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Review

Does the hip powder of *Rosa canina* (rosehip) reduce pain in osteoarthritis patients? – a meta-analysis of randomized controlled trials

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Summary

Objective: Meta-analysis of randomized controlled trials (RCTs) – of a hip powder of *Rosa canina* (rosehip) preparation for symptomatic treatment of osteoarthritis (OA), in order to estimate the empirical efficacy as a pain reducing compound.

Method: RCTs from systematic searches were included if they explicitly stated that OA patients were randomized to either rosehip or placebo. The primary outcome was reduction in pain calculated as effect size (ES), defined as the standardized mean difference (SMD). As secondary analysis the number of responders to therapy was analyzed as Odds Ratios (OR), and expressed as the Number Needed to Treat (NNT). Restricted Maximum Likelihood (REML) methods were applied for the meta-analyses using mixed effects models.

Results: The three studies (287 patients and a median trial-duration of 3 months) – all supported by the manufacturer (Hyben-Vital International) – showed a reduction in pain scores by rosehip powder (145 patients) compared to placebo (142 patients): ES of 0.37 [95% confidence interval (CI): 0.13–0.60], $P = 0.002$. Test for homogeneity seemed to support that the efficacy was consistent across trials ($I^2 = 0\%$). Thus it seems reasonable to assume that the three studies were measuring the same overall effect. It seemed twice as likely that a patient allocated to rosehip powder would respond to therapy, compared to placebo (OR = 2.19; $P = 0.0009$); corresponding to a NNT of six (95% CI: 4–13) patients.

Conclusions: Although based on a sparse amount of data, the results of the present meta-analysis indicate that rosehip powder does reduce pain; accordingly it may be of interest as a nutraceutical, although its efficacy and safety need evaluation and independent replication in a future large-scale/long-term trial.

Key words: *Rosa canina*, Rosehip, Meta-analysis, Osteoarthritis, Dietary supplements, Knee, Hip, Herbal therapy.

Introduction

Osteoarthritis (OA) is a common joint disorder and may occur in any synovial joint in the body, although the condition is most common in hands, knees, hips and spine[1]. The clinical problems, along with the pathological and radiographic changes, include joint pain, stiffness, movement with a restricted range and cracking of joints (crepitus)[2]. OA has traditionally been regarded as a non-inflammatory condition[3], but improved detection methods show that inflammatory pathways are up-regulated in OA[4]; with, e.g., a low-level increase by groups in C-reactive protein (CRP)[5]. Drug therapy in OA consists mainly of analgesics and non-steroidal anti-inflammatory drugs (NSAIDs). Paracetamol is the oral analgesic of first choice, and if successful, the preferred long-term oral analgesic. However, NSAIDs must be considered in patients with no response to paracetamol[6,7]. Disease-modifying OA drug (DMOAD)-therapy remains to be developed in order to slow down disease progression as demonstrated by, e.g., a reduced joint space narrowing on plain X-rays[8].

According to the consensus statement following the outcome measures in rheumatology (OMERACT) III conference, a core set of outcome measures for phase III clinical trials pointed towards four variables which should be evaluated in trials with patients suffering from either knee, hip, or hand OA: pain, physical function (i.e., disability), patient global assessment; and – for studies of 1 year or longer – joint imaging[9]. It is mandatory to perform continuous follow-up on clinical interventions, which are assessed on scales typically referred to as subjective[10,11].

A standardized hip powder of *Rosa canina* made from the seeds and husks of the fruits from a subtype of *R. canina* hip powder (i.e., rosehip), the common wild-briar hedgerow rose, has been evaluated in (short-term) randomized controlled trials (RCTs)[12]. According to the best-evidence synthesis, there are contradictory results with regard to scientific evidence for *R. canina* extracts[13]. Evidence from early *in vitro* studies indicates that *R. canina* hip powder

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preparations exert anti-inflammatory properties *via* reduced chemotaxis of peripheral blood neutrophils and monocytes in healthy subjects, and a reduction in CRP is seen after 4 weeks supplementation in patients with OA[14,15]. The proposed mechanism of action has been focused on the preparations' anti-oxidative capacities, and a specific galactolipid (called GOPO) has been identified (*in vitro*) as anti-inflammatory, and as such possibly the reason for the preparation's proposed pain reducing property[16]. These considerations over active ingredients have recently been confirmed by others, as extracts of *R. canina* fruits have shown potent anti-inflammatory and anti-nociceptive activities[17] and *R. canina* hip powder extracts (an organic solvent) may inhibit both cyclooxygenase (COX)-1 and -2[18]. In a clinical trial it has been shown that *R. canina* hip powder may have some efficacy in hip and knee OA patients[19].

In the present systematic review on clinical efficacy of giving a *R. canina* hip powder preparation for symptomatic treatment of OA, with explicit meta-analysis of the available RCTs[20] – our primary aim was to obtain up-to-date, evidence-based estimates that could provide a detailed view of the symptomatic efficacy of *R. canina* compounds used in the treatment of OA. The results of this analysis may be crucial for the evaluation whether or not these preparations will be relevant for future large-scale (i.e., phase III) clinical trials.

Materials and methods

Study selection, assessment of eligibility criteria, data extraction, and statistical analysis were performed based on a predefined protocol according to the Cochrane Collaboration guidelines (http://www.cochrane.org/resources/handbook/index.htm).

RETRIEVAL OF PUBLISHED STUDIES

RCTs of *R. canina* hip powder treatment vs placebo were identified through a systematic literature search in the following bibliographic databases: Medline *via* PubMed (mid 1950s to October 2007), EMBASE *via* WebSpirs (1980 to October 2007), CINAHL *via* WebSpirs (1982 to October 2007), Biosis Previews *via* WebSpirs (1980 to October 2007), Web of Science (1945–54 to October 2007), Scifinder (1907 to October 2007), Scopus (1966 to October 2007), and the Cochrane Library from 1966 to October 2007. Following the searches, reference lists of original reports and review articles retrieved through the described searches, were thoroughly checked for further relevant studies. Finally, we searched conference abstracts over the past 2 years *via* the established international societies of rheumatology, i.e., the OsteoArthritis Research Society International (OARSI), EUropean League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR). Since the available studies were expected to be few, a broad, less specific search strategy was applied: (Rosehip OR "Rose hip" OR "*Rosa canina*" OR "dog rose" OR Rosaceae OR Litozin OR hyben OR GOPO OR i-flex) AND (OA OR osteoarthrosis). Controlled, randomized and clinical trials were deliberately not part of an explicit search strategy, since we wished to find any work dealing with *R. canina* hip powder in the treatment of OA. With the awareness of a higher proportion of noise in the chosen searches, full references were reviewed for possible RCTs, and full text references were obtained for further scrutiny, where relevant.

INCLUSION AND EXCLUSION CRITERIA

We included RCTs comparing a preparation containing *R. canina* hip powder with a placebo intervention. Studies were selected if the included patients were (explicitly) described as having clinical or radiographic evidence of OA. Two reviewers (RDA, HB) crosschecked and agreed on diagnostic criteria in each trial. We excluded studies in conditions such as non-OA joint pain, rheumatoid arthritis (RA), pain due to surgery or injury, and studies with mixed patient groups such as those with both OA and RA, unless the subgroup data for OA were available. No language restrictions applied.

QUALITY ASSESSMENT

The quality of studies was assessed based on randomization, masking and withdrawal. The complete reports of the RCTs that were selected for inclusion in the meta-analysis were scored by two reviewers for quality (RC, EMB) using a validated instrument[21]. The score was given as follows: if the study was described as randomized (+1); if the study was described as double masked (+1); if there was a (detailed) description of withdrawals and attrition rates/detailed outcome data and the analysis was performed according to the intention-to-treat (ITT) principle (+1). In addition, if the random allocation and the double blinding were properly described and appropriately put into practice, each item received 1 point extra. Conversely, if the methods (randomization and masking) were not considered appropriate, 1 point was subtracted from each item.

DATA EXTRACTION AND OUTCOME MEASURES

Two reviewers (RC, EMB) undertook data extraction independently. Disagreements were resolved by discussion. A customized form was used to record the following: authors of the study, year of publication, trial design, study length, number of patients randomized (i.e., the ITT population, N_{total}), the number of patients for whom detailed outcome data was available for meta-analysis in each group (E/exposed = *R. canina* hip powder and C/control = placebo) included in the individual-study statistical tests (N_E and N_C, respectively), average patient age, sex, site of OA. Note that in order to estimate the relative number of responders to therapy, we included the ITT population (based on the N_{E-ITT} and N_{C-ITT}, respectively) in the denominator. The number of responders *per se*, was assessed as the number of patients in each trial defined by the authors as being a responder; the number of responders in both the *R. canina* hip powder and placebo group were based on the same criterion[11].

As it seemed relevant to consider the available efficacy in cross-over trials as being subjected to carry-over bias[19], we only report (i.e., include) data from the first period. The primary outcome measure was the magnitude of pain reduction[22]. The secondary outcomes were the reported changes in the average level of applied painkillers; the extracted (or estimated) reported number of responders per group following intervention[11]. Disability and patient's global assessment following therapy[9] were not included as outcomes in the present meta-analysis, since we expected that these endpoints would not have been reported consistently.

STATISTICAL ANALYSIS

As a preliminary review of the available data[23] supported the notion that the available cross-over trials had been reporting carry-over bias[24], we chose to include only data from the first period, as any pooled efficacy meta-analysis including data from both periods would imply a risk of (accumulating) carry-over bias[25,26]. For each of the continuous outcomes (i.e., pain and rescue medications), we calculated the test statistics based on the available data, using standard formulae[26,27]. Based on these statistics and the number of observations in each group, we were able to estimate the standardized mean difference (SMD) for each study[28] – which was applied as effect size (ES)[29]. The corresponding variance (SE^2) was calculated based on the individual study SMD and the number of patients included ($SE^2 = 1/N_E + 1/N_C + SMD^2/[2\{N_E + N_C\}]$)[28]. As the unadjusted (Cohen's) SMD in principle does not treat the variance (SE^2) as an estimate, we applied (i.e., *via* multiplication) the Hedges' bias-correction ($J = 1 - 3/[4 \times df - 1]$; i.e., $df = N_E + N_C - 2$) by default – adjusting for small sample bias[30]. SMDs were signed so that positive values (>0) indicated a benefit of *R. canina* hip powder: clinically, $|ES| \geq 0.2$ is considered small, $|ES| \geq 0.5$ is moderate (and would probably be recognized clinically[31]), and $|ES| \geq 0.8$ is large[6,7,32,33]. The Odds Ratio (OR) was estimated for the dichotomous efficacy data (i.e., responders to therapy)[34]. To combine the individual study results we did (generic inverse variance) meta-analyses *via* mixed effects model procedures using SAS software (version 9.1.3, by SAS Institute Inc., Cary, NC, USA)[35]. We applied the restricted maximum likelihood (REML) method[36,37] to estimate the between study variance and the combined efficacy[28,38]. The heterogeneity (between trials) was examined with a standard Q test (testing the hypothesis of homogeneity: $\chi^2_{(k-1)}$)[39]. However, as measures of the extent of heterogeneity might be considered preferable to test of its presence, we evaluated possible inconsistency between effect measures *via* the I^2 statistic[40] – which can be interpreted as the percentage of variability in effect estimates due to heterogeneity[41]. As it is often sensible to use one statistic for meta-analysis and re-express the results using a second more easily interpretable statistic[26], we estimated the Number Needed to Treat (NNT), with 95% confidence intervals (CI) on the basis of the combined OR value[42], since this method enables direct translation into clinical practice[10,43,44]; applying the overall event rate in the placebo group as a *proxy* for baseline risk[45,46]. The software "*Visual Rx*" is designed to calculate NNT (and NNH) from the pooled results of a meta-analysis and produce a graphical display of the result[47]: http://www.nntonline.net/ebm/visualrx/try.asp[48].

Results

CHARACTERISTICS OF TRIALS

The Quality of Reporting of Meta-analyses (QUOROM)-recommended flowchart[20] in Fig. 1 displays the eligibility details of the studies identified by the combined search strategy. Studies with clearly irrelevant objectives/designs as well as abstracts and reviews/theme articles, were separated from possible studies for inclusion: initially the search strategy revealed 37 potential references, which were considered at abstract level. When removing obviously residual literature and abstracts later reported in full, we retrieved 15 studies for further scrutiny – including critical assessment of the reported references[12–19,49–55].

Among these, five papers were excluded as a consequence of being reviews[12,13,50,54,55]; one study only considered intestinal microflora in patients with irritable bowel syndrome[49]; three studies were categorized as *in vitro*[16–18]. Among the remaining six potentially relevant studies[14,15,19,51–53] two were excluded as a consequence of being controlled trials, reported as case-control trials with explicit focus on *in vitro*-inflammatory properties[14], and inhibition of chemotaxis and chemiluminescence[15], respectively. This left four trials[19,51–53] potentially relevant for inclusion in the meta-analysis[23]. However, following personal contact with Dr Winther and Dr Rein, it appeared that the patent registration from Rein *et al.*[51] was based on an unpublished subgroup-analysis of the Norwegian study[52] and was, quote: "*a rehash of a another study*". Accordingly, we were able to include three (assumed) mutually independent RCTs[19,52,53].

Table I shows the baseline characteristics of the included studies. All trials were supported by Hyben-Vital International (Tullebølle, Langeland, Denmark): one study was performed in an outpatient clinic in Norway[52], while the two others included patients (from outpatient clinics) in Denmark[19,53]. Overall, the trials randomized 306 OA patients to either *R. canina* hip powder or placebo, allocating 153 patients to each group. The Danish trials[19,53] applied a cross-over design, and excluded patients with other rheumatic diseases than OA, and those who received glucosamine or intra-articular glucocorticoids 6 weeks prior to the study. The Norwegian study[52] included OA patients with pain for at least 6 months, who were on a waiting list for either hip or knee surgery, or on a list for final evaluation for surgery. As presented in Table I the majority of the participating patients were women (62%) suffering from knee OA (61%) with a median age of 66 years.

PAIN REDUCTION

As presented in Fig. 2(A): the meta-analysis of the three studies reporting changes in pain scores produced a statistically significant ($P = 0.0019$) combined ES of 0.37 (95% CI: 0.13–0.60) – favoring *R. canina* hip powder compared to placebo. Test for homogeneity seemed to support that the efficacy was consistent across trials ($Q = 0.18$; $I^2 = 0\%$). Thus, it seems reasonable to assume that the three (mutually independent) studies measured the same overall effect. Apparently the pain reducing property of *R. canina* hip powder seemed more pronounced in the population examined in the study by Warholm *et al.*[52], which included patients who were on a waiting list for either hip or knee surgery, or on a list for final evaluation for surgery.

USE OF RESCUE MEDICATION

As presented in Fig. 2(B): the meta-analysis of the three studies reporting changes in the use of 'rescue medication' produced a statistically significant ($P = 0.018$) combined ES of 0.28 (95% CI: 0.05–0.51) – favoring *R. canina* hip powder compared to placebo. Test for homogeneity seemed to support that the efficacy was consistent across trials ($Q = 1.25$; $I^2 = 0\%$). Thus it seems reasonable to assume that the three (mutually independent) studies measured the same overall effect. Apparently *R. canina* hip powder did not reduce the patients' consumption of painkillers in the population reported by Warholm *et al.* (i.e., ES < 0.2)[52], while based on the diaries of the consumption of 'rescue medication' investigated

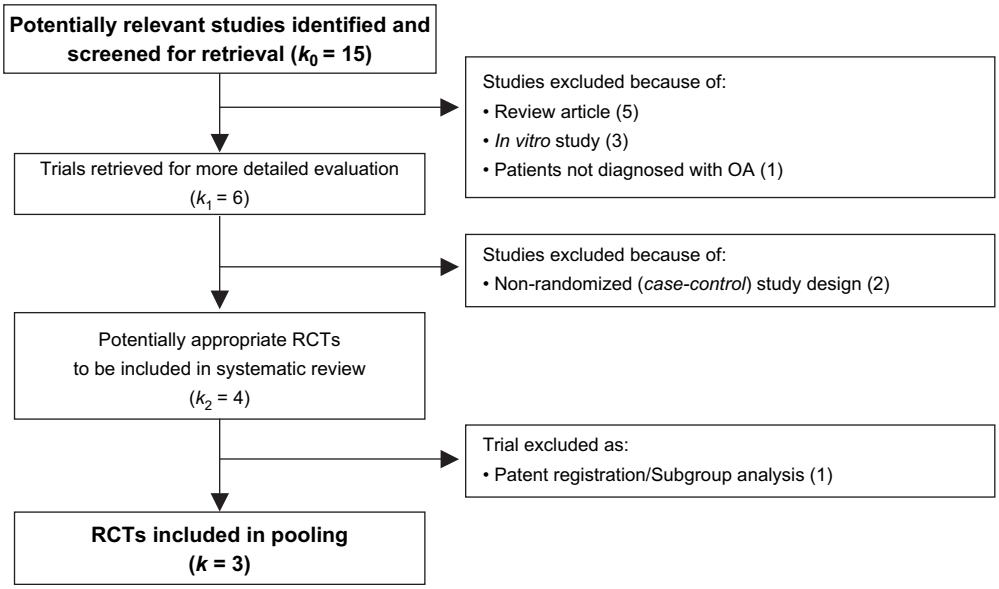

Fig. 1. Flow chart of the search strategy and selection of trials.

Table I
Summary of baseline characteristics of all participants in the eligible trials

Study	Year	QS	Intervention	Design	Duration (months)	ITT	Women (%)	Joint affected	Age (years)	BMI (kg/m^2)	Definite sample size	
											N_E	N_C
Warholm	2003	4	Hyben-Vital®, $2 \times 5 \times 0.5$ g/day = 5 g/day	PG	4	100	65 (65.0%)	K: 56, H: 44 (56% KOA)	65.2 ± 11.1	n.a.	48	48
Rein	2004	4	Hyben-Vital®, $2 \times 5 \times 0.5$ g/day = 5 g/day	CO	3	112	71 (63.4%)	K: 59, H: 46, N: 18, S: 14, Ha: 40 (53% KOA)	67.0 ± 11.7	27.3 ± 5.0	50	47
Winther	2005	5	LitoZin®, $2 \times 5 \times 0.5$ g/day = 5 g/day	CO	3	94	54 (57.4%)	K: 58, H: 21, K&H: 15 (78% KOA)	65.6 ± n.a. [range: 38–92]	27.0 ± n.a. [range: 19–41]	47	47
Overall		Median: 4, Mean: 4.3, SD: 0.5	5 g Rosehip powder/day	32.7% PG	Median: 3, Mean: 3.3, SD: 0.5	306	190 (62.1%)	K: 188 (61.4% KOA)	Median: 65.6	n.a.	145	142

Data are number (%) or mean ± SD. QS: Jadad Quality Score (range: 0–5); PG and CO indicate Parallel-Group and Cross-Over Trial design, respectively. BMI: body-mass index; K: knee OA; H: hip OA; N: neck OA; S: shoulder OA; Ha: hand OA. N_E and N_C are the number of patients included in the analyses in the exposed and control groups (i.e., rosehip and placebo), respectively. n.a.: Data not available.

in the study by Winther *et al.*[19] – the use of *R. canina* hip powder resulted in a significantly reduced use of analgesics, compared to placebo.

NUMBER OF RESPONDERS TO THERAPY

In order to assess this secondary outcome, the arbitrary "responders to therapy", the following data was extracted: (1) Warholm *et al.* used a simple yes-or-no questionnaire (about relief of pain) after 4 months therapy in both groups[52] (*R. canina* hip powder: 31/50 vs placebo: 21/50); (2) Rein *et al.* defined a responder as one who showed at least one category of pain improvement[53] (*R. canina* hip powder: 31/56 vs placebo: 18/56); (3) Winther *et al.* used *any* reduction in western ontario and mcmaster (WOMAC) score for joint pain after the initial 3 weeks of treatment as a response criterion – however, they did not report any explicit numbers following 3 months treatment[19]. We assessed the number of responders (*any* reduction in WOMAC pain) in each group following a Monte-Carlo simulation based on the reported means and standard deviations (SDs) (i.e., table 3[19]) assuming that a univariate normal distribution apply[56] (*R. canina* hip powder: 32/47 vs placebo: 26/47). As presented in Fig. 2(C): the meta-analysis of the studies reporting the number of patients responding to therapy as a dichotomized (yes/no) count, produced a statistically highly significant ($P = 0.00089$) combined OR of 2.19 (95% CI: 1.38–3.48) – favoring *R. canina* hip powder compared to placebo; i.e., it is more than twice as likely that a patient allocated to *R. canina* hip powder will respond to therapy, compared to placebo. Test for homogeneity seemed to support that the observed efficacy was consistent across trials ($Q = 0.52$; $I^2 = 0\%$), supporting the assumption that the three (mutually independent) studies were measuring the same overall effect. In absolute terms: the total number of responders (across the three trials) on *R. canina* hip powder and placebo was 94/153 (61.4%) and 65/153 (42.5%), respectively. On the basis of the average number of responders within the placebo groups, the combined OR corresponded to a NNT of six (95% CI: 4–13) patients.

ADVERSE EVENTS AND SAFETY CONSIDERATIONS

Focusing on adverse events, there seemed to be the same amount of mild cases of gastrointestinal discomfort after intervention vs control[52]. The same number of patients seemed to experience '*acid regurgitation*' in both the study by Rein *et al.*[53] and Winther *et al.*[19]: one case in each group (*R. canina* hip powder and placebo) – both leading to discontinuation. In the study by Winther *et al.*[19], mild unwanted effects (reported as being non-significant) that *did not* cause withdrawal, were explicitly reported; based on these data we re-calculated empirical OR-values with 95% ("exact"[57]) confidence limits for these rare incident cases[58]: (1) '*Frequent voiding*' [OR = 3.07 (0.24–162.65)]; (2) '*Diarrhea*' [OR = 1.00 (0.07–14.07)]; (3) '*Constipation*' [OR = 2.02 (0.10–120.54)]; (4) '*Short episode of mild urticaria*' [OR = 2.02 (0.10–120.51)].

Discussion

The main result of our analysis was a small to moderate short-term efficacy of preparations with *R. canina* hip powder with a small but clinically relevant reduction of pain in

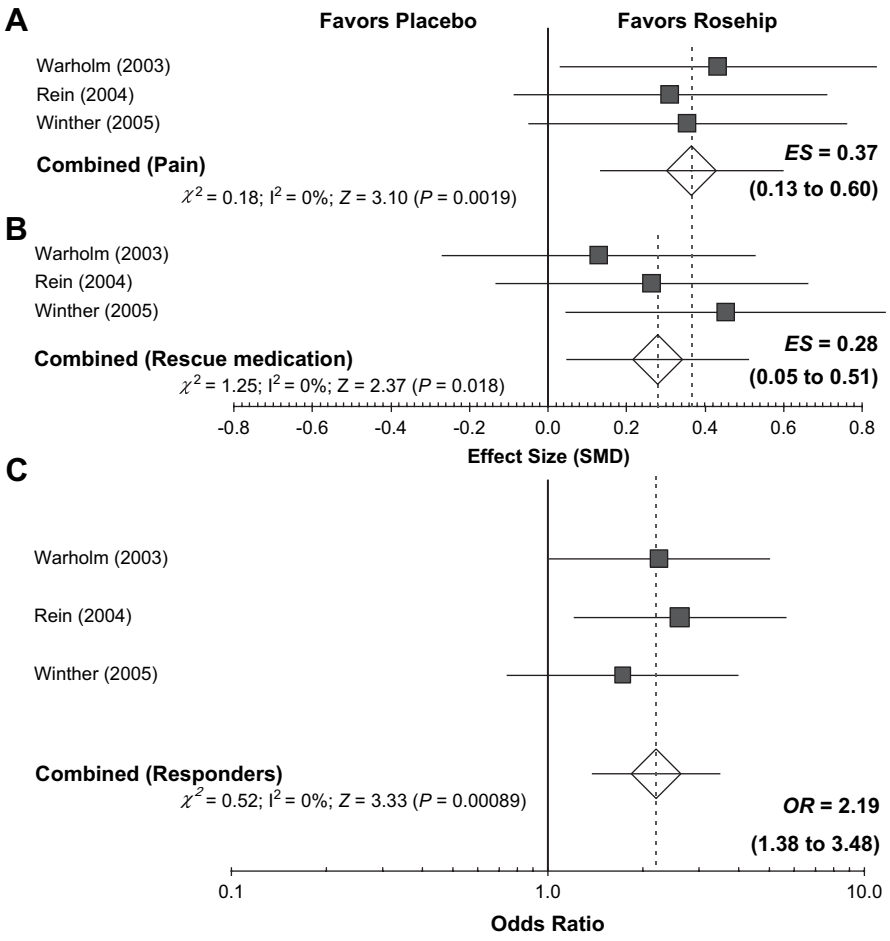

Fig. 2. Efficacy of *R. canina* hip powder (i.e., Rosehip) compared to placebo in OA patients presented as SMDs and OR. (A) Change (i.e., reduction) in self-reported pain; (B) change (i.e., reduction) in self-reported use of analgesics; (C) the number of patients defined/estimated as being a responder. Every square represents the individual study's effect measure with 95% CI indicated by horizontal lines. Square sizes are proportional to the precision of the estimate. The overall estimate from the meta-analysis and its CI are shown at the bottom of each subplot (A–C), represented as a diamond. The center of the diamond represents the pooled point estimate, and its horizontal lines represent the CI.

OA patients. However, the available data are sparse, since we had only three clinical trials evaluating the efficacy in 145 patients after use of *R. canina* hip powder for 3–4 months. One assumption that is prudent in order to make statistical inference following meta-analysis, is that the eligible studies included can be assumed to be mutually independent, which might be an issue within the context of clinical efficacy of *R. canina* hip powder. Dr Rein had access to the original data from Warholm *et al.*[52] – enabling a patent registration[51] prior to the publication by Rein *et al.*[53]; recalling that Dr Winther was the co-author on this paper[53] before the Winther *et al.* paper was published in 2005[19]. However, meta-analyses are depending on the international peer-review system, which has been applied in all of the included papers[19,52,53]. A combined analysis (i.e., meta-analysis) of homogeneous results, quantifies the magnitude of clinical efficacy *per se*[59]. Thus, it seems possible that the empirical magnitude of clinical efficacy following use of *R. canina* hip powder is comparable to other nutraceuticals available[60]. Our meta-analysis supports the conclusion previously stated by Chrubasik: "*Moderate evidence exists for the use of a powder of the seeds and husks of a Rosa canina subspecies in patients suffering from osteoarthritis*"[12].

We are confident that the efficacy estimate is robust *per se*, as it is based on very consistent findings ($I^2 = 0\%$) – thus, a new trial (of the same duration) would be expected to result in a similar magnitude of small to moderate clinical efficacy (ES $\approx$ 0.4). In an (assumed) average knee OA population[61,62], this ES would correspond to a mean reduction in the visual analog scale (VAS) for pain (0–100 mm) of 6 mm; i.e., approximately 10% pain reduction. Apparently the use of *R. canina* hip powder leads to a significant reduction in the use of rescue medication, corresponding to a small clinical efficacy. This does not allow more detailed interpretation, although it seems likely that a reduction in analgesics could have an impact on a major public health scale[63]. When focusing on the explicit, although arbitrary outcome 'responders to therapy', it seems that an OR of 2.19 corresponding to an ES of 0.43[64] – indicates a small to moderate clinical efficacy[6,7,33]. When translated into the number of patients who would need *R. canina* hip powder therapy (compared to placebo) in order to "treat" one patient, the combined estimated NNT was six patients. The magnitude of *R. canina* hip powder as a pain reducing agent is more pronounced than the primary analgesic of choice in clinical practice, paracetamol/acetaminophen, which compared to placebo has an ES of 0.13 (95% CI:

0.04−0.22), and thus of questionable clinical significance[65]. Hence *R. canina* hip powder might have an impact as an over-the-counter (OTC) preparation in the future. The patients studied in the present meta-analysis (see Table I)[19,52,53] represent a fairly homogenous OA population with a clinically relevant age distribution. The exact degree of OA (i.e., radiographic data) was not given in the studies, in one study[52], however, patients were presumably end-stage, which might be the reason for a continuous use of pain medication in this study, in spite of a significant effect of *R. canina* hip powder on self-reported pain.

An increasing interest has been noted over the last years for dietary supplements for OA[54] with a special emphasis on glucosamine and chondroitine[66,67]. Glucosamine only shows significant efficacy in Rottapharm-supported pivotal trials, of which three well conducted trials had a pooled efficacy of ES = 0.27 (95% CI: 0.12−0.43)[68]. Never the less the efficacy of glucosamine has been heavily debated, among many things because of the great heterogeneity between efficacy outcomes[69−71].

In the present analysis of *R. canina* hip powder, the lack of heterogeneity between studies gives credit to an efficacy. The drawback of this observation is − as with the Rottapharm product − that the same company sponsored all three studies on *R. canina* hip powder. Ideally, other similar products from other manufacturers should be tested to substantiate the outcome or even better, the presumed active ingredient (e.g., GOPO) should be isolated, patented, and tested in a strictly controlled clinical trial, following guidelines for Good Clinical Practice (GCP) and consolidated standards of reporting trials (CONSORT)[72]. Such initiatives would increase the external validity of any proposed herbal therapy[73]. Patients with chronic painful diseases seek complementary-alternative therapy for various reasons. Ramsey *et al.* has previously reported from a US cohort, that alternative medicine use is highly prevalent among those with OA (47%) and that levels of expenditure for those who do consume these services ($1,127 per year) approximate expenditures on more traditional medical care ($1,148 per year)[74]. The traditional medical approach has only been able to offer slight improvements with regard to pain[65,75] with a definite problem of a rather frightening list of adverse events[75,76]. In contrast, alternative medications are repeatedly found (i.e., report) to have almost no adverse effects; this has been shown for both glucosamine[77], chondroitin[78], avocado/soybean unsaponifiables (ASU)[79] among many − as well as *R. canina* hip powder.

We turn to the question: whether treatment of OA *via* prescription of anti-oxidants is dream or reality?[80] In a short-term cross-over trial 1 g of calcium ascorbate for either knee or hip OA was given for 14 days, resulting in a small to moderate (statistically significant) pain reduction compared to placebo[81], which is equivalent to our results for *R. canina* hip powder. It is, however, noteworthy that data have been presented that the anti-inflammatory properties of *R. canina* hip powder is unrelated to its vitamin C content[14,15]. In regard to anti-oxidants, however, a recent large-scale meta-analysis found that treatment with β-carotene, vitamin A, and vitamin E may increase mortality, while a potential role for vitamin C remains to be clarified[82]. By consequence, large-scale trials on anti-oxidants are still relevant, and no final conclusion may be drawn regarding safety.

Alternative therapy should be subjected to a similar scrutiny of effect vs adverse effects as ordinary medications[42,83]. The alternative OTC market is huge[74] whether it is efficacious or not[54], and with an inevitable influence on both direct and indirect costs[84]. With regard to *R. canina* hip powder a large-scale trial is justified by the magnitude of clinical efficacy demonstrated in this meta-analysis of short-term trials − an efficacy in the area of 0.4 SMD-points. In a parallel group design this would correspond to 133 OA patients in each group in order to assess a statistically significant effect ($P < 0.05$, two-tailed) with a proper statistical power (90%)[85]. In order to monitor the clinical efficacy applying these *R. canina* hip powder products, the next RCT should be of at least half a year duration, although a 1-year trial with sufficient imaging would be even better[9]. We emphasize the need for future studies applying empirically validated outcomes (e.g., WOMAC[86], knee and osteoarthritis outcome core (KOOS)[87] or the Lequesne index[88])[11], and that these studies explicitly report the number of so-called responders according to the OMERACT−OARSI response criterion[11,89]. Also, a study should strictly adhere to the CONSORT statement[72,73,90], and be subjected to central registration (e.g., http://www.clinicaltrials.gov).

In conclusion, the dry powder of *R. canina* L. fruit (i.e., *R. canina* hip powder) seems to have a consistent, small to moderate efficacy on pain in OA patients; however, an efficacy only observed in short-term clinical trials (3−4 months). The adverse events were similar to placebo in the available literature, and it seems safe to apply this herbal remedy, though long-term safety remains to be tested. The results of the present meta-analysis − that *R. canina* hip powder *does* reduce pain − should be further substantiated in a large-scale (i.e., phase III) trial.

Conflicts of interest

RC is statistical editor in the *Cochrane Musculoskeletal Group* (CMSG, Australian editorial base); the present meta-analysis is not a Cochrane review. The funding agencies (The Danish Rheumatism Association and 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 is affiliated with or funded by any manufacturer of a *R. canina* hip powder agent.

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