Mirheidari M, Mansouri H, *et al*. Oral intake of purple passion fruit peel extract reduces pain and stiffness and improves physical function in adult patients with knee osteoarthritis. Nutr Res 2010;30:601–6.
19. Henrotin Y, Priem F, Mobasheri A. Curcumin: a new paradigm and therapeutic opportunity for the treatment of osteoarthritis: curcumin for osteoarthritis management. SpringerPlus 2013;2:56.
20. Kuptniratsaikul V, Dajpratham P, Taechaarpornkul W, Buntragoolpoontawee M, Lukkanapichonchut P, Chootip C, *et al*. Efficacy and safety of *Curcuma domestica* extracts compared with iboprofen in patients with knee osteoarthritis: a multicenter study. Clin Interv Aging 2014;9:451–8.
21. Panahi Y, Rahimnia AR, Sharafi M, Alishiri G, Saburi A, Sahebkar A. Curcuminoid treatment for knee osteoarthritis: a randomized double-blind placebo-controlled trial. Phytother Res 2014, http://dx.doi.org/10.1002/ptr.5174.
22. McAlindon TE, Bannuru RR, Sullivan MC, Arden NK, Berenbaum F, Bierma-Zeinstra SM, *et al*. OARSI guidelines for the non-surgical management of knee osteoarthritis. Osteoarthritis Cartilage 2014;22:363–88.
23. Long L, Soeken K, Ernst E. Herbal medicines for the treatment of osteoarthritis: a systematic review. Rheumatology 2001;40:779–93.
24. De Silva V, El-Metwally A, Ernst E, Lewith G, Macfarlane GJ. Evidence for the efficacy of complementary and alternative medicines in the management of osteoarthritis: a systematic review. Rheumatology 2011;50:911–20.
25. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, *et al*. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. PLoS Med 2009;6(7):e1000100.
26. Nuesch E, Trelle S, Reichenbach S, Rutjes AW, Burgi E, Scherer M, *et al*. The effects of excluding patients from the analysis in randomised controlled trials: meta-epidemiological study. BMJ 2009;339:b3244.
27. Elbourne DR, Altman DG, Higgins JP, Curtin F, Worthington HV, Vail A. Meta-analyses involving cross-over trials: methodological issues. Int J Epidemiol 2002;31(1):140–9.
28. Juhl C, Lund H, Roos EM, Zhang W, Christensen R. A hierarchy of patient-reported outcomes for meta-analysis of knee osteoarthritis trials: empirical evidence from a survey of high impact journals. Arthritis 2012;2012:136245.
29. Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K, *et al*. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Ann Intern Med 2004;141(10):781–8.
30. Normand SL. Meta-analysis: formulating, evaluating, combining, and reporting. Stat Med 1999;18(3):321–59.
31. Cohen J. Statistical Power Analysis for the Behavioral Sciences. 2 edn. Philadelphia: Lawrence Earlbaum Associates; 1988.
32. Curtin F, Altman DG, Elbourne D. Meta-analysis combining parallel and cross-over clinical trials. I: continuous outcomes. Stat Med 2002;21(15):2131–44.
33. Hedges LV. Distribution theory for Glass's estimator of effect size and related estimators. J Educ Stat 1981;6(2):107–28.
34. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7(3):177–88.
35. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21(11):1539–58.
36. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003;327(7414):557–60.
37. Wang MC, Bushman B. Intergrating Results through Meta-analytic Review Using SAS Software. 1st edn. Cary, NC: SAS Institute Inc; 1999.
38. Littell RC, Milliken GA, Stroup WW, Wolfinger RD, Schabenberger O. SAS for Mixed Models. 2nd edn.. Cary, NC: SAS Institute Inc; 2006.
39. Hamblin L, Laird A, Parkes E, Walker AF. Improved arthritic knee health in a pilot RCT of phytotherapy. J R Soc Promot Health 2008;128(5):255–62.
40. Drozdov VN, Kim VA, Lazebnik LB. Modern approach to the prevention and treatment of NSAID-gastropathy. Eksp Klin Gastroenterol 2011;2:106–10.
41. Altman RD, Marcussen KC. Effects of a ginger extract on knee pain in patients with osteoarthritis. Arthritis Rheum 2001;44(11):2001.
42. Bliddal H, Rosetzsky A, Schlichting P, Weidner MS, Andersen LA, Ibfelt HH, *et al*. A randomized, placebo-controlled, cross-over study of ginger extracts and Ibuprofen in osteoarthritis. Osteoarthritis Cartilage 2000;8(1):9–12.
43. Haghighi M, Khalvat A, Toliat T, Jallaei S. Comparing the effects of ginger (Zingiber officinale) extract and ibuprofen on patients with osteoarthritis. Arch Iran Med 2005;8:267–71.
44. Wigler I, Grotto I, Caspi D, Yaron M. The effects of Zintona EC (a ginger extract) on symptomatic gonarthritis. Osteoarthritis Cartilage 2003;11(11):783–9.
45. Zakeri Z, Izadi S, Bari Z, Soltani F, Narouie B, Ghasemi-Rad M. Evaluating the effects of ginger extract on knee pain, stiffness and difficulty in patients with knee osteoarthritis. JMed Plants Res 2011;5(15):3375–9.
46. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, *et al*. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. J Clin Epidemiol 2011;64(4):383–94.
47. Guyatt GH, Oxman AD, Kunz R, Brozek J, Alonso-Coello P, Rind D, *et al*. GRADE guidelines 6. Rating the quality of evidence–imprecision. J Clin Epidemiol 2011;64(12):1283–93.
48. Pogue JM, Yusuf S. Cumulating evidence from randomized trials: utilizing sequential monitoring boundaries for cumulative meta-analysis. Control Clin Trials 1997;18(6):580–93.
49. Guyatt G, Oxman AD, Sultan S, Brozek J, Glasziou P, Alonso-Coello P, *et al*. GRADE guidelines 11-making an overall rating of confidence in effect estimates for a single outcome and for all outcomes. J Clin Epidemiol 2013;66(2):151–7.

50. Zhang W, Jones A, Doherty M. Does paracetamol (acetaminophen) reduce the pain of osteoarthritis? A meta-analysis of randomised controlled trials. Ann Rheum Dis 2004;63(8):901–7.
51. Bartels EM, Bliddal H, Schondorff PK, Altman RD, Zhang W, Christensen R. Symptomatic efficacy and safety of diacerein in the treatment of osteoarthritis: a meta-analysis of randomized placebo-controlled trials. Osteoarthritis Cartilage 2010;18(3):289–96.
52. Stam W, Jansen J, Taylor S. Efficacy of etoricoxib, celecoxib, lumiracoxib, non-selective NSAIDs, and acetaminophen in osteoarthritis: a mixed treatment comparison. Open Rheumatol J 2012;6:6–20.
53. Trijau S, Avouac J, Escalas C, Gossec L, Dougados M. Influence of flare design on symptomatic efficacy of non-steroidal anti-inflammatory drugs in osteoarthritis: a meta-analysis of randomized placebo-controlled trials. Osteoarthritis Cartilage 2010;18(8):1012–8.
54. Bjordal JM, Ljunggren AE, Klovning A, Slordal L. Non-steroidal anti-inflammatory drugs, including cyclo-oxygenase-2 inhibitors, in osteoarthritic knee pain: meta-analysis of randomised placebo controlled trials. BMJ 2004;329(7478):1317.
55. Bliddal H, Christensen R. The treatment and prevention of knee osteoarthritis: a tool for clinical decision-making. Expert Opin Pharmacother 2009;10(11):1793–804.
56. Blandizzi C, Tuccori M, Colucci R, Fornai M, Antonioli L, Ghisu N, *et al*. Role of coxibs in the strategies for gastrointestinal protection in patients requiring chronic non-steroidal anti-inflammatory therapy. Pharmacol Res 2009;59(2):90–100.
57. Weidner MS, Sigwart K. Investigation of the teratogenic potential of a zingiber officinale extract in the rat. Reprod Toxicol 2001;15(1):75–80.
58. Weidner MS, Sigwart K. The safety of a ginger extract in the rat. J Ethnopharmacol 2000;73(3):513–20.
59. Ulbricht C, Chao W, Costa D, Rusie-Seamon E, Weissner W, Woods J. Clinical evidence of herb-drug interactions: a systematic review by the natural standard research collaboration. Curr Drug Metab 2008;9(10):1063–120.
60. Terry R, Posadzki P, Watson LK, Ernst E. The use of ginger (Zingiber officinale) for the treatment of pain: a systematic review of clinical trials. Pain Med 2011;12:1808–18.
61. Moneret-Vautrin DA, Morisset M, Lemerdy P, Croizier A, Kanny G. Food allergy and IgE sensitization caused by spices: CICBAA data (based on 589 cases of food allergy). Allerg Immunol 2002;34(4):135–40.
62. Tewtrakul S, Subhadhirasakul S. Anti-allergic activity of some selected plants in the Zingiberaceae family. J Ethnopharmacol 2007;109(3):535–8.
63. Shalansky S, Lynd L, Richardson K, Ingaszewski A, Kerr C. Risk of warfarin-related bleeding events and supratherapeutic international normalized ratios associated with complementary and alternative medicine: a longitudinal analysis. Pharmacotherapy 2007;27(9):1237–47.
64. Jiang XM, Blair EYL, McLachlan AJ. Investigation of the effects of herbal medicines on warfarin response in healthy subjects: a population pharmacokinetic-pharmacodynamic modeling approach. J Clin Pharmacol 2006;46(11):1370–8.
65. Young HY, Liao JC, Chang YS, Luo YL, Lu MC, Peng WH. Synergistic effect of ginger and nifedipine on human platelet aggregation: a study in hypertensive patients and normal volunteers. Am J Chin Med 2006;34(4):545–51.
66. Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, *et al*. GRADE guidelines: 5. Rating the quality of evidence – publication bias. J Clin Epidemiol 2011;64(12):1277–82.
67. Nuesch E, Reichenbach S, Trelle S, Rutjes AW, Liewald K, Sterchi R, *et al*. The importance of allocation concealment and patient blinding in osteoarthritis trials: a meta-epidemiologic study. Arthritis Rheum 2009;61(12):1633–41.
68. Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, onso-Coello P, *et al*. GRADE guidelines: 4. Rating the quality of evidence – study limitations (risk of bias). J Clin Epidemiol 2011;64(4):407–15.
69. Leach MJ, Kumar S. The clinical effectiveness of Ginger (Zingiber officinale) in adults with osteoarthritis. Int J Evid Based Health 2008;6(3):311–20.
70. Nagendra chari KL, Manasa D, Srinivas P, Sowbhagya HB. Enzyme-assisted extraction of bioactive compounds from ginger (Zingiber officinale Roscoe). Food Chem 2013;139(1–4):509–14.
71. Ghasemzadeh A, Jaafar HZ. Effect of CO(2) Enrichment on synthesis of some primary and secondary metabolites in ginger (Zingiber officinale Roscoe). Int J Mol Sci 2011;12(2):1101–14.
72. Catchpole OJ, Grey JB, Perry NB, Burgess EJ, Redmond WA, Porter NG. Extraction of chili, black pepper, and ginger with near-critical CO2, propane, and dimethyl ether: analysis of the extracts by quantitative nuclear magnetic resonance. J Agric Food Chem 2003;51(17):4853–60.
73. Eurovita A/S, inventor; Eurovita A/S, assignee. Pharmaceuticals, Dietary Supplements and Cosmetic Compositions, and the Use of Certain Mixtures for Preparing a Medicament or a Dietary Supplement for the Treatment or Prevention of Inflammation, Hypersensitivity Reactions or Pain. 6482421 2003.
74. Harris P, Rees R. The prevalence of complementary and alternative medicine use among the general population: a systematic review of the literature. Complement Ther Med 2000;8(2):88–96.
75. Harris PE, Cooper KL, Relton C, Thomas KJ. Prevalence of complementary and alternative medicine (CAM) use by the general population: a systematic review and update. Int J Clin Pract 2012;66(10):924–39.
76. Thomas KJ, Nicholl JP, Coleman P. Use and expenditure on complementary medicine in England: a population based survey. Complement Ther Med 2001;9(1):2–11.
77. Bailey RL, Gahche JJ, Lentino CV, Dwyer JT, Engel JS, Thomas PR, *et al*. Dietary supplement use in the United States, 2003–2006. J Nutr 2011;141(2):261–6.
78. Posadzki P, Watson LK, Alotaibi A, Ernst E. Prevalence of use of complementary and alternative medicine (CAM) by patients/consumers in the UK: systematic review of surveys. Clin Med 2013;13(2):126–31.
79. Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, *et al*. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res 2012;64(4):465–74.