Research Article

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Comparing different preparations and doses of rosehip powder in patients with osteoarthritis of the knee: an exploratory randomized active-controlled trial

Aim: We compared original rosehip powder consisting of whole rosehips including seeds, with two different doses of a novel enhanced rosehip powder of rosehips without their seeds, for patients with knee osteoarthritis (OA). **Methods:** A total of 150 patients with symptomatic knee OA were randomly assigned to original powder (six capsules/day), enhanced powder (six capsules/day) or enhanced powder (three capsules/day). The primary outcome was change from baseline in the Knee Injury and Osteoarthritis Outcome Score (KOOS) item, 'pain during walking on flat surface', assessed after 12 weeks. Statistical analyses were based on the intention-to-treat population. **Results:** During the trial period the change in the primary outcome was comparable across groups. Changes in the KOOS symptoms supported a potential superiority of enhanced powder versus original powder, with a difference of 5.97 KOOS points (95% CI: 0.92–11.02; p = 0.02). **Conclusion:** Enhanced rosehip powder is at least as good, even taken as three capsules/day, as the original rosehip product for patients with symptomatic OA.

Keywords: dietary supplements • knee • osteoarthritis • pain • randomized controlled trial • rosehips

Robin Christensen*[,1,2], Simon Tarp[1], Roy D Altman[3], Marius Henriksen[1], Else M Bartels[1], Louise Klokker[1], Mikael Boesen[1,4], Daniel E Furst[5], Christian C Holm[1], Bente Danneskiold-Samsøe[1] & Henning Bliddal[1]

[1]The Parker Institute, Department of Rheumatology, Copenhagen University Hospitals, Bispebjerg & Frederiksberg, Copenhagen, Denmark

[2]Institute of Sports Science & Clinical Biomechanics, University of Southern Denmark, Odense M, Denmark

[3]The David Geffen School of Medicine, University of California, Los Angeles, CA 90024, USA

[4]Department of Radiology, Copenhagen University Hospitals, Bispebjerg & Frederiksberg, Copenhagen, Denmark

[5]Department of Rheumatology, University of California at Los Angeles, Los Angeles, CA, USA

*Author for correspondence: robin.christensen@frh.regionh.dk

Osteoarthritis (OA) is a common joint disorder and may occur in any synovial joint in the body, although the condition is most frequent in the hands, knees, hips and spine [1]. For the knee OA patient, pain is the most important problem; treatment must first address pain relief if function is to be maintained at habitual levels [2]. To manage OA symptoms, patients and healthcare providers often resort to multiple approaches, including lifestyle modifications, medication, exercise or surgery [2–5]. Complementary or alternative therapies (i.e., nutraceuticals – functional ingredients sold over the counter as powders, tablets and other medicinal formulations not generally associated with food [6]) for OA are commonly used: healthcare providers need to be aware of the evidence supporting their claims [7].

One proposed nutraceutical that has shown promising results in OA patients is rosehip powder made from *Rosa canina* L. [8]. Rosehips, particularly those of dog rose, have traditionally been used to prevent and treat infections and inflammatory diseases [9]. A rosehip powder of *R. canina* L. made from the seeds and husks from dog rose was previously assessed for pain relief of OA in randomized controlled trials [8]. According to *in vitro* studies, *R. canina* preparations exert anti-inflammatory properties via reduced chemotaxis of peripheral blood neutrophils and monocytes in a small number of healthy subjects. Moreover, a reduction in C-reactive protein has been observed in patients with OA following intake of rosehip powder [10,11]. A specific galactolipid, monogalactosyldiacylglycerol 1, identified (*in vitro*) as anti-inflammatory, is also present in rosehips and could possibly explain some of the preparation's supposed pain-reducing property [12].

A previous meta-analysis on specialized rosehip powder from *R. canina* trials for symptomatic treatment of OA showed a

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small but potentially clinically relevant reduction of pain and a statistically significant reduction in use of analgesics [8]. The included studies were all based on a rosehip powder made from the seeds and husks of the fruits from *R. canina* L. The dose shown effective in clinical trials is six capsules/day. Such a large number of capsules presents a challenge with regard to compliance. Increasing the potency of the rosehip powder is therefore desirable in order to improve product compliance [13]. One way to increase potency is to concentrate the active compounds of rosehip. An *in vitro* study comparing the anti-inflammatory and radical scavenging properties of two rosehip preparations with and without seeds, respectively, showed that extracts derived from powdered rosehip without seeds were more effective in all assays, compared with extracts derived from powdered rosehip with seeds. Thus, the active compounds responsible for the anti-inflammatory properties are more abundant in the fleshy peels of rosehip than in the seeds [14].

Our objective was to compare the efficacy and safety of the original rosehip powder consisting of whole rosehips including seeds, with two different doses of a novel enhanced rosehip powder without seeds, for patients with knee OA.

Methods

Design & eligibility criteria

The trial was a physician- and partly patient-blinded, single-center, 12-week exploratory randomized active-controlled trial, on rosehip powder for OA (the REPORT study) [30]. After randomization, a third of the patients were informed to take only three capsules/day, consistent with the numbers of capsules in the prepacked, sequentially numbered drug containers. In contrast to a confirmatory trial, our objective was not to test any specific null hypothesis, rather to explore various aspects of efficacy and safety of a novel rosehip preparation. The study was neither designed as a superiority nor a noninferiority/equivalence study of the new formulations versus the older one with seeds. Thus, this trial cannot provide formal proof of efficacy, although it may contribute to the decision whether to perform a subsequent Phase III-like trial.

Patients were recruited from the outpatients' clinic at the Department of Rheumatology at Frederiksberg Hospital (Copenhagen, Denmark). Eligible patients were at least 40 years of age and had clinical evidence (diagnosed according to the American College of Rheumatology criteria [15]) and radiographic evidence of OA according to Kellgren and Lawrence [16]. Biplane, weight-bearing, semi-flexed, nonfluoroscopic radiographs were taken at a 15° knee flexion, one in the anteroposterior and one in the lateral view. Eligible patients had a self-reported overall pain level corresponding to at least 40 mm on a 100-mm visual analog scale (VAS) when entering the study. Patients were ineligible if they were morbidly obese (having a BMI >40 kg/m^2), had concurrent medical or arthritic conditions that could confound evaluation of the index joint, or had a coexisting disease that could preclude successful completion of the trial. Finally, patients who already used rosehip powder as a dietary supplement, were unable to speak Danish fluently, or had a mental state impeding compliance with the program, were not included.

All participants gave written informed consent for the study, which was approved by the ethics committee of the Capital Region of Denmark (H-1-2011-018) and registered with ClinicalTrials.gov (NCT01430481). The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000.

Interventions

In general, rosehips are harvested when they are mature. The rosehip powder used in the novel enhanced rosehip formulation does not include the seeds, which are removed after harvesting. The fleshy peels are dried and the dried peels are milled to a fine powder in a patent pending milling process before being processed and packaged. The original rosehip powder includes the seeds; the rosehips are frozen directly after harvesting, defrosted before drying, and milled to a fine powder before being packaged into jars or capsules for use as a food supplement. Seeds constitute between 40 and 60% of the weight of the rosehip, the main component of the seeds being oil rich in polyunsaturated fatty acids [17,18]. The new formulation of a rosehip powder without seeds employs a patent pending manufacturing process that refines the network of anti-inflammatory substances present in rosehip fleshy peels: flavonoids, carotenes, triterpene acids and galactolipids. The formulation is standardized with added vitamin C to a content of 80 mg per daily dosage to increase the otherwise low content of naturally occurring vitamin C in rosehips, producing the Rosenoids® (Axellus A/S, Ishøj, Denmark) complex. Rosenoids are patented as consisting of vitamin C, flavonoids, carotens, triterpene acids and galactolipids and the sum of these gives 4% of the formulation. The amount of the individual substances cannot be specified as these will differ in the rosehip (natural variation).

The rosehip powder contains a number of achenes, which are fruits holding a seed. The achenes are surrounded by the receptacle, which becomes the fleshy

part of the ripe rosehip. A rosehip powder consisting of the flesh (receptacle) with the seeds (achenes) removed added with 80 mg vitamin C per daily dosage is referred to as the novel 'enhanced rosehip formulation'. In the study, two different dosages of this product was tested. A rosehip powder consisting of the whole rosehip (flesh and seeds) added with 80 mg vitamin C per daily dosage is referred to as the 'original rosehip powder'. The new seedless powder was made in two variants so that the dosage of vitamin C remained constant (80 mg) and only the dosage of rosehip powder varied (4.5 vs 2.25 g; Supplementary Material; see online at www.futuremedicine.com/doi/suppl/10.2217/ijr.14.13).

Patients received a 12-week intervention with rosehips in the form of identically appearing capsules. Patients were randomly allocated to either:

- Treatment A: original rosehip powder, 4500 mg of whole rosehip powder with seeds plus 80 mg vitamin C once daily in the form of six capsules/day;
- Treatment B: enhanced rosehip powder, 4500 mg of the new seedless rosehip powder plus 80 mg vitamin C once daily (six capsules/day);
- Treatment C: enhanced rosehip powder in half dose of 2250 mg of the new seedless rosehip powder plus 80 mg vitamin C once daily (three capsules/day).

Enhanced rosehip powder is defined based on *in vitro* studies showing that extracts derived from rosehip powder without seeds are more effective in all assays carried out compared with extracts derived from rosehips with seeds (anti-inflammatory and radical scavenging properties). The active principles responsible for these effects are more abundant in rosehip flesh than in the seeds. Therefore the effect has been enhanced in the new formulation by removing the inactive seeds and thereby increasing the potency per weight of the powder (half dosage). The only difference between treatments B and C was that patients in treatment C were informed to take only three capsules/day, consistent with the number of capsules in the prepacked, sequentially numbered drug containers corresponding to 1 month of capsules necessary between the milestones.

Randomization & allocation concealment

Eligible participants, who signed an informed consent form, were randomly assigned in permuted blocks of three and six, according to a secret computer-generated list of random numbers; the randomization was stratified according to sex. The clinical research center was given 150 sealed, opaque envelopes for each consecutive patient (either male or female). These envelopes contained detailed pharmacist instructions for the particular course of treatment (A, B or C). During data collection, neither the rheumatology department nor the coordinating center (The Parker Institute, Copenhagen, Denmark) had access to the randomization codes or statistical summaries of follow-up data. To prevent subversion of the allocation sequence, a unique patient identification (according to the name and date of birth) was written on the envelope and stored together with the individual informed consent form. Treatment assignment was thus concealed and masking was successfully achieved during the study; no sealed envelope was opened voluntarily or accidentally or was tampered with during the study.

Outcome measures

The exploratory primary outcome measure consisted of change from baseline to week 12 in the single-item 'pain during walking on flat surface' score, according to the pain subscale in the Knee Injury and Osteoarthritis Outcome Score (KOOS) [19,20], with individual items graded on a five-point Likert scale from 0 to 4. Secondary outcome measures, selected *a priori* in accordance with the recommendations of the Osteoarthritis Research Society International (OARSI) task force included the following: results on all five KOOS subscales [19,20]; the patient's global assessments of disease status obtained with the use of a 100-mm VAS on which higher scores indicate more severe disease; and scores on the Medical Outcomes Study 36-item Short-Form General Health Survey (SF-36), which reflect health-related quality of life [21,22]. For compliance, we applied a proxy measure for the different allocated rosehip therapies, assessed on the basis of simple capsule counts. The KOOS (assessed every 4 weeks) is a self-administered patient-reported outcome measure, assessing five domains of importance to patients with knee OA: pain, symptoms, activities of daily living, sport and recreation function, and knee-related quality of life [19,20,23]. Except for the SF-36 (which was only assessed at baseline and at the 12-week end point), all outcome measures were assessed at each of the three study visits required every 4 weeks during the 12-week trial period.

Finally, another outcome of this study that related to efficacy was the number of patients responding to therapy according to the Outcome Measures in Rheumatology (OMERACT)-OARSI responder criteria, based on the combination of the higher and lower level of response definition [24]. These criteria are defined as high improvement in pain or function (≥50%) and an absolute change ≥20%, or an improvement in at least two of the three following indicators: pain ≥20% and absolute change ≥10%; function ≥20% and absolute

change ≥10%; and patient's global assessment ≥20% and absolute change ≥10% [25]. In this trial, the three items of the OMERACT–OARSI responder criteria were assessed using 100-mm VAS separately for pain, disability and patient global evaluation.

Reports of adverse events were elicited with non-leading questions according to good clinical practice; all events were coded according to the Medical Dictionary for Regulatory Activities, as currently required by all regulatory authorities, including the US FDA and the EMA. We also used a questionnaire with some suggestive leading questions, assessing general adverse events, but not necessarily adverse effects in a generic framework [26] using options based on OA standards applied previously [27].

Sample size

This trial was designed as an exploratory study, evaluating which dose of the novel rosehip preparation to include in a later Phase III-like confirmatory efficacy trial on rosehip powder for treating OA. We decided for practical reasons to include 50 patients in each group [28]. Randomized controlled trials with 50 patients in each group have previously been considered to provide gold evidence in musculoskeletal research [29]. For exploratory purposes, the two pairwise comparisons (A vs B and A vs C, respectively) were assessed independent of any overall analysis. For a two-sample pooled t-test of a normal mean difference with a two-sided significance level of 0.05, assuming a common standard deviation of 20 mm, a sample size of 50 patients per group has a power of 80% to detect a group mean difference of 11.3-mm VAS (SAS Power and Sample Size, v. 3.1; SAS Institute Inc., NC, USA).

Statistical analysis

Analyses were carried out according to a pre-established analysis plan. All analyses were carried out applying SAS software (v. 9.2 Service Pack 4; SAS Institute Inc.). Descriptive statistics and tests are reported in accordance to the recommendations of the Enhancing the Quality and Transparency of Health Research network (i.e., various forms of the Consolidated Standards of Reporting Trials statement apply) [30–32]. Analyses were based on the intention-to-treat population, whereby all randomized patients are included in the analysis in the group to which they were allocated, regardless of the treatment received. Missing values were imputed for continuous outcomes by carrying forward the most recent nonmissing value (last observation carried forward) [33]. All reported p-values are two-sided; a p-value ≤0.05 was considered statistically significant. The longitudinal part of this exploratory study included repeated measurements in a mixed linear model [34]. Data were modeled and analyzed using 'PROC MIXED' based on restricted maximum likelihood estimates of the parameters [35]: 'Patient' was included as a random effects factor. The assessment of the main effects for 'Treatment' and 'Time' [36], as well as the possible interaction ('Treatment × Time') were all included in the same model as fixed factors. The baseline value was applied as a covariate to further reduce random variation [37] and increase statistical power [38]. The continuous outcome measures, such as SF-36 scores, which were not repeated over time, were analyzed using analysis of covariance adjusted for baseline value [37]. For the purpose of sensitivity analysis, all of the above models were also performed conditional on the randomization stratification criteria sex, although without any influence on the estimates.

Results

Study flow & patient characteristics

Recruitment began 23 August 2011 at the Parker Institute, Department of Rheumatology, Frederiksberg Hospital (Copenhagen, Denmark). The study was completed on 20 March 2012. A total of 259 patients were screened and 150 underwent randomization (Figure 1). Among the 52 potential participants who were screening failures, the most common reason for exclusion was a VAS pain score of less than 40 mm (in 19 patients); only two possible participants were unable to meet radiographic criteria. Most of the patients (73%) were women, with a mean age of 64.7 years and a mean BMI (the weight in kilograms divided by the square of the height in meters) of 29.2 kg/m^2. The groups had similar clinical characteristics at baseline (Table 1). The treatment adherence details of the participants are shown in Figure 1. There were no significant differences in the number of patients who withdrew for various reasons (Fisher's exact test: p = 0.93). Adherence to the assigned treatment regimen among the participants who completed the trial period, measured by capsule count at each visit, ranged from 18 to 115% (i.e., some participants took more capsules than prescribed). There were no apparent differences in capsule compliance among the A, B and C groups (Kruskal–Wallis test: p = 0.13) for medians 99.6, 97.0 and 98.8%, respectively.

Clinical outcomes

As illustrated in Figure 2, the primary (exploratory) outcome measure – change in pain on walking – showed no significant treatment effect over time (p = 0.95), but indicated a possible statistical interaction between treatment and time (Treatment × Time: p = 0.075), revealing a possible difference between

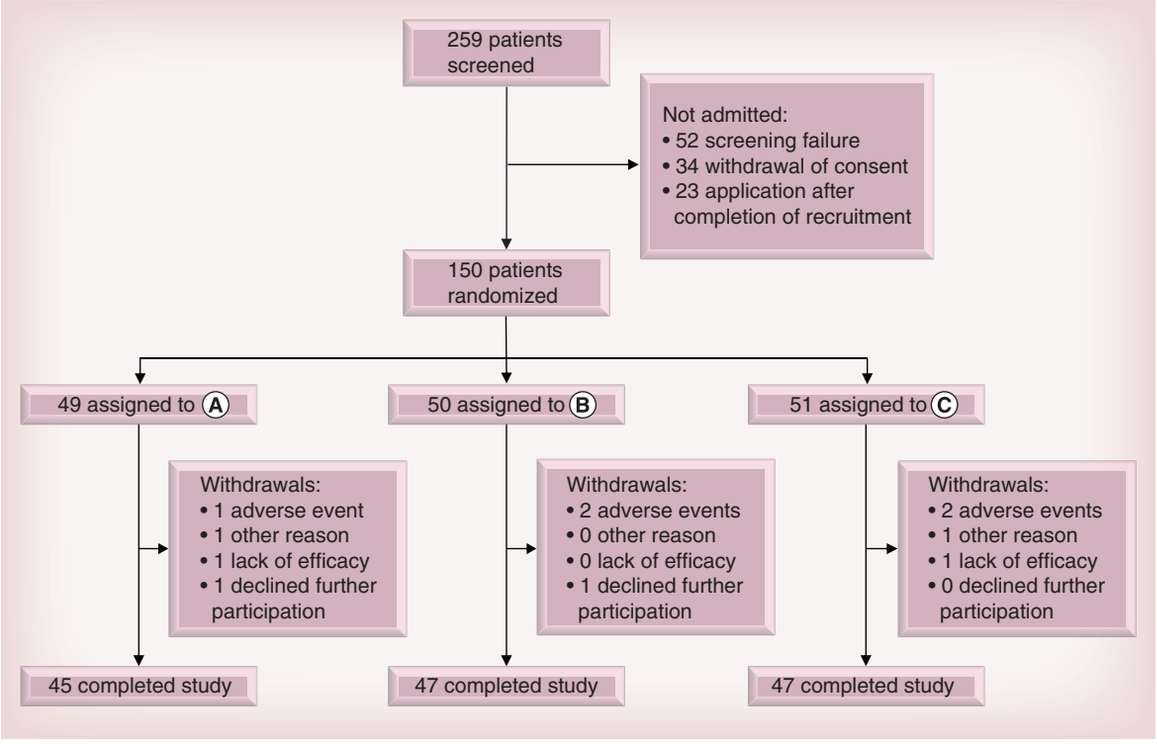

Figure 1. Trial profile. (A) Original rosehip (six capsules); **(B)** enhanced rosehip (six capsules); **(C)** enhanced rosehip (three capsules).

the response to different rosehip preparations over time. Table 2 presents the change from baseline at 12 weeks; we were unable to detect a difference in pain on walking between the original rosehip powder and the enhanced rosehip powder (six capsules): -0.06 (95% CI: -0.35–0.22; p = 0.66) and enhanced rosehip powder (three capsules): -0.14 (95% CI: -0.42–0.15; p = 0.34) assessed as changes on a five-point Likert scale from 0 (no pain) to 4 (extreme pain).

When evaluating the overall pain domain (according to the KOOS), we found no statistical differences among the groups: original rosehip powder and enhanced rosehip powder (six capsules): 4.06 KOOS points (-1.40–9.53; p = 0.14) and enhanced rosehip powder (three capsules): 1.29 KOOS points (-4.16–6.73; p = 0.64). Overall, all three rosehip preparations seemed equally efficacious, independent of the choice of secondary outcome. However, as demonstrated in Table 2, there were two exceptions from this finding: KOOS symptoms improved more from the enhanced rosehip powder (three capsules) than from the original rosehip powder (difference: 5.97 [0.92–11.02] KOOS points; p = 0.020). Apparently, changes in the participants' quality of life (mental component) were statistically better in the group receiving enhanced rosehip powder (six capsules) compared with the original rosehip powder (difference: 3.33 [0.62–6.04] SF-36 points; p = 0.016).

Adverse events

Overall, the number of adverse events reported during treatment was considered similar in all three groups (Table 3). Some side effects occurred more often in group B and C rather than in group A, although not statistically significantly different; the observed proportions on B and C compared with A could indicate a potential difference in the mode of action. Table 3 shows the most frequent adverse events reported during the 12-week intervention. Collected among abdominal and intestinal symptoms, nausea could be an issue (6 [12%], 15 [30%] and 11 [22%], respectively for groups A, B, and C; p = 0.098), potentially indicating an increased risk with increasing (active) dose of the enhanced rosehip powder. Within the area of musculoskeletal symptoms, sciatic pain was potentially more likely, although counterintuitive, in patients allocated three capsules/day compared with the six capsules/day, of the enhanced rosehip powder. Finally, there was a trend (p = 0.069) towards more urticaria events in the group receiving enhanced rosehip powder in the six capsules/day compared with the other two groups.

Ancillary analyses

As part of the statistical analysis plan, we generated an exploratory null hypothesis that three capsules of the enhanced rosehip powder would be equally good

Table 1. Patient characteristics at baseline.

Variable	Group A (n = 49)†	Group B (n = 50)†	Group C (n = 51)†
Demographics			
Mean age, years (SD)	65.4 (8.9)	63.6 (10.1)	65.1 (8.6)
Females, n (%)	36 (73)	37 (74)	37 (73)
Mean duration of OA symptoms, years (SD)	10 (8)	11 (7)	10 (8)
Mean height, cm (SD)	167.5 (7.8)	169.0 (10.0)	169.4 (8.8)
Mean bodyweight, kg (SD)	82.1 (18.9)	85.8 (19.8)	81.5 (15.9)
Mean BMI, kg/m^2 (SD)	29.2 (6.2)	30.2 (7.3)	28.3 (4.7)
Kellgren and Lawrence radiographic reading			
Worst compartment: grade 1, n (%)	8 (16)	10 (20)	7 (14)
Worst compartment: grade 2, n (%)	15 (31)	8 (16)	22 (43)
Worst compartment: grade 3, n (%)	14 (29)	22 (44)	15 (29)
Worst compartment: grade 4, n (%)	12 (24)	10 (20)	7 (14)
KOOS			
Pain, walking on flat surface, range: 0–4 (SD)	1.4 (0.8)	1.3 (0.8)	1.3 (0.8)
Function in daily living, range: 0–100 (SD)	60.0 (16.6)	62.5 (17.9)	64.1 (16.4)
Knee-related quality of life, range: 0–100 (SD)	34.9 (16.2)	39.6 (17.6)	40.0 (16.6)
Pain, range: 0–100 (SD)	54.3 (14.7)	54.4 (14.8)	58.5 (18.8)
Function in sport and recreation, range: 0–100 (SD)	24.4 (22.1)	27.0 (21.4)	30.0 (22.5)
Symptoms, range: 0–100 (SD)	60.3 (19.0)	61.0 (19.1)	61.4 (19.7)
SF-36 score(s)			
Mental component summary, range: 0–100 (SD)	55.0 (9.5)	56.3 (9.1)	56.7 (9.0)
Physical component summary, range: 0–100 (SD)	36.3 (9.0)	37.5 (9.2)	39.5 (9.1)
Questions applicable for the OMERACT–OARSI response			
VAS pain, range: 0–100 (SD)	57.4 (19.6)	53.6 (17.6)	55.4 (21.3)
VAS disability, range: 0–100 (SD)	50.3 (23.3)	48.3 (24.5)	47.4 (23.1)
VAS patient global assessment of disease status, range: 0–100 (SD)	44.1 (25.6)	41.7 (23.4)	37.7 (24.9)
Physician's global assessment of disease status (VAS), range: 0–100 (SD)	48.2 (22.2)	42.6 (17.9)	41.8 (18.5)

†Group A: original rosehip (six capsules); group B: enhanced rosehip (six capsules); group C: enhanced rosehip (three capsules).
KOOS: Knee Injury and Osteoarthritis Outcome Score; OA: Osteoarthritis; OARSI: Osteoarthritis Research Society International; OMERACT: Outcome Measures in Rheumatology; SD: Standard deviation; SF-36: 36-item Short-Form General Health Survey; VAS: Visual analog scale.

to the original (six capsules) used in previous trials [8]. To reject the null hypothesis that the response to these two interventions differs by a clinically unimportant amount, we specified a minimal important difference of 0.37 effect sizes (i.e., standard deviation units) [39], as previously proposed by Wandel *et al.* [40]. Estimates varied to some extent, depending on the outcome domain of interest, but they were consistent, indicating they were in favor of enhanced rosehip powder (three capsules). With the 95% CIs from the calculated effect sizes being within the lines of minimal important difference, the two preparations were judged equally efficacious on a *post hoc* level.

After finalizing the protocol of our study, Tubach *et al.* published minimum clinically important improvement (MCII) values for four generic outcomes in five rheumatic diseases [41]. As a *post hoc* effect measure, we evaluated how many patients had achieved an absolute (15 of 100 units) and relative (20%) MCII in KOOS pain at end point. Overall, differences between groups

were small according to both the absolute and relative MCII criteria:

- Absolute MCII: at least improving 15 KOOS pain units. Original rosehip powder: 15/49 (31%); enhanced rosehip powder (six capsules): 15/50 (30%); and enhanced rosehip powder (three capsules): 17/51 (33%; $\chi^2 = 0.148$; $p = 0.93$).
- Relative MCII: patients having at least 20% improvement from baseline. Original rosehip powder: 19/49 (39%); enhanced rosehip powder (six capsules): 20/50 (40%); and enhanced rosehip powder (three capsules): 17/51 (33%; $\chi^2 = 0.544$; $p = 0.76$).

Discussion

The results of the REPORT study agree with existing literature showing that different preparations and doses of rosehip powder in patients with OA of the knee all reduce pain while walking on a flat surface. We found no evidence of clinically relevant differences in efficacy among the three evaluated preparations/doses in the analysis of the primary outcome, or in most of the analyses of secondary outcomes. However, among the secondary outcomes, the KOOS symptoms domain indicated that the enhanced rosehip powder (three capsules/day) may be superior to the original rosehip formulation (six capsules/day).

The REPORT study data support the use of a novel enhanced rosehip powder, based on only the fleshy peel rather than the traditional product that is derived from whole rosehips, including both the fleshy peels and the seeds, thereby enabling a three capsule/day-dose regimen. Thus, the anticipated analgesic properties of rosehip powder were maintained using the enhanced rosehip powder, which includes a number of potentially active substances such as flavonoids, carotenes, triterpene acids, galactolipids and vitamin C.

The reason for our somewhat surprising finding of an inverse relationship with dosage of the enhanced rosehip powder remains to be explained. A physiological rather than incidental finding is supported by the delayed onset of the effect in the low-dose group, indicating a loading period for some of the effective components. A psychological advantage of having to ingest a smaller number of capsules cannot be ruled out. On the other hand, capsule counts in our study pointed towards similar compliance with the study in all three groups.

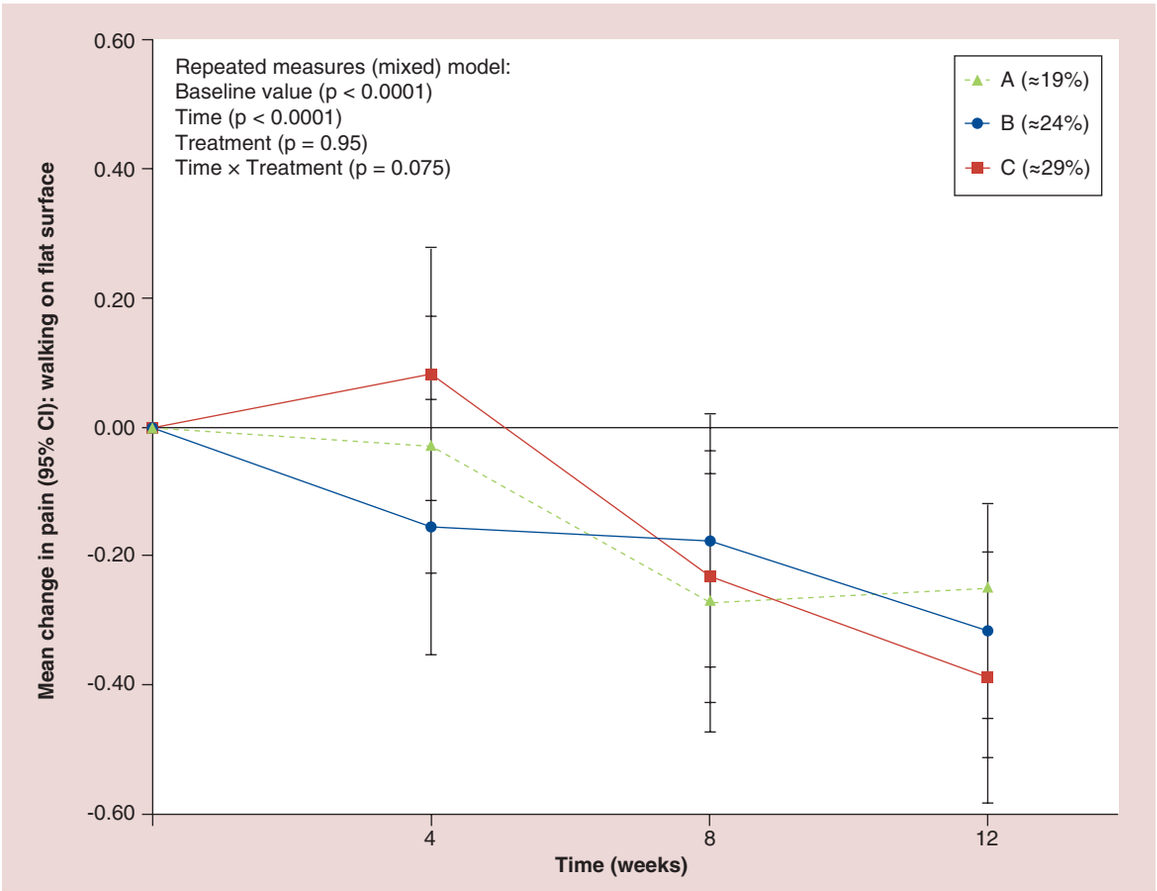

Figure 2. Longitudinal clinical efficacy: change in the primary outcome.

Table 2. Primary and secondary outcomes: change from baseline after 12 weeks.

Variable	Group A (n = 49)†	Group B (n = 50)†	Group C (n = 51)†	MD (95% CI)	
				Group B vs group A	*Group C vs group A*
KOOS					
Δ pain, walking on flat surface (SE)	-0.3 (0.1)	-0.3 (0.1)	-0.4 (0.1)	-0.06 (-0.35–0.22)	-0.14 (-0.42–0.15)
Δ function in daily living (SE)	5.4 (1.8)	7.4 (1.8)	6.6 (1.8)	1.97 (-3.16–7.09)	1.15 (-3.95–6.26)
Δ knee-related quality of life (SE)	7.8 (1.7)	7.8 (1.7)	9.3 (1.7)	0.00 (-4.73–4.73)	1.49 (-3.21–6.20)
Δ pain (SE)	6.1 (2.0)	10.2 (1.9)	7.4 (1.9)	4.06 (-1.40–9.53)	1.29 (-4.16–6.73)
Δ function in sport and recreation (SE)	9.4 (2.2)	8.7 (2.2)	8.4 (2.2)	-0.76 (-6.89–5.37)	-1.06 (-7.16–5.05)
Δ symptoms (SE)‡	2.1 (1.8)	6.4 (1.8)	8.0 (1.8)	4.33 (-0.75–9.40)	5.97 (0.92–11.02)
SF-36 score(s)					
Δ mental component summary (SE)§	-1.44 (0.97)	1.89 (0.96)	-0.65 (0.95)	3.33 (0.62–6.04)	0.80 (-1.91–3.49)
Δ physical component summary (SE)	1.60 (0.95)	2.86 (0.94)	2.34 (0.93)	1.26 (-1.37–3.89)	0.74 (-1.91–3.38)
OMERACT–OARSI response					
Δ VAS pain (SE)	-9.4 (3.0)	-10.7 (3.0)	-16.6 (2.9)	-1.30 (-9.62–7.02)	-7.22 (-15.50–1.05)
Δ VAS disability (SE)	-4.3 (2.9)	-5.7 (2.8)	-9.0 (2.8)	-1.42 (-9.37–6.53)	-4.67 (-12.58–3.24)
Δ VAS patient global assessment of disease status (SE)	-1.8 (2.9)	-1.3 (2.9)	-8.2 (2.9)	0.45 (-7.76–8.66)	-6.43 (-14.61–1.75)
OMERACT–OARSI response, n (%)	26 (53)	23 (46)	28 (55)	-7% (-27–13)	2% (-18–21)

†Group A: original rosehip (six capsules); group B: enhanced rosehip (six capsules); group C: enhanced rosehip (three capsules).
Values are means and SEs unless otherwise indicated.
‡Statistically significant difference between enhanced rosehip powder (three capsules) and original rosehip powder (p = 0.0199), potentially in favor of enhanced powder.
§Statistically significant difference between enhanced rosehip powder (six capsules) and original rosehip powder (p = 0.0164), potentially in favor of enhanced powder.
KOOS: Knee Injury and Osteoarthritis Outcome Score; MD: Mean difference; OARSI: Osteoarthritis Research Society International; OMERACT: Outcome Measures in Rheumatology; SE: Standard error; SF-36: 36-item Short-Form General Health Survey; VAS: Visual analog scale.

Recently, the American College of Rheumatology published its recommendations on nonpharmacologic and pharmacologic therapies for OA [42]. Pharmacologic modalities conditionally recommended for the initial management of patients with knee OA included acetaminophen, oral and topical NSAIDs, tramadol, intra-articular corticosteroid/hyaluronate injections, duloxetine and opioids [42]. The conditional recommendation of these interventions is partly due to the fact that they show inconsistent effect sizes, and all known pharmaceutical products have varying risks of adverse effects [2]. By contrast, nutraceuticals are products derived from food sources claiming that they provide extra health benefits, apparently without significant adverse effects. Surveys from the USA suggest that approximately 90% of arthritic patients use alternative therapies such as herbal medicines [43]. 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. The adverse events are comparable with placebo in the available literature, and it seems safe to apply this herbal remedy [8]. As reported in the present study, the adverse events collected by a standardized questionnaire covered a range of rather common complaints, all at low frequency. An understandable potential dose relationship was indicated with only one of these reported events. The tendency of more frequent complaint of nausea with six in comparison to three capsules of the enhanced rosehip powder was not consistent with other items of the gastrointestinal adverse effects domain. Urticaria was reported only in the group with six capsules of enhanced rosehip powder, whereas a similar tendency was not present with other items of skin reactions.

Limitations of the inference from the REPORT study and the subsequent interpretation include the lack of a placebo-control group. The clinical value of the study can be difficult to assess from the current design and observations in view of an absent placebo, or even an active control of NSAID (e.g., naproxen) would have been useful and maybe more ethical than a placebo. The placebo group was omitted when designing this study to reduce the number of participants in this first trial of another rosehip product, but placebo should be added in future further testing of the enhanced rosehip powder.

Table 3. Adverse events among patients in the intention-to-treat population during 12-week intervention.

Variable	Group A, n (%)†	Group B, n (%)†	Group C, n (%)†	p-value
Abdominal and intestinal symptoms				
Nausea	6 (12)	15 (30)	11 (22)	0.098
Diarrhea	10 (20)	11 (22)	14 (27)	0.695
Constipation	8 (16)	11 (22)	13 (25)	0.542
Wind/flatulence	18 (37)	14 (28)	19 (37)	0.558
Epigastric pain	14 (29)	14 (28)	20 (39)	0.426
Vomiting	2 (4)	2 (4)	5 (10)	0.510
Abdominal pain	12 (24)	12 (24)	19 (37)	0.270
Heartburn	7 (14)	8 (16)	8 (16)	1.000
Biliary symptoms	1 (2)	2 (4)	4 (8)	0.504
Musculoskeletal symptoms				
Cramps	13 (27)	7 (14)	12 (24)	0.282
Joint paint	9 (18)	9 (18)	12 (24)	0.788
Back pain	12 (24)	15 (30)	21 (41)	0.200
Swollen joints	14 (29)	12 (24)	10 (20)	0.584
Sciatic pain	11 (22)	5 (10)	14 (27)	0.070
CNS and psychiatric symptoms				
Dizziness	13 (27)	11 (22)	13 (25)	0.890
Headache	11 (22)	17 (34)	13 (25)	0.427
Anxiety	5 (10)	4 (8)	5 (10)	0.941
Sleeplessness	8 (16)	14 (28)	15 (29)	0.258
Fatigue	9 (18)	9 (18)	17 (33)	0.137
Mood changes	10 (20)	9 (18)	11 (22)	0.935
Depressive tendencies	11 (22)	6 (12)	6 (12)	0.272
Skin and subcutaneous symptoms				
Dry skin	14 (29)	7 (14)	11 (22)	0.216
Allergic rash	6 (12)	8 (16)	5 (10)	0.648
Redness	9 (18)	8 (16)	4 (8)	0.259
Eczema	2 (4)	4 (8)	6 (12)	0.395
Perianal itching	10 (20)	13 (26)	11 (22)	0.782
Skin irritation	6 (12)	7 (14)	8 (16)	0.956
Urticaria	0 (0)	3 (6)	0 (0)	0.069
Miscellaneous symptoms				
Sensitive to cold	13 (27)	11 (22)	9 (18)	0.565
Influenza	10 (20)	10 (20)	7 (14)	0.624
Hair loss	3 (6)	3 (6)	4 (8)	1.000
Bad breath	3 (6)	8 (16)	10 (20)	0.129
Toothache	11 (22)	5 (10)	6 (12)	0.183

†Group A: original rosehip (six capsules); group B: enhanced rosehip (six capsules); group C: enhanced rosehip (three capsules).

Another limitation is the apparent lack of double blinding: a third of the patients were, as a consequence of the randomization, informed to take only three capsules/day. Thus, these particular patients knew they were on the new formulation, which is why the study could not be designed as a double-blind trial. The study was designed as neither an equivalence nor a superiority study; rather, it was designed as an exploratory dose-finding study. The present study builds on the premise, and does not confirm, that rosehip powder reduces pain better than a placebo [8]. However, this exploratory study with focus on three capsules/day of enhanced rosehip powder is reassuring with all the 95% CIs being within the *post hoc* defined limits for minimal clinically important difference proposed by Rutjes *et al.* [44].

According to the presented MCII values, a 30–40% of participants having a clinical improvement in pain do not necessarily indicate effectiveness since the 'placebo effect' may be up to 50% of the participants. As the design the REPORT study also includes what would be referred to as a 'placebo effect', one could argue that none of the powders was effective. Furthermore, from pharmacokinetics, we would have expected the same dose of shell powder (4500 mg) to be more effective than the hip and seed powder (4500 mg) to indicate superiority. These design limitations and subsequent results clearly illustrates why a double-blind, placebo-controlled trial is urgently needed.

Conclusion & future perspective

The enhanced rosehip powder (the novel shell powder) was not superior to the powder previously investigated. Although the exploratory randomized active-controlled trial design of the study cannot confirm that half-dose is not inferior to full dose, we conclude, based on the observed equivalence margins and the apparent benefit on the KOOS symptom domain, that enhanced rosehip powder is as least as efficacious as the traditional rosehip product consisting of whole rosehips including seeds. The enhanced rosehip powder may be used in reduced quantity of three capsules/day. As with other natural products at present, rosehip preparations need further testing in Phase III-like trials.

Author contributions

R Christensen had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. Study design: R Christensen, S Tarp, RD Altman, M Henriksen, L Klokker, B Danneskiold-Samsøe and H Bliddal. Acquisition of data: R Christensen, S Tarp, L Klokker, M Boesen, CC Holm and H Bliddal. Analysis and interpretation of data: R Christensen, S Tarp, M Henriksen, RD Altman, DE Furst, EM Bartels, L Klokker, M Boesen, CC Holm, B Danneskiold-Samsøe and H Bliddal. Manuscript preparation: All authors. Statistical analysis: R Christensen, M Henriksen and CC Holm.

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Executive summary

Background

- Osteoarthritis (OA) is a common joint disorder; the condition is most frequent in the hands, knees, hips and spine.
- Pain is the most important problem for the knee OA patient; treatment must first address pain relief.
- Nutraceuticals are commonly used by patients to relief the pain from OA.
- Trials on a rosehip powder of *Rosa canina* L. made from the seeds and husks from dog rose show a small but clinically relevant pain relief in OA patients.
- The dose shown effective in clinical trials is six capsules/day. Increasing the potency of the rosehip powder is therefore desirable in order to improve product compliance.

Methods

- In a randomized trial, we compared the original rosehip powder consisting of whole rosehips including seeds (six capsules/day), with two different doses of a novel enhanced rosehip powder without seeds (six or three capsules/day), in patients with knee OA.

Results

- Pain during walking decreased during the trial period (12 weeks); the pain reduction was comparable across groups.
- Changes in the Knee Injury and Osteoarthritis Outcome Score symptoms indicated potential superiority of enhanced rosehip powder (three capsules/day) versus original rosehip powder (six capsules/day).

Conclusion

- Enhanced rosehip powder was at least as good, even in three capsules, as the original product.

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No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

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