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, placebo-controlled, 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

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Received 19 August 2004
Accepted 7 January 2005

DOI: 10.1080/03009740510018624

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 improve 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, placebo-controlled, 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 rose-hip 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

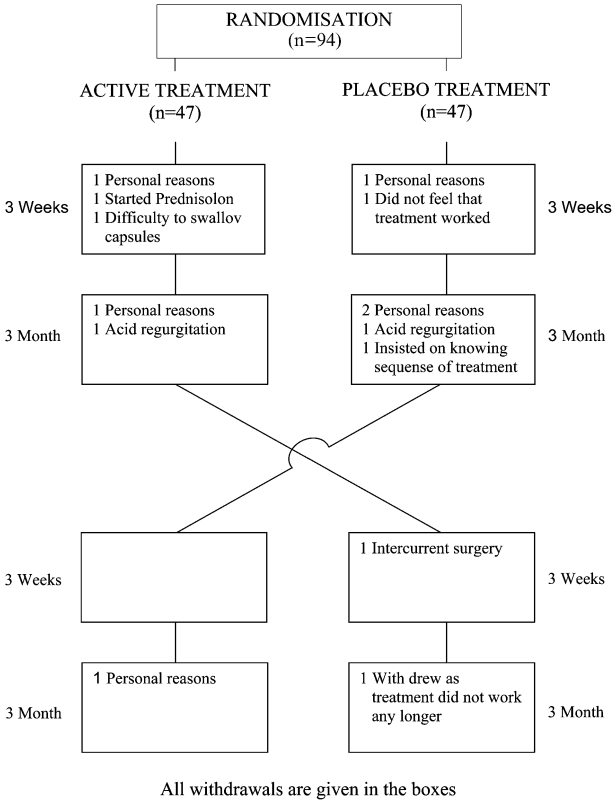

Figure 1. Flow diagram.

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*. 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 co-interventions 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.

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=47) or active treatment first and then placebo (group B, n=47). There were no significant differences in gender or age on comparing the A and B groups (data not given). In the entire group the mean body mass index (BMI) was 27 kg/m^2 (range 19–41). In group A the BMI was 27.3 kg/m^2 (range 19–39) and in group B, 26.6 kg/m^2 (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.

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$14.9 mm ($p<0.001$), compared to a change from 33.7$\pm$19.4 to 35.3$\pm$21.5, a delta

Table 1. Characterization of osteoarthritis.

	All patients (n=94)	Placebo–Active (n=47)	Active–Placebo (n=47)	p-value PA vs. AP
Knee osteoarthritis	58	29	29	NS
Hip osteoarthritis	21	11	10	NS
Hip and knee osteoarthritis	15	7	8	NS
Initial WOMAC scores				
Pain	33.7 (19.4)	30.4 (18.1)	37.0 (20.4)	NS
Stiffness	39.2 (19.4)	35.6 (22.0)	42.5 (26.2)	NS
ADL	35.3 (21.6)	34.0 (21.1)	36.7 (22.2)	NS
PGAD	43.9 (24.4)	43.6 (22.6)	44.3 (26.8)	NS

Table 2. WOMAC scores for pain, stiffness, daily activities (ADL), and patients' evaluation of disease severity (PGAD) in all the included patients (n=94). Data given are mean values with SD in parentheses.

							p-value placebo vs. active	
		Start	3 weeks	Delta value	3 months	Delta value	3 weeks	3 months
Pain	Placebo	33.7 (19.4)	35.3 (21.5)	2.1 (16.8)	35.6 (20.4)	5.1 (18.3)[1]	0.014	0.125
	Active	33.7 (19.4)	29.4 (18.3)	7.4 (14.9)[2]	32.8 (20.6)	7.0 (19.7)[3]		
Stiffness	Placebo	39.2 (24.4)	40.0 (24.2)	3.3 (19.0)	41.2 (24.1)	5.0 (23.2)	0.198	0.038
	Active	39.2 (24.4)	34.0 (20.5)	7.5 (16.7)[4]	36.8 (23.7)	8.0 (21.6)[5]		
ADL	Placebo	35.3 (21.6)	39.7 (25.3)	−0.7 (−21.4)	41.9 (27.5)	−0.2 (25.5)	0.165	0.018
	Active	35.3 (21.6)	35.9 (27.7)	2.2 (22.7)[6]	35.0 (20.7)	6.4 (17.5)[7]		
PGAD	Placebo	43.9 (24.4)	42.3 (21.2)	8.2 (25.1)[8]	45.2 (22.8)	7.8 (28.8)[9]	0.682	0.035
	Active	43.9 (24.4)	39.2 (22.4)	8.2 (22.6)[10]	41.2 (32.1)	14.1 (28.1)[11]		

[1]$p<0.005$, [2]$p<0.001$, [3]$p<0.003$, [4]$p<0.001$, [5]$p<0.006$, [6]$p<0.002$, [7]$p<0.003$, [8]$p<0.004$, [9]$p<0.031$, [10]$p<0.002$, [11]$p<0.001$. The p-values given are relative to pretreatment values (initial values).

change of 2.1 ± 16.8 ($p<0.299$), 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 treatment 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 ($p<0.052$).

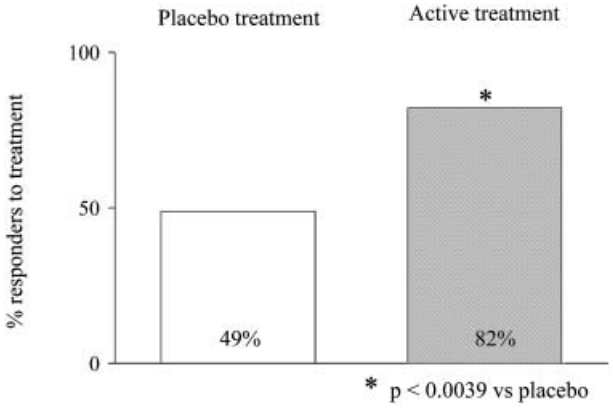

Figure 2. Percentage of patients experiencing a reduction in the WOMAC score for joint pain after 3 weeks of treatment in the group initially given placebo and in the group initially given active treatment.

When a Mann–Whitney subanalysis was applied on the consumption of paracetamol in each of the two groups, during the first 3 month of treatment, rose-hip 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.

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 ($p<0.035$) when active treatment was given, as compared to placebo. The were no significant difference 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

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=47)									
Pain	30.4 (18.1)	34.5 (23.1)	−2.5 (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)	−1.4 (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)	−0.3 (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=47)									
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)	6.5 (23.7)[(16)]
ADL	36.7 (22.2)	38.0 (34.2)	−0.4 (28.2)	37.0 (18.1)	5.3 (15.0)[(17)]	43.6 (27.9)	−1.2 (29.1)	45.3 (32.7)	−2.7 (32.6)
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)	10.7 (28.1)[20]

[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 parantheses indicate borderline significance.

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 carry-over (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).

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

	Placebo	Active	p-value
Dropped out during treatment	7	7	NS
Reasons for dropout	2	0	NS
Felt that treatment did not work	3	3	NS
For personal reasons	1	1	NS
Acid regurgitation	0	1	NS
Difficulty to swallow capsules	0	1	NS
Started prednisolone treatment	0	1	NS
Intercurrent surgery	1	0	NS
Insisted on knowing kind of treatment			
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 receiving 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 rose-hip 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 rose-hip 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 neutrophil 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 rose-hip 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 rose-hip.

Acknowledgements

We are grateful to Hyben-Vital International, Langeland, Denmark for providing capsules containing placebo and rose-hip powder.

References

1. Reginster JY, Deroisy L, Rovati LC, Lee RL, Lejeune E, Bruyere O, et al. Long-term effect of glucosamine sulphate on osteoarthritis progression: a randomised, placebo-controlled clinical trial. Lancet 2001;357:251–6.
2. Hochberg MC, Altman RD, Brandt KD, Clark BM, Dieppe PA, Griffin MR, et al. Guidelines for the management of osteoarthrosis (parts 1 and 2). Arthritis Rheum 1985;38:1535–46.
3. Vane JR, Botting RM. Anti-inflammatory drugs and their mechanism of action. Inflamm Res 1998;47:578–87.
4. Mukherjee D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective Cox-2 inhibitors. J Am Med Assoc 2001;286:954–9.
5. Rodriques LAC, Hernandes-Diaz S. Relative risk of upper gastrointestinal complications among users of acetaminophen and non-steroidal anti-inflammatory drugs. Epidemiology 2001;12:570–6.
6. Altman RD, Markussen KC. Effect of ginger extract on knee pain in patients with osteoarthritis. Arthritis Rheum 2001;44:2531–8.

7. Appelboom T, Schuermans J, Verbruggen G, Henrotin Y, Reginster JY. Symptoms modifying effect of avocado/soybean unsaponifiables (ASU) in knee osteoarthritis. Scand J Rheumatol 2001;30:242–7.
8. Winther K, Rein E, Kharazmi A. The anti-inflammatory properties of rose-hip. Inflammopharmacology 1999;7:63–8.
9. Kharazmi A, Winther K. Rose-hip inhibits chemotaxis and chemiluminescence of human blood neutrophils in vitro and reduces certain inflammatory parameters in vivo. Inflammopharmacology 1999;7:377–86.
10. Altman R, Asch E, Bloch D, Borenstein D, Brandt K, et al. Development of criteria for the classification and reporting of osteoarthritis. Classification of osteoarthritis of the knee. Arthritis Rheum 1986;29:1039–49.
11. Altman R, Alarcon G, Appelrouth D. The American College of Rheumatology criteria for the classification and reporting of osteoarthritis of the hip. Arthritis Rheum 1991;34:505–14.
12. Bellamy N, Buchanan WB, Goldschmidt CH, Campbell J, Stitt LW. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to antirheumatic drug therapy in patients with osteoarthritis of the hip and knee. J Rheumatol 1988;15:1833–40.
13. Warholm O, Skaar S, Hedman E, Mølmen HM, Eik L. The effects of a standardised herbal remedy made from a subtype of Rosa canina in patients with osteoarthritis: a double-blind, randomised, placebo-controlled clinical trial. Curr Therap Res 2003;64:21–31.
14. Rein E, Kharazmi A, Winther K. A herbal remedy, Hyben Vital, reduces pain and improves general wellbeing in patients with osteoarthritis – a double-blind, placebo-controlled, randomised trial. Phytomedicine 2004;11:383–91.
15. Thamsborg GM, Apel K, Rein E, Winther K. A randomized, doubleblind, placebo-controlled, crossover trial of the herbal remedy HybenVital in patients with osteoarthritis. THU0214 EULAR, Stockholm, Sweden, 10–15 June 2002.
16. Larsen E, Kharazmi A, Christensen LP, Christensen SB. An antiinflammatory galactolipid from rose-hip (Rosa canina) that inhibits chemotaxis of human blood neutrophils in vitro. J Nat Prod 2003;66:994–5.
17. McAlindon TE, Jacques P, Zhang Y, Hannan MT, Aliabadi P, Weissmann B, et al. Do anti-oxidant micronutrients protect against the development and progression of knee osteoarthrosis? Arthritis Rheum 1996;39:648–56.
18. Jensen NH. Reduced pain from osteoarthritis in hip joint or knee joint during treatment with calcium ascorbate. A randomised, placebo-controlled, crossover trial. Ugeskr Laeger 2003;165:2563–6.
19. Rein E, Kharazmi A, Winther K. Rose-hip given as a standardised dry powder exerts anti-inflammatory properties, without influencing platelet aggregation and the coagulation cascade. 1st International Congress on Heart Disease, Washington, May 1999.
20. Brandt K, Aakeson B. Health promoting compounds in vegetables and fruit. Plant Prod 2002;29:43–44.