

SCIENTIFIC COMPENDIUM ON ROSE HIP POWDER

A new Opportunity for **Joint Health**

THE EVIDENCE FOR CLINICAL EFFICACY OF ROSE HIP AND SEED: A SYSTEMATIC REVIEW

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Background: The objective of this review is to evaluate whether clinical research has gained any evidence of effectiveness of *Rosa canina* preparations.

Methods: Several databases and other sources were searched to identify randomized controlled trials of *Rosa canina* preparations.

Results: Trials were described in a narrative way, taking into consideration methodological quality scores. Four trials were included in this review and two were identified as subgroup analyses.

Conclusion: Moderate evidence exists for the use of a powder of the seeds and husks of a *Rosa canina* subspecies in patients suffering from osteoarthritis. Copyright © 2006 John Wiley & Sons, Ltd.

Keywords: osteoarthritis; pain; rose hip and seed; nutraceutical.

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Study population

The German Commission E Monograph (Blumenthal, 1998) summarizes the indications for rose hip and seed in traditional medicine which include the prevention and treatment of colds and influenza-like infections, infectious diseases, prophylaxis and therapy of vitamin C deficiencies, fever, for increase in the immune mechanism during general exhaustion, gastric spasms, gastric acid deficiency, prevention of inflammation of the gastric mucosa and gastric ulcers, as 'stomach tonic', for intestinal diseases, for diarrhea, as prophylaxis of intestinal catarrhs, as a laxative, for gallstones, gall- and discomforts and ailments, diseases and discomforts of the lower urinary tract, dropsy, as a 'tonic for kidneys', as a diuretic, for gout, disorders of uric acid metabolism, arthritis, sciatica, diabetes, inadequate peripheral circulation, as an astringent, for lung ailments, and as an eye rinse.

The monograph stated that the effectiveness of the herb for most of its claimed applications was not documented. Investigations in rats and rabbits failed to demonstrate an increased diuresis and a hypoglycaemic effect, respectively (Anon., 1998). However, a potent antioxidative effect was seen in vitro (Anon., 1998).

The aim of this study was to evaluate whether in the meantime clinical research has gained any evidence of efficacy for rose hip and seed.

Methodes

Computerized literature searches were carried out by the authors (MEDLINE, PUBMED, COCHRANE COLLABORATION LIBRARY, EMBASE (Ovid technologies) back to 1985 and also manually to identify randomized controlled studies (RCT) investigating preparations of *Rosa canina* ('or' rosehip 'or' rose hip 'or' rose hip and seed, Hagebutte (MEDLINE *Rosa* 'or' fruit; drug effects)). The following data were extracted from each study: authors' names; date of publication; country of origin; type of study, including number of study centres; participants (numbers, disease(s), characteristics of the study population (age, size, weight, gender)); duration of acute exacerbation or chronic disease; baseline values with details on pain and previous treatments; additional treatments; types of outcome measures; summary statistics; timing of outcome assessment; withdrawals and drop-outs; and adverse events. Methodological quality and level of evidence were assessed as described in a previous review (Gagnier et al., 2004): Quality items: (A) eligibility criteria specified, (B) randomization appropriate, (C) treatment allocation concealed, (E) similarity at baseline, (F) outcome measures and control interventions explicitly described, (G) co-interventions comparable, (H) outcome measures relevant, (I) adverse events and (J) drop-outs fully described, (K) sample size based on a priori power calculation, (L) intention-to-treat analy-

sis, (N) point estimates and measures of variability presented for the primary outcome measure, (O) appropriate timing giving a Total Score (TS) of 13; levels of evidence strong – pooling of data or at least 2 confirmatory studies (considering items K and N) demonstrating a clinical

relevant effect, moderate – consistent findings among one confirmatory study with a clinical relevant effect and/ or multiple exploratory RCTs, insufficient – one low quality RCT, conflicting – inconsistent findings among multiple trials, no evidence from trials – no RCTs

Table 1. (A) eligibility criteria specified, (B) randomization appropriate, (C) treatment allocation concealed, (E) similarity at baseline, (F) outcome measures and control interventions explicitly described, (G) co-interventions comparable, (H) outcome measures relevant, (I) adverse events and (J) drop-outs fully described, (K) sample size based on a priori power calculation, (L) intention-to-treat analysis, (N) point estimates and measures of variability presented for the primary outcome measure, (O) appropriate timing giving a Total Score (TS) of 13

	Phytomedicine 2004; 11: 383–391		Osteoarthritis Cartilage 2004; 12 Suppl 2	
	Curr Ther Res Clin Exp 2003; 64: 21–31		80 (subgroup)	145 (subgroup)
	n = 112	n = 100	n = 94 (112)	n = 32 (112)
	5 g/day vs placebo	5 g/day vs placebo	5 g/day vs placebo	5 g/day vs placebo
	Cross-over	Parallel	Cross-over	Cross-over
	Over 3 months	Over 4 months	Over 3 months	Over 3 months
A	OA multiple sites	Hip, knee	Hip, knee	Hand
B	Yes	Yes	Yes	Yes
C	Yes	Yes	Yes	Yes
E	Yes	Don't know	Yes	Yes
F	Yes	Yes	Yes	Yes
G	Yes	Yes	Yes	Yes
H	Yes	Yes	Yes	Yes
I	Yes	Yes	Yes	Yes
J	Yes	Yes	Yes	Yes
K	Yes	Yes	No	No
L	Yes	Yes	Yes	Yes
N	No	No	No	No
O	Yes	Yes	Yes	Yes
TS	11	10	11	11

Results

A total of 88 (30 PUBMED, 24 MEDLINE), citations were screened and 4 RCTs identified (Warholm et al., 2003; Rein et al., 2004a, b; Winther and Kharazmi, 2004), however, two were identified as subgroup analyses (Rein et al., 2004a; Winther and Kharazmi, 2004). All trials were carried out with a powder of the seeds and husks of a *Rosa canina* subspecies in patients suffering from osteoarthritis. A full description of the studies is placed on the webpage <http://remed-chrubasik.uniklinikfreiburg.de>. The two main studies were of high quality (TS 10, 11, Table 1), but not confirmatory. Relief of joint pain was greater after 3 and 4 months of treatment with 5 g powder/day compared with placebo, respectively (n = 112, p < 0.01; n = 100, p < 0.05). Likewise, activities of daily living were more improved and consumption of rescue medication was significantly less.

Discussion

Our systematic review shows that clinical evidence of effectiveness has only been gained in

the field of osteoarthritis. There is evidence that nutritional supplementation with a dry powder of a *Rosa canina* subspecies may decrease both osteoarthritic pain and the consumption of additional synthetic pain medications. The proprietary powder has a potent antioxidative effect (Daels-Rakotoarison et al., 2002), inhibited chemotaxis and chemiluminescence of human peripheral blood neutrophils in vitro and reduced certain inflammatory parameters in vivo (Kharazmi and Winther, 1999; Winther et al., 1999). A galactolipid contributes to the antiinflammatory principle (Larsen et al., 2003). Painful arthritis is usually treated with nonsteroidal antiinflammatory drugs (NSAIDs) (Pincus et al., 2000), although their use is often associated with adverse gastrointestinal events that may be life threatening in some patients (Smalley et al., 1995). The cost of health care resources spent on preventing and managing these side-effects was calculated to be around one Canadian dollar for every day of NSAID treatment (Rahme et al., 2001). Safer therapies are therefore required and have led to the introduction

of selective COX-2 inhibitors for the treatment of chronic pain (Grainger and Cicuttini, 2004). However, recently, rofecoxib (Vioxx®) although associated with a statistically significantly lower incidence of upper gastrointestinal bleedings (Watson et al., 2004) was voluntarily withdrawn from the market due to increased risk of cardiovascular events (Davies and Jamali, 2004). Some nutraceuticals may be promising alternatives to synthetic medications in the treatment of musculoskeletal pain, although conclusive studies are required for all of them: proprietary preparations from devil's claw (Gagnier et al., 2004), willow bark (Chrubasik et al., 2000a, b), ginger (Chrubasik et al., 2005), avocado-soybean (Ernst, 2003) and glucosamine supplemented with and without shark chondroitin (McAlindon et al., 2000). Confirmatory studies (considering items K and N) are also required for the proprietary rose hip and seed preparation in order to prove the effectiveness beyond any doubt in the treatment of osteoarthritis. More research is needed to clarify the other supposed rose hip and seed effects.

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A POWDER MADE FROM SEEDS AND SHELLS OF A ROSE-HIP SUBSPECIES (*ROSA CANINA*) REDUCES SYMPTOMS OF KNEE AND HIP OSTEOARTHRITIS: A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED CLINICAL TRIAL

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Objective: The aim of this study was to determine whether a herbal remedy made from a subspecies of rose-hip (*Rosa canina*) might reduce symptoms of osteoarthritis and consumption of rescue medication in patients suffering from osteoarthritis.

Methods: Ninety-four patients with osteoarthritis of the hip or knee were enrolled in a randomized, placebocontrolled, double-blind crossover trial. Forty-seven patients were given 5 g of the herbal remedy daily for a period of 3 months and the remaining patients were given a similar amount of placebo. The group initially treated with placebo was then changed to rose-hip and vice versa for another 3-month period. Upon inclusion and after 3 weeks and 3 months of each treatment period, pain, stiffness, disability, and global severity of the disease were scored on a Western Ontario and McMaster Universities (WOMAC) questionnaire. After 3 weeks of treatment, patients, if possible, were allowed to reduce their consumption of 'rescue medication'. Data were analysed on the basis of intention to treat.

Results: Rose-hip resulted in a significant reduction in WOMAC pain ($p < 0.014$) as compared to placebo, when testing after 3 weeks of treatment. The consumption of 'rescue medication' significantly declined as a result of active treatment ($p < 0.027$). WOMAC disability, stiffness, and global assessment of severity of the disease were not altered by 3 weeks but decreased significantly ($p < 0.018$, $p < 0.038$, and $p < 0.035$, respectively) after 3 months of treatment.

Conclusion: The data suggest that the present herbal remedy can alleviate symptoms of osteoarthritis and reduce the consumption of 'rescue medication'.

Osteoarthritis is a disease that reaches younger sportspersons of both sexes, many middle-aged people, and the majority of the older population. It has recently been claimed that long-term treatment with glucosamine sulfate can repair the destroyed cartilage, which is normally thought to be the main element of the disease (1). However, most treatment is still directed against symptoms of the disease, such as pain and stiffness, which are responsible for the main reduction in daily activities often reported in osteoarthritis.

Non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid, and glucocorticoids are often used for treatment of such symptoms, although treatments can result in serious side effects such as bleeding, gastric erosions, and liver and kidney damage (2, 3). Cyclooxygenase-2 inhibitors, which selectively inhibit the enzyme cyclooxygenase, have also exerted unfavourable effects (4) and the daily cost of the treatment is still very high. Paracetamol, which for a decade was regarded as a safe drug, was recently reported to enhance the risk of upper gastrointestinal problems (5). For these reasons there has been a search for new compounds that could minimize pain and stiffness without the serious side effects mentioned above. Various herbal remedies, especially extracts of ginger and avocado/soybean unsaponifiables, have shown promising results in patients with osteoarthritis (6, 7). More focus on remedies of a herbal origin might therefore, in the future, change the treatment of patients with osteoarthritis by a consumption pattern with fewer side effects.

Inflammatory cells such as polymorphonucleated leucocytes participate in inflammation and tissue damage by liberating proteolytic and hydrophilic enzymes as well as oxygen radicals. We have found that a standardized dry powder made from seeds and shells of a subtype of rose-hip (*Rosa canina*) reduces the migration rate of polymorphonucleated leucocytes in vitro and the serum concentration of C-reactive protein in humans (8), an effect unrelated to the high vitamin C content of rose-hip (9).

Moreover, some of the osteoarthritic volunteers who participated in these preliminary studies claimed that their pain symptoms were dramatically reduced after a period of treatment (8). This encouraged us to investigate whether a standardized powder made from the same wild type of rose-hip (*Rosa canina*) would alleviate symptoms such as pain and stiffness and impro-

ve daily functions in osteoarthritic patients. We also wanted to evaluate whether an effect, if present, was of sufficient magnitude to influence the daily consumption of pain relieving medicine.

Patients and methods

Study population

Patients were recruited from the outpatient clinics of the Department of Rheumatology of Copenhagen University Hospital in Glostrup and of the Institute for Clinical Research. The study was approved by the Ethics Committee of Vejle and Copenhagen counties (no. 9980042 PMC). Patients were recruited after announcements in local newspapers. The primary inclusion criteria were age over 35 years and symptomatic knee or hip osteoarthritis. Osteoarthritis of the knee or hip was diagnosed according to the clinical and radiological criteria of the American College of Rheumatology (10, 11). Major exclusion criteria were inflammatory arthritis, fibromyalgia, depression, and substantial abnormalities in haematological, hepatic, renal, or metabolic functions. Furthermore, we excluded patients who received glucosamine sulfate, chondroitin sulfate, intra-articular hyaluronate, or systemic or intra-articular glucocorticoids in the 6 weeks preceding enrolment.

Design and treatment

The study was a randomized, double-blind, placebocontrolled, crossover trial with three successive periods: a 14-day run-in period and two subsequent treatment periods of 3 months. After the run-in period, patients were allocated to receive active medication and placebo in random order in the two treatment periods (Figure 1). Allocation was carried out in blocks of four by a computer program. Active medication comprised biologically standardized rosehip powder (LitoZin). All capsules were produced from the same batch. Identical capsules containing an inactive powder of similar taste, smell, and colour were produced for placebo. The dosage was a total of 5 g of rose-hip powder administered daily as five capsules each of 0.5 g of the rose-hip or placebo, to be taken in the morning and again in the evening along with a meal. Compliance with study treatment was established by asking the patient about missed doses and by counting the number of returned capsules.

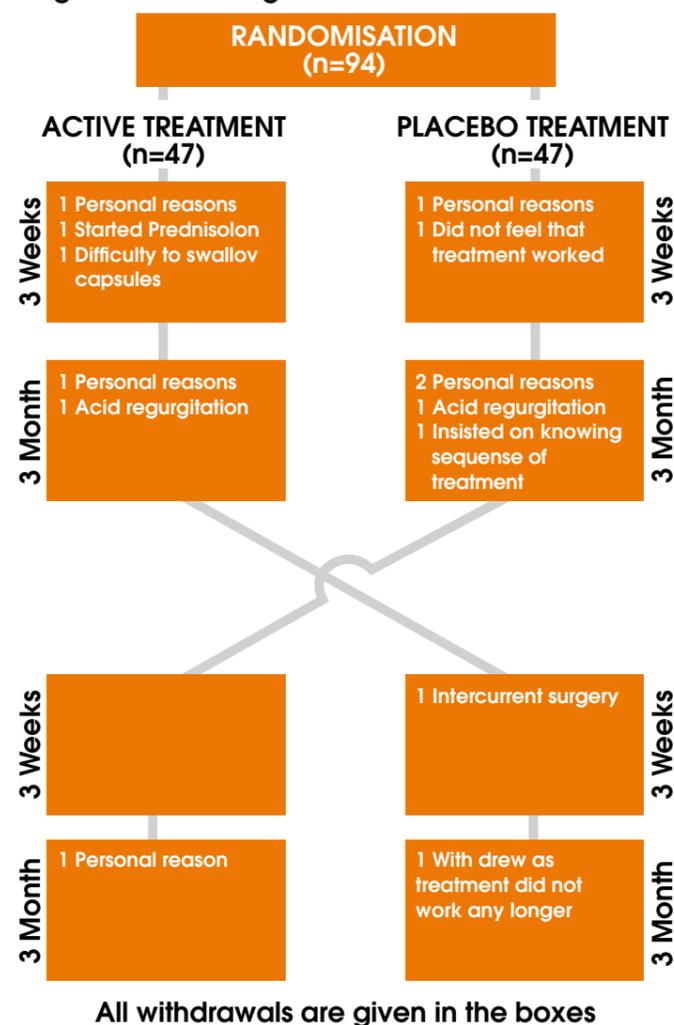
The rose-hip powder used has been on the market as a herbal remedy in the Scandinavian countries for almost a decade. It is produced from fruits of a selected subtype of *Rosa canina*.

na. The plants are always grown in standardized fields according to good agricultural practice and harvesting takes place only when the fruits are mature. Immediately after harvesting, the fruits are frozen. When the fruits are thawed later on, a special laser technique is used to ensure optimal fruits for the production of powder. A computerized technique ensures that the drying process never exceeds 40°C and the dry powder, which contains elements of the seeds as well as the shells of the rose-hip, is controlled regarding vitamin and mineral content. Patients using NSAIDs regularly were advised to continue using the same dosage during the entire study. However, patients were advised to reduce intake of other analgesics if possible, such as paracetamol or synthetic opioids after the first 3 weeks of each of the two treatment periods. During the study period, the patients were instructed not to change to another generic type of the same analgesic or to use similar tablets containing a different quantity of the same painkiller. Neither was patients allowed to start up any new type of pain relieving medication. The consumption of analgesics was recorded daily by the patients in a diary. The change in consumption of analgesics, in each of the two treatment periods, was estimated by subtracting the consumption of medication in the past 2 weeks from that of the initial 2 weeks. No other cointerventions for osteoarthritis were allowed during the entire study period.

Outcome measures

Symptoms of osteoarthritis were assessed by the Western Ontario and McMaster Universities (WOMAC) osteoarthritis index, a validated, disease-specific questionnaire addressing severity of joint pain (five questions), stiffness (two questions), limitation of physical function (17 questions), and patients' global assessment of disease severity referring to the 48 h before assessment (11). The visual analogue scale version of the index was used, that is with the patient assessing each question by a 100 mm visual analogue scale. A higher WOMAC score represents worse symptom severity, with 2500 mm being the worst possible total score (12). WOMAC scores were assessed at the beginning, after 3 weeks, and at the end of each of the two treatment periods. WOMAC score of joint pain was the primary outcome measure together with the consumption of analgesics taken during the two different treatment periods. WOMAC scores of stiffness, limitation of physical function, and patients' global assessment of disease severity and occurrence of adverse events were secondary outcome measures.

Figure 1. Flow diagram.



Statistical analysis

Based on a within-patients SD of 10%, we calculated that a sample size of 90 patients in a crossover design would give a power of 90% in detecting more than a 15% difference in the WOMAC score of joint pain at the 5% level of significance. Statistical analysis was based on the intention-to-treat principle with last observation carried forward. The Wilcoxon test for matched pairs was used throughout. Subanalysis comparing parallel groups was performed using the Mann-Whitney test. Data are given as mean values \pm SD.

Results

Patients

A total of 94 patients, comprising 54 women (mean age 66 years; range 38–92) and 40 men (mean age 65 years; range 48–85) were enrolled in the study and randomized to either receive placebo first and then active treatment (group A, n=547) or active treatment first and then placebo (group B, n=547). There were no significant differences in gender or age on com-

paring the A and B groups (data not given). In the entire group the mean body mass index (BMI) was 27 kg/m² (range 19–41). In group A the BMI was 27.3 kg/m² (range 19–39) and in group B, 26.6 kg/m² (range 22–41), a non-significant difference. In group A 13 of the patients were taking NSAIDs, 18 paracetamol, 10 synthetic opioids such as tramadol and codeine, and 19 did not use any rescue medication at all. In group B the corresponding numbers of patients were: NSAID 15, paracetamol 21, synthetic

opioids 6, and no medication at all 17. These values were not significantly different from the values reported in group A. There was no significant difference in the number of patients dropping out of the study when comparing the two different treatments or the A and B groups (for details see Figure 1). There were no significant differences in osteoarthritic characterization on comparing the A and B groups, as detailed in Table 1. Compliance was 92.5% with Hyben-Vital and 90.5% with placebo.

Table 1. Characterization of osteoarthritis.

	All patients (n=594)	Placebo-Active (n=547)	Active-Placebo (n=547)	p-value PA vs. AP
Knee osteoarthritis	58	29	29	29
Hip osteoarthritis	21	11	10	10
Hip and knee osteoarthritis	15	7	8	8
Initial WOMAC scores				
Pain	33.7 (19.4)	30.4 (18.1)	37.0 (20.4)	37.0 (20.4)
Stiffness	39.2 (19.4)	35.6 (22.0)	42.5 (26.2)	42.5 (26.2)
ADL	35.3 (21.6)	34.0 (21.1)	36.7 (22.2)	36.7 (22.2)
PGAD	43.9 (24.4)	43.6 (22.6)	44.3 (26.8)	44.3 (26.8)

Table 2. WOMAC scores for pain, stiffness, daily activities (ADL), and patients' evaluation of disease severity (PGAD) in all the included patients (n594). Data given are mean values with SD in parentheses.

		Start	3 weeks	Delta value	3 months	Delta value	p-value placebo vs. active	
							3 weeks	3 months
Pain	Placebo	33.7 (19.4)	35.3 (21.5)	2.1 (16.8)	2.1 (16.8)	5.1 (18.3) ¹	0.014	0.125
	Active	33.7 (19.4)	29.4 (18.3)	7.4 (14.9) ²	7.4 (14.9) ²	7.0 (19.7) ³		
Stiffness	Placebo	39.2 (24.4)	40.0 (24.2)	3.3 (19.0)	3.3 (19.0)	5.0 (23.2)	0.198	0.038
	Active	39.2 (24.4)	34.0 (20.5)	7.5 (16.7) ⁴	7.5 (16.7) ⁴	8.0 (21.6) ⁵		
ADL	Placebo	35.3 (21.6)	39.7 (25.3)	-20.7 (22.4)	-20.7 (22.4)	-20.2 (25.5)	0.165	0.018
	Active	35.3 (21.6)	35.9 (27.7)	2.2 (22.7) ⁶	2.2 (22.7) ⁶	6.4 (17.5) ⁷		
PGAD	Placebo	43.9 (24.4)	42.3 (21.2)	8.2 (25.1) ⁸	8.2 (25.1) ⁸	7.8 (28.8) ⁹	0.682	0.035
	Active	43.9 (24.4)	39.2 (22.4)	8.2 (22.6) ¹⁰	8.2 (22.6) ¹⁰	14.1 (28.1) ¹¹		

¹pv0.005, ²pv0.001, ³pv0.003, ⁴pv0.001, ⁵pv0.006, ⁶pv0.002, ⁷pv0.003, ⁸pv0.004, ⁹pv0.031, ¹⁰pv0.002, ¹¹pv0.001. The p-values given are relative to pretreatment values (initial values).

Primary outcome measure

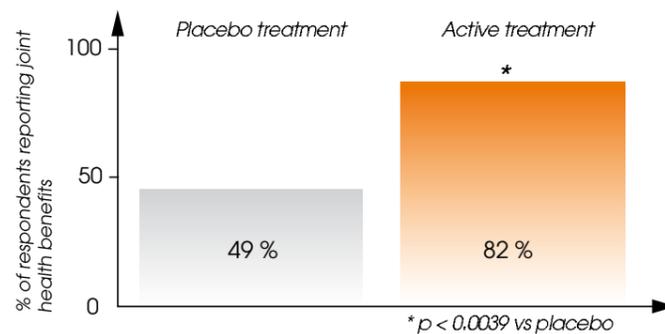
WOMAC scores for joint pain, for the entire study population, are given in Table 2. After 3 weeks of active treatment, WOMAC scores for joint pain declined from 33.7 \pm 19.4 to 29.4 \pm 18.3, a delta reduction of 7.4 \pm 14.9 mm (pv0.001), compared to a change from 33.7 \pm 19.4 to 35.3 \pm 21.5, a delta change of 2.1 \pm 16.8 (pv0.299), when placebo treatment was given (Table 2). The change comparing the two different groups was statistically significant at the p<0.014 level. After 3 months of treatment, the same pattern was observed, although the changes were not statistically significant (p<0.125). The percentage of patients experiencing a reduction in the WOMAC score for joint pain after the initial 3 weeks of treat-

ment was significantly higher when active treatment was given (82%) than when placebo was given (49%) (p<0.004) (Figure 2). After 3 months of treatment, the percentages of responders in the two groups, although still in favour of active treatment, did not differ significantly.

Diaries of the consumption of 'rescue medication' indicated, in accordance with the study design, that the intake of NSAIDs was unchanged during the two different treatment periods (p<0.803) (data not given). A decline of 40% in the consumption of paracetamol (data available in 21 patients) was observed as a result of active treatment (p<0.052).

When a Mann–Whitney subanalysis was applied on the consumption of paracetamol in each of the two groups, during the first 3 months of treatment, rosehip powder resulted in a significant reduction in the number of tablets taken during a 2-week period (14.0 ± 24.0 ; $p < 0.031$) compared to an insignificant increase of 7.9 ± 15.5 tablets observed as a result of placebo treatment. The between-group difference was 51% ($p < 0.027$). The consumption of weak opioids (data available in only seven patients) showed a similar reduction in the consumption during active treatment ($p < 0.0313$) (data not given). As relatively fewer patients were taking weak opioids, a subanalysis was not performed on weak opioids.

Figure 2. Percentage of patients experiencing a reduction in the WOMAC score for joint pain after 3 weeks of treatment in the group initially given placebo and in the group initially given active treatment.



Secondary outcome measures

WOMAC scores for stiffness, limitation of physical function, and patients' global assessment of disease severity for the entire study population are given in Table 2. After 3 months of treatment, there was a significant reduction in WOMAC symptom scores for stiffness ($p < 0.037$), WOMAC scores for limitation of physical function improved ($p < 0.018$), whereas patients' global assessment of disease severity declined

Table 3. WOMAC scores for pain, stiffness, daily activity (ADL), and patients' evaluation of disease severity (PGAD) in group A (placebo first, then active treatment) and in group B (active treatment first, then placebo). Data given are mean values with SD in parentheses.

	Initial value	3 weeks	Delta value	3 months	Delta value	3 weeks	Delta value	3 months	Delta value
Group A (n=547)									
Pain	30.4 (18.1)	34.5 (23.1)	-22.5 (13.6)	36.3 (20.4)	2.3 (14.9)	29.9 (17.7)	5.1 (15.6) ¹	31.9 (23.4)	5.9 (21.9)
Stiffness	35.6 (22.0)	37.1 (25.9)	-21.4 (19.3)	38.0 (23.6)	3.2 (22.8)	31.4 (19.0)	5.9 (19.2) ²	33.8 (25.5)	6.8 (21.9) ³
ADL	34.0 (21.1)	36.1 (22.3)	-20.3 (10.5)	38.3 (20.3)	2.5 (14.7)	33.5 (17.6)	5.3 (13.8) ⁴	33.0 (23.0)	7.6 (19.9) ⁵
PGAD	43.6 (22.6)	40.2 (22.3)	8.1 (23.5)	48.9 (25.5) ⁶	5.2 (29.6)	41.1 (21.5)	9.6 (25.5) ⁷	38.1 (22.9)	15.3 (28.6) ⁸
Group B (n=547)									
Pain	37.0 (20.4)	28.9 (19.0)	9.6 (13.9) ⁹	33.8 (17.6)	8.1 (17.4) ¹⁰	36.0 (20.0)	7.0 (18.5) ¹¹	34.9 (20.6)	7.8 (20.9) ¹²
Stiffness	42.5 (26.2)	36.2 (21.7)	8.9 (14.4) ¹³	39.8 (21.6)	9.2 (21.4) ¹⁴	42.8 (22.4)	7.8 (18.0) ¹⁵	44.0 (24.5)	7.8 (18.0) ¹⁵
ADL	36.7 (22.2)	38.0 (34.2)	-20.4 (28.2)	37.0 (18.1)	5.3 (15.0) ¹⁷	43.6 (27.9)	-21.2 (29.1)	45.3 (32.7)	-21.2 (29.1)
PGAD	44.3 (26.8)	37.6 (23.3)	6.8 (19.4) ¹⁸	44.4 (39.3)	12.6 (28.0) ¹⁹	44.5 (20.2)	9.3 (27.4)	41.5 (19.3)	9.3 (27.4)

($p < 0.035$) when active treatment was given, as compared to placebo. There were no significant differences in the alleviation of symptoms comparing patients with osteoarthritis of the hip to patients with osteoarthritis of the knee. As a carry-over effect can blunt the impact of treatment in a crossover design, we also analysed, separately, the group initially treated with placebo and then actively treated (group A) and the group initially given active treatment and then placebo (group B). Group A showed a significant improvement in activities of daily living (ADL) function and a reduction in patients' overall feeling of discomfort from their disease patients' global assessment of disease severity (PGAD) after 3 weeks and 3 months of active treatment. The impact on pain and stiffness, although present, did not attain statistical significance (Table 3).

Patients in group B showed a statistically significant reduction in pain, stiffness, and PGAD as a result of active treatment. These changes, however, did not return to pretreatment levels during the following placebo treatment period, suggesting carryover (Table 3). A comparison of the A and B groups regarding pain and stiffness yielded Mann–Whitney p -values of 0.001 and 0.016, respectively, when evaluating after the initial 3 weeks of treatment. Although this comparison between groups was still also in favour of active treatment after the first 3 months of treatment, statistical significance was not obtained and further statistically significant changes in WOMAC parameters were not observed when comparing the initial 3-month periods of the two different treatments. An identical pattern as described for WOMAC data was also observed for rescue medication (data not given). There was no significant difference in dropout rate or milder unwanted side effects reported during treatment (Table 4).

¹ $p < 0.042$, ² $p < 0.076$, ³ $p < 0.095$, ⁴ $p < 0.002$, ⁵ $p < 0.025$, ⁶ $p < 0.018$, ⁷ $p < 0.022$, ⁸ $p < 0.001$, ⁹ $p < 0.001$, ¹⁰ $p < 0.011$, ¹¹ $p < 0.031$, ¹² $p < 0.012$, ¹³ $p < 0.001$, ¹⁴ $p < 0.022$, ¹⁵ $p < 0.037$, ¹⁶ $p < 0.084$, ¹⁷ $p < 0.068$, ¹⁸ $p < 0.044$, ¹⁹ $p < 0.010$, ²⁰ $p < 0.049$. P -values given are relative to pretreatment values. P -values given in parentheses indicate borderline significance.

Table 4. Dropout rate and unwanted effects in patients after 3 months while on placebo or active treatment.

	Pla- cebo	Ac- tive	p - value
Dropped out during treatment	7	7	NS
Reasons for dropout			
Felt that treatment did not work	2	0	NS
For personal reasons	3	3	NS
Acid regurgitation	1	1	NS
Difficulty to swallow capsules	0	1	NS
Started prednisolone treatment	0	1	NS
Intercurrent surgery	0	1	NS
Insisted on knowing kind of treatment	1	0	NS
Milder unwanted effects reported during treatment that did not cause withdrawal			
Frequent voiding	1	3	NS
Diarrhoea	2	2	NS
Constipation	1	2	NS
Short episode of mild urticaria	0	1	NS

Discussion

This study shows that a standardized rose-hip powder, made from a subtype of *Rosa canina*, has a beneficial symptomatic effect in patients with knee and hip osteoarthritis. The percentage of patients who reported at least some reduction in WOMAC pain after 3 weeks of active treatment was 82% compared to a 49% reduction in the group treated with placebo. A placebo effect of the same magnitude as reported here was also reported in a recent study evaluating the impact of a ginger extract on pain from osteoarthritis of the knee (6). In that study, which reported a 50% reduction in pain during placebo compared to a 66% reduction during active treatment, early testing was also performed. The placebo impact, in both studies, might have declined if the studies had been running for a longer period of time.

We used a validated, disease-specific, and very sensitive questionnaire and were able to demonstrate a reduction in joint pain and stiffness as well as an improved physical function in these patients after treatment with the present rose-hip powder. Pain that was significantly reduced after 3 weeks of treatment did not attain statistical significance when tested after 3 months. During the course of the 3-month treatment period in which the patients received active treatment, there was, however, a significant reduction in the consumption of traditional painkillers such as paracetamol and synthetic opioids as compared to the group re-

ceiving placebo. We suggest that this change in consumption of additional painkillers, which patients were allowed to reduce after the first 3 weeks of treatment, may explain the lack of significance when pain was evaluated after 3 months of treatment. Furthermore, the powder was well tolerated and did not give rise to any serious adverse effects; in fact, stiffness and global assessment of disease severity significantly declined and daily activities significantly improved after 3 months of active treatment. Our results are supported by the findings in a recent Norwegian study in which treatment with powder from the same subtype of rosehip resulted in improved joint mobility and less joint pain in patients on a waiting list for either hip or knee surgery due to osteoarthritis (13).

There are, however, reservations to our conclusion. The dose was possibly not optimal and a long-term study is needed to confirm that the reduction in symptoms is persistent, and that long-term treatment does not result in side effects different from what was observed with placebo.

The present data, however, seem to fit well into earlier, more basic, reports from our laboratory indicating that the present version of rose-hip powder, when used in higher doses, reduces pain in osteoarthritis and affects mechanisms of importance to joint disease (8, 9). It is also encouraging to note that in another study aiming to test patients with osteoarthritis, on the waiting list for hip or knee replacement, the present powder, given in a similar dose, reduced pain and improved mobility, suggesting that the powder may work in both the early and late stages of osteoarthritis (13).

When responders to treatment were asked about the time before some alleviation of pain occurred, the earliest response reported was within 2 weeks. Moreover, a certain carry-over effect was demonstrated in the present study, and carry-over was also demonstrated in another study using the same rosehip powder and an identical study design (14). This may indicate that the present powder does not work like the traditional painkillers normally used in the treatment of osteoarthritis. As reported earlier, one mode of action might be an anti-inflammatory action mediated by leucocyte neutrophils (8, 9). Indeed, we were able to show that C-reactive protein and also the chemotaxis of neutr-

phil leucocytes were decreased in vitro as well as in vivo, using concentrations of the present subtype of rose-hip, comparable to the dose used in this study (8, 9). Chemotaxis of leucocyte neutrophils also significantly declined when measured in a subfraction of the present patients (15). It seems likely therefore that one mechanism of the present powder might be of an anti-inflammatory origin. Indeed, the anti-inflammatory hypothesis seems to be receiving increased attention. We have shown that the anti-inflammatory impact of the present subtype of rose-hip was not related to vitamin C and suggested that another possibly unknown active ingredient might be found in the rosehip powder (8). An active ingredient that can inhibit the chemotaxis of human neutrophil leucocytes has been isolated recently from the present subtype of rose-hip, making the anti-inflammatory hypothesis more likely (16). A Framingham study and, more recently, a Danish study indicate that patients with osteoarthritis might benefit from vitamin C (17, 18). As the present powder is rich in natural vitamin C, an additional mechanism might be of vitamin C origin.

The powder does not seem to be involved in the arachidonic acid pathway as platelet aggregation was not affected when the powder was tested in healthy volunteers and patients on warfarin treatment (19). This is different from the anti-inflammatory agents referred to in the introduction of this paper and we suggest that this might help to explain why side effects in this study were comparable to that of the placebo.

In summary, we suggest that the present standardized powder, made from a subtype of *Rosa canina*, can alleviate pain to an extent that can influence the consumption of rescue medication. It should be emphasized that the present data may not apply to any type of rose-hip, as species can be different regarding biological activity (20). Further research should aim to find the optimal dose, test the impact of long-term treatment and compare that with the impact of NSAIDs, and evaluate the biological activity of different subtypes of rosehip.

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A HERBAL REMEDY, HYBEN VITAL (STANDARD. POWDER OF A SUBSPECIES OF ROSA CANINA FRUITS), REDUCES PAIN AND IMPROVES GENERAL WELLBEING IN PATIENTS WITH OSTEOARTHRITIS—A DOUBLE-BLIND, PLACEBO-CONTROLLED, RANDOMISED TRIAL

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Abstract

The treatment of osteoarthritis, a disease that eventually affects the majority of the older population, involves the alleviation of symptoms such as pain and stiffness, and the reduction of inflammation. The double-blind, placebocontrolled, crossover study reported here examined the effect of Hyben Vital, a herbal remedy made from a subtype of *Rosa canina* and recently reported to have anti-inflammatory properties, on the symptoms of osteoarthritis. One hundred and twelve patients with osteoarthritis were randomly allocated to treatment with either Hyben Vital 5 g daily or an identical placebo for 3 months, followed immediately by the alternative treatment. The patients assessed changes in joint pain and stiffness after each treatment period on a 5-point categorical scale. General wellbeing, including mood, sleep quality and energy were also assessed and recorded in a personal diary.

The results in the two arms of the crossover differed markedly. Group A (placebo first) showed significantly more improvement from Hyben Vital than from placebo, $p=0.0078$ for pain and $p=0.0025$ for stiffness. But Group B (Hyben Vital first) revealed a positive effect of the same order as for Hyben Vital in group A, not only from the active drug, but also from placebo (difference not significant). An identical pattern was observed when we evaluated general wellbeing from the diary records. When patients, on the basis of reduction in joint pain, were divided into responders and nonresponders, the first 3 months of active treatment (group A) showed a response rate of 31/47 (66%) compared to that of placebo (group B) 18/50 (36%), $p=0.0185$: No major side effects occurred in either group. The data indicate that Hyben Vital reduces the symptoms of osteoarthritis. We interpret the marked differences in the responses of the two groups as indicating a strong "carryover" effect of Hyben Vital.

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Introduction

Inflammatory cells such as polymorphonuclear leukocytes are known to be causally involved in inflammation, in pain and tissue damage. The damage is caused by release of proteolytic and hydrophilic enzymes as well as toxic, reactive oxygen radicals derived from cells activated in the tissues and joints (Harris, 1988). The non-surgical therapy of osteoarthritis, a disease that attacks many of the middle-aged and the majority of the older population, involves alleviation of the symptoms associated with the disease, such as pain and stiffness, and the reduction of inflammation. Acetylsalicylic acid and a range of non-steroidal anti-inflammatory drugs including ibuprofen, indomethacin and naproxen, as well as glucocorticoids, have been used for the treatment of arthritis (Hochberg et al., 1995; Vane and Botting, 1998). These drugs have a variety of toxic and unwanted effects, including interference with haemostasis, gastric erosion and adverse effects on the liver and kidneys (Hochberg et al., 1995; Vane and Botting, 1998). Selective inhibitors of the cyclooxygenase-2 system have recently shown promising analgesic and anti-inflammatory properties, without the side effects mentioned. They are, however, still expensive and a negative effect on the circulatory system cannot be excluded (Mukherjee et al., 2001). Recently, acetaminophen was shown to worsen the risk of upper gastrointestinal complications (Rodrigues and Hernandez-Diaz, 2001). There is, therefore, still a need for a safe, low-cost remedy for the long-term treatment of symptoms in osteoarthritis. We have earlier shown that a standardised dry powder, Hyben Vital, made from the hips of a particular subtype of *Rosa canina*, reduced both chemotaxis and the generation of oxygen radicals in polymorphonuclear cells (Winther et al., 1999; Kharazmi and Winther, 1999).

The plants used for the current preparation of Hyben Vital powder are grown in standardised fields according to good agricultural practice.

Harvesting takes place when the fruits are mature and all fruits are brought to freezing facilities without delay. Later, the selection of optimal fruits for production of the powder is made by a laser technique and the temperature of the subsequent controlled drying process never exceeds 40 °C. The powder contains seeds as well as husks (*Rosae pseudofructus cum fructibus*) from a certain subtype of *R. canina*, by name LiTo, and is finally standardised to contain at least 500 mg Vitamin C per 100 g Hyben Vital powder. Further constituents are: pectins (total) 58.0 mg/g, β -carotene 57.9 mg/kg, β -sitosterol 0.5 mg/g, folic acid 1.6 mg/kg, Vitamin E 4.6 mg/100 g, Mg 170 mg/100 g, Zn 1.0 mg/100 g, copper 10.9 mg/100 g and non-quantified but reported flavonoids. The anti-inflammatory effect of the powder is not related to the well-known high vitamin C content of Rose hip extracts (Kharazmi and Winther, 1999). But we have earlier shown that, Hyben Vital modifies inflammation by reducing both chemotaxis and the generation of oxygen radicals in polymorphonuclear white cells (Winther et al., 1999; Kharazmi and Winther, 1999). Moreover, many volunteers have claimed that pain from osteoarthritis was diminished after a few weeks of treatment with the powder (Winther et al., 1999; Kharazmi and Winther, 1999). All these findings encouraged us to investigate whether Hyben Vital, in a larger controlled trial as now reported, would affect pain, stiffness and general wellbeing and the consumption of pain-reducing medicines, in particular paracetamol and the synthetic opioid Tramadol, in patients with osteoarthritis.

Methods

Patients

After we had obtained approval for the trial from the local Ethical Committee, 125 Caucasian out patients were enrolled through advertisements in local newspapers. The study was performed according to good clinical practice

and designed to accord, as far as possible, with the guidelines on conduct of clinical trials on osteoarthritis devised by the Osteoarthritis Research Society International. The only notable exception was that the study included patients with arthritis of various joints instead of confining it to a single joint (Altman et al., 1996). The volunteers all gave their oral and written informed consent. They had all been earlier diagnosed by their own general practitioner or local rheumatologist as suffering from osteoarthritis, and were reported to have an X-ray verified diagnosis and symptoms of primary osteoarthritis in the hip, knee, hand, shoulder or neck, or some combination of these, for at least the last 12 months. All reported pain of the affected joints of at least mild to moderate severity. We excluded patients with liver or kidney disease and those known to suffer from allergy or a history of drug or alcohol abuse. We also excluded patients with cancer, rheumatoid arthritis, fibromyalgia, gout, serious cardiovascular disease, asthma requiring treatment with steroids, and any other disease which would substantially influence the patients' quality of life. Likewise, we excluded those who had received intra-articular hyaluronate, glucosamine sulphate, immunosuppressive drugs such as gold or penicillamine or injections of glucocorticoids within the 6 weeks prior to the study, and patients who were found to be unable to co-operate after the first evaluation.

Trial design

The trial was of a double-blind, placebo-controlled, crossover design, and randomisation of treatment allocation was performed in blocks of four with the block size unknown to the investigators. The design had three immediately successive periods: a 14 days run-in period followed by randomised allocation of the two treatment periods of 3 months each. The two primary efficacy parameters were: change in joint pain and the alteration of consumption of concomitant "rescue" medication for alleviating pain, evaluated after each of the two, blinded, 3-months treatment periods. The three secondary efficacy parameters were: joint stiffness, general wellbeing including mood, energy and sleep quality, and a subjective overall evaluation of preference for one or other of the study medications. The run-in period was intended primarily for patients to become accustomed to the ideas of the trial, and to be instructed in and practise the daily subjective assessment/ record-keeping required, rather than as a formal "baseline". However, we took the opportunity during this period to measure

blood pressure and removed a routine blood sample for measurement of haemoglobin, creatinine, sodium and potassium, blood glucose and cholesterol. The patients were then randomly allocated, in blocks of four, by a computer-generated allocation schedule, to receive capsules containing either a biologically standardised rose hip powder (Hyben Vital) or an identical placebo. The capsules were kept in numbered containers. The daily dosage was five 0.5 g capsules a.m. and p.m. One or other of the responsible investigators enrolled all patients. The patients as well as the research team were kept blind throughout the study. After 3 months, the groups switched immediately to the alternative treatment for a further 3 months. Immediately after each of the two treatment periods, a further routine blood sample was taken and blood pressure was measured. When the trial had been completed, all data were entered onto the spreadsheet, after which the treatment code was broken and patients were separated into two groups according to the treatment sequence they had received. It transpired that Group A started out with 56 randomised patients who took placebo first, followed by Hyben Vital, while Group B comprised the same number of randomised patients who took Hyben Vital first, followed by placebo (Fig. 1). The data for the two groups separately were also entered on the spreadsheet, which was then mailed to the statistician, who was also kept blind as to the treatment code.

Methods of assessing clinical effect

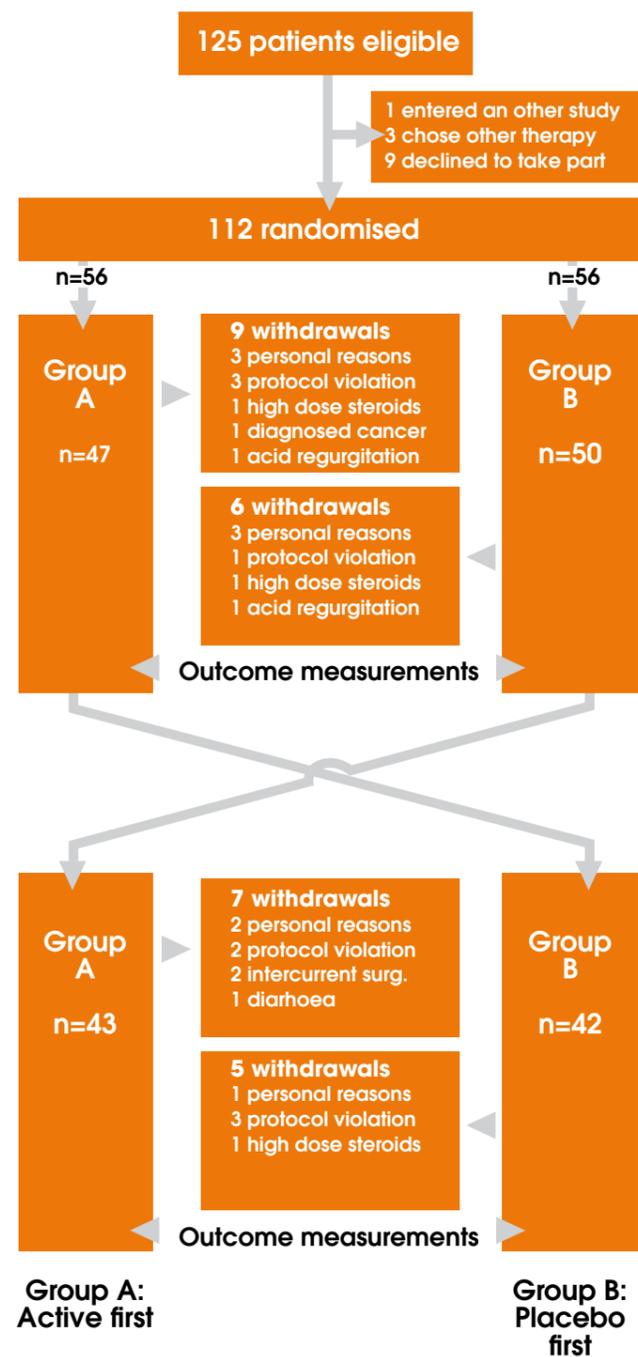
Primary efficacy parameters

The cardinal item of information obtained was the end-of-treatment subjective assessments of any changes in pain that had occurred during each of the treatments. These were estimated by the patients on a 5-step categorical scale ranging from 0 (no change) to 4 (almost total relief of pain). Here, the higher the score the greater the clinical benefit, a rise of 1 category representing 25% improvement. This technique also allowed us to calculate the number of responders and non-responders in each group.

Each type of "rescue" analgesic consumed was noted daily by the volunteers in a diary. All patients taking NSAIDs regularly on prescription from their general practitioners were advised to continue such treatment, without any change in dosage, throughout the study. Three weeks into each of the two treatment periods we recommended the patients to reduce their consumption of concomitant pain-relieving medicine, if at all possible. Consumption of such medication

was recorded daily in a diary, and at the end of each 3-months treatment period we calculated the consumption of each type of non-trial pain-relieving medicine. As patients normally use a wide range of rescue medications, we simplified accounting of them by transformation into paracetamol equivalents, as devised by the Danish Health Authorities (Lægemiddelkataloget, 2002). Thus 25 mg of Tramadol and 25mg of codeine would be considered as equivalent to 1000 mg paracetamol and aspirin would be considered equal to paracetamol.

Fig. 1. Flow-chart showing the dropout rate of the different time points of the study.



Secondary efficacy measures

The patients made a subjective assessment of joint stiffness at the end of each treatment period, on a 5-step categorical scale ranging from 0 (no change) to 4 (almost total relief of the symptom), as devised for pain. In addition, the patients made a daily subjective assessment of the severity of joint pain (in the morning and later in the day), stiffness (in the morning and later in the day) and the state of wellbeing, sleep, energy, and mood was recorded by the patient in a diary. Each aspect was assessed and recorded on a separate 10-point categorical scale, where an increasing score denoted increasing disability. An average of each kind of measurement was taken for statistical comparison of treatments.

Patients' overall evaluation of the study medication

On the final day of the trial, before the treatment code had been broken, the supervising physician asked this question of the patient: Taking all aspects into consideration, did you develop a definite preference for one of the treatments, or not?

Statistical techniques

We based the sample size on results from an earlier clinical trial using the same dry powder. Data from all the randomised patients were entered on the spreadsheet. Statistical evaluation was based on the intention to treat (ITT), with the last value carried forward. We applied Wilcoxon's test for matched pairs when evaluating the study as a simple crossover trial and when we compared effects occurring within the same group of patients. The Mann-Whitney test was applied to comparison of groups A and B after 3-months treatment. The only exceptions were simple yes/no questions, to which Fisher's test was applied. Data given are mean \pm SD. Any p value equal to or <0.05 was regarded as statistically significant.

Results

Description of patients

Of the 125 eligible patients who responded to our advertisement, we eventually enrolled 112, including 71 women, mean age 68 years (range 33–93) and 41 men, mean age 64 years (range 35–89) (see flow diagram of Fig. 1).

Matching of groups

Details are given in Table 1. The two groups were virtually identical in their demographic data, in the severity and distribution of osteoarthritis and in their consumption of rescue medication; in-

deed, there was no significant between-group difference in any of the 16 items of Table 2. The mean body mass index for the included patients was 26.9, range 18–42 kg/m². Although only 85 patients completed the trial, the two final groups of per-protocol patients were still not significantly different. We consider the groups therefore to have been very well matched (Table 1).

Fifteen patients dropped out before the first 3 months period was finished, leaving 97 patients for the second part of the study and 85 completed both treatment periods (Fig. 1). Before the code was broken, a further 5 were excluded because of protocol violation detected on evaluation of the patient's record form before the data were entered on the spreadsheet. This left 80 patients, 46 women and 34 men, for a per-protocol analysis. Of the randomised pati-

ents, 59 had arthritis of the knee, 46 of the hip, 40 had involvement of the hands, 18 of the neck and 14 of the shoulder or a combination of these different joints. The dropouts were correspondingly represented by all the different joints mentioned and there were no major disagreements between the ITT and the per-protocol analysis—hence we refer only to the ITT analysis if not otherwise stated. Of the included patients, 40 were taking NSAIDs regularly, 40 paracetamol, 12 Tramadol, 3 codeine, 2 Aspirin, 2 morphine, and 1 dextropropoxyphen. Thirty of the patients took no rescue medication whatever. When a subanalysis of the initial values of the placebo-first group (n = 56) versus the active treatment first group (n = 56) were made, there were no significant differences in body mass index, age, sex, joints involved, consumption of NSAID and rescue medication (Table 1).

Table 1. Baseline demographic and osteoarthritic characteristics of the study population

	Intention-to-treat population		Per-protocol-population	
	Placebo treatment (n = 56)	Active treatment (n = 56)	Placebo treatment (n = 39)	Active treatment (n = 56)
Age (years)	66.8 \pm 11.8	67.1 \pm 11.6	67.5 \pm 10.6	67.0 \pm 10.8
Sex				
Women	34	37	21	26
Men	21	20	18	15
BMI (kg/m ²)	26.8 \pm 5.0	27.7 \pm 4.9	27.7 \pm 4.9	27.5 \pm 5.5
No. of patients with OA of the hip	20	26	15	21
No. of patients with OA of the knee	30	29	24	24
No. of patients with OA of the neck	11	7	10	6
No. of patients with OA of the shoulder	7	7	6	6
No. of patients with OA of the hand	17	23	15	19
No. of patients on NSAIDs	20	20	17	19
No. of patients on paracetamol	21	19	18	16
No. of patients on tramadol	7	5	6	4
No. of patients on codein	1	2	0	0
No. of patients on aspirin	1	1	1	1
No. of patients on morphine	1	1	1	1
No. of patients on dext. ppoxy. phen.	1	0	0	0
No. of patients with no medication	26	24	19	18

Compliance

Compliance, as calculated from the proportion of study medication (number of capsules) returned by the patients, was 92.8 \pm 11% for Hyben Vital and 90.6 \pm 11% for placebo (nonsignificant difference). Compliance in the placebo-first group was 92.3 \pm 10.0% and for active treatment first 90.5 \pm 8.0% (nonsignificant difference).

Primary efficacy measures: pain

Details are given in Table 2. The most important item of clinical information—the patients' final evaluations of change in pain—showed a remarkable difference between the groups. In group A (placebo first), there was a highly significant difference in favour of Hyben Vital—a

mean rise from 1.02 \pm 1.45 after placebo (an improvement of 25%), to 1.91 \pm 1.43 (an improvement close to 50% of the improvement scale) observed after 3 months of Hyben Vital treatment, $p < 0.0078$. But group B (starting with active treatment) showed no significant difference between the two treatments: 1.45 \pm 1.28 units for active treatment, as compared with 1.72 \pm 1.37 for placebo, $p = 0.6084$. Table 2, upper panel, and the histograms of Figs. 2A and B illustrate the large between-treatment differences, when groups A and B are compared. Group A patients showed a marked difference between the two treatments at every degree of response, while B showed no consistent pattern of difference between treatments. The carryover effect that we postulate as re-

sponsible for this between-groups discrepancy (see also Discussion) likewise blunted the level of significance when the two treatment groups were lumped together: there was again no significant difference between the effects of the two treatments ($p < 0.0991$), data not shown. An evaluation of between-group differences after only 3-months treatment did not attain statistical significance, although an improvement of 50% was observed in favour of active treatment ($p < 0.101$) data not shown.

We also made an alternative analysis of the data by identifying two categories of subject—“responders” who by definition showed at least one category of improvement and “non-responders”, who showed less improvement than this. If we compare the A and B groups after the first 3 months of treatment, the overall outcome of the analysis is that 31/47 (66%) of subjects responded to Hyben Vital, while 18/50 (36%) responded to placebo and this was significant at $p < 0.0128$. The corresponding per-protocol evaluation yielded a p value of 0.0428.

Table 2. Pain given on a scale from 0 (no reduction) to 4 (almost total relief of pain), consumption of rescue medication given as paracetamol equivalents (g)

	Placebo	Active treatment	p-value
Group A: Placebo first, then active treatment			
Pain	1.02 ± 1.45	1.91 ± 1.43	0.0078
Rescue medication	227.40 ± 249.50	127.90 ± 143.30	0.0024
Stiffness	0.91 ± 1.38	1.91 ± 1.25	0.0025
Group B: Active treatment, then placebo			
Pain	1.45 ± 1.28	1.72 ± 1.37	0.6084
Rescue medication	127.50 ± 94.00	77.70 ± 51.1	0.1452
Stiffness	1.28 ± 1.35	1.71 ± 1.47	0.3850

Stiffness estimated on a scale from 0 (no reduction) to 4 (almost total relief of stiffness) is given for groups A and B. Data given are mean ±SD.

Primary efficacy measures: pain

Twenty-three patients handed in medical diaries adequate for ITT analysis of their use of NSAIDs in accordance with the protocol. Consumption during the two treatment periods was found to be identical (data not shown). Paracetamol and acetylsalicylic acid were administered as 500 mg tablets and Tramadol and codeine as 50 and 25 mg tablets, respectively. Twenty-five patients handed in medical diaries adequate for ITT analysis of their daily use of paraceta-

mol and seven and four and two patients, respectively, handed in diaries adequate for ITT analyses of their daily use of Tramadol, codeine and Aspirin. A pattern very much like that previously described for pain, occurred. Group A, placebo first, data available from 12 patients, showed after 3 months a mean consumption of 227.4 ± 249.5 g. However, this consumption was reduced to 127.9 ± 143.3 g after 3 months of active drug treatment. This decline of 99.4 ± 163.9 g ($p < 0.0024$) comprised a 44% reduction. The B group, active treatment first, with data available from 15 volunteers, showed after the first 3 months of active treatment a mean value of 129.50 ± 91.00 g, a value close to what was observed in the second active treatment phase of the group A patients (see Table 2). A further 3 months placebo treatment, in the B group, resulted in a non-significant decline to 77.70 ± 51.1 g (Table 2). No significant change was present when the two groups were lumped together ($p < 0.1420$), data not shown. An evaluation of the two groups after 3-months treatment showed placebo values of 227.4 ± 249.5 g and active values of 128.4 ± 94.3 g. The reduction, in favour of active treatment, was 44%, but was not statistically significant. When, however, a subanalysis was made on the delta change in consumption of rescue medication from the beginning of each of the two 3-months treatment periods (the two initial weeks of treatment) to the end of each of the respective periods (the final two weeks of the 3-month treatment period), there was a significant reduction in consumption of rescue medication from active treatment, when comparing placebo and active treatment ($p < 0.006$), data not shown.

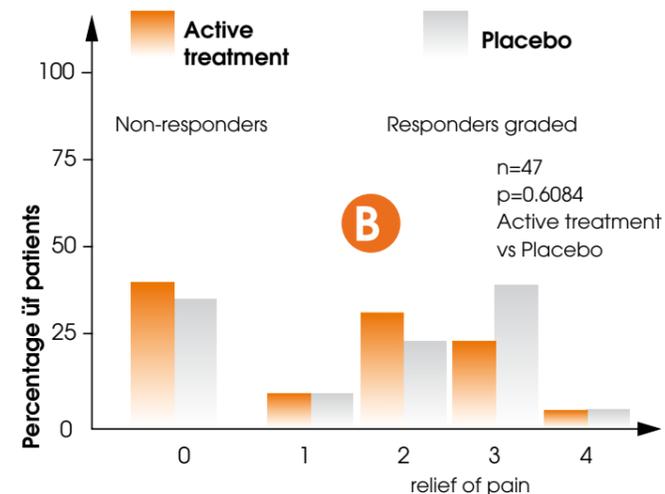
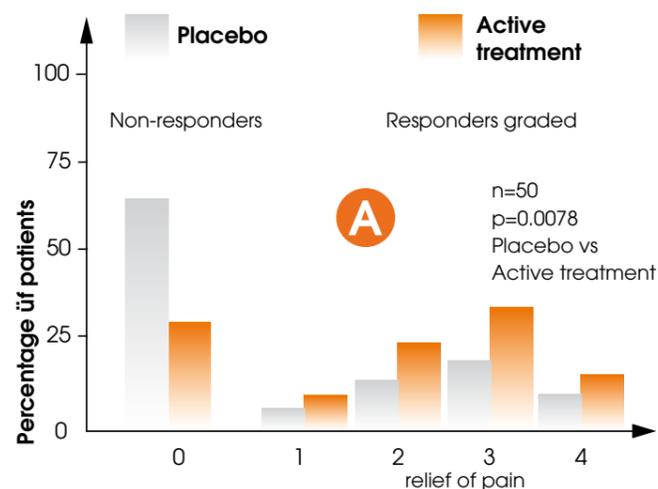


Fig. 2. (A) Histograms comparing, in group A subjects (placebo first then Hyben Vital), the degree of improvement in pain relief from placebo (white columns) as compared with Hyben Vital (shaded columns). The height of each column indicates the percentage of patients who experienced pain relief of category 0, 1, 2, 3 or 4, corresponding to 0%, 25%, 50%, 75% or 100% relief of pain (p value refers to the added scores comparing the two different treatments). (B) Histograms comparing in group B subjects (Hyben Vital first then placebo), the degree of improvement in pain relief from Hyben Vital (shaded columns) as compared with placebo (white columns). The height of each column indicates the percentage of patients who experienced a given pain relief of category 0, 1, 2, 3 or 4, corresponding to 0%, 25%, 50%, 75% or 100% relief of pain (p value refers to the added scores comparing the two different treatments).

Secondary efficacy measures

Joint stiffness, tested on a scale from 0 (no improvement at all) to 4 (almost total relief of stiffness) revealed an almost identical pattern to that found for pain. In group A, the initial placebo value was 0.91 ± 1.38 (an improvement of 23% on the scale) as compared to 1.91 ± 1.25 (an improvement of 48%) while on Hyben Vital therapy), $p < 0.0025$. Group B, however, showed no significant difference between treatments: Hyben Vital 1.28 ± 1.35 versus placebo 1.71 ± 1.47, $p < 0.3850$ (Table 2). Nor was there any significant difference when the two groups were taken together ($p < 0.1612$), data not shown. A comparison of the two groups after 3 months of treatment, although in favour of active treatment, did not attain statistical significance ($p < 0.153$), data not shown. The diary records of joint pain and stiffness in the morning and later in the day, wellbeing, mood, energy and sleep, available in diaries from 47 patients, showed the

same sharp distinction between groups as for the primary parameters. The placebo-first group A ($n = 26$) showed, in all measurements a distinct difference in favour of Hyben Vital. The change was highly significant, stiffness and pain in the morning giving p values of 0.0016 and 0.0127, respectively, and sleep quality, mood and general wellbeing, 0.0096, 0.0124 and 0.0164, respectively. But in the Hyben-first group B, the two sets of results appeared indistinguishable, and there was not a single instance of anything approaching a statistically significant difference between the two treatment groups, as shown by a mean p level of more than 0.50 (details not shown). The majority of the significant changes observed in favour of active treatment in the placebo-first group, were confirmed, when subanalysis comparing the A and B group after 3-months treatment was made: stiffness in the morning, $p < 0.054$; pain in the morning, $p < 0.036$; general wellbeing, $p < 0.012$; mood, $p < 0.017$; and sleep quality, $p < 0.005$.

Patients' preference for treatment

The separate groups again showed a large difference, similar in pattern to that described above. In group A, 24 patients reported that they felt most improvement from Hyben Vital, while 8 patients preferred placebo and 9 were not sure ($p < 0.0070$). In group B, 12 patients preferred the first treatment (Hyben Vital) whereas 20 voted for placebo treatment and 8 did not have any preference ($p < 0.2153$). Comparison of the A and B groups (Fisher's test) gave a p value of < 0.0040 in favour of Hyben Vital.

Routine screening tests

Haemoglobin, blood glucose, creatinine and sodium and potassium levels were unaffected by either treatment. Nor were there any changes when those patients with blood glucose levels above 5.5 mmol/l were analysed separately. An unexpected finding was that Hyben Vital resulted in a small but significant 8.5% fall of total cholesterol.

Unwanted effects

Although 27 of the original 112 subjects recruited dropped out during the 6-months treatment period, only 3 of these defaulted because of adverse effects: acid regurgitation occurred in one patient during placebo therapy and in one during active treatment, and one other patient with diarrhoea dropped out while on placebo; for details see Fig. 1. In the remaining group there were 12 who reported milder unwanted effects. These were as follows: frequency of micturition 4 (three while on active treatment and

one while on placebo); waterbrash 3 (present in both treatments); diarrhoea 2 (present in both treatments); constipation 2 (1 during placebo and 1 during both treatments); urticaria 1 (while on placebo). There were no major side effects of any kind in the whole group.

Discussion

Interpretation of trial results

The chief advantage of a crossover trial, as used here, is that in comparing the effects of two successive treatments on the same "arm" of the trial, each patient acts as his/her perfect control, so concern about mismatching of the groups—an important source of error—can be forgotten. A wholly uncomplicated crossover trial with a positive result can be expected to yield three pieces of information: a within-group significant comparison of the two test substances—one from each of the two arms of the trial (and more or less identical with each other), and a significant between-groups comparison at the crossover point, provided that the groups have been well matched, since in this case the patients do not act as their own controls.

Looking at the results of the trial described here, it is obvious that they are far from this idealised pattern. That arm of the trial given placebo first does show a significant, clear-cut difference between the effects of the two test substances. So far so good, but the other arm—active substance first, placebo second—shows no significant difference between the two. We believe that by far the most likely explanation of this discrepancy between the two arms of the trial is a strong "carryover" effect of Hyben Vital. This is a common, major complication of crossover trials and the reason for the inclusion of a "washout" period after crossover.

The usual tactical response is to write off all data after the crossover point and to supplement the single withingroup result obtained in the placebo-first arm, with a between-groups comparison at the crossover point. But this, using the primary efficacy data of Table 2, also gave a non-significant result. This raises the possibility that a carryover effect is not the whole explanation—a slow onset of the active drug effect could be another factor. The strength and significance of the difference between placebo and active drug seen in Group A is supported by several ancillary aspects. If the reduction in pain sensation was evaluated after 3-month treatment on a yes/no basis, there was a significant reduction of pain from active treatment when compared

to placebo. In agreement with this finding, preference for treatment A or B was also in favour of active treatment and the diary recordings on pain, general wellbeing, mood and sleeping quality were all statistically significant in favour of active treatment. Taken together these findings seem to fully justify confirmation of the action of Hyben Vital by a large-scale, parallel, placebo-controlled, blind study, and this is our intention.

R. canina (the "dog rose", the common wild-briar rose of English hedgerows) is said to have been so named because the ancient Greeks believed its root to be effective against the bite of a mad dog (Brewer, 1981). In this context, Pliny the Elder used the plant's classical Greek name "cynorrhodos", combining the verbal roots of "dog" and "red" (Pliny, 1966). Although Hyben Vital has been marketed in Scandinavia for several years, modern European interest in the plant has been concentrated on preparations made from the hips rather than the root, mainly because of their high content of vitamin C, and herbal tea infusions of "cynorrhodon" are still used today.

It is widely known that rose hips contain significant amounts of vitamin C, but it seems highly unlikely that this accounts for much, or indeed any, of the activity of Hyben Vital in this trial. A large-scale study in 1996 on the Framingham population group showed that the middle and highest tertiles of daily dietary vitamin C intake did protect against the long-term progression of knee osteoarthritis (especially against loss of cartilage). But the lowest intake tertile—a daily mean of 81 mg for men and 94 for women—had no such protective effect (McAlindon et al., 1996). The vitamin C content of a Hyben Vital dosage of 5 g daily, as used in this trial, is only 26 mg, i.e. only one-third of the Framingham lowest tertile and therefore very unlikely to contribute significantly to the action of Hyben Vital.

We have earlier shown that Hyben Vital significantly reduces the migration of neutrophils, when estimated after 1 month of treatment (Winther et al., 1999; Kharazmi and Winther, 1999). One explanation for the lessening of symptoms during Hyben Vital treatment could therefore be a reduction of the inflammation that is an integral part of the pathogenesis of osteoarthritis (Harris, 1988). This hypothesis has gained increasing interest, as an active ingredient that inhibits neutrophil chemotaxis, has now been isolated from the present subtype of Rose hip (Larsen et al., 2003). If the present suggestion is

correct, it could also explain the pronounced carryover effect; once inflammation has subsided, it requires a certain interval of time before the process can be reactivated. As rose hips have been used in daily household use for centuries, it is surprising that their anti-inflammatory property has not been detected before now. A possible explanation is that different species of Rose hip vary in their anti-inflammatory properties (Brandt and Akesson, 2002). In another study testing a possible interaction between Rose hip and warfarin, we could not show any effect on coagulation and platelet aggregability (Winther, 2000). This suggests that Rose hip, unlike NSAID, aspirin and ginger—another natural remedy also used for symptoms of osteoarthritis (Altman and Markussen, 2001)—does not affect the arachidonic acid and cyclo-oxygenase system. This could explain why the incidence of side effects is lower for Hyben Vital than for the therapies mentioned above.

Conclusion

We have found that the herbal remedy Hyben Vital has a moderate alleviating effect on joint pain and improves general wellbeing, sleep quality and mood in patients with osteoarthritis, without producing any side effects. We consider that the results warrant a largescale double-blind, long-term, placebo-controlled and parallel study of Hyben Vital.

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THE EFFECTS OF A STANDARDIZED HERBAL REMEDY MADE FROM A SUBTYPE OF ROSA CANINA IN PATIENTS WITH OSTEOARTHRITIS: A DOUBLE-BLIND, RANDOMIZED, PLACEBO-CONTROLLED CLINICAL TRIAL

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Background: A standardized rose-hip powder produced from the seeds and husks of fruit from a subtype of *Rosa canina* has been reported to inhibit leukocyte functions that cause cell injury in osteoarthritis.

Objective: The aim of this study was to assess the impact of standardized rose-hip powder on mobility of the hip and knee joints, activities of daily living, quality of life, and pain in patients with osteoarthritis.

Methods: Patients with a diagnosis of osteoarthritis of either the hip or knee, verified on radiography, participated in this randomized, placebo-controlled, double-blind study. Half of the patients were given five 0.5-g capsules of standardized rose-hip powder twice daily for 4 months, and the other half received identical placebo capsules twice daily for the same period. Mobility of the hip or knee was measured in both groups after the initial screening and again after 4 months of therapy.

Results: One hundred patients (65 women, 35 men; mean (SD) age, 65.2 (11.1) years) were divided into 2 treatment groups of 50 patients each. Hip joint mobility improved significantly in the treatment group compared with the placebo group ($P=0.033$). Similarly, pain decreased significantly in the treatment group compared with the placebo group ($P=0.035$). Two patients (4%) from each group withdrew during the early stages of the trial for reasons not related to treatment.

Conclusions: In this study population, standardized rose-hip powder reduced symptoms of osteoarthritis, as 64.6% of patients reported at least some reduction of pain while receiving treatment. Standardized rose-hip powder may improve hip flexion and reduce pain in patients with osteoarthritis. (Curr Ther Res Clin Exp. 2003;64:21–31) Copyright © 2003 Excerpta Medica, Inc.

Key words: osteoarthritis, stiffness, pain, rose-hip powder, *Rosa canina*.

Introduction

During the past decade, the commonly used drugs for osteoarthritic pain were aspirin, other nonsteroidal anti-inflammatory drugs (NSAIDs), and corticosteroids. 1 However, side effects have been associated with prolonged use of these drugs. During the past 5 years, selective inhibitors of cyclooxygenase-2 (an enzyme involved in the synthesis of proinflammatory cytokines) have shown promising analgesic and anti-inflammatory actions without serious adverse effects. 2 However, these drugs are expensive, and the need remains for a lowcost, safe remedy for long-term treatment of osteo-

oarthritis. As a possible alternative, a standardized rose-hip powder* made from the seeds and husks of fruit from a subtype of *Rosa canina* is available. This powder inhibits leukocyte functions that cause cell injury in osteoarthritis. The plants are grown according to good agricultural practice in standardized fields in Denmark and Sweden. When the fruits are mature, they are harvested and frozen immediately. Selection of optimal fruits for later production of powder is made by a laser technique, and the computerized drying process does not exceed 40 C. The vitamin and mineral content of the powder is controlled. Uncontrolled exploratory trials^{3,4} of

this standardized dry rose-hip powder showed analgesic action in patients with osteoarthritis. This finding was evidenced by a mean (SD) decrease in the serum concentration of C-reactive protein from 8.25 (4.9) mg/L before treatment to 6.67 (2.6) mg/L after treatment, and inhibition of polymorphonuclear chemotaxis. These findings were sufficient to encourage the present trial. The aim of this study was to assess the impact of the standardized rose-hip powder on mobility of the hip and knee joints, activities of daily living (ADLs), quality of life, and pain in patients with osteoarthritis.

Patient and methods

This was a single-center, double-blind, randomized, placebo-controlled study. All patients had a diagnosis of osteoarthritis of the hip or knee, verified on radiography, within 12 months before the study. Patients with pain for 6 months and who were on a waiting list for either hip or knee surgery, or on a list for final evaluation for surgery, were included. Patients who reported allergy to plant products or who had severe asthma or liver disease were excluded. All patients provided written informed consent to participate, and approval from the ethics committee of the study site (an outpatient clinic in Norway) was obtained.

Patients were randomized in groups of 10 using an independent computerized system. One group was randomized to treatment with five 0.5-g capsules of standardized rose-hip powder twice daily for 4 months. The other group received the same quantity of placebo capsules (identical in appearance, taste, and smell to the rose-hip powder capsules) for the same time period as the active treatment group.

Primary Outcome Measures

Mobility of the hip or knee was measured in both groups after the initial screening and again after 4 months of therapy. Mobility measurements included the full range of external and internal rotation of the hip; maximum flexion and extension of the hip and knee measured using a goniometer (Gallus Plesner, Oslo, Norway) during passive movement; and active voluntary rotation, flexion, and extension by the patient. Goniometry can result in some variation if the test is not conducted by the same researcher at each visit. For that reason, all measurements were taken by the same investigator and data given are expressed as the mean of 3 test episodes. The measurements of joint movement are presented in 2 ways: as the numeric measurements taken and also as a degree of restriction, calcu-

lated by subtracting these measurements from a standard value of 125° for hip flexion, 140° for knee flexion, and 45° for external and internal hip rotation.⁵

Secondary Outcome Measures

At the start of the trial and again after 1, 2, and 4 months of treatment, patients recorded any difficulties in performing ADLs, such as walking, getting into and out of a car, shopping, and getting up and down from the lavatory. The difficulty was estimated on a visual analog scale ranging from 0 (no difficulty) to 10 (great difficulty). After 4 months of therapy, patients gave their overall assessment of the effectiveness of the study medication on relief of joint pain using a categorical scale of 0 (no improvement) to 4 (almost total relief of pain). The patients also were asked about relief of pain on a simple yes-or-no questionnaire after 1, 2, and 4 months of treatment.

During the trial, patients were asked to maintain their daily dosage of NSAIDs. Any changes that did occur were to be recorded in a diary. Compliance was estimated by counting the number of capsules returned by patients. Adverse events were recorded on the case-report forms completed at each visit.

Statistical Analysis

Statistical analysis was performed on an intent-to-treat basis. Results in the 2 groups were compared using the Mann-Whitney test for parallel data. The Wilcoxon signed rank test for matched pairs was used to compare baseline findings with those after 1, 2, and 4 months of treatment in each group separately. The chi-square test was used for the questionnaires. All data are presented as mean (SD). Statistical significance was set at $P<0.05$.

Results

One hundred patients (65 women, 35 men; mean (SD) age, 65.2 (11.1) years) were enrolled. The treatment group comprised 34 women and 16 men (mean (SD) age, 65.1 (12.2) years). The placebo group comprised 31 women and 19 men (mean (SD) age, 65.3 (9.9) years). The demographic and osteoarthritic characteristics of the 100 patients entering the study (intent-to-treat population) and of the 96 patients who completed the study (per-protocol population) are shown in Table I. The demographic characteristics and consumption of medicine were similar in the intent-to-treat and per-protocol populations. At baseline, active flexion of the hip, however, was significantly different in

the active-treatment group versus the placebo group in both the intent-to-treat and the per-protocol populations. Active external rotation of the hip was significantly different in the active-treatment group compared with the placebo group only in the intent-to-treat population. All passive movements were comparable between groups.

Among the 100 patients, there were 44 hip joints (25 in the treatment group, 19 in the placebo group) and 56 knee joints (25 in the treatment group, 31 in the placebo group) involved in the trial. All patients had experienced osteoarthritic pain for 2 to 12 years. Four patients (4%)

withdrew during the early stages of the trial: 1 woman and 1 man in the placebo group because of cardiac problems and a sore throat, respectively, and 1 woman and 1 man in the treatment group due to the possibility of hip surgery earlier than expected and because of the desire not to continue, respectively. These 4 patients comprised 3 hip joints (1 in the treatment group and 2 in the placebo group) and 1 knee joint (in the treatment group). The baseline demographic characteristics, medication, and osteoarthritic characteristics of the 2 groups were similar, except for range of motion for active hip flexion and active external hip rotation ($P=0.041$ for treatment group vs placebo group).

Table I. Baseline demographic and osteoarthritic characteristics of the study population.

	Intent-to-Treat Population		Per-Protocol Population	
	Placebo (n=50)	SRHP (n=50)	Placebo (n=48)	SRHP (n=48)
Age, y*	65.3 (9.9)	65.1 (12.2)	65.8 (14.7)	65.5 (14.2)
Sex, no. (%)				
Woman	31 (62.0)	34 (68.0)	29 (60.4)	33 (68.8)
Man	19 (38.0)	16 (32.0)	19 (39.6)	15 (31.3)
No. (%) of patients with OA of the hip	19 (38.0)	25 (50.0)	17 (35.4)	24 (50.0)
No. (%) of patients with OA of the knee	31 (62.0)	25 (50.0)	31 (64.6)	24 (50.0)
Hip joint movement, deg*				
Passive flexion	111.05 (12.76)	116.00 (13.92)	111.47 (13.20)	115.62 (14.09)
Active flexion	97.63 (15.49)	105.60 (13.10) [†]	97.94 (16.01)	105.42 (13.34) [†]
Passive external rotation	19.72 (11.56)	26.40 (9.74)	20.00 (16.01)	25.62 (9.13)
Active external rotation	13.06 (10.17)	20.00 (9.79) [§]	13.44 (10.76)	19.17 (9.05)
Passive internal rotation	28.61 (11.61)	28.80 (13.17)	29.37 (12.09)	28.75 (13.45)
Active internal rotation	21.39 (10.68)	21.20 (12.61)	22.19 (11.10)	21.04 (12.85)
Knee joint movement, deg*				
Passive flexion	128.71 (14.37)	132.40 (9.14)	128.71 (14.37)	132.08 (9.20)
Active flexion	123.55 (14.73)	124.80 (11.77)	120.35 (24.95)	124.58 (11.97)
No. (%) of patients taking concomitant medication				
None	15 (30.0)	11 (22.0)	14 (29.2)	10 (20.8)
NSAIDs	20 (40.0)	24 (48.0)	19 (39.6)	23 (47.9)
Paracetamol	12 (24.0)	14 (28.0)	12 (25.0)	14 (29.2)
Opioids	2 (4.0)	0 (0.0)	2 (4.2)	0 (0.0)
Asthma medication	2 (4.0)	0 (0.0)	2 (4.2)	0 (0.0)
Antihypertensive	2 (4.0)	2 (4.0)	2 (4.2)	2 (4.2)
Heart disease medication	5 (10.0)	3 (6.0)	5 (10.4)	3 (6.3)

SRHP=standardized rose-hip powder; OA=osteoarthritis; NSAIDs=nonsteroidal anti-inflammatory drugs.

*Values are expressed as mean (SD). [†] $P=0.020$ versus placebo. [‡] $P=0.039$ versus placebo. [§] $P=0.041$ versus placebo.

Effects of 4 Months' Treatment on Joint Movement

Patients receiving standardized rose-hip powder showed significant improvements at 4 months in passive hip flexion ($P=0.003$), external rotation ($P=0.006$), and internal rotation ($P<0.001$) (Table II). The placebo group showed a significant improvement in passive hip internal rotation

($P=0.031$), but not in flexion or external rotation. The between-group comparison at 4 months showed a significant difference in improvement in passive hip flexion ($P=0.033$), but not in internal or external rotation.

The same patterns of change in joint movement (and in P values) were found when hip flexion

and rotation were actively performed by the patients (Table III). However, it should be noted that the baseline values for active hip flexion and active external hip rotation were not identical in the 2 groups (Table I), which makes the interpretation of these results difficult.

Changes in passive flexion of the knee did not differ significantly between the 2 groups (data not shown). Active treatment resulted in a mean (SD) improvement of 2.71 (4.42°) ($P=0.012$); this value improvement was 3.75° (5.32°) in the placebo group ($P=0.005$). A similar pattern occurred when flexion was performed actively by the patients at the request of the researcher.

Activities of Daily Living

Changes in difficulty performing ADLs did not differ significantly between the 2 groups. Significant improvement was observed in the following ADLs in the placebo group after 1 month of treatment: walking down the street ($P<0.05$), getting into and out of a car ($P=0.258$), shopping ($P<0.001$), putting on/taking off stockings ($P=0.251$), and getting up and down from the lavatory ($P=0.154$). After 2 months of treatment,

the following improvements were observed in the placebo group: walking down the street ($P<0.05$), getting into and out of a car ($P<0.001$), putting on/taking off stockings ($P<0.001$), and getting up and down from the lavatory ($P=0.274$). These improvements were not found at 4 months of treatment in the placebo group. In contrast, the group treated with the standardized rose-hip powder showed significant changes in the majority of ADL functions after 1 month of treatment, as follows: walking down the street ($P<0.001$), getting into and out of a car ($P<0.05$), shopping ($P<0.001$), putting on/taking off stockings ($P<0.001$), and getting up and down from the lavatory ($P<0.05$). After 2 months of treatment, improvement was found in all of these ADLs ($P<0.001$ for all), and this group continued to show significant improvement in the majority of ADL performances at month 4 compared with baseline, as follows: walking down the street ($P=0.038$), getting into and out of a car ($P=0.054$, borderline significant), shopping ($P=0.024$), putting on/taking off stockings ($P=0.019$), and getting up and down from the lavatory ($P=0.016$).

Table II. Passive hip joint movements before therapy and standardized rose-hip powder (SRHP) and placebo.

Type of Movement	Baseline, deg*	Restriction of Movement, deg	At 4 Months of Therapy, deg*	Improvement, %
Flexion				
SRHP	116.00 (13.92)	9.0	119.37 (14.09) ^{†‡}	40.0
Placebo	111.05 (12.76)	13.9	112.38 (14.27)	6.7
External rotation				
SRHP	26.40 (9.74)	18.6	28.96 (8.84) [§]	17.1
Placebo	19.72 (11.56)	25.3	22.50 (11.40)	10.0
Internal rotation				
SRHP	28.80 (13.17)	16.2	34.38 (13.41)	35.0
Placebo	28.68 (11.61)	16.4	33.13 (12.09)	24.0

*Values are expressed as mean (SD). [†] $P=0.003$ versus pretreatment. [‡] $P=0.033$ versus placebo.

[§] $P=0.006$ versus pretreatment. ^{||} $P=0.001$ versus pretreatment. ^{|||} $P=0.031$ versus pretreatment.

Joint Pain

Significantly greater relief of joint pain was found in the group receiving standardized rose-hip powder than in the placebo group after 4 months of treatment ($P=0.035$; Figure). At month 4, 31 of 48 (64.6%) patients in the active treatment group reported some effect, ranging up to almost total relief of pain, whereas 17 of 48 (35.4%) patients reported no effect. In the placebo group, 27 (56.3%) patients reported no effect of treatment, whereas 21 (43.8%) patients reported various degrees of improvement. When pain relief was assessed on a yes-or-no basis, significantly more patients in the treatment group compared with the placebo group indi-

cated that they had pain relief at both 1 month ($P=0.014$) and 4 months ($P=0.046$) of treatment, but not at 2 months of treatment.

Compliance, Concomitant Medication, and Tolerability

Compliance was 98% in the treatment group and 97% in the placebo group. Although patients were asked to maintain their daily doses of analgesic therapy throughout the study, in the group receiving the standardized rose-hip powder, 7 (14.6%) patients reduced their consumption of NSAIDs, and none increased it. In contrast, 4 (8.3%) patients in the placebo group decreased their consumption of NSAIDs, and 4 (8.3%)

patients increased it. The decrease in NSAID use in the treatment group was statistically significant ($P < 0.016$); however, the between-group difference was not. Three (6.3%) patients in the treatment group and 2 (4.2%) in the placebo group decreased their consumption of paracetamol. In the placebo group, 1 of the 2 (50%) patients taking an opioid drug (tramadol) reduced their consumption of that drug.

The only adverse event reported was mild gastrointestinal discomfort (2 (4.2%) patients in each group).

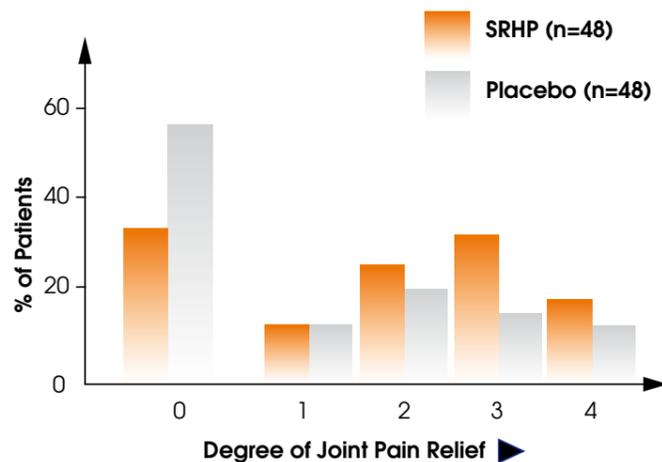


Figure. Degree of joint pain relief on a scale from 0 (no impact) to 4 (almost total relief of pain) after 4 months of treatment with standardized rose-hip powder (SRHP) or placebo. $P=0.035$ for SRHP versus placebo (Mann-Whitney test).

Discussion

The aim of this controlled study was to answer the following questions: Does the standardized rose-hip powder improve mobility of the hip and knee joints? Does it reduce the functional disability in performing ADLs that goes with the restricted hip and knee joint movements? Does it relieve pain? We found that, in the group treated with standardized rose-hip powder, (1) functional capacity of the hip, as assessed by an objective method, was improved; (2) the impact on functional capacity and ADLs, when measured subjectively, was less pronounced; and (3) pain was reduced in approximately two thirds of these patients. This response rate was comparable to that reported for ginger,^{6,7} another natural remedy often used by patients with osteoarthritis.

The difference between the effects on objective measures of hip and knee flexion is difficult to explain. The large-scale, controlled trial⁸ of avo-

cado/soybean unsaponifiables in 101 instances of osteoarthritis of the hip and 62 of the knee showed a similar, sharp difference between the therapeutic response of the 2 joints. The fact that the hip joint is a ball and socket, whereas the knee difference, and the possibility that the pain is differently mediated in the 2 joints is based on unsupported conjecture.

Pain is the cardinal symptom of osteoarthritis. Due to degeneration of the cartilage and lack of joint stability, small intra-articular traumas do occur. Injuries of this kind are reflected in biochemical responses, some of which involve cytokines.⁹ Cytokines have proinflammatory effects that are manifested as episodes of pain, joint swelling, and redness. Our interest in these mechanisms lies in the fact that the standardized rose-hip powder used here inhibits the polymorphonuclear chemotaxis that is a step in the proinflammatory action of various cytokines. This could be the basis of the effects of the standardized rose-hip powder on joint pain.⁴ Further support for an anti-inflammatory action of this compound is that the serum concentration of C-reactive protein, a marker for inflammation, decreases significantly during treatment with the compound, as shown by a mean (SD) decrease from 8.25 (4.9) mg/L to 6.67 (2.6) mg/L.^{3,4} The basic mechanism of the anti-inflammatory action of standardized rose-hip powder does not reside in a blockade of the cyclooxygenase pathway, as is known to be the case for the anti-inflammatory drugs (aspirin and other NSAIDs) and the herbal remedy ginger.^{10,11} This was shown in a study¹² measuring platelet aggregation during treatment with the same standardized rose-hip powder in doses far higher than that used in the present study. In contrast to drugs inhibiting the cyclooxygenase pathway, platelet aggregation was not affected by these high doses. In fact, the powder seems to stabilize cell membranes, as shown by the finding that erythrocytes from individuals treated with the powder, when routinely stored in a blood bank, leak less hemoglobin than expected.¹³

Natural vitamins C and E are present in standardized rose-hip powder. However, it does not seem likely that these vitamins can explain the present findings because vitamin C was not involved in the anti-inflammatory action reported for rose-hip powder,⁴ and vitamin E has been reported to be ineffective for symptomatic relief of osteoarthritis.¹⁴ Also, the prevalence of gastrointestinal adverse events was low in the present trial and similar to that of placebo. Mo-

reover, several years of use of the powder in the Scandinavian countries has not disclosed significant data on any adverse events.

Although a significant increase was found in mobility of the hip joint and a significant decrease in pain was found in the majority of patients who received the standardized rose-hip powder, the clinical benefit of 4 months of treatment should not be overestimated. Future research should include long-term studies to evaluate joint mobility, clinical improvements, and consumption of NSAIDs and other types of concomitant pain-reducing medicine. It is also important to find the active ingredient(s) in rose-hip and clarify whether the content of such active ingredient(s) (as well as the content of vitamins and minerals) differ among subtypes, as species of rose-hip can be very different from each other regarding biological activity.¹⁵

Conclusions

In this study population, standardized rose-hip powder reduced symptoms of osteoarthritis, as 64.6% of patients reported at least some reduction of pain while receiving treatment. Standardized rose-hip powder may improve hip flexion and reduce pain in patients with osteoarthritis.

Acknowledgements

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THE ANTI-INFLAMMATORY PROPERTIES OF ROSE-HIP

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Abstract – The anti-inflammatory properties of **rose-hip** are described in this short report. **Rose-hip** extract reduced chemotaxis of peripheral blood neutrophils and monocytes of healthy subjects in vitro. Daily intake of **rose-hip** powder for four weeks by healthy volunteers and patients suffering from **osteoarthritis**, resulted in reduced serum C-reactive protein (**CRP**) levels and reduced **chemotaxis** of peripheral blood neutrophils. The results indicate that **rose-hip** possesses **anti-inflammatory** properties and might be used as a replacement or supplement for conventional drug therapies in patients with osteoarthritis.

1. INTRODUCTION

There have been undocumented lay claims that rose-hip, normally known for its high vitamin C content, may reduce the pain in patients suffering from osteoarthritis. We have recently shown that rose-hip extract reduced the chemotaxis of peripheral blood polymorphonuclear leukocytes (PMNs) and monocytes in vitro (1). This activity was independent of the vitamin C content of rose-hip. Furthermore, the level of CRP and the chemotaxis of neutrophils were reduced in healthy subjects under rose-hip treatment. The purpose of this study was to investigate whether the natural product rose-hip, administered as dry powder to volunteers of which four were suffering from clinical osteoarthritis, had any effect on the clinical signs and symptoms and certain inflammatory parameters.

2. SUBJECTS AND METHODS

2.1. Subjects

Eight male volunteers, free from any known allergic, hepatic, cardiovascular or infectious diseases, mean age 52 years (range 47-62), were entered into the study. Four of them had never experienced any pain of muscular or joint origin. The other four had all been engaged in hard physical work in different areas of construction for most of their adult life. One had suffered from clinical osteoarthritis for more than 20 years, with pain especially in the knee and elbow. The pain had been alleviated by injections of steroid directly into the joints and by acetylsalicylic acid and nonsteroid anti-inflammatory drugs (NSAIDs). The second patient had osteoarthritis and moderate pain in the knee and the ankle, periodically relieved by acetylsalicylic acid. The

third patient had pain from osteoarthritis of the ankle and had been periodically treated with NSAIDs and acetylsalicylic acid. The fourth patient had osteoarthritis of the elbow and shoulder of 10 years duration, normally treated with aspirin or paracetamol. The volunteers were treated with 45 grams (high dose) of Hyben Vital rose-hip daily for four weeks. The treatment was withdrawn for at least one month, then followed by another treatment for four weeks at a daily dose of 10 grams (low dose). Rose-hip was taken together with a main meal. After four weeks of the high dose rose-hip intake, at the end of treatment-free intervals and at the end of the low dose intake, the volunteers were asked about the possible side-effects, and blood samples were collected for clinical chemistry and PMN chemotaxis studies. All blood samples were taken between 8 : 30 and 9 : 00 am by the same laboratory technician after 30 minutes of rest, and analyzed immediately. For chemotaxis, heparinized blood was taken using vacuotainers. The time-lapse between blood sampling and chemotaxis was the same for the patients and control subjects.

2.2. Rose-hip

Rose-hip powder of *Rosa canina* was kindly provided by Hyben Vital, Langeland, Denmark. The rose-hip powder used in these studies was a well characterized and standardized batch containing both seeds and shell. During the drying procedure of the rose-hip powder, the temperature never exceeded 40°C. For the in vitro studies, a water extract of rose-hip was prepared. The extraction took place at 4°C

2.3. CRP determination

Serum CRP was estimated by a turbidometric method using a Hitachi 717 turbidometer. CRP antiserum was from Orion Diagnostica, Helsinki, Finland. CRP dilution buffer and human CRP calibrator was purchased from DACO A/S, Glostrup, Denmark. The normal range in our laboratory is ≥ 10 mg/l.

2.4. Chemotaxis

Chemotaxis was carried out using a modified Boyden chamber assay (2). For the in vitro studies, PMNs isolated from peripheral blood of the subjects were preincubated with various dilutions of rose-hip extract for 30 min at 37°C. Following preincubation, chemotaxis of the cells towards the chemotactic peptide f-Met-Leu-Phe (fMLP) at a concentration of 10^{-5} M or zymosan activated serum (ZAS) at a dilution of 1 : 200 was tested. For the in vivo studies, the chemotaxis of peripheral blood neutrophils from healthy control subjects and patients towards fMLP and ZAS was determined. The migrated cells were counted by a computer-assisted image analysis system.

2.5. Statistical analysis

Statistical analysis of the data was performed by using the Wilcoxon test for matched pairs. All data are given as mean \pm SEM. p values of ≤ 0.05 were considered significant.

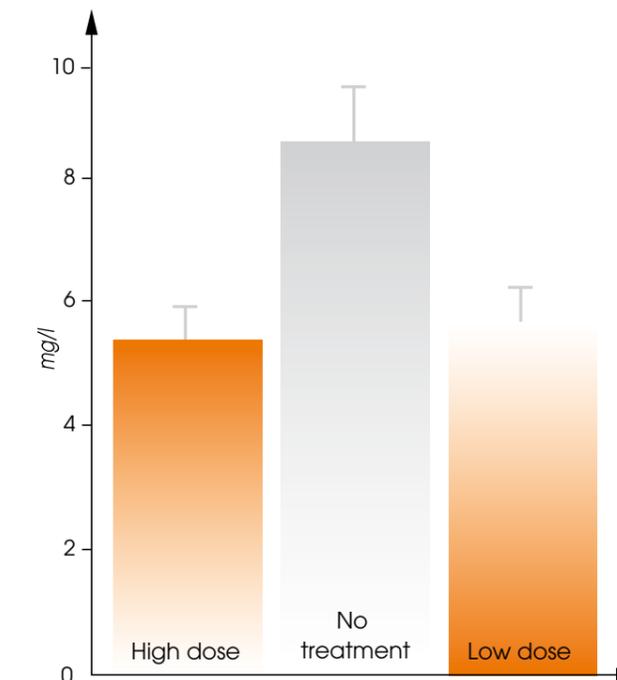


Figure 1. C-reactive protein levels in the serum of eight volunteers given high dose, low dose or no treatment. The values are given as mean \pm SEM in mg/l. There were statistically significant differences between CRP levels from the high dose group and no treatment ($p \leq 0.02$) and low dose group and no treatment ($p \leq 0.05$).

3. Results and discussion

Rose-hip extract at concentrations as low as 100 μ g/ml inhibited the chemotaxis of PMNs in vitro (data not shown). Cell viability after incubation with rose-hip extract was greater than 98%. As shown in Fig. 1, serum CRP levels, although within normal range, declined significantly both in the high-dose ($p \leq 0.02$) and in the low-dose groups ($p \leq 0.05$) as compared to the no-therapy group. The CRP levels (mean \pm SEM) in the patient group were 5.75 ± 2.95 , 6.67 ± 2.67 and 5.75 ± 2.95 with high dose, low dose and no therapy, respectively. In the control group the CRP levels were 4.75 ± 0.75 , 4.00 ± 0.0 and 7.25 ± 1.03 with high dose, low dose and no therapy, respectively. The neutrophil chemotaxis data are shown in Table 1. Chemotaxis towards fMLP declined by approximately 60% and 50%, in the high dose and low dose group, respectively, with p values of 0.01 and 0.02. Chemotaxis towards ZAS also declined in both the high dose ($p \leq 0.01$) and in the low dose groups ($p \leq 0.02$). The decline in chemotaxis of cells from the patients and the controls under treatment with rose-hip was similar. The decline in chemotaxis was observed in all the 8 subjects. The mean \pm SEM values for fMLP were 187 ± 60 compared to 370 ± 39 and for ZAS 414 ± 136 compared to 673 ± 27 in the high dose patient group compared with no therapy. In the high dose control group the mean \pm SEM response to fMLP was 101 ± 45 as compared to 308 ± 22 and to ZAS 272 ± 125 as compared to 600 ± 49 as compared to no therapy.

The salient finding of the present study is that rose-hip, given as dry powder, lowered CRP levels significantly and inhibited chemotaxis of peripheral blood neutrophils in human male volunteers. To our knowledge, this finding has not been reported before. There are very few reports in the literature on other properties of rose-hip. Rose-hip has been used as source of vitamin C in tea and other products (3). Cells such as polymorphonuclear leukocytes (PMNs) and monocytes are involved in the inflammatory process and tissue damage in inflammatory diseases such as arthritis and atherosclerosis (4). The damage is caused by the release of proteolytic and hydrolytic enzymes as well as toxic oxygen radicals (5). Acetylsalicylic acid, nonsteroid anti-inflammatory drugs and glucocorticoids have been used for the treatment of these diseases (6, 7). These drugs have a variety of side effects such as gastric erosion and kidney disturbances. The present study demonstrates that administration of rose-hip to patients with osteoarthritis, diagnosed on a clinical basis,

reduced the levels of the acute phase protein CRP and peripheral blood neutrophil chemotaxis. Similar results were found in the four healthy subjects who had never experienced pain of osteoarthritis origin. Symptoms were assessed as pain severity on a scale of 1-10 and change in limitation of joint movement. Alleviation of physical symptoms by rose-hip in the patients correlated very well with the reduced chemotaxis of peripheral blood neutrophils and reduced level of CRP. After the volunteers stopped taking rose-hip, the chemotaxis of neutrophils and the levels of CRP rose to the untreated values. It is interesting to note that the initial CRP values were higher in the patient than the control group. The inhibition of chemotaxis observed in our study was comparable to that observed with acetylsalicylic acid as reported by Matzner et al. (8). On the other hand Kemp and Smith (9) showed that incubation of neutrophils in vitro with sodium salicylate increased the chemotaxis of these cells. A similar increased response was observed in normal individuals after ingestion of sodium salicylate (9). Some non-steroid anti-inflammatory drugs such as ibuprofen at in vivo obtainable concentrations inhibited neutrophil locomotion by 50%, similar to our findings with rose-hip (10-12). The patients who complained of mild pain of osteoarthritis origin, reported that their pain declined after 14 days of rose-hip intake. The pain relieving effect of rose-hip in these patients was comparable to that of NSAID and acetylsalicylic acid. In all cases the pain returned 12-14 days after stopping intake. No allergic reactions or gastrointestinal disturbances were observed during therapy. There was no major difference between the pain alleviating effect of rose-hip given at the two different doses. Three patients had total pain relief from rose-hip and were unable to distinguish the difference between the high dose and the low dose. However, one patient felt that high dose gave him total relief whereas low dose decreased the pain dramatically but not completely.

Table 1. Chemotaxis of peripheral blood neutrophils from the eight volunteers at the end of high dose intake, 28 days after cessation of intake and at the end of low dose intake of rose-hip powder. The results are given as mean \pm SEM

	High dose	No therapy	Low dose
Chemotaxis (fMLP)	144 \pm 38.7 ^a	339 \pm 24.0	172 \pm 18.0 ^b
Chemotaxis (ZAS)	343 \pm 89.7 ^a	637 \pm 29.3	432 \pm 39.9 ^b

^a Comparison of high dose with no therapy $p \leq 0.01$.

^b Comparison of low dose with no therapy $p \leq 0.02$.

In conclusion, the anti-inflammatory and pain-relieving properties of the natural product rose-hip, combined with its safety, low price and ease of administration, provide an attractive strategy to use rose-hip as part of a supplement to a therapeutic regimen for osteoarthritis. A large scale placebo-controlled clinical study will be required to extend confirmation of the anti-inflammatory effect of rose-hip.

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ROSE HIP INHIBITS CHEMOTAXIS AND CHEMILUMINESCENCE OF HUMAN PERIPHERAL BLOOD NEUTROPHILS IN VITRO AND REDUCES CERTAIN INFLAMMATORY PARAMETERS IN VIVO

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Abstract – Objective and Design: The objective of this study was to investigate the leucocyte-related antiinflammatory properties of rose hip.

Materials and Methods: The effect of rose hip on a number of inflammatory parameters was evaluated using the following models: (1) The effect of rose hip extract on chemotaxis and chemiluminescence of peripheral blood polymorphonuclear leucocytes (PMNs) from healthy subjects in vitro; (2) The effect of rose hip administered to healthy subjects on serum levels of creatinine and C-reactive protein and on chemotaxis and chemiluminescence of peripheral blood PMNs.

Results: Rose hip extract at concentrations higher than 500 μ g/ml inhibited the chemotaxis and chemiluminescence of peripheral blood polymorphonuclear leucocytes in vitro. Daily intake of rose hip powder at doses of 45 grams or lower by healthy subjects resulted in reduced chemotaxis of peripheral blood PMNs and reduced the level of serum creatinine and acute phase protein CRP.

Conclusions: These results indicate that rose hip possesses antiinflammatory properties and might be used as a replacement or supplement for conventional drug therapies in some inflammatory diseases such as arthritis.

Key words: Rose hip; *Rosa canina*; neutrophil; chemotaxis; CRP; antiinflammatory.

1. Introduction

Inflammatory diseases such as arthritis involve a broad spectrum of different clinical manifestations. Inflammatory cells such as polymorphonuclear leucocytes have been shown to be involved in the inflammatory process and tissue damage. Inflammatory cytokines such as TNF appear to be involved in the amplification of the disease process. The damage is caused by the release of proteolytic and hydrolytic enzymes as well as toxic reactive oxygen radicals from these cells activated in the tissue and joints (Harris, 1988). Therapy of inflammatory diseases involves alleviation of the symptoms associated with the disease, such as, relief of pain, reduction of inflammation and increase of motion. Acetylsalicylic acid (aspirin) and other non-steroid anti-inflammatory drugs such as ibuprofen, methotrexate and naproxen, and glucocorticoids have been used for the treatment of arthritis (Hochberger et al., 1995a, b; Ridker, et al., 1997). Control of the symptoms with these drugs requires long term daily treatment. These drugs have a variety of toxic and other side effects, such as gastric erosion and adverse effects on kidneys and liver. Some of these drugs, particularly the glucocorticoids, inhibit the immune response to infections. Therefore, there is a great need for alternative therapies for the management of arthritis which can eliminate the need for conventional drugs and their side-effects, particularly for prolonged daily use. In a short communication we have reported on the anti-inflammatory activity of rose hip in four subjects suffering from mild osteoarthritis (Winther et al., 1999). The purpose of this study was to investigate in more detail the anti-inflammatory property of the natural product rose hip, utilizing in vitro methods in a larger number of healthy subjects.

2. Materials and methods

2.1. Rose hip

The extract was prepared by incubating 80 mg of Hyben Vital rose hip (Langeland, Denmark) dry powder from *Rosa canina* with 4 ml of minimal essential medium (MEM) containing 50 units/ml of penicillin and 0.05 mg/ml of streptomycin, for 19 h at 4°C. The extracts were prepared from either the whole fruit powder, the shells or the seeds. The shells and the seeds were separated from each other by splitting the dried fruit and separating the shells from the seeds manually. They were then ground in a mortar. Chemical analyses of Hyben Vital rose hip was performed by Steins Laboratorium A/S, Holstebro, Denmark. Following incubation of the powders in MEM, the mixtures were centrifuged

at 4000 rpm for 10 min. The supernatants were collected, sterile filtered and diluted further. The pH of extract preparations was adjusted to pH 7.2 before use.

2.2. Chemotaxis

The chemotaxis assay was performed using a modified Boyden chamber technique as previously described (Jensen and Kharazmi, 1991). PMNs isolated from peripheral blood of healthy subjects were preincubated with different dilutions of rose hip extract for 30 min at 37°C. Following preincubation, the chemotaxis of the cells towards the chemotactic peptide f-Met-Leu-Phe (fMLP) or zymosan activated serum (ZAS) were tested. The migrated cells were counted by a computer-assisted image analysis system.

2.3 Chemiluminescence

Chemiluminescence assay was used as a measure of oxygen radical generation by activated PMNs. The method was performed as previously described (Kharazmi et al., 1984). PMNs were preincubated with different dilutions of rose hip extract and then stimulated with either fMLP or opsonized zymosan. The oxidative burst response of the activated cells was measured by a luminometer (1250-LKB Wallace).

2.4. Subjects

Thirteen healthy volunteers represented by both sexes with a mean age of 47 years (range 30-59 years) were included in this study. All the subjects included were without known cardiovascular, immunological, kidney, liver, allergic, rheumatological or haematological disorders. The volunteers were treated with 45 g of Hyben vital rose hip daily for 28 days (high dose), followed for another 28 days during which Hyben vital rose hip was not taken. At the end of this period, the volunteers received another treatment of rose hip at a dose of 10 g daily for 28 days (low dose). Before inclusion, all volunteers went through a screening procedure to assure that none of the above mentioned diseases were present. Moreover, before inclusion blood samples were taken for C-reactive protein (CRP) measurement to assure that none of the included volunteers suffered from unknown infectious diseases.

2.5. Blood chemistry

Blood potassium, sodium, serum creatinine, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, bilirubin, hemoglobin and total cholesterol were also measured

before initiation of the treatment. All measurements were performed according to the conventional laboratory routine. All the above mentioned parameters except serum creatinine and CRP were repeated after 5, 10, 21 and 28 days of treatment, 28 days after stopping rose hip therapy and again at the end of low dose treatment. Serum creatinine and C-reactive protein (CRP) were tested before therapy, after 10 and 28 days of treatment, 28 days following cessation of the treatment and finally at the end of low dose treatment. Rose hip was taken together with a meal at 12.00 noon. On the days of blood sampling rose hip was taken together with a light meal at 09.00 a.m., two hours before blood sampling. Blood sampling was always performed after 15 min at rest sitting in a chair.

2.6. Statistical analysis

Statistical analysis of the data was performed by using Wilcoxon test for matched pairs, p values of < 0.05 were considered significant.

3. RESULTS

3.1. Analysis of rose hip

Table 1 shows the chemical analyses of the commercially available Hyben Vital Rose hip. Rose hip powder contains proteins, carbohydrates, a low amount of fat and several vitamins such as vitamin A, vitamin B, vitamin C, vitamin E and vitamin K. The powder also contains several minerals. Uptake of vitamin C present in Hyben vital powder was as good as, or even better than, that of vitamin C when given in tablet form. The concentrations and kinetics of uptake through the gastrointestinal tract of the equivalent of 250 mg vitamin C in rose hip powder was similar to 500 mg vitamin C in tablet form. The better absorption of vitamin C in rose hip powder may be due to a larger surface area of rose hip powder as compared to vitamin C tablets.

3.2. Chemotaxis

Initial dose-response experiments were performed and it was found that the extract of rose hip at concentrations equivalent to 500 µg/ml and higher inhibited chemotaxis of PMNs in vitro. As shown in Fig. 1, rose hip extract at concentrations of 500 µg/ml and higher inhibited chemotaxis of human peripheral blood neutrophils; pH-adjusted rose hip extract at these concentrations was as strongly inhibitory as the non-pH-adjusted rose hip extract. The two major parts of rose hip – shells and seeds – were tested separately for their activity on PMN chemotaxis. It was shown that by far most of the inhibitory activity resided in the shells (Fig. 1).

The inhibition of chemotaxis by rose hip shells at both the 1000 µg/ml and 500 µg/ml levels was significantly higher than that of seeds ($p \leq 0.01$ and $p \leq 0.04$, respectively). When comparing rose hip shells with whole powder, there was significantly higher inhibition by rose hip shells at 500 µg/ml ($p \leq 0.03$) but not at 1000 µg/ml.

3.3. Chemiluminescence

As shown in Table 2, rose hip extract inhibited the chemiluminescence of PMNs activated by opsonized zymosan. Adjustment of pH to physiological values in the extract did not influence the inhibitory effect markedly. Vitamin C in crystalline form used as control up to a concentration of 5000 µg/ml had almost no effect on PMN chemiluminescence when the pH of vitamin C solution was adjusted to the physiological pH 7.2. Vitamin E (alpha-tocopherol) was also used as a known antioxidant control. Vitamin E at a concentration of over 1 µg/ml inhibited chemiluminescence.

Table 1. Chemical analyses of the commercially available Hyben Vital rose hip powder. The values are given for 100 g of dry powder

Protein	6.2 g
Carbohydrate	39.0 g
Fat	4.0 g
Vitamin C	560 mg
Energy	916 kJ

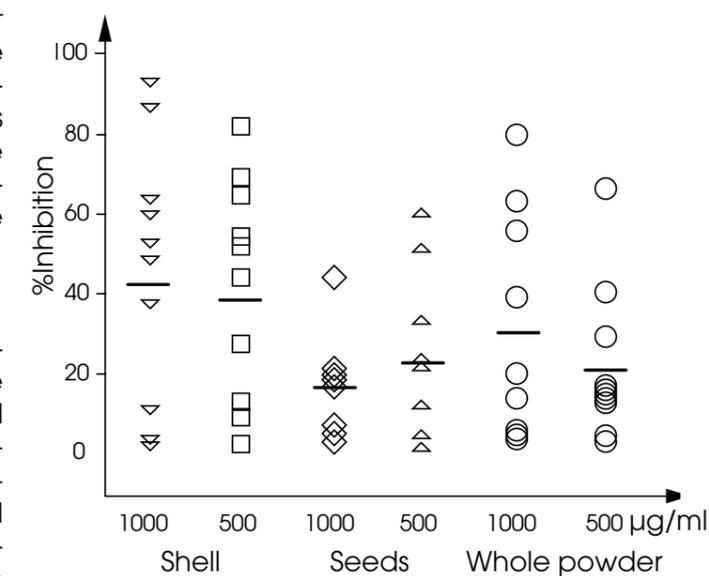


Figure 1. Effect of rose hip extract on polymorphonuclear leukocytes (PMN) chemotaxis in vitro. Cells were preincubated with various concentrations of rose hip powder as given in the X-axis for 30 min. The data are presented as percent inhibition of PMN chemotaxis for each subject tested.

Table 2. Effect of rose hip extract on human peripheral blood polymorphonuclear leucocyte (PMN) chemiluminescence. The data are presented as percent inhibition as compared with control

Rose hip extract concs (µg/ml)	1 Subject	2 Subject	3 Subject
2500	37	27	57
1000	8	8	12
500	0	0	ND

ND: Not determined.

4. Ex vivo studies

4.1. Blood chemistry

No significant changes occurred in potassium, sodium, alanine aminotransferase, alkaline phosphatase, lactate dehydrogenase, bilirubin, haemoglobin or total cholesterol comparing values from before intake to values obtained after 5, 10, 21 and 28 days of high dose therapy, values obtained 28 days after stopping intake and those obtained at the end of low dose therapy (data not shown).

Serum creatinine, however, declined significantly compared with initial value given as mean $4 \pm \text{SEM}$ ($90.0 \pm 2.1 \mu\text{mol/l}$) to values obtained after 10 days: ($87.4 \pm 1.8 \mu\text{mol/l}$) and 28 days ($84.9 \pm 1.9 \mu\text{mol/l}$) of intake, respectively 3 ($p < 0.001$). When treatment had been stopped for 28 days the serum creatinine levels significantly increased ($93.2 \pm 1.9 \mu\text{mol/l}$) ($p < 0.001$) and were similar to values obtained before intake.

The data on C-reactive protein are given in Fig. 2. Similar to the findings on serum creatinine, CRP values were also decreased during intake of rose hip. The initial mean $4 \pm \text{SEM}$ values of CRP were $5.38 \pm 0.4 \text{ mg/l}$ and declined to $3.31 \pm 0.49 \text{ mg/l}$ and $4.31 \pm 0.47 \text{ mg/l}$, after 10 and 28 days of intake respectively ($p < 0.05$). After stopping therapy for 28 days, the levels increased to $5.75 \pm 0.54 \text{ mg/l}$ ($p < 0.051$) as compared with that previously.

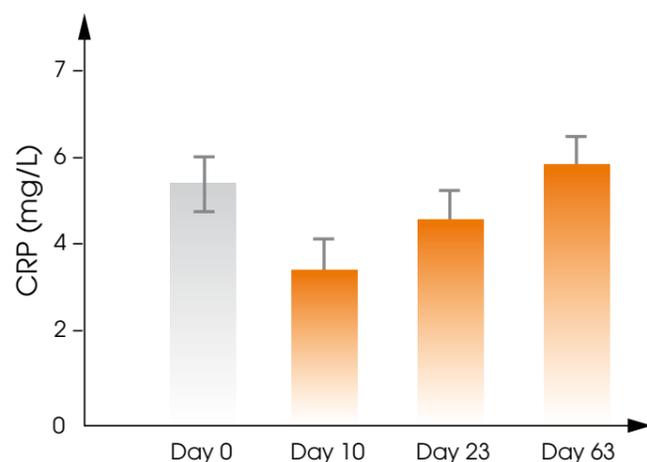


Figure 2. Levels of serum C-reactive protein (CRP) as given in mg/l from subjects on the start (Day 0), 10 days and 28 days during intake of rose hip and 35 days after cessation of treatment (Day 63) with 45 g daily intake of rose hip. The results are given as mean $4 \pm \text{SEM}$ values from 13 subjects. The mean value on day 10 was significantly lower than that on day 0 and day 63 ($p \leq 0.05$).

4.2. Chemotaxis

PMN chemotaxis in the period during which the volunteers had not taken any rose hip powder was compared with values obtained in the preceding 28 days (Figs 3 and 4). The mean $\pm \text{SEM}$ value of PMN chemotaxis towards the chemotactic peptide fMLP was 103.6 ± 60.0 when tested on day 28 of treatment with rose hip as compared with 298.9 ± 26.2 when blood samples were taken 28 days after cessation of rose hip intake ($p < 0.001$). The mean $\pm \text{SEM}$ values for PMN chemotaxis towards zymosan activated serum (ZAS) which contains the biologically active chemotactic factor C5a was 218 ± 60.0 as compared to 529.9 ± 39.9 when tested 28 days after cessation of treatment with rose hip ($p < 0.001$). The decline in chemotaxis response to fMLP was 65% in 12 out of 13 volunteers: a considerable decline of chemotaxis response. The decline in chemotactic response to ZAS was 59%, also a considerable decline in 12 out of 13 volunteers. It was the same subject who did not respond to therapy in both assays.

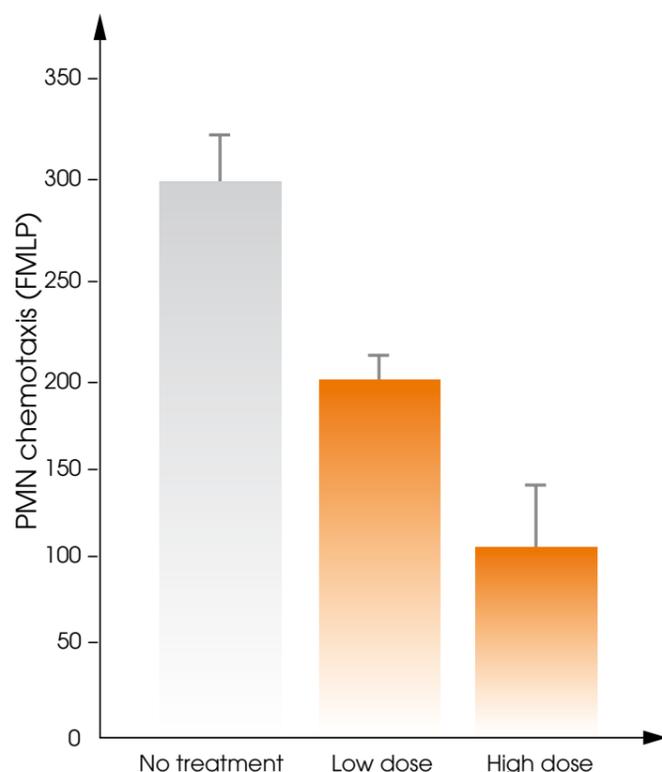


Figure 3. Chemotaxis of peripheral blood polymorphonuclear leukocytes (PMN) from subjects during and 28 days after cessation of treatment with 45 g (high dose) or 10 g (low dose) daily intake of rose hip for 28 days or no treatment. The chemotaxis is determined towards the chemotactic peptide FMLP. The results are given as mean $\pm \text{SEM}$ number of cells migrated from 13 subjects. The mean chemotaxis values for both low dose and high dose were significantly lower than that for no treatment group ($p \leq 0.01$ and $p \leq 0.001$, respectively).

4.3. Clinical findings

No allergic reactions or any other side-effects were observed during therapy. Only two volunteers complained of mild gastrointestinal gas disturbances at the end of the study, while on the high dose.

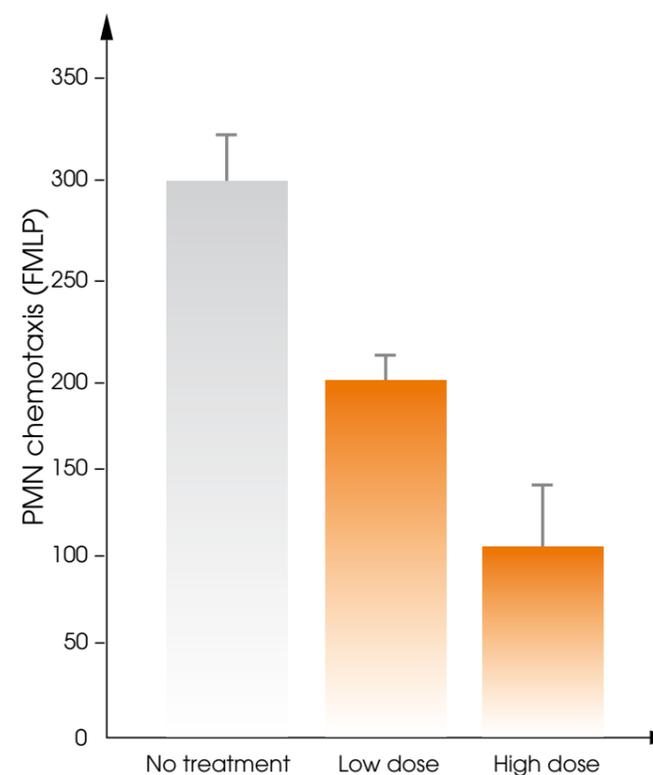


Figure 4. Chemotaxis of peripheral blood polymorphonuclear leukocytes (PMN) from subjects during and 28 days after cessation of treatment with 45 g (high dose) or 10 g (low dose) daily intake of rose hip for 28 days or no treatment. The chemotaxis is determined towards zymosan activated serum (ZAS). The results are given as mean $\pm \text{SEM}$ number of cells migrated from 13 subjects. The mean chemotaxis value for high dose was significantly lower than that for no treatment group ($p \leq 0.001$),

5. DISCUSSION

The studies described in this communication demonstrate that the extract from rose hip inhibited, in vitro, the chemotaxis and oxidative burst response of the human peripheral blood polymorphonuclear leukocytes, important and abundant inflammatory cells involved in the pathogenesis of arthritis. Furthermore, administration of rose hip to healthy volunteers for a period of 28 days inhibited the chemotactic response of neutrophils by approximately 60% or higher. Moreover, rose hip lowered the level of serum creatinine and the acute phase protein C-reactive protein in volunteers with values within normal range, which is below 10 mg/l . Serum creatinine levels were within the normal range in all the volunteers (males $55\text{-}125$ and females $45\text{-}100 \mu\text{mol/l}$). However, the decline was statistically significant and might indicate enhanced glomerular filtration. The blood chemistry data presented in this study showed that intake of rose hip had no harmful effect on any of the liver functions determined in this study.

Studies on the inhibition of neutrophil oxidative burst response by rose hip extract showed that this effect was not due to vitamin C content of the extract. This is shown by the inability of pH-adjusted vitamin C to inhibit chemiluminescence whereas pH-adjusted rose hip extract was still as inhibitory as non-pH-adjusted extract. In order to determine which part of rose hip exhibited the inhibitory effect on chemotaxis the extract from shells, seeds and the whole powder were prepared and tested in PMN chemotaxis assay. As shown in Fig. 1 the major inhibitory activity was found to reside in the shells. It will be interesting to identify the compound(s) responsible for the anti-inflammatory activity of rose hip. The inhibition of chemotaxis observed in our study was comparable to that observed with acetylsalicylic acid as reported by Matzner et al. (1984). On the other hand Kemp et al. (1982) showed that incubation of neutrophils in vitro with sodium salicylate increased the chemotaxis of these cells. Similar increased response was observed in normal individuals after ingestion of sodium salicylate (Kemp et al., 1982). Some non-steroid anti-inflammatory drugs such as ibuprofen at attainable concentrations during therapy has been shown to inhibit neutrophil locomotion by 50%; a finding which is similar to our findings with rose hip (Rivkin et al., 1976; Kaplan et al., 1984; Maderazo et al., 1984).

6. CONCLUSION

Rose hip possesses anti-inflammatory and antioxidant properties. These properties are important in alleviation of tissue damage in the inflammatory sites. As a natural product, rose hip has no side effects, is safe and can be administered easily. It can be designed for daily consumption as supplemental part of a therapeutic regimen for some inflammatory diseases, or as a prophylactic regimen for individuals having a genetic or environmental predisposition to these diseases. A large scale placebo-controlled clinical study will be required to extend confirmation of the antiinflammatory effect of rose hip described in this report.

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NOTICE

