SYSTEMATIC REVIEW

Safety of Symptomatic Slow-Acting Drugs for Osteoarthritis: Outcomes of a Systematic Review and Meta-Analysis

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Abstract

Background Symptomatic slow-acting drugs for osteoarthritis (SYSADOAs) are an important drug class in the treatment armamentarium for osteoarthritis (OA).

Objective We aimed to re-assess the safety of various SYSADOAs in a comprehensive meta-analysis of randomized placebo-controlled trials, using, as much as possible, data from full safety reports.

Methods We performed a systematic review and random-effects meta-analyses of randomized, double-blind, placebo-controlled trials that assessed adverse events (AEs) with various SYSADOAs in patients with OA. The databases MED-LINE, Cochrane Central Register of Controlled Trials (Ovid CENTRAL) and Scopus were searched. The primary outcomes were overall severe and serious AEs, as well as AEs involving the following Medical Dictionary for Regulatory Activities (MedDRA) system organ classes (SOCs): gastrointestinal, cardiac, vascular, nervous system, skin and subcutaneous tissue, musculoskeletal and connective tissue, renal and urinary system.

Results Database searches initially identified 3815 records. After exclusions according to the selection criteria, 25 studies on various SYSADOAs were included in the qualitative synthesis, and 13 studies with adequate data were included in the meta-analyses. Next, from the studies previously excluded according to the protocol, 37 with mainly oral nonsteroidal anti-inflammatory drugs (NSAIDs) permitted as concomitant medication were included in a parallel qualitative synthesis, from which 18 studies on various SYSADOAs were included in parallel meta-analyses. This post hoc parallel inclusion was conducted because of the high number of studies allowing concomitant anti-OA medications. Indeed, primarily excluding studies with concomitant anti-OA medications was crucial for a meta-analysis on safety. The decision for parallel inclusion was made for the purpose of comparative analyses. Glucosamine sulfate (GS), chondroitin sulfate (CS) and avocado soybean unsaponifiables (ASU; Piascledine®) were not associated with increased odds for any type of AEs compared with placebo. Overall, with/without concomitant OA medication, diacerein was associated with significantly increased odds of total AEs (odds ratio [OR] 2.22; 95% confidence interval [CI] 1.58–3.13; $I^2 = 52.8\%$), gastrointestinal disorders (OR 2.85; 95% CI 2.02–4.04; $I^2 = 62.8\%$) and renal and urinary disorders (OR 3.42; 95% CI 2.36–4.96; $I^2 = 17.0\%$) compared with placebo. In studies that allowed concomitant OA medications, diacerein was associated with significantly more dermatological disorders (OR 2.47; 95% CI 1.42–4.31; $I^2 = 0\%$) and more dropouts due to AEs (OR 3.18; 95% CI 1.85–5.47; $I^2 = 13.4\%$) than was placebo. No significant increase in serious or severe AEs was found with diacerein versus placebo.

Conclusions GS and CS can be considered safe treatments for patients with OA. All eligible studies on ASU included in our analysis used the proprietary product Piascledine® and allowed other anti-OA medications; thus, the safety of ASU must be confirmed in future studies without concomitant anti-OA medications. Given the safety concerns with diacerein, its usefulness in patients with OA should be assessed, taking into account individual patient characteristics.

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1 Introduction

Osteoarthritis (OA) is a progressive disorder of synovial joints of the hand, knee, and hip that causes pain and limitation of function, increasing disability, and progressive cartilage degeneration [1]. OA occurs frequently in adults aged > 50 years, with increasing incidence, and is a major

Key Points

Our meta-analysis of randomized, placebo-controlled trials did not identify any safety issue associated with glucosamine sulfate (GS) or chondroitin sulfate (CS).

Diacerein is associated with significantly more adverse events than placebo, particularly regarding the gastrointestinal and renal and urinary systems. The usefulness of diacerein for patients with OA should therefore be considered, taking into account its benefit:risk profile according to individual patient characteristics.

Avocado soybean unsaponifiables (ASU) as a whole require further investigation in safety studies without any concomitant anti-OA medication; however, our analyses, which included only the proprietary ASU Piascledine® in studies that allowed concomitant anti-OA medications, seem to support the safety of this product, but this remains to be confirmed.

cause of disability worldwide [1–3]. There is currently no established disease-modifying therapy for OA, so treatment relies on a combination of pharmacologic and non-pharmacologic therapies that can manage OA symptoms, primarily pain and loss of function [4]. Symptomatic slow-acting drugs for osteoarthritis (SYSADOAs) are an important class in the pharmacologic treatment armamentarium for OA that have been demonstrated to alleviate the symptoms of pain and functional impairment, with some additional evidence of a disease-modifying effect in the long term [5–7]. The SYSADOAs class comprises many different agents, including glucosamine, chondroitin, diacerein, and avocado soybean unsaponifiables (ASU), which are supported by varying degrees of clinical efficacy data. Meta-analyses of placebo-controlled trials of SYSADOAs treatment lasting up to 3 years provide evidence that prescription-grade crystalline glucosamine sulfate (GS), chondroitin sulfate (CS), and diacerein have small to moderate beneficial effects in patients with OA [5, 8–10].

The European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO) recommends the use of SYSADOAs as step 1 pharmacologic background therapy, specifically prescription-grade GS and CS, with paracetamol as add-on rescue analgesia when needed [4]. However, the level of recommendation afforded to SYSADOAs by other international and national guidelines is less favorable, likely because of the multiple products available, including over-the-counter medications and nutritional supplements that contain the active ingredients but for which the pharmaceutical quality

is considerably reduced [11–14]. Some issues have been raised in the literature regarding several anti-OA preparations that could not be considered clinically equivalent to their SYSADOA counterparts, which could compromise the efficacy and safety of these products [15, 16].

Despite the controversies and non-concordant recommendations about SYSADOAs, they are widely used in many countries as prescription or over-the-counter medications in patients with OA [17, 18]. In this context, it is of primary importance to clearly establish their safety profile. In fact, while some SYSADOAs are considered safe for use in patients with OA, some concerns have been raised about the safety profile of other agents. For example, diacerein may induce loose stools or diarrhea as it is incompletely absorbed in the upper gastrointestinal tract [19].

A Cochrane review found significantly more adverse events (AEs) with diacerein than with placebo after 2–36 months; the AEs were mainly diarrhea (relative risk [RR] 3.5; 95% confidence interval [CI] 2.42–5.11), with an absolute risk increase of 24% (95% CI 12–35) and a number needed to treat for an additional harmful outcome (NNTH) of 4 (95% CI 3–7) [20].

The SYSADOAs GS and CS are generally considered safe medications, with no difference in AEs compared with placebo [6, 7, 21]. Only limited evidence is available on the safety of ASU; however, a meta-analysis of five placebo-controlled trials found no difference in AEs between ASU and placebo [22].

Notably, the meta-analyses that have assessed the safety of SYSADOAs used only published data, and it is well-known that safety data are under-reported in manuscripts. The objective of this study was to re-assess the safety of SYSADOAs in the management of OA in a systematic review and meta-analysis of randomized placebo-controlled trials (RCTs). To better estimate the safety profile of these OA medications, authors of the manuscripts and/or sponsors of studies were contacted to ask for the full report of AEs.

2 Methods

The protocol of this systematic review and meta-analysis was previously registered in the PROSPERO database (registration number: CRD42017069875). The systematic review was performed in accordance with the recommendations in the *Cochrane Handbook for Systematic Reviews of Interventions* [23]. The findings were reported according to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [24]. The entire review process (study selection and risk-of-bias assessment) was undertaken using Covidence, the Cochrane platform for systematic reviews.

2.1 Eligibility Criteria

Randomized, double-blind, placebo-controlled, parallel-group trials that assessed the AEs associated with various SYSADOAs in patients with OA were eligible for inclusion in this meta-analysis. The SYSADOAs considered were limited to GS, CS, hyaluronic acid, collagen derivatives, diacerein, ASU and curcuma, administered orally. The following studies were excluded: crossover studies, reviews or meta-analyses, letters, comments, or editorials. Studies that allowed concomitant anti-OA medications during the trial (other than rescue medication such as paracetamol or aspirin) were also excluded for the main meta-analysis but were kept and used for a parallel analysis.

2.2 Data Sources and Search Strategies

A comprehensive literature search was undertaken in the databases MEDLINE (via Ovid), Cochrane Central Register of Controlled Trials (Ovid CENTRAL), and Scopus. Each database was searched from inception up until 31 May 2017. We searched for RCTs of various SYSADOAs in OA, using a combination of study design-, treatment-, and disease-specific keywords and/or medical subject heading (MeSH) terms. While AEs were the outcomes of interest for this study, we decided to avoid the outcome-specific keywords in the search strategies because of the possibility that a study on the efficacy of a drug may have not mentioned terms related to AEs in its title, abstract, or keywords. The search was limited to English and French publications and to human subjects. Detailed search strategies for MEDLINE/CENTRAL and Scopus databases are reported in the Electronic Supplementary Material (ESM)-1.

Two clinical trials registries, ClinicalTrials.gov (clinicaltrials.gov/) and the World Health Organization's International Clinical Trials Registry Platform Search portal (apps.who.int/trialsearch/) were also checked for trial results that would not have been published. Finally, very recent meta-analyses were also screened for any additional relevant studies. For all studies that responded to the selection criteria, authors of the manuscripts and/or sponsors of studies were automatically contacted to ask for the full report of AEs, as far as there was any way to contact them (email, fax, telephone number or co-author email in another article).

We set up search alerts in the bibliographic databases for any new relevant RCTs that were published from 31 May 2017 until 30 September 2018.

2.3 Study Selection and Data Extraction

Two members of the review team (GH and AG) independently evaluated each title and abstract to exclude only obviously irrelevant studies according to the predefined eligibility criteria. At this step, the criteria related to adverse effects were not considered, as studies focusing on the efficacy of a treatment may not report data about adverse effects in the abstract; this means that all trials mentioning only the efficacy information were retrieved at this step. After this first step, the two investigators (GH and AG) independently reviewed the full text of each of the articles not excluded during the initial screening stage to determine whether the studies met all selection criteria, and those that did not were definitely excluded. All differences of opinion regarding the selection of articles were resolved through discussion and consensus between the two investigators; any persistent disagreement was resolved with the intervention of a third person (VR). A flowchart with the number of included studies at each step was established, including the reasons for excluding studies during the full text reading process.

The full texts of the selected studies were screened for extraction of relevant data using a standard data extraction form. Outcome results data were independently extracted by two investigators of the review team (GH and AG). For each study, the following data were extracted: characteristics of the manuscript, trial, patients, disease, and treatments; study objective and design; AEs (outcomes) reported during the trial; and the main conclusion of the study. The raw data (number of events in each group) were extracted for each outcome. The number of patients who experienced at least once any body system-related AE (e.g., nervous system, gastrointestinal system), as well as specific AEs within each body system (e.g., headache, abdominal pain), were extracted. Intention-to-treat (ITT) data were only used when reported or supplied by the study authors or sponsor.

2.4 Assessment of Risk of Bias in Included Studies

Two review team members (GH and AG) independently assessed the risk of bias in each study, using the Cochrane Collaboration's tool for risk of bias assessment [23]. The following characteristics were evaluated:

- *Random sequence generation* We assessed whether the allocation sequence was adequately generated.
- *Allocation concealment* We assessed the method used to conceal the allocation sequence, evaluating whether the intervention allocation could have been foreseen in advance.
- *Blinding of participants and personnel* We assessed the method used to blind study participants and personnel from knowledge of which intervention a participant received and whether the intended blinding was effective.
- *Blinding of outcome assessment* We assessed the method used to blind outcome assessors from knowledge of which intervention a participant received and whether the intended blinding was effective.

– *Incomplete outcome data* We assessed whether participants' exclusions, attrition, and incomplete outcome data were adequately addressed in the paper.

– *Selective outcomes reporting* We checked whether there was evidence of selective reporting of AEs.

Each item was categorized as having "low" or "high" risk of bias when sufficient information was provided in the manuscript to judge the risk of bias; otherwise, the risk was classed as "unclear." Disagreements were solved by discussion between the two reviewers during a consensus meeting and, when necessary, another member of the review team (VR) was involved for final decision.

2.5 Outcomes of Interest

The main system organ classes (SOCs) that are likely to be affected by the use of various SYSADOAs in the treatment of OA were explored in this meta-analysis. The primary outcomes of interest were Medical Dictionary for Regulatory Activities (MedDRA) SOC-related AEs: gastrointestinal, vascular, cardiac, nervous system, skin and subcutaneous tissue, musculoskeletal and connective tissue (MSCT), renal and urinary, and overall severe and serious AEs. Secondary outcomes were withdrawals due to AEs (i.e., the number of participants who stopped the treatment because of an AE) and total AEs (i.e., the number of patients who experienced any AE at least once).

2.6 Data Analysis

Analyses were performed using STATA 14.2 software. We described harms associated with the treatment as odds ratios (OR) with 95% CIs. We computed an overall effect size for each primary or secondary outcome (AE). Anticipating substantial variability among trial results (i.e., the inter-study variability), we assumed heterogeneity in the occurrence of the AEs, so we planned to use random-effects models for the meta-analyses. We estimated the overall effects and heterogeneity using the DerSimonian and Laird random-effects model [25]. As this method provides biased estimates of the between-study variance with sparse events [26, 27], we also performed the meta-analyses using the restricted maximum likelihood (REML) method [28]. Indeed, we planned in the protocol to use specific methods for rare events analysis if necessary. However, we reported only the results from the DerSimonian and Laird random-effects model, as we found no difference in the effects computed by the two methods. We preferred to report the results obtained with the DerSimonian and Laird method (which uses a correction factor) because it allows for displaying studies with null events on the forest plot, even if those with null event in both the

intervention and the control groups are excluded from the overall effect size computation. Conversely, with the REML method, these studies are not displayed on the forest plot. Additionally, the STATA command, which performs the meta-analysis based on the REML method (metaan) has no option for displaying subgroups on the same graphic, unlike the DerSimonian and Laird method command (metan), which has this option ("by").

We tested heterogeneity using Cochran's Q test. As we performed a random-effects meta-analysis, we used the Tau^2 estimate as the measure of the between-study variance. The I^2 statistic was used to quantify heterogeneity, measuring the percentage of total variation across studies due to heterogeneity [29]. In the case of substantial heterogeneity ($I^2 > 50\%$) [30], we prespecified to undertake subgroup analyses, stratifying the analyses according to participants' age in the intervention group, duration of OA complaint, location of OA (knee, hand, hip), number of joints involved, drug dose, duration of treatment, use of bioavailability enhancer, treatment regimen (single use vs. combination), industry involvement (sponsored vs. non-sponsored), nature of the product (pharmaceutical grade vs. food supplement), and risk of bias (e.g., studies with low risk of bias vs. all other studies).

Funnel plot asymmetry was assessed for publication bias by visual inspection and using the test proposed by Harbord et al. [31], which is more suitable for dichotomous outcomes with effects sizes measured as ORs [32] than the classical Egger's test [33]. In the end, we assessed the certainty of each piece of evidence based on the GRADE approach [34] and prepared summary of findings tables using the GRADE-pro online software [35].

2.7 Additional Analysis

We performed additional post-hoc meta-analyses, in parallel with the main meta-analysis including the studies responding to our pre-defined eligibility criteria. Studies allowing concomitant anti-OA medications, which were excluded based on our eligibility criteria, as well as all studies with or without concomitant anti-OA medications, were considered separately in parallel to the primary meta-analysis. These parallel analyses were conducted according to the same principles described in the data analysis section for the main meta-analysis. However, instead of depicting the results of the parallel analyses in separate forest plots, we prefer to show all the analyses for each outcome on the same figure for ease of comparison. Therefore, considering the rationale of this safety meta-analysis (the exclusion of studies with other anti-OA medication allowed), the parallel analyses on one single forest plot are not to be considered subgroup analyses as for a classical meta-analysis.
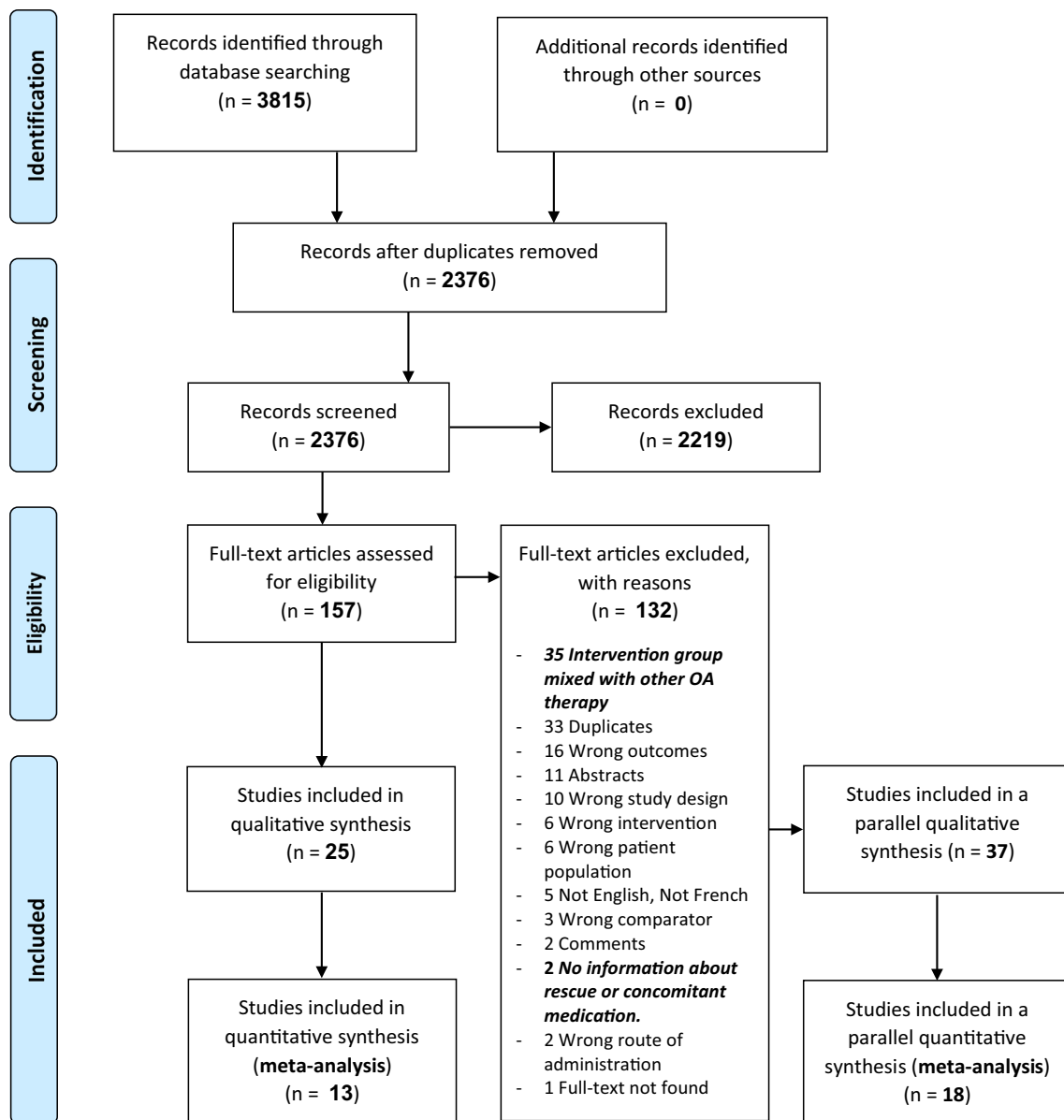
Fig. 1 Flow chart of the study. *OA* osteoarthritis

3 Results

3.1 Initial Study Selection and Characteristics

Database searches initially identified 3815 records; after exclusions (Fig. 1), 157 articles were assessed for eligibility. Of these, 132 studies were excluded for various reasons according to the predefined eligibility criteria (Fig. 1). In total, 25 papers were included in the qualitative synthesis according to our prespecified selection criteria, and 13 studies on various SYSADOAs with adequate data were ultimately included in the meta-analysis [36–60]. These studies

that met our selection criteria included no concomitant anti-OA medication (in accordance with the protocol).

Table 1 presents the characteristics of all the studies included through the systematic review process, according to the predefined selection criteria (those ultimately included in the quantitative synthesis—meta-analysis—are highlighted). The large majority of the studies were in patients with knee OA, with only one including patients with hand OA, one including patients with temporomandibular joint (TMJ) OA, and one involving patients with OA of any joint. In most of the studies, treatment durations varied between 12 and 26 weeks, with the shortest being 4 weeks and the longest 156 weeks.

Among the 25 articles initially selected for inclusion in this study (from trials without any concomitant anti-OA medication), only three had data usable, as published, for the meta-analysis; thus, the risk of selective outcome reporting bias was judged as "high" in > 60% of these studies. Figures 2a and 3a include a summary of the risk of bias assessed for each of the studies included in the primary qualitative synthesis and the risk-of-bias items presented as percentages across all of them. Full data provided by study authors and/or sponsors ultimately enabled us to include 13 studies without any concomitant anti-OA medication in the meta-analyses: five were on GS, six on CS, and two on diacerein. All six studies on CS used the pharmaceutical-grade products manufactured by IBSA, Institut Biochimique SA. The two studies on diacerein used the pharmaceutical-grade product manufactured by TRB Chemedica. Only two of the five studies on GS used the pharmaceutical preparation of crystalline GS manufactured by Rottapharm.

3.2 Post-Hoc Study Selection and Characteristics

From the 132 studies previously excluded according to the protocol, 37 that permitted other pharmacologic OA treatments or that had no information about rescue or concomitant OA medications (Fig. 1) were included in a post hoc parallel qualitative synthesis, from which 18 studies with adequate data were ultimately included in post hoc parallel meta-analyses [61–97].

We a posteriori decided to consider these studies with other pharmacologic OA treatments in parallel analyses because we were surprised by their number compared with those with no concomitant pharmacologic OA treatment allowed. By doing so, we sought to compare the results from these two groups of studies, knowing that our main conclusions regarding the safety profile of each SYSADOA will primarily be based on the results of the analyses using the studies with no concomitant anti-OA medication (those responding to our prespecified selection criteria). Indeed, as this was a meta-analysis on safety, primarily excluding studies that allowed the use of concomitant anti-OA medications was crucial.

Table 2 presents the characteristics of the studies included in the post hoc parallel qualitative synthesis (those included in the parallel meta-analyses are highlighted). These studies largely involved patients with knee joint OA, as seen in the studies with no concomitant anti-OA medication. Conversely, the studies in the parallel qualitative synthesis included more long-term trials (12 studies [32%] with treatment duration ≥ 104 weeks) than the previous studies (4%). Oral nonsteroidal anti-inflammatory drugs (NSAIDs) were the most permitted concomitant medications.

Harms-related data were relatively well reported in only eight studies, sufficient that they could be used for the analyses. Ultimately, in addition to the full data provided by study authors and/or sponsors, we could perform parallel post hoc meta-analyses for GS (four studies), CS (six studies), diacerein (four studies), and ASU (four studies). All the included studies on ASU used the pharmaceutical-grade proprietary product Piascledine® (Expanscience). The raw data sent by study authors and/or sponsors resulted in a substantial decrease of the impact of selective outcome reporting bias in the studies included in the parallel meta-analyses. In fact, for 17 of the 18 studies included in these analyses, the data used were those sent by the study authors and/or sponsors. Originally, almost 70% of the studies included in the parallel qualitative synthesis were associated with a "high" risk of selective outcome reporting bias. Figures 2b and 3b include a summary of the risk of bias assessed for each study included in the parallel qualitative synthesis and the risk-of-bias items presented as percentages across all these studies.

3.3 Glucosamine Sulfate

For the primary outcomes, with or without concomitant anti-OA medications, there was no significant increase in the odds for any SOC-related disorders investigated (gastrointestinal, cardiac, vascular, nervous system, dermatological, MSCT, renal and urinary) with GS compared with placebo, as well as for severe and serious AEs (ESM-2).

Likewise, for the secondary outcomes, there was no significant increase in odds for total AEs reported with GS versus placebo (OR 0.96; 95% CI 0.66–1.41; $I^2 = 29.8\%$) (overall OR) (Fig. 4). In both studies with and those without concomitant anti-OA medications, as well as overall, there were no more withdrawals due to AEs with GS compared with placebo (ESM-2).

3.4 Chondroitin Sulfate

With or without concomitant anti-OA medications, there was no significant increase in the odds with CS versus placebo for any SOC-related disorders investigated or for severe and serious AEs and withdrawals due to AEs (ESM-2). Conversely, fewer AEs pertaining to the renal and urinary system were reported with CS than with placebo, whatever the group of studies considered; these findings reached statistical significance overall (OR 0.40; 95% CI 0.22–0.74) and in studies with concomitant anti-OA medications (OR 0.43; 95% CI 0.23–0.81) (ESM-2).

In studies with no concomitant OA medications allowed, patients receiving CS were significantly less likely to report AEs (total AEs) than were those receiving placebo (OR 0.70; 95% CI 0.51–0.98; $I^2 = 33.3\%$). The same trend was observed in studies with concomitant OA medications

Table 1 Characteristics of the studies included in the systematic review process according to the prespecified selection criteria (without concomitant osteoarthritis medication). Studies are grouped by drug; those studies included in the quantitative synthesis are highlighted in bold type

Study	OA location	Treated groups/ participant age[a]	Compound nature: Pharmaceutical grade or food supplement (manufacturer)	Dose	Treatment duration (weeks)	Data provided in article (type of AE/% of pts considered)	Published data usable for MA? (yes/no)	Full data provided by author/sponsor? (information source)
Glucosamine sulfate[b]								
Cahlin and Dahlstrom [38]	TMJ	Female Active 61.0±16.0 Placebo 58.0±9.0	Manufactured by hospital pharmacy without industrial involvement	400 mg × 3 capsules OD	6 wk	Only GI AEs reported	No	Yes (author)
Chopra et al. [39]	Knee	Active 54.2±8.1 Placebo 54.0±7.7	NA	Two 250 mg capsules BID	16 wk	Per SOC frequencies NP	No	Author contacted: no response
Esfandiari et al. [41]	Any	Active 60.6±11.0 Placebo 58.8±11.5	Pharmaceutical grade (Avicenna Laboratories Inc., Tehran, Iran)	750 mg TID	13 wk	Focus on IOP frequencies	No	Yes (author)
Frestedt et al. [42]	Knee	Active 59.2±8.3 Placebo 58.9±7.4	Food supplement (Pharmachem Labs, NJ, USA)	3 capsules TID (167 mg D-GS potassium salt + 267 mg maltodextrin)	12 wk	All TEAEs seem to have been reported but only per SOC frequencies	Yes	Author contacted: no response
Noack et al. [49]	Knee	Active 55.0±14.0 Placebo 55.0±15.0	Pharmaceutical grade (Opfermann Arzneimittel GmbH, D-5276 Wiehl, Germany)	2 tablets TID (GS 1500 mg/d)	4 wk	Not stated whether all AEs reported but per SOC data provided	Yes	Yes (author)
Pavelka et al. [50]	Knee	Active 61.2±7.3 Placebo 63.5±6.9	Pharmaceutical grade (Rottapharm group)	1×1500 mg/d	156 wk	Reporting per SOC frequencies but incomplete reporting of specific AEs	Yes	No (Rottapharm)
Pujalte et al. [53]	Knee	Active 58.8±2.3 Placebo 64.6±2.3	Pharmaceutical grade (Rotta Pharmaceuticals)	2 capsules TID (250 mg each)	6–8 wk	Summary without details	No	No contact information found
Usha and Naidu[c] [59]	Knee	Active 52.0±8.0 Placebo 50.0±9.0	Nutraceutical (Healers Limited, Chennai, India)	3×500 mg/d	12 wk	Summary without details	No	Clarifications from author insufficient for inclusion in MA
Glucosamine hydrochloride								
Clegg et al. [40] a. GH	Knee	Active 58.6±10.2 Placebo 58.2±9.8	NA (various suppliers)	GH 500 mg TID	24 wk	Summary without details	No	Author contacted: no response

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Table 1 (continued)

Study	OA location	Treated groups/ participant age[a]	Compound nature: Pharmaceutical grade or food supplement (manufacturer)	Dose	Treatment duration (weeks)	Data provided in article (type of AE/% of pts considered)	Published data usable for MA? (yes/no)	Full data provided by author/sponsor? (information source)
Kwoh et al. [46]	Knee	Active 52.2 ± 6.1 Placebo 52.3 ± 6.7	Food supplement (Cargill, Incorporated)	Oral GH 1500 mg, in 16-ounce bottle of diet lemonade	24 wk	Summary without details	No	Author contacted: no response
Chondroitin sulfate[b]								
Bucsi and Poor [37]	Knee	Active 60.6 ± 9.6 Placebo 59.4 ± 9.0	Pharmaceutical grade (IBSA)	800 mg/d	26 wk	Summary without details	No	Yes (IBSA)
Clegg et al. [40] b. Chondroitin sulfate	Knee	Active 58.2 ± 10.0 Placebo 58.2 ± 9.8	NA (various suppliers)	Sodium chondroitin sulfate 400 mg TID	24 wk	Summary without details	No	Author contacted: no response
Gabay et al. [43]	Hand	Active 63.9 ± 8.5 Placebo 63.0 ± 7.2	Pharmaceutical grade (IBSA)	800 mg/d	26 wk	Unclear whether all AEs reported; per SOC frequencies NP	No	Yes (IBSA)
Möller et al. [48]	Knee	Active 58.6 ± 11.4 Placebo 61.0 ± 10.4	Pharmaceutical grade (Bioibérica, S.A., Barcelona, Spain)	Daily CS 800 mg (1 × 2 capsules 400 mg each)	13 wk	Summary without details	No	Author contacted: no response
Reginster [54]	Knee	Active 65.5 ± 8.0 Placebo 64.9 ± 8.0	Pharmaceutical grade (IBSA)	1 × 800 mg OD	26 wk	Summary without details	No	Yes (IBSA)
Uebelhart et al. [57]	Knee	Active 60.0 ± 13.0 Placebo 57.0 ± 11.0	Pharmaceutical grade (IBSA)	2 × 400 mg/d	52 wk	Summary without details	No	Yes (IBSA)
Uebelhart et al. [58]	Knee	Active 63.2 ± 9.1 Placebo 63.7 ± 8.1	Pharmaceutical grade (IBSA)	800 mg chondroitin 4&6 sulfate; 1 sachet/d	26 wk (intermittent administration from entry to mo 3 and between mo 6 and 9)	Summary without details	No	Yes (IBSA)
Zegels et al. [60] a. CS 1200 b. CS 3 × 400	Knee	Active a: 65.4 ± 10.4 Active b: 65.3 ± 8.8 Placebo 64.9 ± 10.6	Pharmaceutical grade (IBSA)	a. 1 oral gel sachet of CS 1200 mg/d b. 1 oral capsule of CS 400 mg TID	13 wk	Summary without details	No	Yes (IBSA)
Combined glucosamine sulfate/chondroitin sulfate								
Roman–Blas et al. [55]	Knee	Active 65.0 ± 8.0 Placebo 67.0 ± 8.0	Pharmaceutical grade (Tedec Meiji Farma)	CS (1200 mg) plus GS (1500 mg) in a single oral daily dose	26 wk	Summary of treatment-related AEs; details NP	No	Yes (author)

Table 1 (continued)

Study	OA location	Treated groups/participant age[a]	Compound nature: Pharmaceutical grade or food supplement (manufacturer)	Dose	Treatment duration (weeks)	Data provided in article (type of AE/% of pts considered)	Published data usable for MA? (yes/no)	Full data provided by author/sponsor? (information source)
Combined glucosamine hydrochloride/chondroitin sulfate								
Clegg et al. [40] c. Combined GH+CS	Knee	Active 58.6±10.6 Placebo 58.2±9.8	NA (various suppliers)	500 mg GH+400 mg CS TID	24 wk	Summary without details	No	Author contacted: no response
Lugo et al. [47] a. Combined GH+CS	Knee	Active 52.6±1.02 Placebo 53.1±1.02	Nutraceuticals (GH: Wellable group, Shishi City, Fujian); CS, bovine-derived: Sioux Pharm, Sioux Center, IA, USA)	Morning and evening doses delivered 750 mg GH+600 mg CS each=1500 mg GH+1200 mg CS daily	26 wk	Listing of all reported individual side effects but per SOC frequencies NP	No	No (author)
Hyaluronic acid								
Kalman et al. [45]	Knee	Active 57.7±10.1 Placebo 54.6±7.7	Dietary ingredient (Bioibérica, Barcelona, Spain)	1×80 mg capsule/d	8 wk	No. of AEs reported (summary)	No	Yes (author)
Collagen derivatives								
Benito-Ruiz et al. [36]	Knee	Active 59.4±10.6 Placebo 58.8±11.4	Food ingredient (Protein SA, Girona, Spain)	10 g CH OD	26 wk	No. of AEs reported	No	Author contacted: no response
Jiang et al. [44]	Knee	Active 60.9±8.8 Placebo 60.7±6.2	Food ingredient (Rousselot)	Daily oral dose 8 g collagen peptides (Peptan®B 2000)	26 wk	AEs assessed but results NP	No	Clarifications from author insufficient for inclusion in MA
Lugo et al. [47] b. Undenatured type II collagen	Knee	Active 53.5±0.99 Placebo 53.1±1.02	Nutraceuticals (Chick Cart Inc., Fort Smith, AR, USA)	2 capsules×20 mg each of UC-II totaling 40 mg=1.2 mg UC-II	26 wk	Listing of all reported individual side effects, but per SOC frequencies NP	No	No (author)

Table 1 (continued)

Study	OA location	Treated groups/ participant age[a]	Compound nature: Pharmaceutical grade or food supplement (manufacturer)	Dose	Treatment duration (weeks)	Data provided in article (type of AE/% of pts considered)	Published data usable for MA? (yes/no)	Full data provided by author/sponsor? (information source)
Schauss et al. [56]	Hips and/or knee joints	Active 54.3 ± 8.69 Placebo 54.5 ± 9.79	Nutraceutical grade (BioCell Technology, Newport Beach, CA, USA)	2 × 2 capsules (1 g) of BCC/d. Each capsule = 500 mg BCC (300 mg hydrolyzed collagen type II + other compounds)	10 wk	No. AEs reported	No	Author contacted: no response
Diacerein[b]								
Pavelka et al. [51]	Knee	Active 63.5 ± 8.39 Placebo 63.8 ± 8.09	Pharmaceutical grade (TRB Chemedica)	50 mg diacerein capsules BID	13 wk	Summary of most common AEs	No	Yes (TRB Chemedica)
Pelletier et al. [52] a. 50 mg/day b. 100 mg/day c. 150 mg/day	Knee	Active a: 62.9 ± 8.4 Active b: 64.2 ± 8.0 Active c: 62.3 ± 10.2 Placebo 64.5 ± 8.6	Pharmaceutical grade (TRB Chemedica)	a. 25 mg BID b. 50 mg BID c. 75 mg BID	16 wk	AEs that occurred in ≥ 5% of patients; but per SOC frequencies NP	No	Yes (TRB Chemedica)

Where published data were adequate for inclusion in MA and full safety report also provided by the author/sponsor, we preferably used the full data obtained from the author/sponsor

AE adverse event, *BCC* BioCell collagen, *BID* twice daily, *CS* chondroitin sulfate, *d* day, *GH* glucosamine hydrochloride, *GI* gastrointestinal, *IBSA* Institut Biochimique SA, *IOP* intraocular pressure, *MA* meta-analysis, *mo* month, *NA* not available, *NP* not provided, *OA* osteoarthritis, *OD* once daily, *pts* patients, *SOC* system organ class, *TEAE* treatment-emergent adverse event, *TID* three times daily, *TMJ* temporomandibular joint, *UC-II* undenatured type II collagen, *wk* week(s)

[a] Data presented as mean ± standard deviation or median (P25–P75)

[b] Drug with sufficient data for "individual MA"

[c] Not stated in the paper whether glucosamine sulfate or glucosamine hydrochloride was used

Fig. 2 a Summary of risk of bias in studies without any concomitant anti-osteoarthritis medication (studies meeting prespecified selection criteria): review authors' judgements about each risk-of-bias item for each study included in the initial qualitative synthesis. **b** Risk-of-bias summary in studies with concomitant anti-osteo-arthritis medication (studies included in the post hoc parallel qualitative synthesis): review authors' judgements about each risk-of-bias item for each study included in the parallel qualitative synthesis. *OA* osteoarthritis

Fig. 3 a Risk-of-bias graph in studies without any concomitant anti-osteoarthritis medication: review authors' judgements about each risk-of-bias item presented as percentages across all studies included in the initial qualitative synthesis. **b** Risk-of-bias graph for studies with concomitant anti-oste-oarthrits medication: review authors' judgements about each risk-of-bias item presented as percentages across all studies included in the parallel qualita-tive synthesis
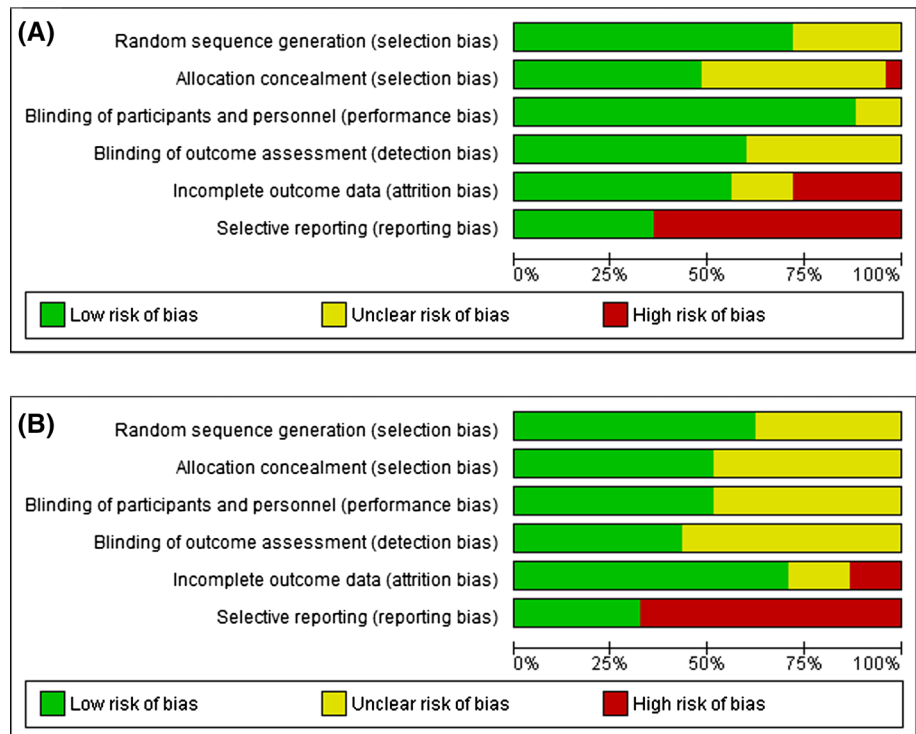
permitted, and overall, but this did not reach statistical sig-nificance (Fig. 5).

3.5 Avocado Soybean Unsaponifiables

No statistically significant difference was found between ASU treatment and placebo for any SOC-related disorder investigated or for severe and serious AEs and withdrawals due to AEs (ESM-2).

All ASU studies allowed concomitant oral NSAIDs during the trials (Table 2). Using data from these tri-als, ASU was no more likely than placebo to be associ-ated with AEs (total AEs) (OR 1.09; 95% CI 0.81–1.46; $I^2 = 0$%) (Fig. 6).

3.6 Diacerein

Significantly more gastrointestinal disorders were reported with diacerein than with placebo (OR 2.85; 95% CI 2.02–4.04; $I^2 = 62.8$%), whether concomitant OA medi-cations were allowed in the treatment protocol (OR 3.25; 95% CI 2.05–5.16; $I^2 = 51.3$%) or not (OR 2.53; 95% CI 1.43–4.46; $I^2 = 73.6$%) (Fig. 7). Diarrhea, abdominal pain, soft stools, and colitis were the most frequently reported gastrointestinal AEs.

The odds of nervous system disorders (mostly dizziness) were significantly increased with diacerein but only among studies that did not allow concomitant pharmacologic OA treatment (OR 3.46; 95% CI 1.44–8.32; $I^2 = 0$%) (Fig. 8).

Significantly increased odds of skin and subcutaneous tissue disorders were reported with diacerein in studies that allowed concomitant OA medications (OR 2.47; 95% CI 1.42–4.31; $I^2 = 0.0$%), with eczema, rash, pruritus, and urti-caria being the most reported specific events. There were also more skin and subcutaneous tissue disorders with diacerein than with placebo in studies that did not allow concomitant OA medications, but this did not reach statisti-cal significance (Fig. 9).

The odds of having renal and urinary disorders was significantly increased with diacerein versus placebo (OR 3.42; 95% CI 2.36–4.96; $I^2 = 17.0$%), whether concomitant OA medications were used (OR 3.40; 95% CI 1.18–9.82; $I^2 = 68.2$%) or not (OR 3.16; 95% CI 1.93–5.15; $I^2 = 0.0$%) (Fig. 10). Urine discoloration and urinary tract infection were the most frequently reported specific AEs.

A reduced odds of MSCT disorders was observed with diacerein versus placebo when concomitant OA medica-tions were not allowed during the trials (OR 0.53; 95% CI 0.35–0.82; $I^2 = 2.2$%). This was not observed when con-comitant OA medications were allowed (OR 1.19; 95% CI 0.82–1.73; $I^2 = 0$%) (ESM-2).

Overall, and specifically in studies with or without con-comitant OA medications, there were no increased odds of serious and severe AEs with diacerein compared with pla-cebo (ESM-2).

Table 2 Characteristics of studies included in the parallel qualitative synthesis (trials with concomitant osteoarthritis medication allowed). Studies are grouped by drug; those studies included in the quantitative synthesis are highlighted in bold type

Study	OA location	Treated groups/participant age[a]	Compound nature: Pharmaceutical grade or food supplement (manufacturer)	Dose	Treatment duration (weeks)	Concomitant OA medication allowed	Data provided in article (type of AE/% of pts considered)	Published data usable for MA? (yes/no)	Full data provided by author/sponsor? (information source)
Glucosamine sulfate[b]									
Cibere et al. [64]	Knee	Mean (range) Active 64.0 (40.0–83.0) Placebo 65.0 (43.0–88.0)	Nutritional supplement (Vita-Health, Canada)	Variable: maximum 1500 mg/d	26 wk	NSAIDs	Summary without details	No	Yes (author)
Drovanti [67]	Any joints	Mean ± SEM Active 61.3 ± 2.1 Placebo 58.7 ± 2.5	Pharmaceutical grade (Rotta Pharmaceuticals, Italy)	2 × 250 mg TID (total 1.5 g)	4 wk	No information about rescue medication	Unclear whether all AEs reported (seems to be a summary)	No	No (Rottapharm)
Fransen et al. [68] a. GS	Knee	Active 61.2 ± 7.7 Placebo 60.6 ± 8.1	Dietary supplement (Supplied by Sanofi-Aventis Consumer Healthcare)	2 × 753 mg OD	104 wk	Opioids, NSAIDs	Only AEs leading to withdrawal specified	No	Yes (author)
Giordano et al. [69]	Knee	Active 57.2 ± 7.2 Placebo 58.09 ± 8.3	Manufactured by Department of Pharmacology Giorgio Segre of the University of Siena	1500 mg GS/d	12 wk	Diclofenac 150 mg, piroxicam 20 mg, naproxen 750 mg, aceclofenac 200 mg	Frequency of most common AEs but per SOC frequencies NP	No	Yes (author)
Herrero-Beaumont et al. [70]	Knee	Active 63.4 ± 6.9 Placebo 64.5 ± 7.2	Pharmaceutical grade (Rottapharm)	1500 mg OD	26 wk	Ibuprofen max 4 × 400 mg/d	Summary of AEs occurring in ≥3 pts in any group; per SOC frequencies NP	No	No (Rottapharm and author)
Hughes and Carr [71]	Knee	Active and placebo 62.28 ± 9.12	Nutrient supplement (Health Perception UK)	3 × 500 mg/d	26 wk	NSAIDs	Listed all reported individual side effects, but per SOC frequencies NP	No	No (author)
Reginster et al. [89]	Knee	Active 66.0 ± 8.1 Placebo 65.5 ± 7.5	Pharmaceutical grade (Rotta Research Group, Monza, Italy)	1 × 1500 mg/d	156 wk	NSAIDs (diclofenac, piroxicam or proglumeta-cin)	AEs with ≥5% frequency, but per SOC frequencies NP	No	No (Rottapharm)

Table 2 (continued)

Study	OA location	Treated groups/ participant age[a]	Compound nature: Pharmaceutical grade or food supplement (manufacturer)	Dose	Treatment duration (weeks)	Concomitant OA medication allowed	Data provided in article (type of AE/% of pts considered)	Published data usable for MA? (yes/no)	Full data provided by author/sponsor? (information source)
Rindone et al. [90]	Knee	Active 63.0±12.0 Placebo 64.0±11.0	NA (Applehart Laboratories, Bedford, NH, USA)	3×500 mg/d	9 wk	NSAIDs, hydrocodone	Summary without details	No	No (author)
Rozendaal et al. [91]	Hip	Active 63.1±9.5 Placebo 63.7±8.5	Dietary supplement (Nutricia Manufacturing USA, Greenville, SC, USA)	2×750 mg OD	104 wk	NSAIDs, tramadol	All TEAEs seem to have been reported	Yes	Yes (author)
Zenk [97]	NA	Active 57±13 Placebo 58±13	Dietary supplement (NA)	3×500 mg/d	6 wk	Naproxen 220 mg, ibuprofen 200 mg	All TEAEs seem to have been reported, but per SOC frequencies NP	No	Data sent by colleague of author but after completion of our analyses
Chondroitin sulfate[b]									
Bourgeois et al. [63] a. CS 1200 mg b. CS 3×400 mg	Knee	Active a: 63.0±11.0 Active b: 63.0±9.0 Placebo 64.0±8.0	Pharmaceutical grade (IBSA)	a. 1 oral gel sachet 1200 mg CS/d b. 3 capsules×400 mg CS/d	13 wk	NSAIDs	Per SOC frequencies of AEs reported; no details about specific AEs	Yes	Yes (Laboratoires Genevrier)
Fransen et al. [68] b. CS	Knee	Active 59.5±8.0 Placebo 60.6±8.1	Dietary supplement (TSI Health Sciences, Australia)	2×400 mg OD	104 wk	Opioids, NSAIDs	Only AEs leading to withdrawal specified	No	Yes (author)
Kahan et al. [72]	Knee	Active 62.9±0.5 Placebo 61.8±0.5	Pharmaceutical grade (Genévrier Laboratories, France & IBSA, Switzerland)	800 mg OD	104 wk	NSAIDs	Summary without details	No	Yes (IBSA)
Mathieu [78]	Knee	Active 62.5±9.1 Placebo 63.1±10.7	Pharmaceutical grade (Laboratoires Genévrier)	1×800 mg/d	104 wk	NSAIDs	Only numbers of withdrawal due to AEs specified	No	Yes (Laboratoires Genevrier)

Table 2 (continued)

Study	OA location	Treated groups/participant age[a]	Compound nature: Pharmaceutical grade or food supplement (manufacturer)	Dose	Treatment duration (weeks)	Concomitant OA medication allowed	Data provided in article (type of AE/% of pts considered)	Published data usable for MA? (yes/no)	Full data provided by author/sponsor? (information source)
Mazieres et al. [79]	Hip or knee	Active 64.5±1.14 Placebo 63.3±1.07	NA	2×1000 mg/d	13 wk	NSAIDs (diclofenac, flurbiprofen, ibuprofen, indometacin, ketoprofen, naproxen, piroxicam, tenoxicam)	All TEAEs seem to have been reported, but per SOC frequencies NP	No	No (Pierre Fabre)
Mazieres et al. [80]	Knee	Active 67.3±7.8 Placebo 66.9±8.0	NA	2×500 mg/d	13 wk	NSAIDs (diclofenac, ketoprofen, naproxen)	Summary without details	No	No (Pierre Fabre)
Mazieres et al. [81]	Knee	Active 66.0±8.8 Placebo 66.0±7.7	NA	2×500 mg/d	24 wk	NSAIDs	Numbers of AEs reported, not incidences	No	No (Pierre Fabre)
Michel et al. [83]	Knee	Active 62.5±9.1 Placebo 63.1±10.7	Pharmaceutical grade (IBSA)	1×800 mg/d	104 wk	NSAIDs	Frequencies of ≥5% in one of two study groups provided for specific AEs; per SOC frequencies NP	No	Yes (IBSA)
Railhac et al. [88]	Knee	Active 63.6±8.2 Placebo 66.5±8.1	Pharmaceutical grade - Structum®	2×500 mg/d	48 wk	NSAIDs	Summary without details	No	No (Pierre Fabre)
Wildi et al. [96]	Knee	Active 59.7±9.4 Placebo 64.9±9.5	Pharmaceutical grade (Bioibérica S.A., Barcelona, Spain)	2×400 mg/d	26 wk	NSAIDs	Not specified whether all AEs reported; per SOC frequencies provided	Yes	Yes (author)
Combined glucosamine sulfate/chondroitin sulfate									
Fransen et al. [68] a. Glucosamine –Chondroitin	Knee	Active 60.7±8.4 Placebo 60.6±8.1	Dietary supplements (GS: Sanofi-Aventis Consumer Healthcare; CS: TSI Health Sciences, Australia)	1500 mg GS + 800 mg CS, OD	104 wk	Opioids, NSAIDs	Only AEs leading to withdrawal specified	No	Yes (author)

Table 2 (continued)

Study	OA location	Treated groups/ participant age[a]	Compound nature: Pharmaceutical grade or food supplement (manufacturer)	Dose	Treatment duration (weeks)	Concomitant OA medication allowed	Data provided in article (type of AE/% of pts considered)	Published data usable for MA? (yes/no)	Full data provided by author/sponsor? (information source)
Combined glucosamine hydrochloride/chondroitin sulfate									
Das et al. [65]	Knee	Active 64.5±9.8 Placebo 66.0±1.5	Dietary supplements (Nutramax Laboratories Inc., Baltimore, MD, USA)	1×(500 mg GH+400 mg CS+76 mg manganese), BID	26 wk	NSAIDs	All TEAEs seem to have been reported	Yes	No contact information found
Collagen derivatives									
Kumar et al. [73] a. PCP vs. placebo PCP b. BCP vs. placebo BCP	Knee	Active a: NA Placebo a: NA Active b: NA Placebo b: NA	NA (PCP: Nitta Gelatin Inc., Japan; BCP: Nitta Gelatin India Ltd)	2×5 g/d	13 wk	Aceclofenac sodium 100 mg	Summary without details	No	Author contacted: no response
McAlindon et al. [82]	Knee	Active 58.9±8.0 Placebo 60.3±8.5	NA – Fortigel (Gelita AG)	1×10 g CH/d	48 wk	Analgesics or NSAIDs	Summary without details	No	Yes (author)
Stančík et al. [94]	Knee	Active 53.4±8.6 Placebo 54.5±8.1	Dietary supplement – Colafit® (Dacom Pharma s.r.o., Czech Republic)	1×8 mg pure lyophilized collagen type I in capsule	13 wk	No information about concomitant medication use	All AEs seem to have been reported	Yes	Corresponding author unable to provide any information
Diacerein[b]									
Dougados et al. [66]	Hip	Active 63.0±6.7 Placebo 62.1±7.0	NA	50 mg BID	156 wk	Analgesics and/or NSAIDs	Most commonly observed AEs; per SOC frequencies reported	Yes	Yes (TRB Chemedica)
Lequesne et al. [74]	Knee or hip	Mean Active 63.6 Placebo 59.5	NA	50 mg BID	26 wk	NSAIDs	Summary without details	No	Yes (TRB Chemedica)
Nguyen et al. [85]	Hip	Active 63.0±10.0 Placebo 65.0±11.0	Pharmaceutical grade (Negma Pharma, Ltd., Buc, France)	1×50 mg/d	8 wk	Hypnotic drugs and/or muscle relaxants	Frequencies given for specific AEs, but not for body systems	No	Data provided by TRB Chemedica, but reported as number of AEs and not frequencies. Not usable for M-A

Table 2 (continued)

Study	OA location	Treated groups/ participant age[a]	Compound nature: Pharmaceutical grade or food supplement (manufacturer)	Dose	Treatment duration (weeks)	Concomitant OA medication allowed	Data provided in article (type of AE/% of pts considered)	Published data usable for MA? (yes/no)	Full data provided by author/sponsor? (information source)
Pham et al. [87]	Knee	Active 64.5±7.8 Placebo 64.9±7.7	NA	50 mg BID	52 wk	NSAIDs	Most commonly seen AEs reported. By SOC report for some SOCs, and only specific AEs for GI	Yes	No (Laboratoires NEGMA)
Shin et al. [92]	Hand	Active 57.0±7.0 Placebo 58.6±7.0	Pharmaceutical grade (Myung-moon Pharmaceutical Co, Ltd, Seoul, Korea)	1×50 mg/d	12 wk	Nabumetone (unclear whether this was considered protocol violation)	Frequencies of specific AEs, but per SOC frequencies NP	No	Yes (author)
Vignon et al. [95]	Hip	Active NA Placebo NA	NA	50 mg BID	156 wk	Analgesics and/or NSAIDs	Summary without details	No	No contact information found
Avocado soybean unsaponifiables (ASU)[b]									
Appelboom et al. [61] a. ASU 300 mg b. ASU 600 mg	Knee	Active a: 63.4±8.6 Active b: 65.2±8.5 Placebo 66.3±8.1	Pharmaceutical grade (Pharmascience)	a. 1×300 mg/d b. 1×600 mg/d	13 wk	Analgesics and NSAIDs	Incidence of side effects according to body systems; no details about specific AEs	Yes	Yes (Expanscience)
Blotman et al. [62]	Knee	Active 63.3±7.6 Placebo 65.1±6.9	Pharmaceutical grade (Pharmascience)	1×300 mg capsule/d ASU	13 wk	NSAIDs	Frequencies for specific AEs reported; per SOC frequencies NP	No	Yes (Expanscience)
Lequesne et al. [75]	Hip	Active 63.3±8.7 Placebo 63.0±8.8	Pharmaceutical grade (Pharmascience)	1×300 mg capsule ASU OD	104 wk	NSAIDs	Summary without details	No	No (Expanscience)
Maheu et al. [76]	Knee or hip	Active 63.3±7.6 Placebo 65.1±6.9	Pharmaceutical grade (Pharmascience)	1×300 mg capsule ASU OD	26 wk	NSAIDs	Incidences of AEs reported for active but not placebo group	No	Yes (Expanscience)
Maheu et al. [77]	Hip	Active 61.6±7.9 Placebo 62.7±8.0	Pharmaceutical grade (Laboratoires Expanscience)	1×300 mg capsule ASU OD	156 wk	Analgesics and NSAIDs	Summary without details	No	Yes (Expanscience)

Table 2 (continued)

Study	OA location	Treated groups/participant age[a]	Compound nature: Pharmaceutical grade or food supplement (manufacturer)	Dose	Treatment duration (weeks)	Concomitant OA medication allowed	Data provided in article (type of AE/% of pts considered)	Published data usable for MA? (yes/no)	Full data provided by author/sponsor? (information source)
Curcuma									
Nakagawa et al. [84]	Knee	Active 71.9±5.3 Placebo 66.1±7.2	Therapeutic food material (Theravalues, Tokyo, Japan)	6 capsules of Theracurmin/d, containing curcumin 180 mg (BID)	8 wk	Oral celecoxib and pain relief patches	Incomplete reporting (missing data for some events)	No	Yes (author)
Panahi et al. [86]	Knee	Active 57.3±8.8 Placebo 57.6±9.1	Dietary supplement (Sami Labs Ltd, Bangalore, India)	C3 complex®, 3×500 mg/d	6 wk	Naproxen	Summary without details	No	No (author)
Srivastava et al. [93]	Knee	Active 50.2±8.1 Placebo 50.3±8.6	NA (Himalaya Drug Company Bangalore, India)	2×500 mg/d	17 wk	Diclofenac 50 mg/day	Unclear whether frequencies or numbers of AEs reported	No	No (author)

Where published data were adequate for inclusion in meta-analysis and full safety report also provided by the author/sponsor, we preferably used the full data obtained from the author/sponsor

AE adverse event, *ASU* avocado soybean unsaponifiables, *BCP* collagen peptides isolated from bovine bone, *BID* twice daily, *CH* collagen hydrolysate, *CS* chondroitin sulfate, *d* day, *GI* gastrointestinal, *GS* glucosamine sulfate, *IBSA* Institut Biochimique SA, *MA* meta-analysis, *NA* not available, *NP* not provided, *NSAID* nonsteroidal anti-inflammatory drug, *OA* osteoarthritis, *OD* once daily, *PCP* collagen peptides isolated from pork skin, *pts* patients, *SEM* standard error of the mean, *SOC* system organ class, *TEAEs* treatment-emergent AEs, *wk* week

[a]Mean±standard deviation or median (P25–P75) unless otherwise indicated

[b]Drug with sufficient data for 'individual MA

Glucosamine sulfate: Any adverse event

Study	n Active	N Active	n Placebo	N Placebo	Odds Ratio (95% CI)	% Weight
Without concomitant anti-OA medication						
Cahlin 2011	12	30	4	29	4.17 (1.15, 15.04)	7.42
Esfandiari 2017	5	44	2	44	2.69 (0.49, 14.69)	4.57
Frestedt 2008	12	15	14	16	0.57 (0.08, 4.01)	3.55
Noack 1994	8	126	13	126	0.59 (0.24, 1.48)	12.54
Pavelka 2002	67	101	65	101	1.09 (0.61, 1.95)	22.12
Subtotal (I-squared = 45.9%, p = 0.117)					1.24 (0.62, 2.46)	50.20
.						
With concomitant anti-OA medication						
Cibere 2004	13	68	20	66	0.54 (0.24, 1.21)	15.15
Giordano 2009	11	30	12	30	0.87 (0.31, 2.46)	10.38
Rozendaal 2008	57	111	59	111	0.93 (0.55, 1.58)	24.27
Subtotal (I-squared = 0.0%, p = 0.540)					0.80 (0.53, 1.20)	49.80
.						
Overall (I-squared = 29.8%, p = 0.190)					0.96 (0.66, 1.41)	100.00

NOTE: Weights are from random effects analysis

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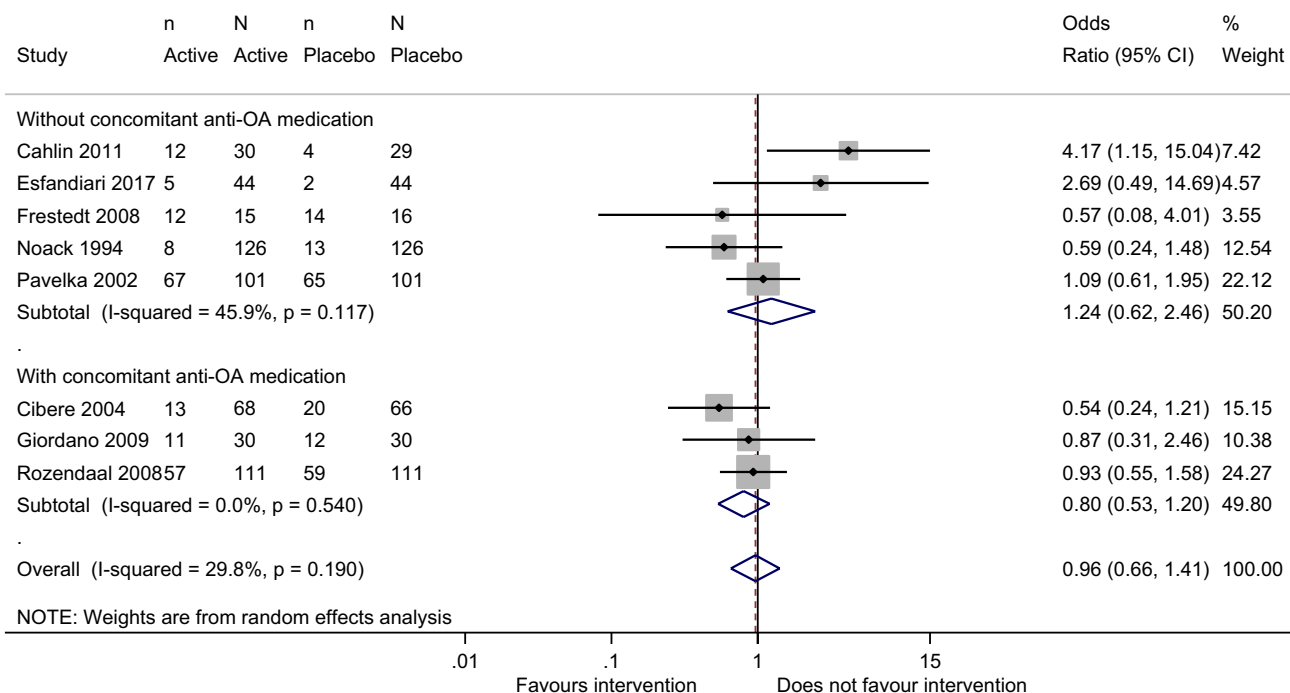Favours intervention   Does not favour intervention

Fig. 4 Forest plot displaying the results of the meta-analyses comparing total adverse events with glucosamine sulfate versus placebo in patients with osteoarthritis: overall analysis and analyses of studies with and without concomitant anti-OA medication allowed. *CI* confidence interval, *OA* osteoarthritis

Overall, diacerein was associated with significantly higher odds of any AE (total AEs), with or without concomitant OA treatment, compared with placebo (OR 2.22; 95% CI 1.58–3.13; $I^2 = 52.8\%$) (Fig. 11). In studies without any concomitant OA medications, diacerein was not associated with increased withdrawals due to AEs compared with placebo. However, more withdrawals due to AEs were seen with diacerein when concomitant anti-OA treatments were allowed (OR 3.18; 95% CI 1.85–5.47; $I^2 = 13.4\%$) (Fig. 12).

No significant increase in serious or severe AEs was found with diacerein compared with placebo (ESM-2).

3.7 Assessment of Publication Bias

We assessed funnel plot asymmetry for publication bias for each of the primary or secondary outcomes for GS, CS, ASU, and diacerein if there were sufficient data for each outcome. Only CS had sufficient studies for the Harbord's test for funnel plot asymmetry. Visual inspection of funnel plots (for all compounds) and formal test for funnel plot asymmetry with CS (Harbord's test) showed no evidence of publication bias, whatever the treatment. For each compound,

funnel plots for "total AEs" are depicted in Fig. 13. All the other funnel plots are provided in ESM-3.

3.8 GRADE Assessment of Findings

Using the GRADE approach [34], we assessed the certainty of evidence for each of the outcomes for GS, CS, ASU, and diacerein. Overall, for all of the outcomes considered for CS, ASU, and diacerein, the certainty of evidence was "high." For diacerein, this was downgraded to "moderate" for a few outcomes in studies with or without concomitant anti-OA medications (data not shown), because of the large CIs around the estimates. We found "moderate" certainty of evidence for severe and serious AEs with GS (overall) and for some other outcomes in studies with or without concomitant anti-OA medications (data not shown) because of wide CIs (imprecision) due to the low number of events (null events were reported in most of the included studies); for other outcomes, the certainty of evidence was "high" with GS. The detailed results for the main outcomes for each of these compounds are depicted in the summary of findings tables using data from "overall" meta-analyses (Tables 3, 4, 5, 6).

Chondroitin sulfate: Any adverse event

Study	n Active	N Active	n Placebo	N Placebo	Odds Ratio (95% CI)	% Weight
Without concomitant anti-OA medication						
Bucsi 1998	2	39	3	46	0.77 (0.12, 4.89)	2.09
Gabay 2011	34	81	34	82	1.02 (0.55, 1.90)	10.47
Reginster 2017	100	199	110	205	0.87 (0.59, 1.29)	15.27
Uebelhart 1998	1	21	3	21	0.30 (0.03, 3.15)	1.33
Uebelhart 2004	8	54	6	56	1.45 (0.47, 4.49)	4.77
Zegels 2013 (a)	61	117	84	117	0.43 (0.25, 0.74)	11.98
Zegels 2013 (b)	68	119	84	117	0.52 (0.30, 0.90)	11.97
Subtotal (I-squared = 33.3%, p = 0.174)					0.70 (0.51, 0.98)	57.88
.						
With concomitant anti-OA medication						
Bourgeois 1998 (a)	3	40	8	44	0.36 (0.09, 1.49)	3.36
Bourgeois 1998 (b)	2	43	8	44	0.22 (0.04, 1.10)	2.64
Kahan 2009	203	309	206	313	0.99 (0.71, 1.39)	16.67
Mathieu 2002	2	150	0	150	5.07 (0.24, 106.45)	0.81
Michel 2005	113	150	103	150	1.39 (0.84, 2.31)	12.69
Wildi 2011	19	35	23	34	0.57 (0.21, 1.51)	5.94
Subtotal (I-squared = 46.7%, p = 0.095)					0.85 (0.53, 1.38)	42.12
.						
Overall (I-squared = 44.6%, p = 0.041)					0.78 (0.59, 1.03)	100.00

NOTE: Weights are from random effects analysis

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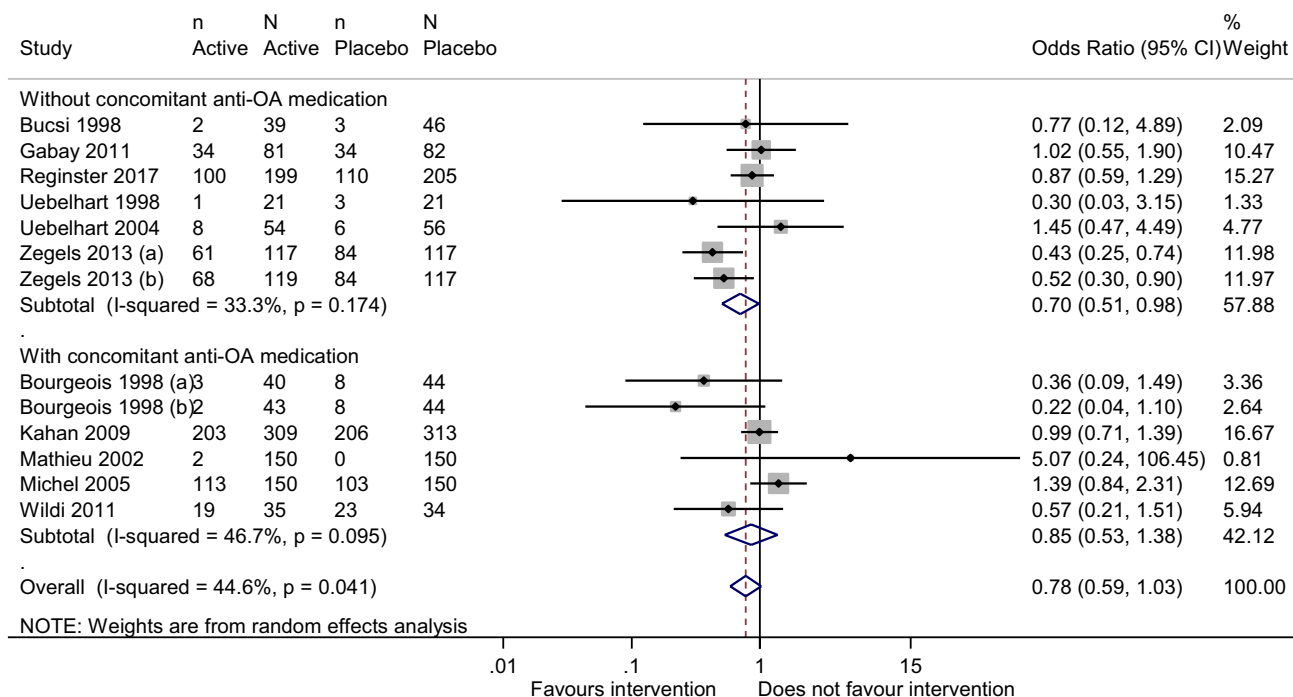Favours intervention   Does not favour intervention

Fig. 5 Forest plot displaying the results of the meta-analyses comparing total adverse events with chondroitin sulfate versus placebo in patients with osteoarthritis: overall analysis and analyses of studies with and without concomitant anti-osteoarthritis medication allowed. *CI* confidence interval, *OA* osteoarthritis

4 Discussion

In our analysis, we found no statistically significant increase in odds between either GS, CS, or ASU, each compared with placebo, for any of the SOC-related disorders investigated, including gastrointestinal, cardiac, vascular, nervous system, skin and subcutaneous tissue, MSCT, and disorders of the renal and urinary systems. In addition, we found no statistically significant difference in odds between either GS, CS, or ASU treatment and placebo for severe and serious AEs or for withdrawals due to AEs. Almost all of this new evidence was predominantly associated with "high" certainty; "moderate" certainty of evidence was found with two outcomes overall (only with GS) and with a few other outcomes with or without concomitant anti-OA medication (mainly with GS and diacerein) because of imprecision (wide CIs around the estimates).

Overall, this meta-analysis found no statistically significant increase in odds for total AEs reported with GS (with or without concomitant anti-OA -medication) versus placebo, and we found reduced odds for total AEs with CS compared with placebo, particularly in studies in which no concomitant OA medications were permitted. These findings agree with those of previous meta-analyses that have demonstrated GS and CS to be as safe as placebo, with no

significant increase in odds for total AEs or dropouts due to AEs [6, 7, 21]. In a network meta-analysis, Zeng et al. [98] found no statistically significant increase in odds of specific AEs between GS and CS, each compared with placebo. The specific AEs investigated in that study were gastrointestinal, cardiovascular, central nervous system, infection, musculoskeletal and skin AEs.

A reduced odds of reporting renal and urinary disorders was found with CS compared with placebo in all the groups of studies analyzed, which was statistically significant overall (OR 0.40; 95% CI 0.22–0.74) and in studies with concomitant anti-OA medications (OR 0.43; 95% CI 0.23–0.81) (ESM-2). Likewise, as previously stated, the rate of total AEs was lower with CS than with placebo, and the difference in odds was statistically significant with studies with no concomitant anti-OA medication (OR 0.70; 95% CI 0.51–0.98). However, the data available from the studies included in these analyses did not allow us to identify the specific events reported more frequently in patients receiving placebo, particularly in the Kahan et al. [72] study in which renal and urinary disorders were significantly more frequent in the placebo group (26 of 313 patients) compared with the CS group (9 of 309 patients). If these results are not due to chance, whether CS has potential for a protective effect against renal and urinary disorders deserves further

Avocado/soybean unsaponifiables: Any adverse event

Study	n Active	N Active	n Placebo	N Placebo	Odds Ratio (95% CI)	% Weight
With concomitant anti-OA medication						
Appelboom 2001 (a)	26	86	23	88	1.22 (0.63, 2.37)	20.03
Appelboom 2001 (b)	25	86	23	88	1.16 (0.60, 2.25)	19.81
Blotman 1997	9	80	10	83	0.93 (0.36, 2.41)	9.56
Maheu 1998	23	85	22	79	0.96 (0.48, 1.91)	18.62
Maheu 2014	158	189	173	210	1.09 (0.65, 1.84)	31.98
Subtotal (I-squared = 0.0%, p = 0.983)					1.09 (0.81, 1.46)	100.00
.						
Overall (I-squared = 0.0%, p = 0.983)					1.09 (0.81, 1.46)	100.00

NOTE: Weights are from random effects analysis

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        .01        .1         1      5    20
          Favours intervention   Does not favour intervention
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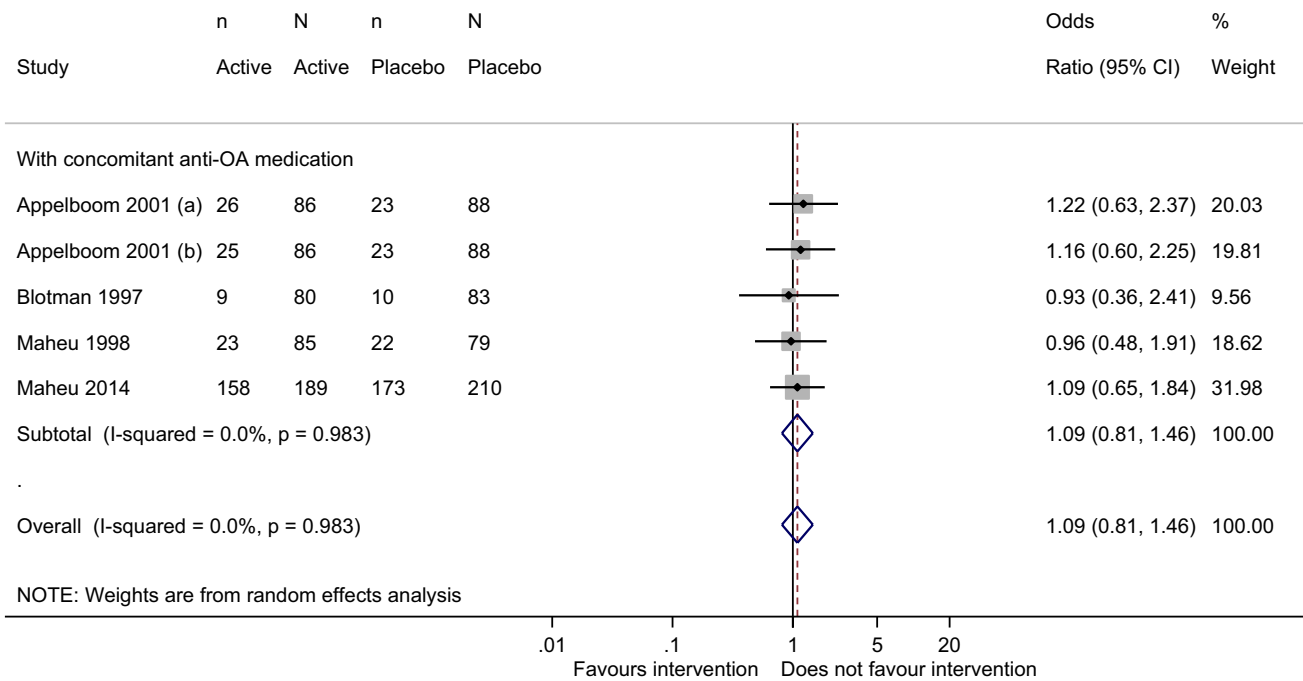
Fig. 6 Forest plot displaying the result of the meta-analysis comparing total adverse events with avocado soybean unsaponifiables versus placebo in patients with osteoarthritis: analysis of studies with concomitant anti-osteoarthritis medications allowed. *CI* confidence interval, *OA* osteoarthritis

investigation. The specific action of CS on the renal and urinary system needs to be identified, and the biological explanation of such an effect should also be clarified if this effect is confirmed by other studies.

With regards to ASU, all studies included in our analysis allowed concomitant oral NSAID treatment. However, ASU was not likely to be associated with more AEs than placebo. A recent Cochrane meta-analysis found no difference in risk of AEs with ASU versus placebo from data reported in five RCTs ($N = 1050$) (RR 1.04; 95% CI 0.97–1.12) [22]. The analysis also found no difference between ASU and placebo in withdrawals due to AEs (one study, $N = 398$) (RR 1.14; 95% CI 0.73–1.80) or in serious AEs (one study, $N = 398$) (RR 1.22; 95% CI 0.94–1.59). In this Cochrane review, the analyses were only based on published and incomplete data. In our meta-analysis, we were able to include the raw data from the full safety reports of all the studies considered; these data were provided by the manufacturer of the compound (Table 2). ASU is a complex mixture of many natural vegetable extracts taken from avocado and soybean oils, including fat-soluble vitamins, sterols, triterpene alcohols, and furan fatty acids [99]; analysis of commercially available ASU supplements demonstrates variation in the sterol content [99, 100]. However, there is no concern about content variety of ASU in the current meta-analysis, as all

the studies included through our systematic review process used the pharmaceutical-grade proprietary ASU product Piascledine® (Expanscience) (Table 2). Therefore, our findings regarding the safety profile of ASU may not apply to other preparations of ASU.

In a post-marketing safety analysis using data provided by the French spontaneous reporting system via the network of national pharmacovigilance centers, AEs affecting the skin, liver, gastrointestinal tract, and platelet aggregation (some being serious) have been reported with ASU [101]. This raises concerns about the safety of ASU supplements, particularly in real life, and requires further investigation.

In our safety analysis, the odds of any AE with diacerein were significantly higher than with placebo, with or without concomitant OA treatment (OR 2.22; 95% CI 1.58–3.13). This was largely due to the increased odds of gastrointestinal AEs with diacerein versus placebo (OR 2.85; 95% CI 2.02–4.04), diarrhea, abdominal pain, soft stools, and colitis being frequently reported, and a considerable increase in the odds of renal and urinary disorders with diacerein (OR 3.42; 95% CI 2.36–4.96), urine discoloration being the most reported effect. These results were found in both studies with and without concomitant OA medications and are in agreement with a Cochrane meta-analysis, which found an increased risk of AEs with diacerein versus placebo:

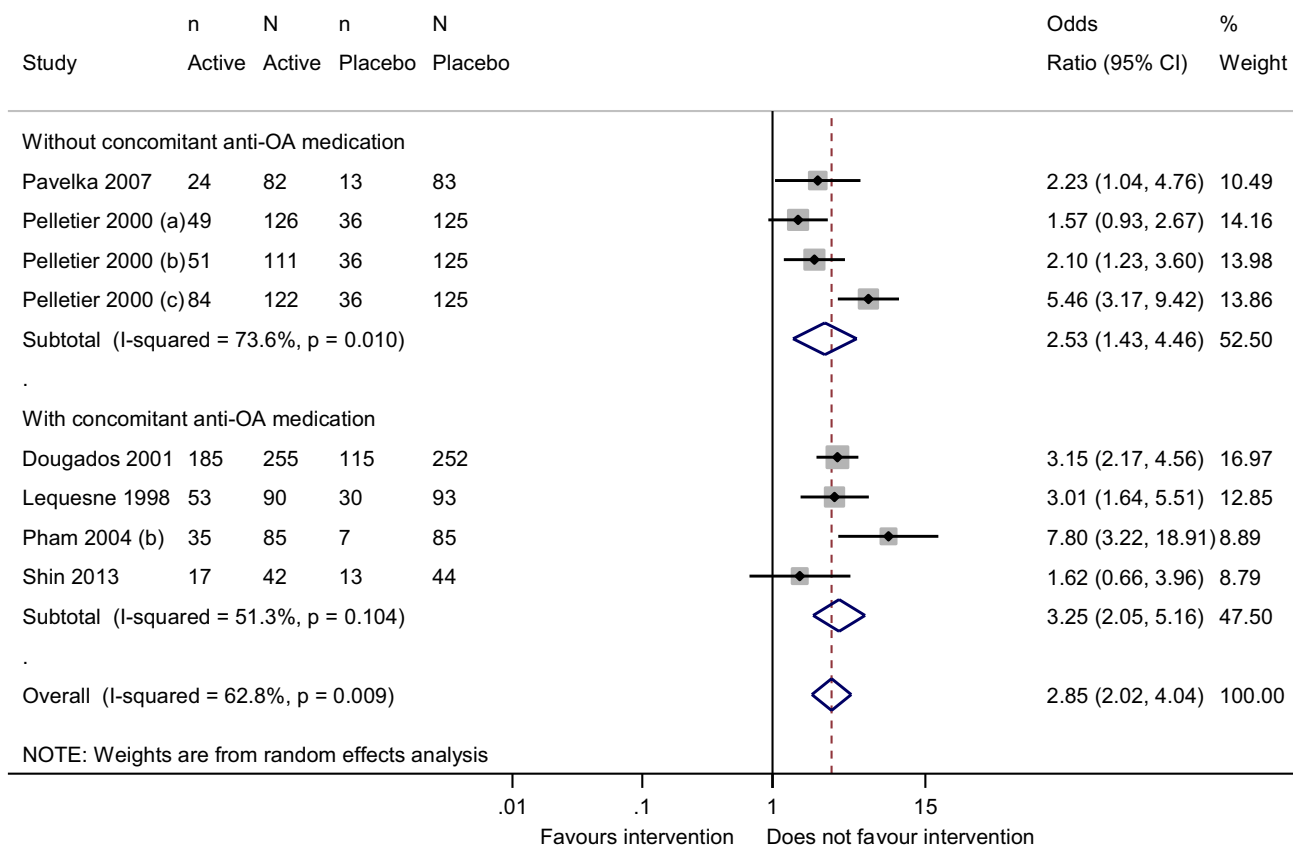## Diacerein: Gastrointestinal disorders

Study	n Active	N Active	n Placebo	N Placebo		Odds Ratio (95% CI)	% Weight
Without concomitant anti-OA medication							
Pavelka 2007	24	82	13	83		2.23 (1.04, 4.76)	10.49
Pelletier 2000 (a)	49	126	36	125		1.57 (0.93, 2.67)	14.16
Pelletier 2000 (b)	51	111	36	125		2.10 (1.23, 3.60)	13.98
Pelletier 2000 (c)	84	122	36	125		5.46 (3.17, 9.42)	13.86
Subtotal (I-squared = 73.6%, p = 0.010)						2.53 (1.43, 4.46)	52.50
.							
With concomitant anti-OA medication							
Dougados 2001	185	255	115	252		3.15 (2.17, 4.56)	16.97
Lequesne 1998	53	90	30	93		3.01 (1.64, 5.51)	12.85
Pham 2004 (b)	35	85	7	85		7.80 (3.22, 18.91)	8.89
Shin 2013	17	42	13	44		1.62 (0.66, 3.96)	8.79
Subtotal (I-squared = 51.3%, p = 0.104)						3.25 (2.05, 5.16)	47.50
.							
Overall (I-squared = 62.8%, p = 0.009)						2.85 (2.02, 4.04)	100.00

NOTE: Weights are from random effects analysis

.01   .1   1   15

Favours intervention   Does not favour intervention

Fig. 7 Forest plot displaying the results of the meta-analyses comparing gastrointestinal disorders with diacerein versus placebo in patients with osteoarthritis: overall analysis and analyses of studies with and without concomitant anti-osteoarthritis medication allowed. *CI* confidence interval, *OA* osteoarthritis

diarrhea (RR 3.52; 95% CI 2.42–5.11), urine discoloration (RR 13.01; 95% CI 5.96–28.40), and rash or pruritus (RR 1.99; 95% CI 0.94–4.23) [20]. In a meta-analysis of RCTs, Bartels et al. [5] also found a significantly increased risk of diarrhea with diacerein.

We also found significantly increased odds of dermatological disorders with diacerein versus placebo, overall (OR 2.18; 95% CI 1.40–3.42), and specifically eczema, rash, pruritus, and urticaria; these odds significantly increased when concomitant anti-OA treatment was allowed (OR 2.47; 95% CI 1.42–4.31) but not when there was no concomitant anti-OA medication (OR 1.74; 95% CI 0.82–3.70). Oral NSAIDs were the rescue or concomitant anti-OA medications allowed during the trials for both the diacerein and the placebo groups (Table 2).

The odds of withdrawals due to AEs were significantly higher with diacerein than with placebo, overall (OR 1.85; 95% CI 1.13–3.02; $I^2 = 52.1\%$), and the increase was more important when concomitant anti-OA medications were allowed (OR 3.18; 95% CI 1.85–5.47; $I^2 = 13.4\%$), but no

significant increase was found without concomitant anti-OA medications (OR 1.22; 95% CI 0.80–1.87; $I^2 = 0.0\%$). As shown by these results, there is moderate but statistically significant heterogeneity with the overall analysis ($I^2 = 52.1\%$, $p = 0.04$), which was eliminated when the studies with ($I^2 = 13.4\%$, $p = 0.33$) or without ($I^2 = 0.0\%$) concomitant anti-OA medications were considered separately. These results could suggest that the use of oral NSAIDs as rescue or concomitant medication might have played a role in the significantly increased number of withdrawals observed in patients receiving diacerein compared with those receiving placebo. However, we could not clinically explain this, as no drug interaction concern has been described with the coadministration of diacerein and NSAIDs [102]. This warrants further investigation given that similar results have been obtained regarding skin and subcutaneous tissue disorders, with eczema, rash, pruritus, and urticaria being the most reported specific events.

Whatever the group of studies considered (overall, with or without concomitant anti-OA medications), there was
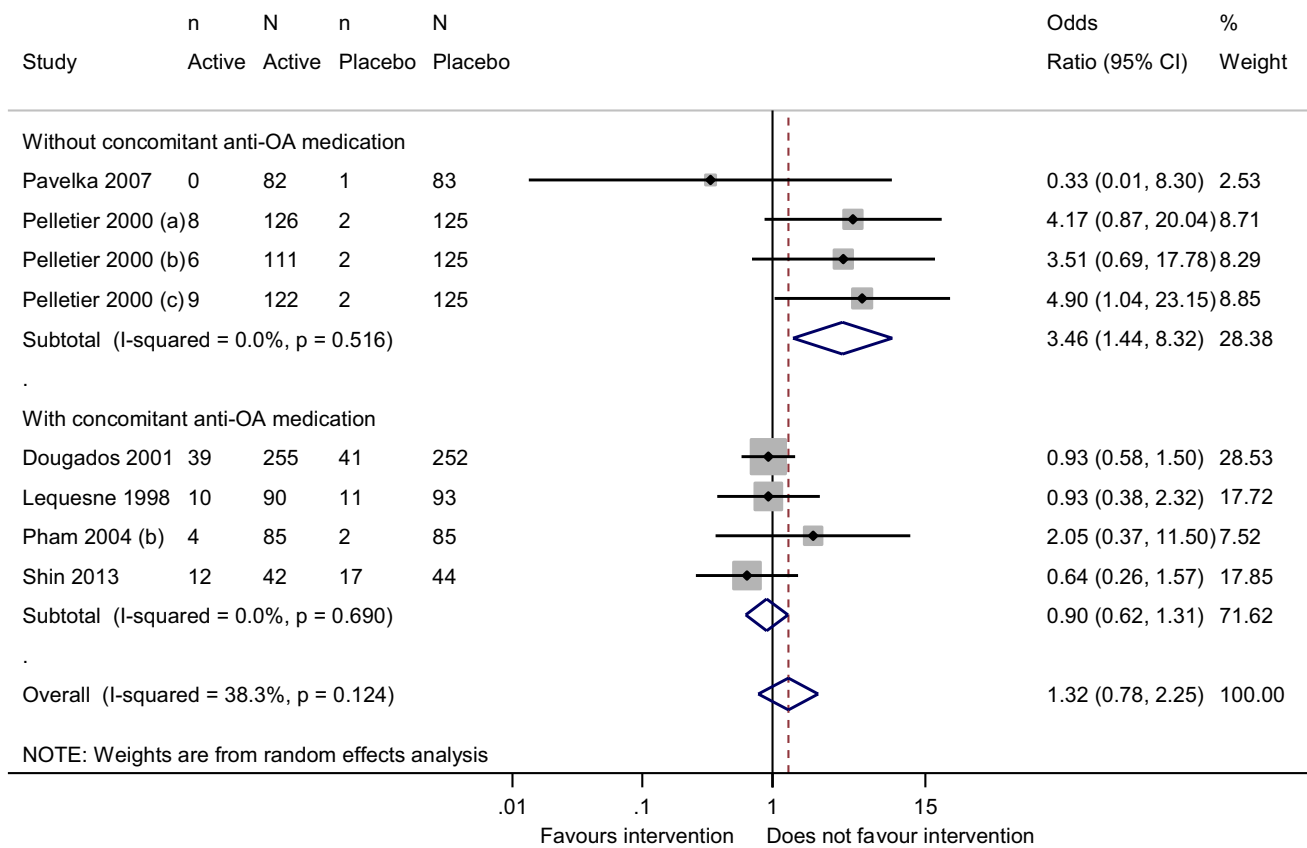
Diacerein: Nervous system disorders

Study	n Active	N Active	n Placebo	N Placebo		Odds Ratio (95% CI)	% Weight
Without concomitant anti-OA medication							
Pavelka 2007	0	82	1	83		0.33 (0.01, 8.30)	2.53
Pelletier 2000 (a)	8	126	2	125		4.17 (0.87, 20.04)	8.71
Pelletier 2000 (b)	6	111	2	125		3.51 (0.69, 17.78)	8.29
Pelletier 2000 (c)	9	122	2	125		4.90 (1.04, 23.15)	8.85
Subtotal (I-squared = 0.0%, p = 0.516)						3.46 (1.44, 8.32)	28.38
.							
With concomitant anti-OA medication							
Dougados 2001	39	255	41	252		0.93 (0.58, 1.50)	28.53
Lequesne 1998	10	90	11	93		0.93 (0.38, 2.32)	17.72
Pham 2004 (b)	4	85	2	85		2.05 (0.37, 11.50)	7.52
Shin 2013	12	42	17	44		0.64 (0.26, 1.57)	17.85
Subtotal (I-squared = 0.0%, p = 0.690)						0.90 (0.62, 1.31)	71.62
.							
Overall (I-squared = 38.3%, p = 0.124)						1.32 (0.78, 2.25)	100.00

NOTE: Weights are from random effects analysis

.01   .1   1   15

Favours intervention   Does not favour intervention

Fig. 8 Forest plot displaying the results of the meta-analyses comparing nervous system disorders with diacerein versus placebo in patients with osteoarthritis: overall analysis and analyses of studies with and without concomitant anti-osteoarthritis medication allowed. *CI* confidence interval, *OA* osteoarthritis

no increase in severe or serious AEs with diacerein versus placebo. Unlike previous meta-analyses on the safety of diacerein in the treatment of OA that used only the published data, we were able to use the full safety reports data for five of six studies analyzed (Tables 1 and 2), which makes our estimates more precise than these previous estimates.

The safety of diacerein was called into question following case reports of severe diarrhea and rare cases of serious hepatotoxicity; however, the reported cases of liver disorders involved patients aged ≥ 65 years [103–105]. The European Medicines Agency (EMA) considered these safety issues and concluded that the benefit-risk balance of diacerein remained positive for hip and knee OA, particularly in patients aged < 65 years [106]. It is advised that patients start treatment on half the normal dose (i.e., 50 mg instead of 100 mg daily) and stop taking diacerein if diarrhea occurs. The limited number of studies on diacerein in our meta-analysis meant we were unable to perform a dose–response effect analysis through subgroup analyses. However, the results of individual studies, as depicted by

Fig. 7, clearly indicated that gastrointestinal disorders were dose-dependent (detailed dose information in Tables 1 and 2). Indeed, for the five studies for which we used the full safety report data, the individual ORs for gastrointestinal disorders increased with the dose of diacerein (Fig. 7), from 50 mg daily in the first arm (a) of the study by Pelletier et al. [52] to 100 mg in the studies by Pavelka et al. [51], Dougados et al. [66], and Lequesne et al. [74] and 150 mg in the third arm (c) of the study by Pelletier et al. [52]. This potential dose–response effect may explain the heterogeneity observed, whatever the group of studies considered (Fig. 7).

Unlike the adverse effects associated with diacerein, a recent RCT in patients with inadequately controlled type 2 diabetes mellitus (T2DM) showed that diacerein improved glycemic control; this led the authors to conclude that diacerein would be an adequate adjunct treatment option for patients with OA and T2DM [107]. Another recent RCT in patients with T2DM also concluded that diacerein could be

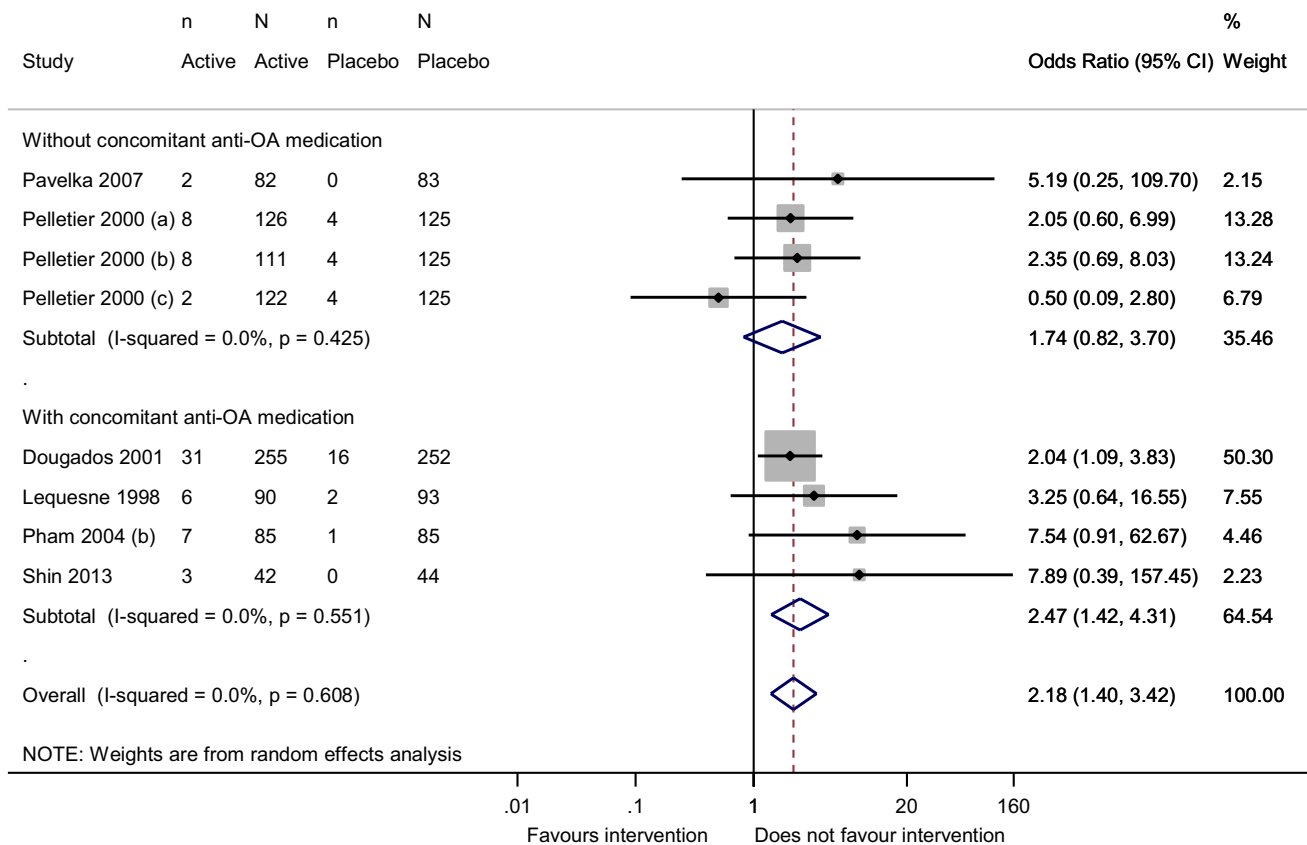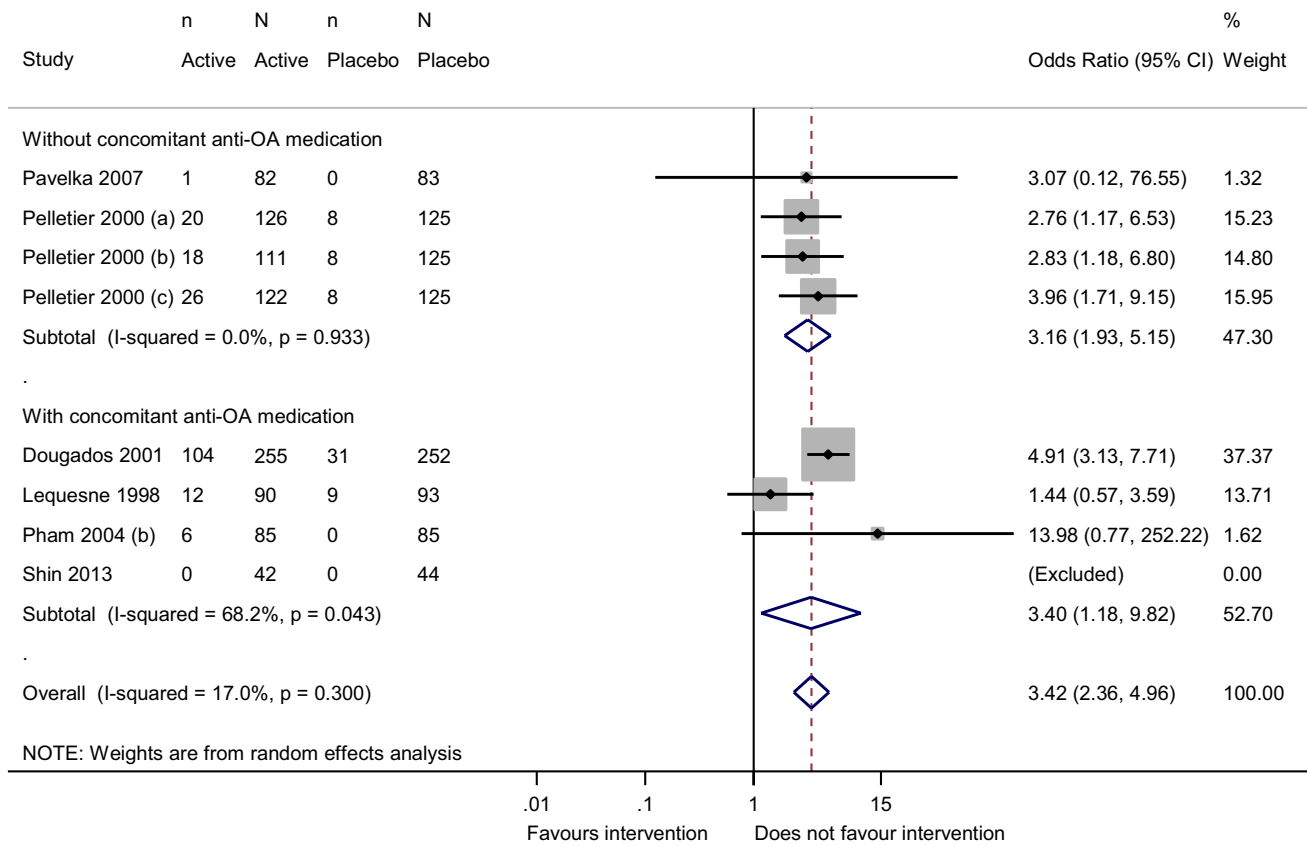## Diacerein: Skin and subcutaneous tissue disorders

Study	n Active	N Active	n Placebo	N Placebo	Odds Ratio (95% CI)	% Weight
Without concomitant anti-OA medication						
Pavelka 2007	2	82	0	83	5.19 (0.25, 109.70)	2.15
Pelletier 2000 (a)	8	126	4	125	2.05 (0.60, 6.99)	13.28
Pelletier 2000 (b)	8	111	4	125	2.35 (0.69, 8.03)	13.24
Pelletier 2000 (c)	2	122	4	125	0.50 (0.09, 2.80)	6.79
Subtotal (I-squared = 0.0%, p = 0.425)					1.74 (0.82, 3.70)	35.46
.						
With concomitant anti-OA medication						
Dougados 2001	31	255	16	252	2.04 (1.09, 3.83)	50.30
Lequesne 1998	6	90	2	93	3.25 (0.64, 16.55)	7.55
Pham 2004 (b)	7	85	1	85	7.54 (0.91, 62.67)	4.46
Shin 2013	3	42	0	44	7.89 (0.39, 157.45)	2.23
Subtotal (I-squared = 0.0%, p = 0.551)					2.47 (1.42, 4.31)	64.54
.						
Overall (I-squared = 0.0%, p = 0.608)					2.18 (1.40, 3.42)	100.00

NOTE: Weights are from random effects analysis

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        .01        .1         1        20      160
        Favours intervention   Does not favour intervention
```

Fig. 9 Forest plot displaying the results of the meta-analyses comparing dermatological adverse events with diacerein versus placebo in patients with osteoarthritis: overall analysis and analyses of studies with and without concomitant anti-osteoarthritis medication allowed. *CI* confidence interval, *OA* osteoarthritis

a good treatment option in patients with T2DM with chronic kidney disease [108].

Given the warnings about adverse liver reactions, the current status or history of liver disease should be considered when prescribing diacerein. However, further investigation regarding the adverse liver effects of diacerein in patients with OA is warranted. In fact, a very recent study in rats with induced abnormal liver function concluded that rhein (the metabolite of diacerein) had a hepatoprotective effect, suggesting its possible concomitant use in patients receiving methotrexate, a treatment associated with kidney and liver function abnormalities [109].

Given the adverse effects associated with the use of diacerein, as shown by our analyses, and its positive effect on glycemic control, as reported by other studies, the usefulness of this compound in patients with OA should be assessed for each patient according to their individual characteristics, provided that its real benefit in terms of efficacy is proven.

4.1 Strengths

Our study has some specific strengths. First, we included only RCTs versus placebo, so the real effect was not underestimated. Second, we investigated many SOCs, not only "total AEs," "serious AEs," or "gastrointestinal AEs," as reported in many previous meta-analyses. Third, to avoid double counting of AEs, for each SOC, we considered the number of patients who experienced at least once any related AE. For total AEs, we considered the number of patients who experienced at least once any AE during the study.

4.2 Limitations

Our study also had some limitations. Many of the identified studies that met the inclusion criteria did not provide

Diacerein: Renal and urinary disorders

Study	n Active	N Active	n Placebo	N Placebo	Odds Ratio (95% CI)	% Weight
Without concomitant anti-OA medication						
Pavelka 2007	1	82	0	83	3.07 (0.12, 76.55)	1.32
Pelletier 2000 (a)	20	126	8	125	2.76 (1.17, 6.53)	15.23
Pelletier 2000 (b)	18	111	8	125	2.83 (1.18, 6.80)	14.80
Pelletier 2000 (c)	26	122	8	125	3.96 (1.71, 9.15)	15.95
Subtotal (I-squared = 0.0%, p = 0.933)					3.16 (1.93, 5.15)	47.30
.						
With concomitant anti-OA medication						
Dougados 2001	104	255	31	252	4.91 (3.13, 7.71)	37.37
Lequesne 1998	12	90	9	93	1.44 (0.57, 3.59)	13.71
Pham 2004 (b)	6	85	0	85	13.98 (0.77, 252.22)	1.62
Shin 2013	0	42	0	44	(Excluded)	0.00
Subtotal (I-squared = 68.2%, p = 0.043)					3.40 (1.18, 9.82)	52.70
.						
Overall (I-squared = 17.0%, p = 0.300)					3.42 (2.36, 4.96)	100.00

NOTE: Weights are from random effects analysis

.01　　　.1　　　1　　　15
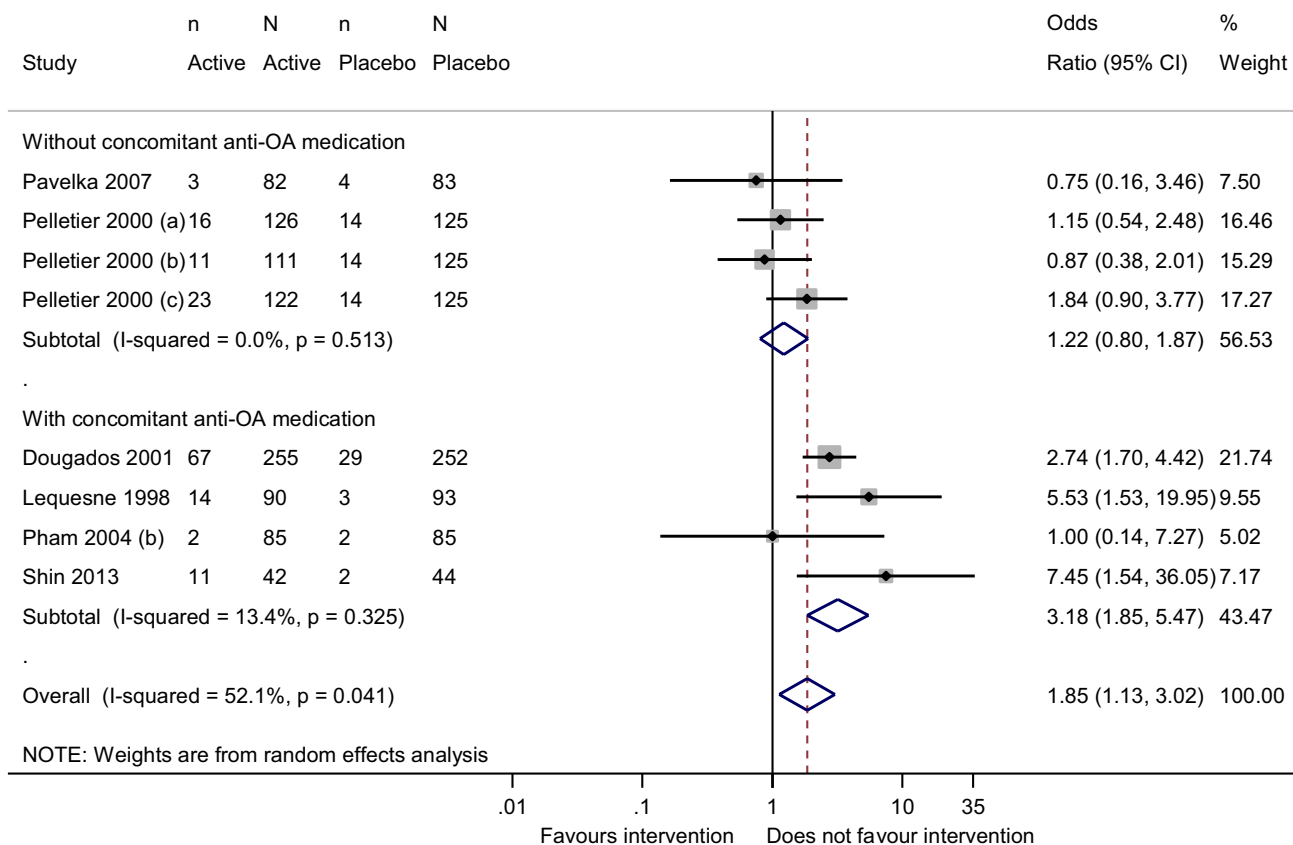
Favours intervention　　Does not favour intervention

Fig. 10 Forest plot displaying the results of the meta-analyses comparing renal and urinary disorders with diacerein versus placebo in patients with osteoarthritis: overall analysis and analyses of studies with and without concomitant anti-osteoarthritis medication allowed. *CI* confidence interval, *OA* osteoarthritis

AE data suitable for inclusion in the meta-analysis and the authors/sponsors did not provide us with the full safety data.

The current meta-analysis contains a unit-of-analysis error issue. However, the analyses on GS were not affected by this issue, and its impact on the results for the other compounds was very marginal. In fact, a unit-of-analysis problem arises in studies with multiple arms when the same group of participants is included twice in the same meta-analysis (e.g., if "dose 1 vs. placebo" and "dose 2 vs. placebo" are both included in the same meta-analysis, with the same original number of patients receiving placebo in both comparisons) [23]. The Cochrane handbook proposes various approaches to include multiple groups from a single study in the same meta-analysis. For the current meta-analysis, one of these proposed methods was suitable, consisting of splitting the "shared" group into two or more smaller

samples and including two or more comparisons. However, we decided not to apply this method, as we found that it only marginally and not significantly altered our results and did not modify our conclusions. Additionally, we wanted to obtain each comparison (active vs. placebo) with its real effect estimate and 95% CI as if we chose to select only one pair of interventions.

5 Conclusions

The SYSADOAs GS and CS can be considered safe treatments for patients with OA. The harmlessness of ASU must be confirmed in future studies without concomitant anti-OA medication, but current evidence seems to support its safety. Our findings regarding ASU are based on the proprietary

Diacerein: Any adverse event

Study	n Active	N Active	n Placebo	N Placebo	Odds Ratio (95% CI)	% Weight
Without concomitant anti-OA medication						
Pavelka 2007	36	82	24	83	1.92 (1.01, 3.67)	13.20
Pelletier 2000 (a)	82	126	74	125	1.28 (0.77, 2.14)	15.96
Pelletier 2000 (b)	71	111	74	125	1.22 (0.72, 2.07)	15.62
Pelletier 2000 (c)	100	122	74	125	3.13 (1.75, 5.61)	14.41
Subtotal (I-squared = 57.2%, p = 0.072)					1.72 (1.12, 2.65)	59.18
.						
With concomitant anti-OA medication						
Dougados 2001	242	255	211	252	3.62 (1.89, 6.93)	13.08
Lequesne 1998	71	90	54	93	2.70 (1.41, 5.18)	13.04
Pham 2004 (b)	78	85	69	85	2.58 (1.00, 6.65)	8.59
Shin 2013	38	42	29	44	4.91 (1.47, 16.38)	6.11
Subtotal (I-squared = 0.0%, p = 0.782)					3.17 (2.15, 4.70)	40.82
.						
Overall (I-squared = 52.8%, p = 0.038)					2.22 (1.58, 3.13)	100.00

NOTE: Weights are from random effects analysis

.01   .1   1   15

Favours intervention   Does not favour intervention

Fig. 11 Forest plot displaying the results of the meta-analyses comparing total adverse events with diacerein versus placebo in patients with osteoarthritis: overall analysis and analyses of studies with and without concomitant anti-osteoarthritis medication allowed. *CI* confidence interval, *OA* osteoarthritis

product Piascledine®, as all the studies included in this systematic review used that preparation. Consequently, our conclusion regarding the safety of ASU may not apply to other preparations. Given the safety issues highlighted in this meta-analysis, the usefulness of diacerein for patients with OA should be considered, taking into account its dosage and patient characteristics. This is in accordance with the EMA recommendations. The safety profile for coadministration of diacerein and oral NSAIDs requires further investigation. Finally, these results, which are based on data from RCTs, must be confirmed with pharmacovigilance data.

Diacerein: Withdrawals due to adverse events

Study	n Active	N Active	n Placebo	N Placebo	Odds Ratio (95% CI)	% Weight
Without concomitant anti-OA medication						
Pavelka 2007	3	82	4	83	0.75 (0.16, 3.46)	7.50
Pelletier 2000 (a)	16	126	14	125	1.15 (0.54, 2.48)	16.46
Pelletier 2000 (b)	11	111	14	125	0.87 (0.38, 2.01)	15.29
Pelletier 2000 (c)	23	122	14	125	1.84 (0.90, 3.77)	17.27
Subtotal (I-squared = 0.0%, p = 0.513)					1.22 (0.80, 1.87)	56.53
.						
With concomitant anti-OA medication						
Dougados 2001	67	255	29	252	2.74 (1.70, 4.42)	21.74
Lequesne 1998	14	90	3	93	5.53 (1.53, 19.95)	9.55
Pham 2004 (b)	2	85	2	85	1.00 (0.14, 7.27)	5.02
Shin 2013	11	42	2	44	7.45 (1.54, 36.05)	7.17
Subtotal (I-squared = 13.4%, p = 0.325)					3.18 (1.85, 5.47)	43.47
.						
Overall (I-squared = 52.1%, p = 0.041)					1.85 (1.13, 3.02)	100.00

NOTE: Weights are from random effects analysis

.01   .1   1   10   35
Favours intervention   Does not favour intervention

Fig. 12 Forest plot displaying the results of the meta-analyses comparing withdrawals due to adverse events with diacerein versus placebo in patients with osteoarthritis: overall analysis and analyses of studies with and without concomitant anti-osteoarthritis medication allowed. *CI* confidence interval, *OA* osteoarthritis

Compliance with Ethical Standards

All authors meet the ICMJE criteria for authorship for this manuscript, take responsibility for the integrity of the work as a whole, and have given final approval to the version to be published.

(A) Glucosamine sulfate

Glucosamine sulfate: Any adverse event

(B) Chondroitin sulfate

Chondroitin sulfate: Any adverse event

Harbord's test: p = 0.54

(C) Diacerein

Diacerein: Any adverse event

(D) Avocado/soybean unsaponifiables

Avocado/soybean unsaponifiables: Any adverse event
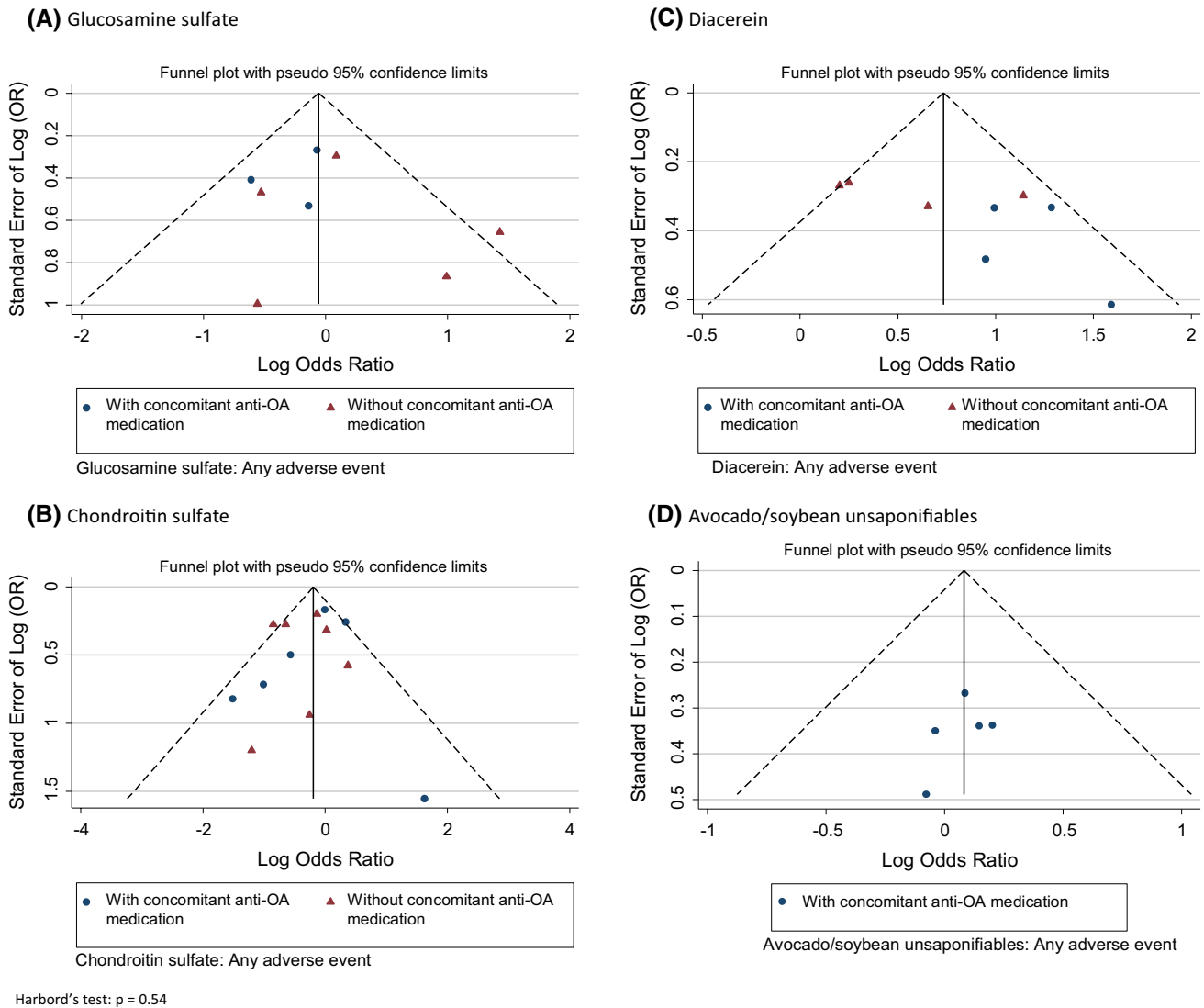
Fig. 13 Assessment of publication bias: funnel plots using data for the meta-analyses comparing total adverse events with **a** glucosamine sulfate, **b** chondroitin sulfate (Harbord's test: $p = 0.54$), **c** diacerein, and **d** avocado/soybean unsaponifiables, each versus placebo, in patients with osteoarthritis. *OA* osteoarthritis, *OR* odds ratio

Table 3 Summary of findings for glucosamine sulfate vs. placebo in patients with osteoarthritis

Outcomes	No. of participants (studies), follow-up	Certainty of the evidence (GRADE)	Overall relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with glucosamine sulfate
Gastrointestinal AEs	1351 (9 RCTs)	⊕⊕⊕⊕ High	OR 1.02 (0.74–1.40)	150 per 1000	3 more per 1000 (34 fewer to 48 more)
Skin and subcutaneous tissue disorders	1351 (9 RCTs)	⊕⊕⊕⊕ High	OR 0.80 (0.43–1.48)	39 per 1000	7 fewer per 1000 (22 fewer to 17 more)
Renal and urinary disorders	1149 (8 RCTs)	⊕⊕⊕⊕ High	Not estimable	0 per 1000	0 fewer per 1000 (0 fewer to 0 fewer)
Severe AEs	1351 (9 RCTs)	⊕⊕⊕◯ Moderate[a]	OR 1.46 (0.26–8.13)	12 per 1000	5 more per 1000 (9 fewer to 77 more)
Serious AEs	1351 (9 RCTs)	⊕⊕⊕◯ Moderate[a]	OR 2.04 (0.37–11.36)	3 per 1000	3 more per 1000 (2 fewer to 30 more)
Withdrawals due to AEs	1351 (9 RCTs)	⊕⊕⊕⊕ High	OR 0.86 (0.51–1.42)	52 per 1000	7 fewer per 1000 (25 fewer to 20 more)

GRADE Working Group grades of evidence: *High certainty* we are very confident that the true effect lies close to that of the estimate of the effect; *Moderate certainty* we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; *Low certainty* our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect: *Very low certainty* we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

AE adverse event, *CI* confidence interval, *OR* odds ratio, *RCT* randomised controlled trial

[a]Wide confidence interval because of low number of events

Table 4 Summary of findings for chondroitin sulfate vs. placebo in patients with osteoarthritis

Outcomes	No. of participants (studies), follow-up	Certainty of the evidence (GRADE)	Overall relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with chondroitin sulfate
Gastrointestinal AEs	2877 (12 RCTs)	⊕⊕⊕⊕ High	OR 0.77 (0.59–1.00)	159 per 1000	32 fewer per 1000 (58 fewer to 0 fewer)
Skin and subcutaneous tissue disorders	2877 (12 RCTs)	⊕⊕⊕⊕ High	OR 1.07 (0.62–1.84)	31 per 1000	2 more per 1000 (11 fewer to 24 more)
Renal and urinary disorders	2877 (12 RCTs)	⊕⊕⊕⊕ High	OR 0.40 (0.22–0.74)	26 per 1000	15 fewer per 1000 (20 fewer to 7 fewer)
Severe AEs	2877 (12 RCTs)	⊕⊕⊕⊕ High	OR 0.82 (0.47–1.45)	86 per 1000	14 fewer per 1000 (44 fewer to 34 more)
Serious AEs	2877 (12 RCTs)	⊕⊕⊕⊕ High	OR 1.13 (0.84–1.52)	75 per 1000	9 more per 1000 (11 fewer to 35 more)
Withdrawals due to AEs	2877 (12 RCTs)	⊕⊕⊕⊕ High	OR 0.72 (0.44–1.16)	56 per 1000	15 fewer per 1000 (31 fewer to 8 more)

GRADE Working Group grades of evidence: *High certainty* we are very confident that the true effect lies close to that of the estimate of the effect; *Moderate certainty* we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; *Low certainty* our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect: *Very low certainty* we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

AE adverse event, *CI* confidence interval, *OR* odds ratio, *RCT* randomised controlled trial

Table 5 Summary of findings for diacerein vs. placebo in patients with osteoarthritis

Outcomes	No. of participants (studies), follow-up	Certainty of the evidence (GRADE)	Overall relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with diacerein
Gastrointestinal AEs	1595 (6 RCTs)	⊕⊕⊕⊕ High	OR 2.85 (2.02–4.04)	314 per 1000	252 more per 1000 (166 more to 335 more)
Skin and subcutaneous tissue disorders	1595 (6 RCTs)	⊕⊕⊕⊕ High	OR 2.18 (1.40–3.42)	34 per 1000	37 more per 1000 (13 more to 73 more)
Renal and urinary disorders	1595 (6 RCTs)	⊕⊕⊕⊕ High	OR 3.42 (2.36–4.96)	70 per 1000	135 more per 1000 (81 more to 203 more)
Severe AEs	1088 (5 RCTs)	⊕⊕⊕⊕ High	OR 1.39 (0.78–2.48)	40 per 1000	15 more per 1000 (8 fewer to 53 more)
Serious AEs	1595 (6 RCTs)	⊕⊕⊕⊕ High	OR 0.95 (0.68–1.33)	128 per 1000	6 fewer per 1000 (37 fewer to 35 more)
Withdrawals due to AEs	1595 (6 RCTs)	⊕⊕⊕⊕ High	OR 1.85 (1.13–3.02)	79 per 1000	58 more per 1000 (9 more to 127 more)

GRADE Working Group grades of evidence: *High certainty* we are very confident that the true effect lies close to that of the estimate of the effect; *Moderate certainty* we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; *Low certainty* our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; *Very low certainty* we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

AE adverse event, *CI* confidence interval, *OR* odds ratio, *RCT* randomised controlled trial

Table 6 Summary of findings for avocado/soybean unsaponifiables vs. placebo in patients with osteoarthritis

Outcomes	No. of participants (studies), follow-up	Certainty of evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with ASU
Gastrointestinal AEs	986 (4 RCTs)	⊕⊕⊕⊕ High	OR 0.91 (0.65–1.27)	174 per 1000	13 fewer per 1000 (54 fewer to 37 more)
Skin and subcutaneous tissue disorders	986 (4 RCTs)	⊕⊕⊕⊕ High	OR 0.91 (0.26–3.14)	41 per 1000	4 fewer per 1000 (30 fewer to 78 more)
Renal and urinary disorders	986 (4 RCTs)	⊕⊕⊕⊕ High	OR 1.12 (0.43–2.87)	20 per 1000	2 more per 1000 (11 fewer to 35 more)
Severe AEs	986 (4 RCTs)	⊕⊕⊕⊕ High	OR 0.89 (0.61–1.30)	157 per 1000	15 fewer per 1000 (55 fewer to 38 more)
Serious AEs	986 (4 RCTs)	⊕⊕⊕⊕ High	OR 1.31 (0.85–2.00)	120 per 1000	31 more per 1000 (16 fewer to 94 more)
Withdrawals due to AEs	986 (4 RCTs)	⊕⊕⊕⊕ High	OR 0.97 (0.55–1.70)	48 per 1000	1 fewer per 1000 (21 fewer to 31 more)

GRADE Working Group grades of evidence: *High certainty* we are very confident that the true effect lies close to that of the estimate of the effect; *Moderate certainty* we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; *Low certainty* our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect; *Very low certainty* we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect

The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI)

AE adverse event, *CI* confidence interval, *OR* odds ratio, *RCT* randomised controlled trial

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