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PHYTOMEDICINE
ROSE HIP HERBAL REMEDY IN PATIENTS WITH RHEUMATOID ARTHRITIS – A RANDOMISED CONTROLLED TRIAL

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abstract

Objective: To investigate if standardised powder made from rose-hip (Rosa canina) can reduce the symptom score in patients with rheumatoid arthritis.
Methods: In a double-blind placebo-controlled trial, patients with rheumatoid arthritis (RA) according to ARA/ACR criteria were randomised to treatment with capsulated rose-hip powder 5 g daily or matching placebo for 6 months at two outpatient clinics in Berlin and Copenhagen. Primary outcome variable was Health Assessment Questionnaire (HAQ) at 6 months, secondary outcome included DAS-28, physician's global evaluation of disease activity, RAQoL, SF-12 and concomitant pain medication.
Results: In a total of 89 patients (90% female, mean age 56.6+11.3 years, mean disease duration 12.8+9.6 years) HAQ-DI in the rose-hip group improved by 0.105 7 0.346, whereas in the placebo group it worsened by 0.039 7 0.253 (p adjusted=0.032). In the HAQ Patient Pain Scale no significant differences were observed between both groups. In the HAQ Patient Global Scale a trend was seen favouring rose-hip (p=0.078). The DAS-28 score yielded improvement in the rose-hip group of 0.897 1.32 and in the placebo group of 0.34 7 1.27 (p=0.056) indicating moderate clinical relevance. The Physicians Global Scale demonstrated more improvement in the rose-hip compared to the placebo group (p=0.012). RAQoL and SF-12 physical score improved significantly in the rose-hip group compared to placebo, whereas SF-12 mental score remained unchanged. Intake of pain medication was not different between the groups. Per-protocol analysis confirmed these results.
Conclusion: The results indicate that patients with RA may benefit from additional treatment with rose hip powder.

Introduction

Rheumatoid arthritis (RA) is a chronic, inflammatory and autoimmune disorder that affects the joints in a polyarticular manner. The most prominent symptoms are pain on palpation, arthralgia, swollen joints, stiffness of joints and loss of function. If the diagnosis is established, treatment is usually started with disease-modifying anti-rheumatic drugs (DMARDs) such as methotrexat or leflunomide. For reducing pain and stiffness in RA patients the therapy is often supplemented with pain medication such as paracetamol or non-steroidal anti-inflammatory drugs, if necessary including COX-2 inhibitors. Many of the different treatments are expensive for the society as well as for the patient. A recent study in Germany for example estimated that the RA related direct cost during one year were 2312 Euro per patient (Ruof et al. 2003). Furthermore all these different types of medication each have potential side effects (Vane and Botting 1998 ; Rodriquez and Hernandez-Diaz 2000 ; Mukherjee et al. 2001).

It seems therefore of relevance to develop new strategies for treating pain in muscle and joints including medication that should be affordable and associated with a minimum of side effects. Evening primrose oil containing gamma linolenic acid (GLA) has been claimed to reduce morning stiffness and global assessment of disease severity in patients with rheumatoid arthritis. Evening primrose oil however, has well known side-effects such as gastric complications e.g. loose stool, nausea and beside this also headache (Leventhal et al. 1993 ; Leventhal et al. 1994 ; Zurier et al. 1996). Fish oil (n-3 fatty acid) was suggested to reduce pain and stiffness in patients suffering from RA (Fortin et al. 1995). In addition vegetarian diet has also been shown to reduce symptoms in RA (Kjeldsen-Kragh et al. 1991).

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A standardised powder from rose hip (Rosa canina) was reported to inhibit chemotaxis of neutrophils and to lower C-reactive protein in healthy volunteers and in patients with osteoarthritis (Kharazmi and Winther 1999). These findings were followed by randomised clinical studies in patients with osteoarthritis indicating that rose hip powder reduced pain moderately and improved physical activity (Warholm et al. 2003 ; Winther et al. 2005).

The aim of the present randomised trial was to evaluate the efficacy of rose hip powder on symptoms in patients with RA.

MATERIALS AND METHODS

Study design and population

The study design was randomized, double-blind, placebo-controlled and parallel. Patients were randomised centrally (computer-generated) in blocks of four. The study was approved by the local ethics committees and performed according to the guidelines for Good Clinical Practice. Included were patients aged 18 years and over with RA according to the revised American Rheumatism Association criteria for the classification of rheumatoid arthritis (Arnett et al. 1988), who gave written informed consent. Exclusion criteria were as follows: Lupus erythematosus present, patients with known allergy to plant products, patients with kidney or liver disease, drug abusers, patients with psychiatric disease and pregnancy. The participants were recruited from 04/2005 to 08/2006 at one outpatient clinics-in Berlin, Germany and two clinics in Denmark.

Intervention

Participants were instructed to take 5 capsules in the morning and 5 capsules in the evening, each capsule containing 0,5 g of rose hip powder or placebo of a similar taste, appearance and smell. In addition, usual care was continued in both groups. Active treatment comprised biological standardised rose hip powder produced by HybenVital, Langeland, Denmark, trade name LitoZin/i-flex. Details regarding the production of the present standardized rose hip powder are provided elsewhere (Winther et al. 2005).

Outcomes

The primary outcome was the Health Assessment Questionnaire (HAQ) disability index (DI) (Wolfe 2001) at 6 months. The HAQ-DI is derived from a questionnaire comprising eight subscales: dressing, arising, eating, walking, reaching, gripping, hygiene, and carrying out common activities. The highest scores in each category are the summed up with requirement of aids or devices taken into consideration and divided by the number of categories yielding a disability index that ranges from 0-3 with higher scores indicating more disability. The HAQ also includes two visual analogue scales (VAS), a patient pain scale and a patient's global scale both raging from 0-100.

Additional outcomes included the disease activity score (DAS-28) is a combined index of swollen and tender joint counts as well as erythrocyte sedimentation rate (ESR) and the patient's self-evaluation of disease activity (Prevoo et al. 1995). Presented as a number between 0 and 10, DAS-28 indicates how active the RA is at this moment (higher scores indicating higher activity). The physician 's evaluation of disease activity is a VAS scale range 0-100. Health-related Quality of Life (QoL) was measured using the Short form (SF)-12 as a generic and also the RA QoL as a disease specific instrument. The SF-12 has a well-documented psychometric history as an excellent measure of HRQoL. The scales are aggregated to comprise the physical component summary (PCS) and the mental component summary (MCS) measures, higher scores indicating better HRQoL. The RAQoL comprises of 30 questions, lower scores indicate a better outcome (De Jong et al., 1997). A hybrid measure that retains inflammation on the ACR 20, ACR 50 and ACR 70, and combine this data with the mean percentage improvement in core set measures was suggested-but not applied. This weakens the study.

Medication was recorded according to the physician 's CRF and a patients' diary, to be documented during the study period.

Evaluation

At the time of study enrolment sociodemographic data were documented and the participants were asked to fill out 3 questionnaires (HAQ, RAQoL, SF-12 [German/Danish version respectively]). The researcher filled out the case record form (CRF) which also included a detailed description of concomitant medication of any kind. Also, the Disease Activity Score (DAS-28) and the physician 's evaluation of disease was recorded. Routine blood samples for haemoglobin, C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were taken and analysed. Finally blood for evaluation of cytokines, tumour necrotic factor alpha (TNF alpha) and lipid profile was isolated and placed in a refrigerator for later analysing. The patient was encouraged to continue unchanged with his/her daily medication. Also the participant was instructed to write down his/her daily consumption of study medication, including any concomitant medication.

Further visits were scheduled after 1 and 3 months for handing out new medication and diaries, monitoring compliance, asking about a change in medication and adverse effects. Also, the HAQ was filled out by the participants at both visits. The RAQoL and SF-12 were also filled out at 3 months. At the final visit at months 6 participants were again asked to fill out the 3 questionnaires (HAQ, RAQoL, SF-12 [German/Danish version respectively]) and the physician filled out the DAS28, the VAS scale and sampled blood.

The participants had to contact the study centres in case of any adverse effects. Patient Compliance was ascertained by counting study medication after each treatment period and by monitoring the use of concomitant medication taken.

Statistical analysis

The protocol stated that a minimum of 80 patients should be randomised into the study, in order to get at least 30 patients, in each arm, who complete the study. In similar studies using the present rose hip powder and placebo on patients with osteoarthritis, this number of patients resulted in clinically relevant differences (Warholm et al. 2003 ; Winther et al. 2005) and the present amount of patients would yield a less than 5% risk of type 1 error and a less than 10% risk of a type 2 error. After finishing this study on patients with rheumatoid arthritis, a sample size estimation yielded 53 subjects in each group to detect with 80% power a difference of 0.22 in HAQ-DI means (considered clinically relevant (Bruce and Fries 2003)) assuming a standard deviation of 0.4 and using a two-sided significance level of 0.05. Data were analysed under blind conditions for 3 populations: (1) Intention to treat (ITT), (2) predefined group of patients who had participated in the trial for at least for 3 month, (3) patients who participated the entire 6 month (per-protocol population). SAS Version 9.1 was used (SAS Institute, Cary, NC). Mann-Whitney and Fisher's Exact

Test were applied to measure differences in baseline characteristics and outcomes.

The main analysis examined differential impact of treatment in an ITT analysis by comparing change scores (3 months minus baseline and 6 months minus baseline) between the two groups using an analysis of covariance (ANCOVA) adjusted for baseline value. For participants who discontinued treatment prior to 6 months, their final values were determined using their last observed value carried forward (LVCF).

Examination of baseline factors to be predictors or effect modifiers were performed by tests ofi nteraction between factor and intervention group.

RESULTS AND DISCUSSION

Patient characteristics

A total of 89 participants were enrolled in the study, 90% female, mean age 56.6 7 11.3 years, mean RA disease duration 12.8 7 9.6 years. At baseline there were no relevant differences between the groups (Table 1). After 6 months a total of 15 participants had dropped out during the trial but were included in the intent-to-treat analysis (Fig. 1).

Outcome

Table 2 shows the mean absolute values of the outcome variables in the treatment and the placebo group at baseline, 3 months and 6 months on an intention-to–treat analysis. The primary outcome mean change in HAQ-DI of patients in the treatment group improved i.e. numerically declined after 3 and 6 months treatment, respectively, whereas in the placebo group it worsened i.e. numerically increased (p=0.014 and p=0.032) comparing groups. In the HAQ Patient Pain Scale no significant differences were observed between groups. In the HAQ Patient Global Scale a trend was seen favouring treatment after 6 month of treatment (p=0.078).

These results were supported by instruments of the physician: after 6 month treatment the DAS28 score yielded a higher improvement in the active treatment group of 0.89 7 1.32 than in the placebo group of 0.34 7 1.27 (p=0.056) indicating moderate clinical relevance. Likewise, the Physicians Global Scale showed strong (about 30%) improvement in the treatment compared to the placebo group (7%) (p=0.012) when evaluated after 6 month treatment. These observations were supported by QoL assessment: SF-12 physical and RAQoL scores improved (p=0.013 and 0.043 respectively) in the actively treated group compared to placebo, whereas SF-12 mental score remained unchanged. Also there was no significant reduction on pain medication.

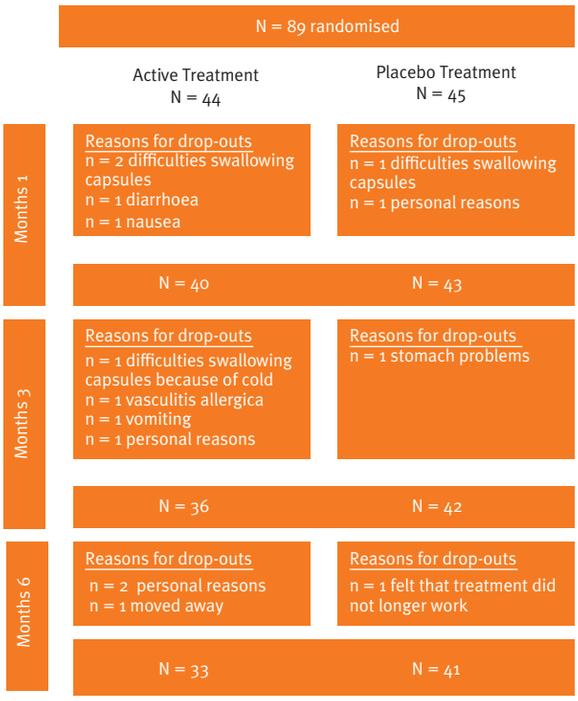

Fig. 1. Flowchart of patients.

Table 1
Baseline characteristics of rheumatoid arthritis participants (N=89).

	Treatment group (N=44)	Placebo (N=45)	p-value
Age (years) (mean 7 SD)	57,0 7 10,6	56,1 7 12,0	0.915
Female sex (%)	86	93	0.315
Disease duration (years) (mean 7 SD)	12,7 7 9,2	13,0 7 9,9	0.935
BMI (kg/m2) (mean 7 SD)	25,7 7 4,3	25,2 7 4,6	0.337
Education (10 years or more) (%)	75	75	1.000
Full-time/part time employment (%)	36	39	0.589
Living alone (%)	30	23	0.628
Smokers (%)	23	11	0.167
Patients using analgesics (%)	46	49	0.830
Patients using NSAID's (%)	64	53	0.390
Patients using Steroids (%)	27	40	0.260
Patients using DMARD's (%)	68	73	0.650
Patients daily consumption of:			
Analgesics (paracetamol units/day)	881 7 1581	961 7 3268	0,924
NSAID's (mg/day)	93,4 7 217	88,9 7 205	0,263
Steroids (mg/day)	1,4 7 3,1	1,7 7 3,0	0,246
DMARD's			
Methotrexat (mg/day)	3,8 7 16,6	3,7 7 15,1	0,695
Leflunomide (mg/day)	1,0 7 4,4	2,0 7 5,7	0,303
Biological anti-rheumatic drugs (mg/day)	5,0 7 22,1	2,8 7 15,3	0,496
Chloroquin (mg/day)	10,0 7 44,1	18,9 7 59,9	0,446

The group "Analgesics" contain paracetamol, tramadol and codeine.

Table 2
Clinical indices of disease activity at baseline, 3 and 6 months in rheumatoid arthritis patients.

	baseline	3 months	6 months	p-value *	p-value * *
HAQ-DI (0-3)					
Active	1.13 7 0.55	1.00 7 0.59	1.03 7 0.58	0.014	0.032
Placebo	1.11 7 0.76	1.13 7 0.71	1.15 7 0.74		
HAQ Pain Scale (VAS)					
Active	44.73 7 22.75	41.50 7 23.36	39.82 7 23.44	0.226	0.209
Placebo	45.56 7 21.98	47.09 7 22.14	45.71 7 23.47		
HAQ Patient ‰s Global Scale (VAS)					
Active	47.55 7 25.96	41.55 7 22.62	39.57 7 25.01	0.225	0.078
Placebo	47.13 7 21.28	46.44 7 25.19	47.18 7 24.13		
DAS28					
Active	4.82 7 1.33	4.18 7 1.22	3.93 7 1.56	0.196	0.056
Placebo	4.71 7 7 1.01	4.47 7 1.46	4.42 7 1.17		
Physician ‰s Global Scale (VAS)					
Active	47.50 7 19.28	40.43 7 22.25	33.57 7 23.72	0.328	0.012
Placebo	48.16 7 18.31	44.89 7 23.44	44.64 7 22.79		
RAQoL					
Active	11.57 7 6.36	10.20 7 6.39	10.18 7 7.22	0.113	0.043
Placebo	10.87 7 6.68	19.73 7 6.75	11.09 7 6.89		
SF-12 physical					
Active	32.91 7 8.77	35.37 7 9.51	36.22 7 9.28	0.515	0.013
Placebo	33.19 7 9.43	35.95 7 10.13	33.78 7 8.86		
SF-12 mental					
Active	49.30 7 10.44	49.63 7 10.94	48.46 7 10.85	0.315	0.954
Placebo	49.13 7 9.34	48.12 7 9.75	48.64 7 9.46		

Data are presented as means 7 SD. Intention-to-treat analysis (N=89).
VAS = Visual Analogue Scale 0–100.

* p-value: from ANCOVA- Difference 3 months to baseline adjusted for baseline values.
* * p-value: from ANCOVA- Difference 6 months to baseline adjusted for baseline values.

Table 3
Clinical indices of disease activity at baseline, 3 and 6 months in rheumatoid arthritis patients.

	baseline	3 months	6 months	p-value *	p-value * *
HAQ-DI (0-3)					
Active	1.12 7 0.53	0.97 7 0.59	1.00 7 0.58	0.008	0.023
Placebo	1.09 7 0.75	1.12 7 0.70	1.14 7 0.73		
HAQ Pain Scale (VAS)					
Active	45.31 7 22.40	40.81 7 23.42	38.75 7 23.44	0.228	0.189
Placebo	44.64 7 21.65	46.29 7 21.89	44.81 7 23.27		
HAQ Patient ‰s Global Scale (VAS)					
Active	48.53 7 25.89	41.14 7 21.81	38.72 7 24.75	0.250	0.083
Placebo	46.10 7 21.03	45.36 7 25.22	46.14 7 24.11		
DAS28					
Active	4.87 7 1.30	4.11 7 1.16	3.81 7 1.56	0.146	0.029
Placebo	4.71 7 1.03	4.45 7 1.50	4.40 7 1.19		
Physician ‰s Global Scale (VAS)					
Active	45.58 7 19.63	36.94 7 22.10	28.56 7 22.33	0.209	0.003
Placebo	47.07 7 18.24	43.60 7 23.54	43.33 7 22.83		
RAQoL					
Active	11.92 7 6.58	10.25 7 6.66	10.22 7 7.64	0.093	0.035
Placebo	10.86 7 6.68	10.71 7 6.75	11.10 7 6.90		
SF-12 physical					
Active	33.19 7 8.24	36.19 7 9.02	37.23 7 8.61	0.428	0.008
Placebo	33.74 7 8.86	36.65 7 9.52	34.30 7 8.24		
SF-12 mental					
Active	48.53 7 10.37	48.96 7 11.02	47.53 7 10.80	0.348	0.858
Placebo	48.66 7 9.45	47.62 7 9.82	48.20 7 9.54		

Data are presented as means 7 SD. Predefined analysis on patients who participated for 3 month or more, last value carried forward (N=78).

* p-value: from ANCOVA-difference 3 months to baseline adjusted for baseline value.
* * p-value: from ANCOVA-difference 6 months to baseline adjusted for baseline value.

A pre-defined analysis of all 78 patients who participated for at least 3 month in the trial (Table 3) and analysis of the 74 patients who completed the trial (data not shown) confirmed these results essentially. In addition the DAS-28 score difference became statistically significant.

Several factors were examined as possible predictors or effect modifiers for the treatment effect: sex, age, BMI, centre and employment status. None of these factors showed a significant result (data not shown).

As shown in Table 1 , there were no statistically significant difference in the pattern of the consumption of analgesics (paracetamol, tramadol and codeine), NSAID's, steroids and DMARD's at baseline. In addition when the consumption of medicine during the 6 month treatment period was calculated, there was no statistically significant change in the consumption of analgesics, NSAID's, steroids and metrotrexate or other DMARD's in either of the two groups or when comparing groups.

Blood sampling

Additionally blood samples at baseline and 6 months were analysed. There was no statistically significant change in haemoglobin, interleukins, tumour necrotic factor alpha (TNF alpha) and cholesterol level (data not shown). ESR declined in the actively treated group as compared to the placebo group, P-values for the ITT population and for patients participating in the study for three months or more were 0.060 and 0.045, respectively. A similar trend, although not significant, was observed for CRP (data not shown).

Adverse effects

There were 14 reports on side effects in the actively treated group and 26 reports in the placebo group (Table 4). There was one serious event (vasculitis allergica) in the treatment group where the code was broken. However, it was not clear whether this event was related to the study medication as the patient was also taking a number of other medications. Four patients in the treatment group dropped out due to adverse effects, compared with 1 patient in the placebo group (Fig. 1). So far this study did not detect adverse events of any kind, which can be related to the present rose hip and seed powder. This seems to be in correspondence with previous studies of the same powder on patients with osteoarthritis (Warholm et al. 2003 ; Winther et al. 2005 ; Christensen et al. 2008).

Table 4
Adverse effects in rheumatoid arthritis patients.

	Active (n)	Placebo (n)
Gastro-intestinal disturbances	5	8
Common cold /Influenza	2	7
Skin Rash /Eczema	2	4
Vasculitis	1	
Elevated diuresis		1
Back problems		1
Swallowing problems	1	
Dizziness		1
Urinary tract infection (UTI)	1	
Headache	1	
Cyst in left breast		1
Pain in hand		1
Weight gain	1	
Sleeping disturbances		1
Elevated blood pressure		1
Total	14	26

Discussion

The present study suggests some benefit of patients with RA treated with the present rose hip powder as indicated in the HAQ-DI and the HAQ Patient Global Scale. The secondary outcomes DAS-28, Physician's Global Scale and QoL assessments RAQoL scores and SF-12 physical support these findings, and no change in the consumption of analgesics, NSAID's, steroids and DMARD's were observed in any of the two groups during the six month treatment period.

The clinical relevant change in HAQ-DI score is given as 0.22 (Bruce and Fries 2003). The average change in the study was a decline of 0.10 in the score of actively treated patients and an increase in the score of 0.04 in the placebo treated group-a modest, although significant change. For that reason a sub analysis was applied on the sub fraction of patients (n=21) who showed a change in HAQ-DI score of 0,22 or more, as the result of 6 month treatment. Fischer's Exact test yielded a table probability (p) of 0.040 in favour of active treatment in the ITT population and of 0.031 in patients who participated in the study for at least 3 month.

There are only few herbal products which were suggested to be effective in RA. A recent Cochrane review concluded that the strongest evidence was found for gamma-linolenic acid (GLA) found in evening primrose oil, borage seed oil and black current seed oil (Little and Parson 2000). All of the GLA studies found some improvement in clinical outcomes but study quality was variable, making it difficult to draw conclusive results. However, the better quality studies suggested potential relief of pain, morning stiffness and joint tenderness. In one study where gamma-linolenic acid was given for 6 month, a time period comparable to the present study, the number of tender joints declined by 36% in patients completing the study (Leventhal et al. 1993). The number of tender joints, which is a part of the DAS-28 score used as direct outcome in the present study, declined by 45% in per protocol patients (p o 0.042). It is interesting to note that both products contain plant fatty acids and the structure of the galacto-lipid, GOPO, isolated from the present rose hip powder has some similarities with gamma-linolenic acid (Larsen et al. 2003).

Fish oil is another product of natural origin which has shown significant improvement in RA. A recent meta-analysis demonstrated that dietary fish oil supplementation significantly reduced tender joint count after long term treatment as compared with placebo (Fortin et al. 1995 ; Cleland et al. 1988). Like the present rose hip powder, fish oil contains long chain fatty acids which act anti-inflammatory. It is encouraging to observe that diet both from fish and from selected plant species can modify the number of tender joints and symptom score in RA.

An inhibition of neutrophil chemotaxis was earlier shown using the present rose hip powder and it was further demonstrated that the inhibitory effect was related to GOPO (Kharazmi and Winther 1999 , Larsen et al. 2003). A recent paper indicates that this standardized rose hip powder contains lipophilic COX inhibiting compounds (Jäger et al. 2007). These findings are further supported by in vivo animal studies showing an anti-inflammatory and anti-nociceptive activity of fruits from rose hip (Orhan et al. 2007) and by studies on human articular cells showing that the present rose hip powder and the galactolipid GOPO in particular show anti-inflammatory and chondro-protective properties (Schwager et al. 2008). It was likewise demonstrated that rose hip, which is rich in bioactive polyphenoles, reduces inflammatory injuries leading to tissue damage in mouse colon (Håkansson et al. 2006). The present study demonstrated a reduction in ESR, suggesting an anti-inflammatory action.

The rose hip powder did not produce side effects different from what was observed for placebo, when added to the already initiated standard RA treatment. This safety profile is consistent with earlier studies on patients with osteoarthritis (Warholm et al. 2003 ; Winther et al. 2005 , Christensen et al. 2008).

Rose hip was shown to have strong anti-oxidant capacity compared with other dietary plants (Halvorsen et al. 2002). Calculated from Halvorsens estimates on different fruits, vegetables and berries it was estimated that there is more than a 1000-fold difference in total antioxidant capacity among various dietary plants with rose hip being the most powerful anti-oxidant of all investigated plants. Extracts from rose hip were also shown to reduce the release of reactive oxygen species from polymorpho-nuclear neutrophils suggesting a protective effect on different tissues (Kharazmi and Winther 1999 ; Daels-Rakotoarison et al. 2002).

Although the pathophysiological background of RA is not fully elucidated, reactive oxygen species appears part ofi ts pathogen-esis (Biemond et al. 1984). Cartilage loss occurs as a consequence of enzymatic degradation by metalloproteinases, the synthesis of which is enhanced by cytotoxic free radicals such as nitric oxide (NO) present in the inflamed areas (Martel-Pelletier et al. 1994 , Murrell et al. 1995). Total plasma antioxidant capacity was also reported to be reduced in RA (Sarban et al. 2005) and it is suggested that anti-oxidants to some extend can prevent symptoms of RA by modifying cartilage destruction (Schwager et al. 2008). This hypothesis may also explain why a sustained vegan diet was observed to reduce the symptom score and number of tender joints in patients with RA (Kjeldsen-Kragh et al. 1991) and why a vegan diet rich in antioxidants were reported to reduce disease activity in patients with RA (Hänninen et al. 2000).

The only parameter with significant effects already after 3 months of treatment was the HAQ-DI. Since after 6 months several further outcome measures, such as DAS-28, physician's global evaluation, HAQoL and SF-12 physical showed improve-ment, a delayed onset of effects of the present remedy is suggested. This is in agreement with observations using other plant and fish fatty acids which also show a slow but sustained onset in RA patients (Leventhal et al. 1993 ; Fortin et al. 1995). The biochemical background for the slow onset still needs to be clarified. A slow onset and carry over effects were detected in a study where the present rose hip powder was given to patients with osteoarthritis (Winther et al. 2005).

From a public health perspective the present results are interesting since they may guide in developing new therapeutic approaches for RA with enhanced clinical effectiveness. Particu-larly in the case of potentially disabling disorders with high medical and economic burden such as RA such new strategies are warranted.

In conclusion: The present trial was small and was not to well powered. And thus, though promising, the values should be taken with precaution. Therefore, studies with higher sample size and adequate power for multivariate analysis are warranted. Future research should also include dose-finding studies and testing of different rose hip extractions.

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References

Arnett, F.C., Edworthy, S.M., Bloch, D.A., McShane, D.J., Fries, J.F., Cooper, N.S., Healey, L.A., Kaplan, S.R., Liang, M.H., Luthra, H.S., 1988. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum. 31, 315–324.

Biemond, P., Swaak, A.J., Koster, J.F., 1984. Protective factors against oxygen free radicals and hydrogen peroxide in rheumatoid arthritis synovial fluid. Arthritis Rheum. 27, 760–765.

Bruce, B., Fries, J.F., 2003. The Stanford health assessment questionnaire: dimensions and practical applications. Health Qual. Life Outcomes 1, 20.

Christensen, R., Bartels, E.M., Altman, R.D., Astrup, A., Bliddal, H., 2008. Does the powder of Rosa canina (rosehip) reduce pain in osteoarthritis patients?A meta-analysis of randomized controlled trials. Osteoarthritis Cartilage 16, 965–972.

Cleland, L.G., French, J.K., Betts, W.H., Murphy, G.A., Elliot, M.J., 1988. Clinical and biochemical effect of dietary fish oil supplementation in rheumatoid arthritis. J. Rheumatol. 15, 1471–1475.

Daels-Rakotoarison, D.A., Gressier, B., Trotin, F., Brunet, C., Luyckx, M., Dine, T., Bailleul, F., Cazin, M., Cazin, J.C., 2002. Effects of rosa canina fruit extract on neutrophil respiratory burst. Phytother. Res. 16, 157–161.

De Jong, Z., Van der Heijde, D., McKenna, S.P., Whalley, D., 1997. The reliability and construct validity of the RAQoL: a rheumatoid arthritis-specific quality ofl ife instrument. Br. J. Rheumatol. 36, 878–883.

Fortin, P.R., Lew, R.A., Liang, M.H., Wright, E.A., Beckett, L.A., Chalmers, T.C., Sperling, R.I., 1995. Validation of a meta-analysis: the effects of fish oil in rheumatoid arthritis. J. Clin. Epidemiol. 48, 1379–1390.

Håkansson, Å., Stene, C., Mihaescu, A., Molin, G., Arhné, S., Thorlacius, H., Jeppsson, B., 2006. Rose hip and lactobacillus plantarum DSM 9843 reduce ischemia/reperfusion injury in the mouse colon. Dig. Dis. Sci. 51, 2094–2101.

Halvorsen, B.L., Holte, K., Myhrstad, M.C.W., Barikmo, I., Hvattum, E., Remberg, S.F., Wold, A.-B., Haffner, K., Baugerød, H., Andersen, L.F., Moskaug, J.Ø., Jacobs, D.R., Blomhoff, R., 2002. A systematic screening of total antioxidants in dietary plants. J. Nutr. 132, 461–471.

Hänninen, O., Kaartinen, K., Rauma, A.-L., Neonen, M., Törrönen, R., Häkkinen, S., Adlercreutz, H., Laakso, J., 2000. Antioxidants in vegan diet and rheumatic disorders. Toxicology 30 (155), 45–53.

Jäger, A.K., Eldeen, I.M.S., Standen, J., 2007. COX-1 and COX-2 activity of rose hip. Phytother. Res. 21 (12), 1251–1252.

Kharazmi, A., Winther, K., 1999. Rose hip inhibits chemotaxis and chemilumini-nescence of human blood neutrophils in vitro and reduces certain inflamma-tory parameters in vivo. Inflammopharmacology 7, 377–386.

Kjeldsen-Kragh, J., Haugen, M., Borchgrevink, C.F., Laerum, E., Eek, M., Mowinkel, P., Hovi, K., Førre, Ø., 1991. Controlled trial of fasting and one-year vegetarian diet in rheumatoid arthritis. Lancet 338, 899–902.

Larsen, E., Kharazmi, A., Christensen, L.P., Christensen, S.B., 2003. An antiinflammatory galactolipid from rose hip (rosa canina) that inhibits chemotaxis of human peripheral blood neutrophils in vitro. J. Nat. Prod. 66, 994–995.

Leventhal, L.J., Boyce, E.G., Zurier, R.B., 1993. Treatment of rheumatoid arthritis with gammalinolenic acid. Ann. Int. Med. 119, 867–873.

Leventhal, L.J., Boyce, E.G., Zurier, R.B., 1994. Treatments of rheumatoid arthritis with blackcurrant seed oil. Br. J. Rheumatol. 33, 847–852.

Little, C.V., Parson, T., 2000. Herbal therapy for treating rheumatoid arthritis (Review). Cochrane Database of Systematic Reviews, issue 4. Art. no.:CD002948. Doi:10.1002/14651858.CD002948.

Martel-Pelletier, J., McCollum, R., Fujimoto, N., Obata, K., Cloutier, J.M., Pelletier, J.P., 1994. Excess of metalloproteases over tissue inhibitors of metalloproteases may contribute to cartilage degradation in OA and rheumatoid arthritis. Lab. Invest. 70, 807–815.

Mukherjee, D., Nissen, S.E., Topol, E.J., 2001. Risk of cardiovascular events associated with selective cox-2 inhibitors. JAMA 286, 954–959.

Murrell, G.A., Jang, D., Williams, R.J., 1995. Nitric oxide activates protease enzymes in articular cartilage. Biochem. Biophys. Res. Commun. 206, 15–21.

Prevoo, M.L.L., van't Hof, M.A., Kuper, H.H., van Leeuwen, M.A., van de Putte, L.B., van Riel, P.L., 1995. Modified disease activity scores that include twenty-eight joint counts. Arthritis Rheum. 38, 44–48.

Orhan, D.D., Harteviogiu, A., Küpeli, E., Yesilada, E., 2007. In vivo anti-inflammatory and antinociceptive activity of the crude extract and fractions from Rosa canina L. fruits. J. Ethnopharmacol. 112, 394–400.

Rodriquez, L.A.G., Hernandez-Diaz, 2000. Relative risk of upper gastrointestinal complications among users of acetaminophen and nonsteroidal anti-inflam-matory drugs. Epidemiology 12, 570–576.

Ruof, J., Hulsemann, J.L., Mittendorf, T., Handelmann, S., van der Schulenburg, J.M., Zeidler, H., et al., 2003. Costs of rheumatoid arthritis in Germany: a micro-costing approach based on healthcare payer's data sources. Ann. Rheum. Dis. 62, 544–549.

Sarban, S., Kocyigit, A., Yazar, M., Isikan, U.E., 2005. Plasma total antioxidant capacity, lipid peroxidation, and erythrocyte antioxidant enzyme activities in patients with rheumatoid arthritis and osteoarthritis. Clin. Biochem. 38, 981–986.

Schwager, J., Richard, N., Wolfram, S., 2008. The galactolipid GOPO mediates beneficial effects of rose hip on arthritis by reducing chemokine and

interleukine production in macrophages and chondrocytes. Int. J. Rheum. Dis. 11 (1), A96.
Vane, J.R., Botting, R.M., 1998. Anti-inflammatory drugs and their mechanisms of action. Inflamm. Res. 47, 578–587.
Warholm, O., Skaar, S., Hedman, E., Mølmer, H., Eik, L., 2003. The effect of a standardized herbal remedy made from a subtype of rosa canina in patients with osteoarthritis: a double-blind, randomized, placebo-controlled clinical trial. Curr. Ther. Res. 64, 21–31.
Winther, K., Apel, K., Thamsborg, G., 2005. 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. Scand. J. Rheumatol. 34, 302–308.
Wolfe, F., 2001. Which HAQ is best? A comparison of the HAQ, MHAQ and RA-HAQ, a difficult 8 item HAQ (DHAQ), and a rescored 20 item HAQ (HAQ20): analyses in 2491 rheumatoid arthritis patients following leflunomide initiation. J. Rheumatol. 28, 982–989.
Zurier, R.B., Rossetti, R.G., Jacobson, E.W., DeMarco, D.M., Liu, N.Y., Temming, J.E., White, B.M., Laposata, M., 1996. Gamma-linolenic acid treatment of rheumatoid arthritis. Arthritis Rheum. 39, 1808–1817.

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A ONE-YEAR SURVEY ON THE USE OF A POWDER FROM ROSA CANINA LITO IN ACUTE EXACERBATIONS OF CHRONIC PAIN

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This pilot surveillance included 152 patients with acute exacerbations of chronic pain, 124 (Back group) with non-specific low back pain (NSLBP), 20 with NSLBP overridden by osteoarthritic pain (Knee-Hip group), and eight with specific LBP (included in the safety analysis). Patients were recommended the rose hip and seed powder Litozin [R] at a dose providing up to 3 mg of galactolipid/day for up to 54 weeks. Clinical symptoms and well-being were assessed every 6 weeks. The patients also kept a diary of their pain and the requirement for rescue medication. Data were analysed by intention to treat with last observation carried forward.

Only 77 patients completed the year of surveillance. Multivariate analysis suggested an appreciable overall improvement during the surveillance, irrespective of group, and this was reflected for most of the individual measures in repeated measures ANOVA. The degree and time-course of improvement echoed that seen in similar surveillances of patients receiving an aqueous extract of Harpagophytum . Multiple regression analyses indicated that percentage changes from baseline tended to be greater in patients with greater degrees of pain and disability, but were otherwise largely unrelated to the patients' characteristics. There were no serious adverse events.

The rose hip and seed powder, Litozin [R], seems to deserve further, more definitive studies as a possible option in long-term management of NSLBP with or without osteoarthritic pain. Copyright © 2008 John Wiley & Sons, Ltd.

Keywords: low back pain; osteoarthritis; rose hip and seed; long-term treatment.

INTRODUCTION

Preparations derived from rose hips and seeds were used in medieval times for rheumatic complaints (Anonymous, 1998), but because of insufficient clinical evidence such use has not been recommended in the German Commission E Monographs (Blumenthal, 1998). Since then, two double-blind randomized placebo-controlled studies (Warholm et al., 2003; Rein et al., 2004) of good quality (Chrubasik et al., 2006) have indicated that there may be some benefit to a 3–4 month treatment with a preparation of powdered rose hip and seed. Litozin [R], which contains an anti-inflammatory principle (Winther et al., 1999; Larsen et al., 2003), is a food additive rather than a pharmaceutical. It is presented either as a loose powder, each gram of which contains 0.3 mg of the coactive marker galactolipid. A 5 mL teaspoon holds 2.5 g, which can be mixed, for example into yoghurt. It has also been supplied in capsules containing 0.5 g (now discontinued) or 0.75 g of the powder. To familiarize ourselves with the product in a setting with which we were already familiar, a protocol was adapted that had been developed in two previous surveillances of an aqueous extract of Harpagophytum procumbens (Chrubasik et al., 2005, 2007a) and it was used to undertake a 1 year surveillance of patients offered Litozin [R] for chronic non-specific low back pain (NSLBP). The protocol provides for a baseline assessment and registration and 6 weekly visits for up to 54 weeks for as long as patients wish to remain in the surveillance, backed up by diary records of pain and the requirement for additional medication.

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METHODS

The adaptation of the protocol for Litozin [R] was approved by the Ethics Committee of the University of Freiburg to be in agreement with the German drug regulatory authority guidelines for post-marketing surveillance studies. The surveillance was publicized locally by word of mouth and patients presented to a clinic of one of the authors (SC). Forty-one patients had taken part in our surveillance with the Harpagophytum extract dating back 3–4 years. Patients whose chronic pain had required treatment for at least 6 months and who rated their maximum pain in the previous 2 weeks as at least 5 cm on a 10 cm visual analogue scale were invited to participate in the surveillance for up to 54 weeks. After giving written informed consent, 152 received the Litozin [R]: in 124 of these (the Back group), the predominating symptoms were from their non-specific low back pain (NSLBP) as defined by the IASP

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(Fordyce, 1995); a further 20 (the Knee/Hip group) did have NSLBP but this was heavily overshadowed by osteoarthritic (OA) pain (as defined by the Altman classifications (1986, 1991), either in the knee (9) patients) or hip (11 patients); the remaining eight patients, whose low back pain was attributable to some specific cause, were included at their insistence, but their data were used only in the documentation of possible adverse events (AEs). After the baseline assessments, in the absence of any formal dosage recommendations, but guided by the studies cited above, the patients were recommended a dose of 5 g Litozin [R] per day or 10 of the 0.5 g capsules. After the first dozen patients had started, the 6-week reviews indicated that the pain relief was clearly unacceptable for some, so that, for 75 of the remaining 148 patients, the starting dose was doubled if the presenting symptoms seemed unduly severe or prolonged. Patients were encouraged to adjust their dose upwards or downwards according to their symptoms.

Initially and at each of the 6 weekly visits up to 54 weeks, the same outcome variables were recorded as in the previous surveillances (Chrubasik et al., 2005, 2007a). These consisted of: (i) the Three Item Pain Score (TIPS), comprising [a] current pain at the time of investigation, [b] worst pain and [c] average pain in the preceding 2 weeks, all assessed on a 0–10 visual analogue scale; the Back group gave a TIPS for their back symptoms and the Knee/Hip group did so for their knee or hip pain; (the Back group also answered separate questions about any radiation of pain to their legs which, together with their TIPS constituted the Pain component of the Arhus low back pain score – except for the exclusion of data on the use of analgesics, because these were recorded separately); (ii) the Disability component of the Arhus low back pain score (though this may have been influenced to some extent by the knee or hip pain in the Knee/Hip group); (iii) a modification of the German version of the Health Assessment Questionnaire (HAQ) that added a point for each aid or device that the patient needed to maintain their quality of life; (iv) a 4-point patient global assessment (PGA) of effectiveness of treatment (very good, good, moderate, poor); (v) a 4-point global assessment of tolerability.

All patients were also given a diary to make morning recordings of the pain they had experienced on the preceding day, using a 5-point verbal rating scale (none, mild, moderate, severe, excruciating) and of additional pain treatments expressed in paracetamol, diclofenac or tramadol equivalents based on their recommended daily dosage. A predetermined standardized questionnaire was used to list any adverse events, to assess their severity, intensity and to attempt to contribute cause. The patient and one author (SC) completed the questionnaire together and the information was subsequently discussed with another physician not otherwise involved in the study.

Statistical analysis. The analyses were carried out with the procedures available in the Statistical Analysis System Software package (SAS Institute Inc., Cary, NC). The principal analyses were by Intention to Treat (ITT) with Last available Observation Carried Forward (LOCF) to each subsequent time point under consideration. A limited number of subsidiary Per Protocol analyses were carried out for comparison.

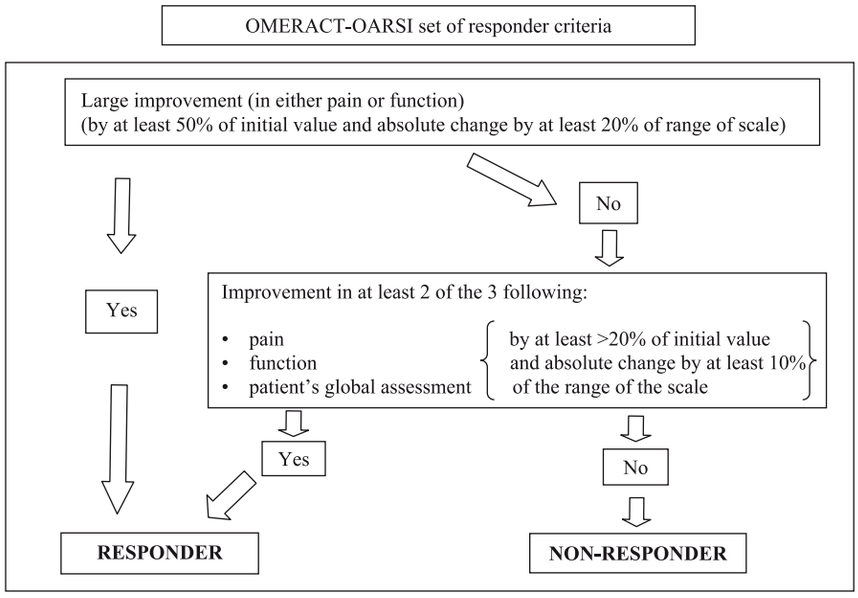
An overall Multivariate Analysis of Variance (MANOVA: GLM procedure) was carried out on the available data, from 122 patients in the Back group and 20 patients in the Knee/Hip group – the patient's gender and group being identified by a dummy variable. The dependent variables were the difference between the initial and last available score for TIPS, Arhus Disability and HAQ: the MANOVA examined for any overall effect and for any differences in effect between the groups. Repeated measures ANOVAs (also with dummy variables to allow for group and gender) were carried out for the individual measures to identify the individual contributions to any overall change. Linear multiple regressions were undertaken for changes between the baseline and each patient's final assessment, with fixed co-variables comprising initial score, initial dose, age, gender, body mass index and duration of acute exacerbation. Weekly averaged daily diary pain scores data were treated as interval (metric) data: because of the relatively slow onset of effect, the average over the first week of treatment was taken as representing the baseline. The indices were calculated as percentage changes from the baseline and the medians of these percentage changes were plotted for each visit.

Patients were classified dichotomously as 'responders' or 'non-responders' to treatment according the general criteria suggested by the OMERACT-OARSI Initiative (Pham et al., 2003, 2004) (Textbox 1) but adapted to the data available to us (Textbox 2). The classification of responder versus non-responder according to the OMERACT-OARSI criteria (Pham et al. 2004) was cross-tabulated against the PGA as 'very good or good' versus 'moderate or poor', and the quality of agreement was assessed in terms of the kappa value. The results of inferential testing were presented as 2-sided p values but with no adjustments made for the numbers of inferential tests.

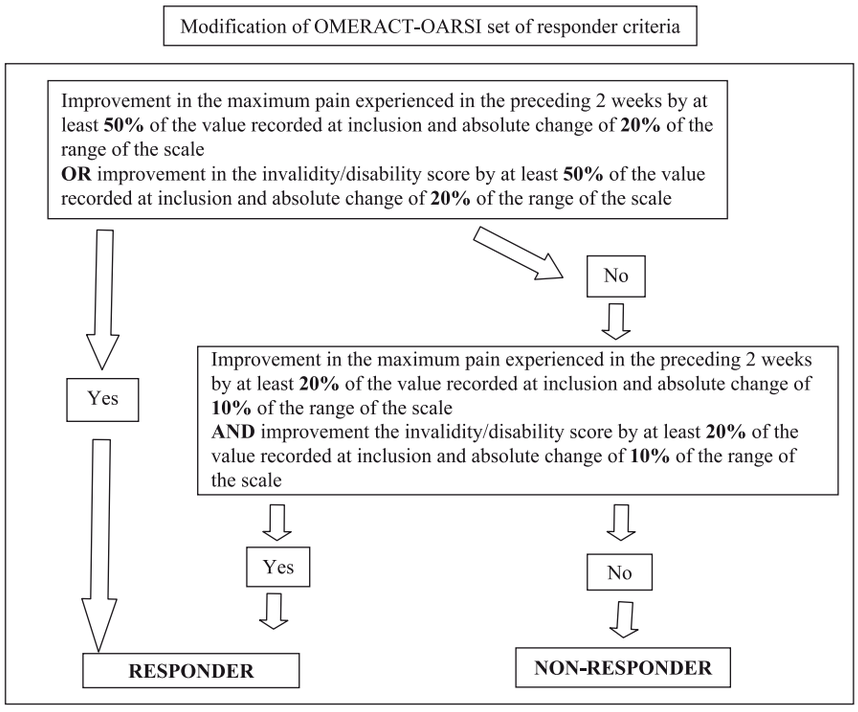
RESULTS

Table 1 summarizes the baseline characteristics of the 33 men and 109 women whose data contributed to the assessment of possible effectiveness (there being no discernible difference between the Back and Knee/Hip groups. It is noteworthy that the duration of their propensity to their chronic pain greatly exceeded the minimum entry requirement of 6 months in almost all patients. http://www.uniklinik-freiburg.de/rechtsmedizin/live/forschung/phytomedicine/originalartikel.html.

Figure 1 illustrates the attrition of patients from the surveillance along with the attritions in our two previous Harpagophytum studies, which were set up in somewhat different circumstances. Of the 75 patients who dropped out of the Litozin [R] surveillance before 54 weeks, 42 did so because of insufficient pain relief, seven because they were so free of pain that they thought continuation pointless, 14 experienced adverse events [seven were deemed unrelated to the study medication (including two patients who underwent hip surgery), seven were deemed possibly related (constipation, constipation and abdominal complaints, irritable bowel syndrome, nausea, meteorism, pruritus and abdominal complaints) or probably related (diarrhoea and abdominal complaints)] and 12 discontinued for other reasons



Textbox 1



Textbox 2

(see webpage). Patients who had participated in our previous surveillances seemed no more or less likely to drop out than those who had not.

Figure 2 shows examples of each week's average of the daily pain scores in six individual patients. The fluctuations seen in individuals were smoothed to a quasi-exponential curve in the grouped averages. Figure 3 shows the results of the ITT analysis of mean weekly average doses taken by the groups who were started on 5 and 10 g per day of Litozin [R]. From week 12, the standard errors of the weekly means (SEMs) varied between 1.86 and 2.58 and the line showing the t-value expresses the difference between the group means for each week in terms of the mean of their SEM. The two groups clearly 'titrate' themselves to a different average dose of Litozin [R]. The PP analysis gives an essentially similar picture. Figures 4a and b, respectively, show the results of the ITT and PP analyses of the averages of the weekly pain scores for the two dosage groups. Whereas the ITT analysis suggests that the two groups are using different doses to titrate themselves to the same average degree of pain, the PP analysis suggests a difference in pain level between the patients in the two groups who remain in the surveillance. The attrition rates from the two groups were very similar (Fig. 5a), and the difference shown in

Table 1. Medians, 25th and 75th centiles for the physical characteristics and baseline assessments of the 142 patients (33 men and 109 women) who contributed data on possible effectiveness of Litozin®

	Median	(25th; 75th centile)
Physical characteristics		
Age (years)	61	(52; 68)
Height (cm)	166	(162; 172)
Weight (kg)	76	(64; 84)
Body mass index	26.9	(23.5; 29.7)
Baseline assessments		
Duration of propensity to pain (months)	180	(120; 240)
Duration of acute exacerbation (weeks)	24	(12; 56)
Arhus Index		
Current pain	4.1	(2.0; 5.6)
Worst pain in the preceding 2 weeks	6.8	(5.3; 8.2)
Average pain in the preceding 2 weeks	4.7	(3.3; 5.4)
Three score index	15.4	(11.3; 19.3)
(1) Pain component of Arhus Index (n = 122)	22.8	(15.4; 34.3)
(2) Disability component	15.0	(11.0; 20.0)
Health Assessment Questionnaire	9.0	(5.0; 16.0)

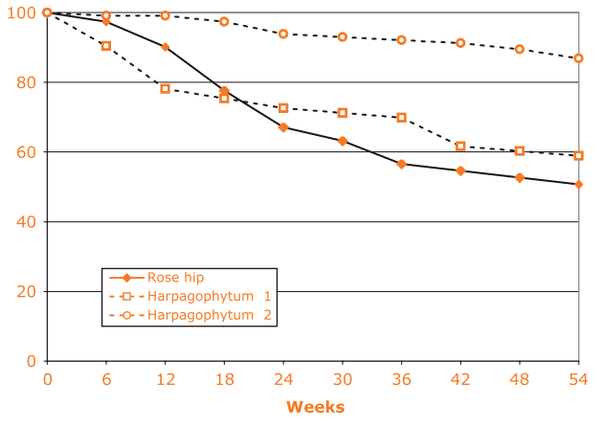


Figure 1. Attrition from the Litozin surveillance and two previous surveillances with a *Harpagophytum* extract.

Fig. 4b arose because the patients who dropped out of the 10 g group did so at a lower average degree of pain than those who dropped out of the 5 g group (Fig. 5b).

Of the 924 patient-days for which patients kept diary records in week 1, the respective percentages with no, mild, moderate, severe and excruciating pain were 3%, 22%, 48%, 22% and 6%, whereas, for each patient's last week of treatment, the respective percentages were 29%, 35%, 24%, 12% and 1%. This is illustrated in Fig. 6 in terms of histograms of the ITT determinations of the averages of the weekly average pain scores for weeks 1, 5, 10, 15, 25, 35 and 50, which is keeping with Fig. 4a. As the surveillance proceeds, there tends to be an increase in the lower values at the expense of the very highest values. The picture is complicated by the entrainment of values by the integer averages, reflecting the increasing stability of pain scores during each week, both for those remaining in the surveillance and for those who drop out and have their last observations carried forward. There does not seem to be a clear dichotomy between patients who respond very well and patients who do not respond at all.

The MANOVA indicated a significant overall improvement ($p < 0.001$) from baseline to the final values of its included indices with no significant influence of group (Back versus Knee/Hip) but with a significant effect of gender. The improvement was reflected in the repeated measures ANOVAs for current Pain, TIPS, (Arhus Disability) and HAQ, but the gender effect was only significant for HAQ and Arhus Disability. Figure 7 is a plot the ITT determinations of median values of the percentage changes from baseline for all four assessments that were included in the MANOVA, along with the OMERACT-OARSI responder rate. The median values declined quasi-exponentially to values of between 35% and 65% of baseline, and the OMERACT-OARSI rose correspondingly to a little over 60%.

There was a reasonable general similarity between this surveillance and our previous two surveillances on the aqueous extract of Harpagophytum in respect of the time-courses of change in the various assessments. However, little importance can be attached to the similarities or otherwise because of the uncertainties engendered by the attrition of patients from the surveillance. The attrition in Litozin® surveillance and the first Harpagophytum surveillance was appreciably greater than in the second Harpagophytum surveillance (Fig. 1), and correspondingly there was a larger difference in these two surveillances between the ITT and PP analyses for each of the component assessments. This difference, expressed in Fig. 8 in terms of the overall OMERACT-OARSI responder rate, gives an indication of the uncertainty in the estimates and this limits the importance that can be attached to the comparisons between surveillances.

Linear multiple regression indicated that there was a high positive correlation between the absolute changes from baseline and the baseline values themselves (the more the initial pain, the more the relief). Some spurious positive correlation would have been expected, because [baseline score – final] is offered to the regressions as the dependent variable and baseline score is also offered as an independent variable. Otherwise, none of the patients' characteristics seemed to have much influence except that women tended to show less improvement in the HAQ and Arhus Disability than men, as seen in repeated measures ANOVA.

Fifty patients took small amounts of additional analgesics (mainly NSAIDS) at various times throughout the year of treatment: 21 of these dropped out

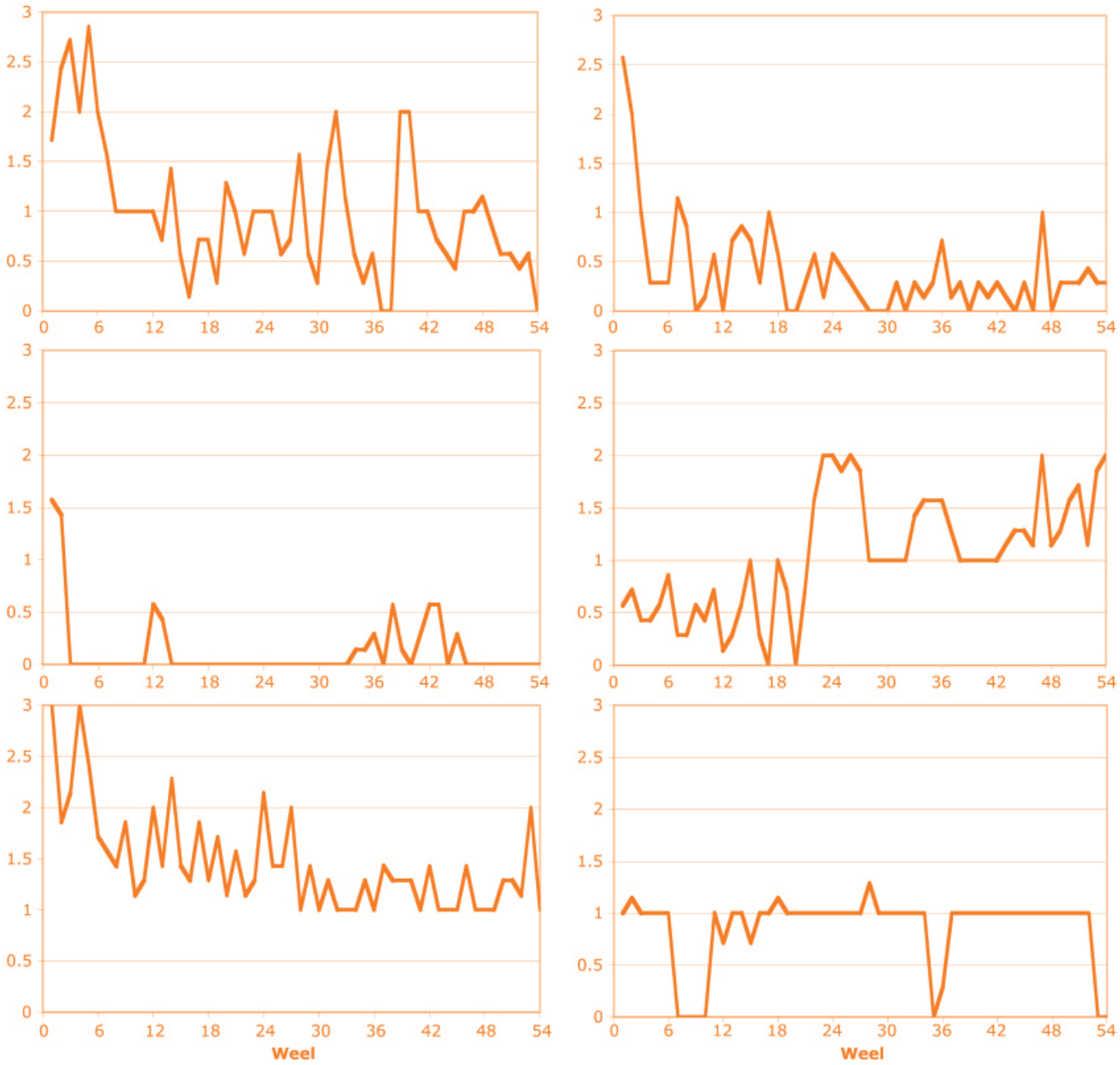


Figure 2. Examples of individual time-courses of the weekly averages of the daily pain scores.

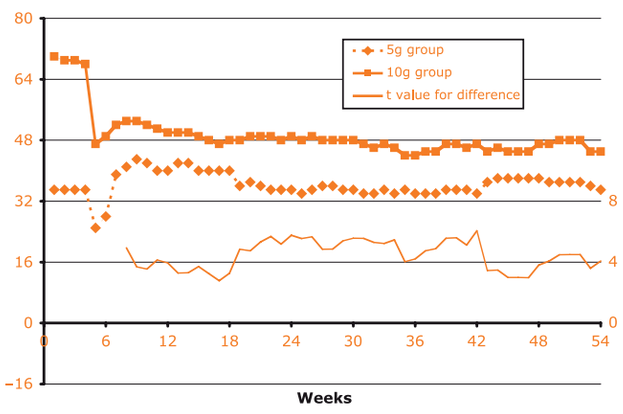


Figure 3. ITT analysis. Averages of the weekly average doses of Litozin [R] taken by the patients who started on 5 g and 10 g. The *t* value expresses the difference between the means for the two groups in terms of the average standard error of the means for each week.

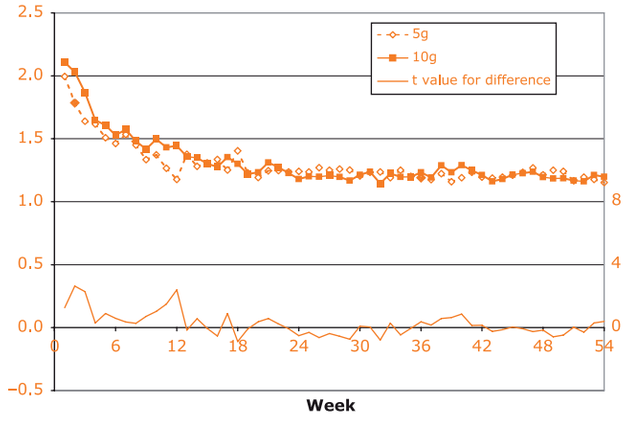


Figure 4a. ITT analysis. Averages of weekly average diary pain scores in the groups who started the surveillance on 5 and 10 g of Litozin [R]. The *t* value expresses the difference between the means for the two groups in terms of the average standard error of the means for each week.

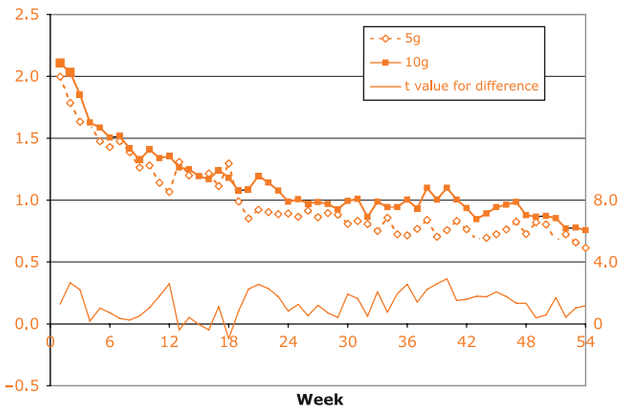


Figure 4b. PP analysis. Averages of weekly average diary pain scores in the groups who started the surveillance on 5 and 10 g of Litozin [R]. The *t* value expresses the difference between the means for the two groups in terms of the average standard error of the means for each week.

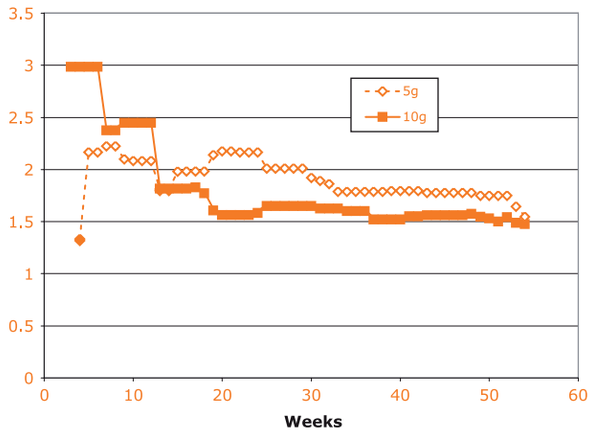


Figure 5b. Averages of weekly average pain scores in the patients who dropped out of in the groups who started the surveillance on 5 and 10 g of Litozin [R].

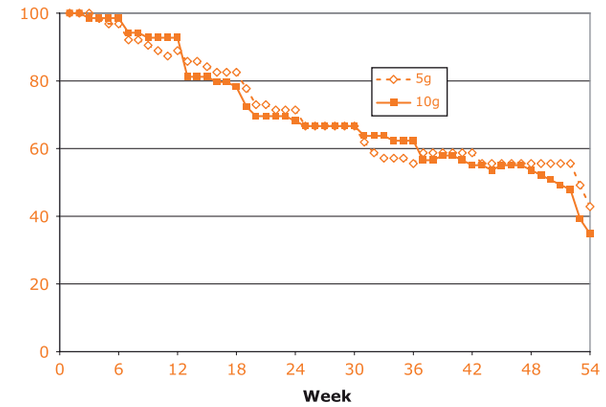


Figure 5a. Attrition rates of patients who started the surveillance in the groups who started the surveillance on 5 and 10 g of Litozin [R].

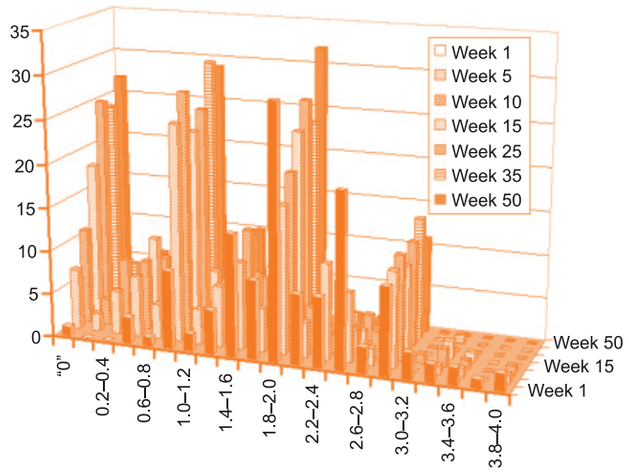


Figure 6. ITT analysis. A series of histograms of the averages of the weekly average pain scores in weeks 1, 5, 10, 15, 25, 35 and 50.

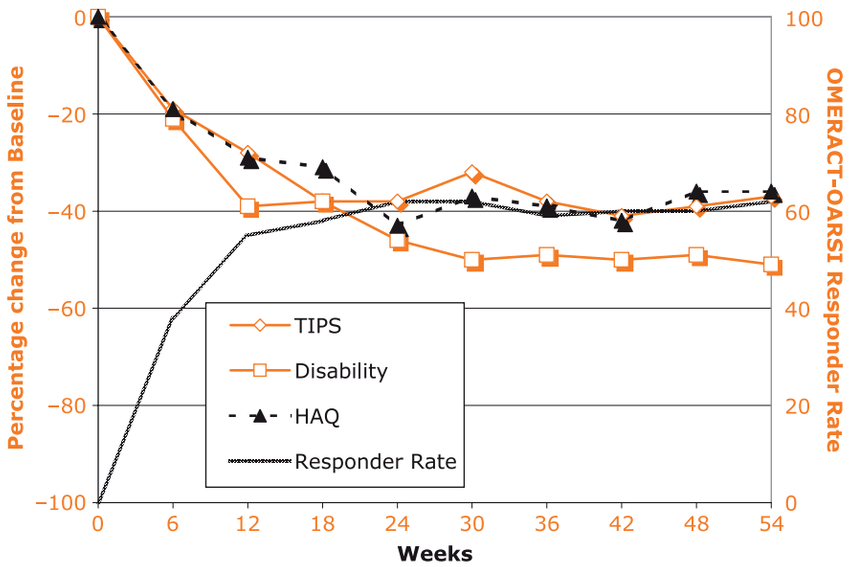


Figure 7. ITT analysis. Time courses of the median percentage changes from baseline of the assessments that were included in the MANOVA, and the OMERACT-OARSI responder rate.

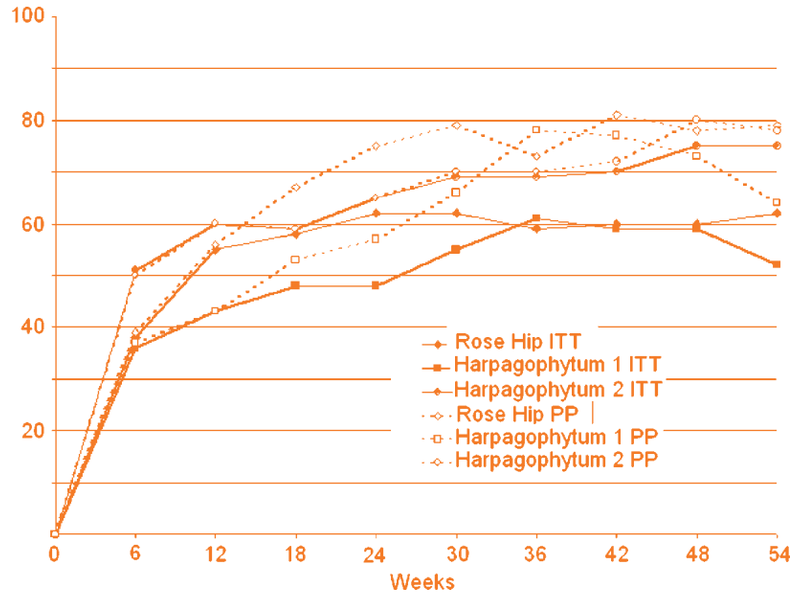


Figure 8. Comparing the ITT and PP analyses of the OMERACT-OARSI responder rates during the current surveillances with Litozin® and the two previous *Harpagophytum* surveillances.

of the surveillance. Only one patient used analgesics continuously, and was one of two patients who remained in the surveillance for the full 54 weeks and met the OMERACT-OARSI criterion for 'response' to treatment despite requiring the equivalent of more than 100 mg diclofenac per day during the 6 weeks leading up to their last visit. (Reclassifying the patients on the grounds that the response was probably to NSAIDs rather than Litozin® made no material difference to the results displayed in Fig. 5). The other six patients who were still taking analgesics at the end of the surveillance (week 54) were using very small amounts (see webpage).

At the 6-week visit 20 of the 142 patients rated the effectiveness as very good, 49 as good, 48 as moderate and 19 as poor. When the patients' final assessments were considered (at whatever time they ceased to take part in the study, the corresponding numbers were: 41 very good; 49 good; 27 moderate and 19 poor. The cross tabulation of patients final perceptions of the effectivenessof treatment against its tolerability showed only poor agreement (Cohens kappa 0.25).

Cross-tabulation of the OARSI/OMERACT 'responders' versus 'non-responders' against the PGA 'very good or good' versus 'moderate or poor' showed about 75% agreement between the two classifications (Cohen's kappa 0.42).

Twenty seven patients experienced a total of 33 adverse events of which one was probably related and 32 were possibly related to Litozin® (see webpage).

DISCUSSION

As in our Harpagophytum surveillances, it is difficult to judge the external validity of the findings. The patients were not a representative sample of any easily definable population, having chosen to respond to largely word of mouth news that the surveillances were on offer. An appreciable proportion in this Litozin® surveillance had taken part in one or other of our previous Harpagophytum surveillances, though there was no convincing evidence that they behaved differently from the remainder either in terms of attrition or improvement during the surveillance. No clear parallels can be drawn between the patients in this surveillance and the 'Inception Cohort' described by Carey et al. (2000) or the one proposed by Costa et al. (2007).

As in the previous surveillances, the absence of a control group denies us any confidence in attributing the observed improvements to the substances that prompted the surveillance. There is no obvious dissimilarity between time-courses of improvement in the three surveillances, given the uncertainties produced by the quite large attrition rates in the Litozin® surveillance and the first Harpagophytum surveillance. Similarity might indicate some similarity in magnitude of effect, but it also prompts an unsettling but intriguing speculation. What would have happened if a placebo had been used in the surveillances, or even if the patients had simply been offered the same degree of personal support through supervision and the same encouragement to record their symptoms, which might have entrained a lifestyle less likely to exacerbate potentially painful processes and more likely to encourage resolution that is part of the natural history of exacerbation? Or what would have happened if they had been left to their own devices or to whatever support would otherwise have been available?

The duration of propensity to low back pain (Table 1) characterizes all of the patients as sufferers from chronic back pain for whom the prospects for return to normal function are generally poor (Carey et al., 2000). They were all experiencing acute exacerbations of varying duration, although we did not determine how many of them could be classed as being in 'unremitting pain' as defined by Carey et al. (2000). However, if they were all experiencing an exacerbation, it follows that they were recruited at a time when their pain was worse than would be considered usual for them, and that there would be some expectation of recovery, at least in some. Although Fig. 4a and b and Fig. 7 give the impression of a smooth reduction in average pain scores, the scores in some individual patients fluctuated appreciably. Since

the peaks and troughs of such fluctuations were asynchronous (Fig. 2), the averaged scores in the sample would be expected to decline as observed – simply as part of the natural history of the disease.

There is relatively good evidence, at least for the short term, that, as symptomatic relief from the pain of acute exacerbations, both Litozin [R] (Chrubasik et al., 2006) and Harpagophytum (Chrubasik et al., 2003a; Gagnier et al., 2007) do provide demonstrable benefit over placebo, and that at least one Harpagophytum product might claim clinical equivalence with conventional NSAID treatment (Chrubasik et al., 2002). Whether this extends to more pronounced or prolonged pain relief with more protracted treatment remains to be demonstrated.

In its guideline for the management of osteoarthritis of the hip and knee, the American College of Rheumatology suggests four goals: (i) control of pain; (ii) improvement in function; (iii) improvement in health-related quality of life; (iv) avoidance of toxicity (www.rheumatology.org/publications/guidelines/oa-mgmt/oa-mgmt.asp?aud=mem). In pursuance of goal (iv) above, non-pharmacological modes of treatment are heavily encouraged. Even if Doloteffin [R] and Litozin [R] contributed nothing to the observed improvement, the discipline provided by the protocol of the surveillance may arguably have done so, and this possibility is something to be pursued. The apparent paucity of side-effects with Litozin [R], as with Harpagophytum products (Chrubasik et al., 2006), should encourage more study of the overall cost-effectiveness in the management of chronic musculoskeletal pain, as has been attempted for another herbal medicine Assalix[R] (Chrubasik et al., 2001).

Though the surveillance was not intended as a dose-finding exercise for Litozin [R], the data shown in Figs 3–5 are interesting. The sudden reduction in dose after the 6 week visit suggests that the patients did follow advice to try reducing the dose if their symptoms seemed to warrant it. The apparent (statistically insignificant) overshoot with respect to the final average level is interesting in that it happened both in patients who were started on 10 g per day and 5 g per day. It is difficult to interpret the difference in the final plateaux of average dose in view of the differences between the ITT and PP analyses of the weekly average pain scores in Fig. 4a and b. However, it is plausible to conclude that, for some patients at least, the dose of 5 g per day that has been used in previous studies will be too small for optimal effect.

The attrition rate of nearly 50% in this surveillance is higher than the 40% seen in our earlier surveillance with Dolotefin [R] and substantially higher than the 10% seen in our second one. This justifies more interest in the comparison between the principal ITT with LOCF analysis and the subsidiary PP analysis, particularly because such a large proportion of the 'drop-outs' did so because of inadequate pain relief. For instance, the final response rate by the OMERACT-OARSI criterion by the PP analysis was 80% as opposed to the 60% seen in the ITT with LOCF analysis (Fig. 8).

In conclusion, though simple surveillances can never claim to be of sufficiently high scientific quality to warrant firm therapeutic recommendations, this one has amply fulfilled our objective of familiarising ourselves with Litozin [R] and raising some interesting questions to pursue in further, more definitive studies.

REFERENCES

Altman R, Alarcon G, Appelrouth D *et al.* 1991. The American College of Rheumatology criteria for classi fication and reporting of osteoarthritis of the hip. *Arthritis Rheum* **34**: 505–514.

Altman R, Asch E, Bloch D *et al.* 1986. Development of criteria for the classi fication and reporting of osteoarthritis. Classi fication of osteoarthritis of the knee. *Arthritis Rheum* **29**: 1039–1049.

Anonymous. 1998. *Rosa canina* L. In *Hagers Handbuch der Pharmazeutischen Praxis,* Bd 3, Blaschek W, H ändel R, Keller K, Reichling J, Rimpler H, Schneider G (eds). Springer: Berlin, 447–452.

Blumenthal M. 1998. *The Complete German Commission E Monographs* . The American Botanical Council: Austin, TX, 369.

Carey TS, Garrett JM, Jackman AM. 2000. Beyond the good prognosis. Examination of an inception cohort of patients with chronic low back pain. *Spine* **25**: 115 –120.

Chrubasik C, Duke RK, Chrubasik S. 2006. The evidence for clinical ef ficacy of rose hip and seed: a systematic review. *Phytother Res* **20**: 1–3.

Chrubasik JE, Roufogalis B, Chrubasik S. 2007b. Systematic review on the safety of *Harpagophytum* preparations for osteoarthritic or low back pain. *Phytother Res* **22**: 149–152.

Chrubasik S, Chrubasik C, K ünzel O, Conradt D, Black A. 2007a. Patient-perceived bene fit during one year of treatment with Dolotef fin[R]. *Phytomedicine* **14**: 371–376.

Chrubasik S, Conradt C, Black A. 2003a. The quality of clinical trials with *Harpagophytum procumbens* . *Phytomedicine* **10**: 613–623.

Chrubasik S, K ünzel O, Acker A, Conradt C, Kerschbaumer F. 2001. Potential economic impact of using a proprietary willow bark extract in outpatients treatment of low back pain: an open non-randomized study. *Phytomedicine* **8**: 241–251.

Chrubasik S, K ünzel O, Thanner J, Conradt C, Black A. 2005. A one-year follow-up after a pilot study with Doloteffn [R] for low back pain. *Phytomedicine* **11** : 470–477.

Chrubasik S, Model A, Pollak S, Black A. 2003b. A randomised double-blind pilot study comparing Dolotef fin and Vioxx in the treatment of low back pain. *Rheumatology* **42**: 141 –148.

Chrubasik S, Thanner J, K ünzel O, Conradt C, Black A, Pollak S. 2002. Comparison of outcome measures during treatment with Dolotef fin[R]. *Phytomedicine* **9**: 181 –194.

Costa LCM, Henschke N, Maher CG *et al.* 2007. Prognosis of chronic low back pain: design of an inception cohort study. *BMC Musculoskelet Disord* **8**: 11.

Fordyce WE. 1995. *Back Pain in the Workplace: Management of Disability in Nonspeci fic Conditions.* A Report of the Task Force on Pain in the Workplace of the International Association for the Study of Pain.

Gagnier JJ, van Tulder MW, Berman B, Bombardier C. 2007. Herbal medicine for low back pain: a Cochrane review. *Spine* **32**: 82–92.

Larsen E, Kharazmi A, Christensen LP, Brogger Christensen S. 2003. An anti-in flammatory galactolipid from rose hip (*Rosa canina* L.) inhibits chemotaxis of human peripheral blood neutrophils *in vitro* . *J Nat Prod* **66**: 994–995.

Pham T, van der Heijde D, Altman RD *et al.* 2004. OMERACT-OARSI Initiative. Osteoarthritis Research Society International set of responder criteria for osteoarthritis clinical trials revisited. *Osteoarthritis Cartilage* **12** : 389–399.

Pham T, Van Der Heijde D, Lassere M *et al.* 2003. OMERACT-OARSI. Outcome variables for osteoarthritis clinical trials: The OMERACT-OARSI set of responder criteria. *J Rheumatol* **30**: 1648 –1654.

Rein E, Kharazmi A, Winther K. 2004. A herbal remedy, Hyben Vital (stand. 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. *Phytomedicine* **11** : 383–391.

Warholm O, Skaar S, Hedman E, Molmen HM, Eik L. 2003. 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. *Curr Ther Res* **64**: 21–31.

Winther K, Rein E, Kharazmi A. 1999. The anti-in flammatory properties of rose-hip. *Inflammopharmacology* **7**: 377–386.

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.

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

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	Curr Ther Res Clin Exp 2003; 64: 21–31	Osteoarthritis Cartilage 2004; 12 Suppl 2	
			80 (subgroup)	145 (subgroup)
	n = 112 5 g/day vs placebo Cross-over Over 3 months	n = 100 5 g/day vs placebo Parallel Over 4 months	n = 94 (112) 5 g/day vs placebo Cross-over Over 3 months	n = 32 (112) 5 g/day vs placebo Cross-over 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://remedchrubasik.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.

References

Anon. 1998. Rosa canina L. In Hager Handbuch der Pharmazeutischen Praxis, 5th edn. Band 4, Hänsel R, Keller K, Rimpler H, Schneider G (eds). Springer-Verlag: Berlin, Heidelberg, New York, 3: 447–452.

Blumenthal M. 1998. The Complete German Commission E Monographs. The American Botanical Council: Austin, Texas, 368–369.

Chrubasik S, Eisenberg E, Balan E, Weinberger T, Luzzati R, Conradt C. 2000a. Treatment of low back pain exacerbations with willow bark extract: a randomized double-blind study. Am J Med 109: 19–14.

Chrubasik S, Kunzel O, Model A, Conradt C, Black A. 2000b. Treatment of low back pain with a herbal or synthetic anti-rheumatic: a randomized controlled study. Willow bark extract for low back pain. Rheumatology 40: 1388–1393.

Chrubasik S, Pittler MH, Roufogalis BD. 2005. Zingiberis rhizome. A comprehensive review on the ginger effect and efficacy profiles. Phytomedicine in press

Daels-Rakotoarison DA, Gressier B, Trotin F et al. 2002. Effects of Rosa canina fruit extract on neutrophil respiratory burst. Phytother Res 16: 157–161.

Davies NM, Jamali F. 2004. COX-2 selective inhibitors cardiac toxicity: getting to the heart of the matter. J Pharm Pharm Sci 7: 332–336.

Ernst E. 2003. Avocado-soybean unsaponifiables (ASU) for osteoarthritis – a systematic review. Clin Rheumatol 22: 285–288.

Gagnier JJ, Chrubasik S, Manheimer E. 2004. Harpagophytum procumbens for osteoarthritis and low back pain: A systematic review. BMC Complement Altern Med 4: 13.

Grainger R, Cicuttini FM. 2004. Medical management of osteoarthritis of the knee and hip joints. Med J Aust 180: 232–236.

Kharazmi A, Winther K. 1999. Rose hip inhibits chemotaxis and chemiluminescence of human peripheral blood neurophils in vitro and reduces certain inflammatory parameters in vivo. Inflammopharmacology 7: 377–386.

Larsen E, Kharazmi A, Christensen LP, Christensen SB. 2003. An antiinflammatory galactolipid from rose hip (Rosa canina) that inhibits chemotaxis of human peripheral blood neutrophils in vitro. J Nat Prod 66: 994–995.

McAlindon TE, LaValley MP, Gulin JP, Felson DT. 2000. Glucosamine and chondroitin for treatment of osteoarthritis: a systematic quality assessment and meta-analysis. J Am Med Assoc 283: 1469–1475.

Pincus T, Swearingen C, Cummins P, Callahan LF. 2000. Preference for nonsteroidal anti-inflammatory drugs versus acetaminophen and concomitant use of both types of drugs in patients with osteoarthritis. J Rheumatol 27: 1020–1027.

Rahme E, Joseph L, Kong SX, Watson DJ, LeLorier J. 2001. Cost of prescribed NSAID-related gastrointestinal adverse events in elderly patients. Br J Clin Pharmacol 52: 185–192.

Rein E, Kharazmi A, Winther K. 2004a. A herbal remedy, Hyben Vital (stand. 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. Phytomedicine 11: 383–391.

Rein E, Kharazmi A, Thamsborg G, Winther K. 2004b. A herbal remedy made from a subspecies of rose-hip Rosa canina, reduces symptoms of knee and hip osteoarthritis. Osteoarthr Cartil 12 (Suppl 2): 80.

Smalley WE, Ray WA, Daugherty JR, Griffin MR. 1995. Nonsteroidal anti-inflammatory drugs and the incidence of hospitalizations for peptic ulcer disease in elderly patients. Am J Epidemiol 141: 539–545.

Warholm O, Skaar S, Hedman E, Molmen HM, Eik L. 2003. 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. Curr Ther Res 64: 21–31.

Watson DJ, Yu Q, Bolognese JA, Reicin AS, Simon TJ. 2004. The upper gastrointestinal safety of rofecoxib vs. NSAIDs: an updated combined analysis. Curr Med Res Opin 20: 1539–1548.

Winther K, Kharazmi A. 2004. A powder prepared from seeds and shells of subtype of rose-hip Rosa canina reduces pain in patients with osteoarthritis of the hand – a double blind, placebo-controlled study. Osteoarthr Cartil 12 (Suppl 2): 145.

Winther K, Rein E, Kharazmi A. 1999. The anti-inflammatory properties of rose-hip. Inflammopharmacology 7: 63–68.

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 pv0.035, 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 avo cado/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 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.

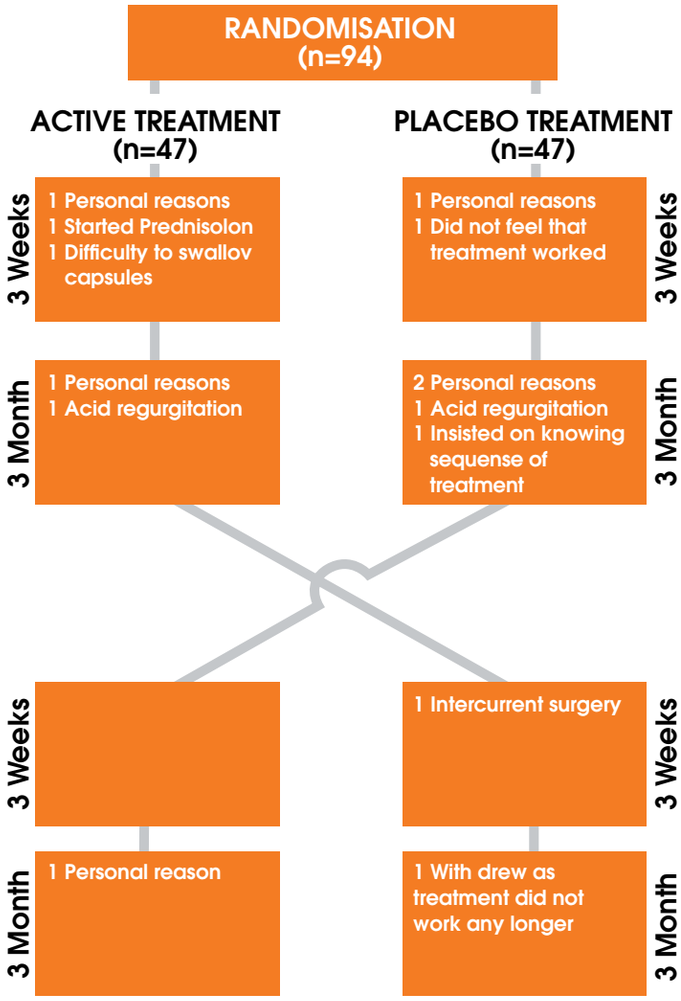
Design and treatment

The study was a randomized, double-blind, 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 cani-

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.

Figure 1. Flow diagram.



All withdrawals are given in the boxes

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 ±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/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.

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 (221.4)	- 20.7 (221.4)	- 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]		

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

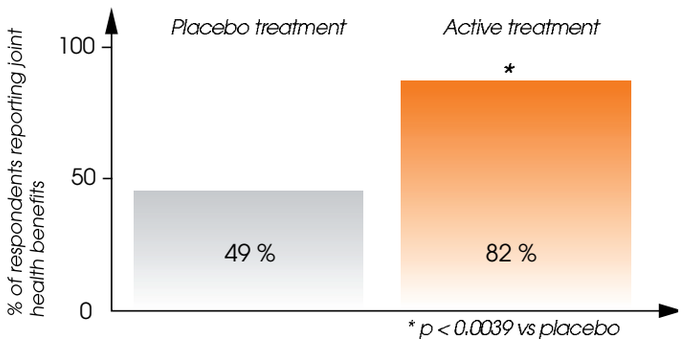
Primary outcome measure

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±19.4 to 29.4±18.3, a delta reduction of 7.4±14.9 mm (pv0.001), compared to a change from 33.7±19.4 to 35.3±21.5, a delta change of 2.1±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 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).

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, 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 suanalysis 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 (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 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).

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)

[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]pv0.022, [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.

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 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 longterm 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 ate 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 trea ment 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-rea tive 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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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-in flammatory properties of rose-hip. Inflammo pharmacology 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.

A **HERBAL REMEDY, HYBEN VITAL (STAND. 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, po0:0078 for pain ando0:0025 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%), po0:0185: 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.

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 ibuprophen, 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 Hernandes- 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, b-carotene 57.9 mg/kg, b-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 antiinflammatory 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

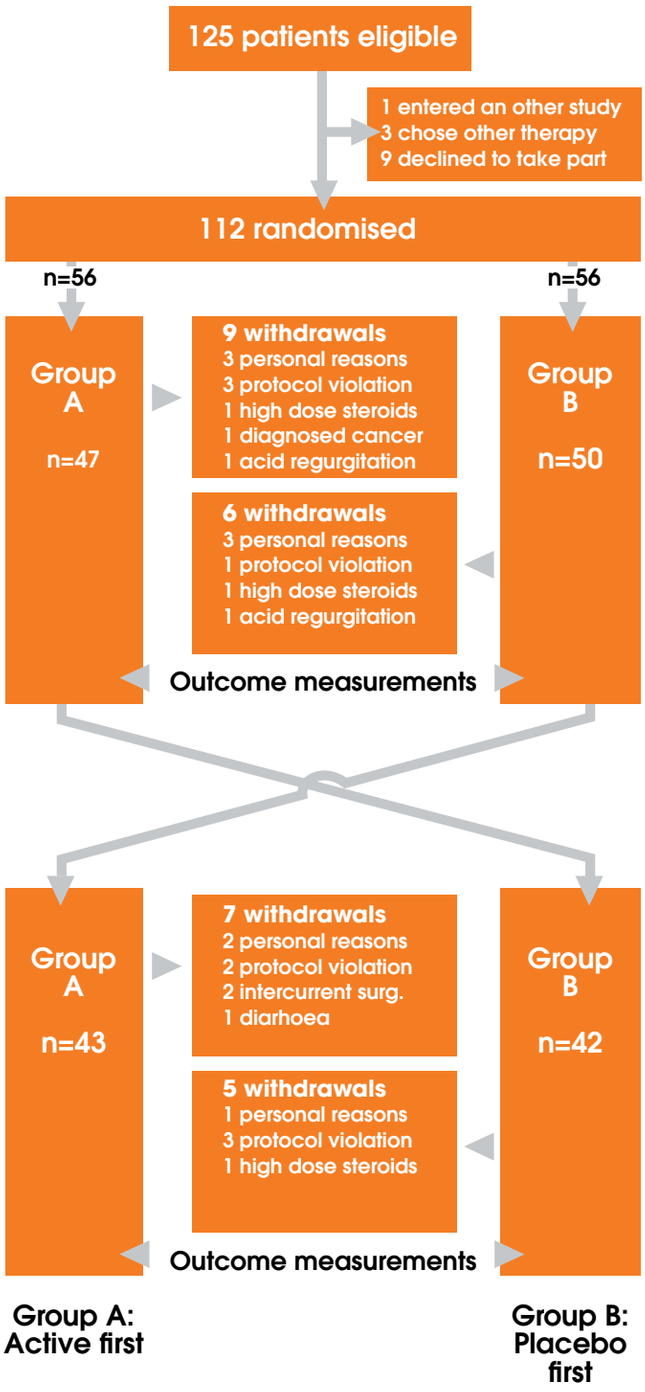
Primary efficacy parameters

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 ±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/m^2. 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 patients, 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 ¼ 56) versus the active treatment first group (n ¼ 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 ± 11.8	67.1 ± 11.6	67.5 ± 10.6	67.0 ± 10.8
Sex				
Women	34	37	21	26
Men	21	20	18	15
BMI (kg/m2)	26.8 ± 5.0	27.7 ± 4.9	27.7 ± 4.9	27.5 ± 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. ppox. 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 ± 11% for Hyben Vital and 90.6 ± 11% for placebo (nonsignificant difference). Compliance in the placebo-first group was 92.3 ± 10.0% and for active treatment first 90.5 ± 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 ± 1.45 after placebo (an improvement of 25%), to 1.91 ± 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 ± 1.28 units for active treatment, as compared with 1.72 ± 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.

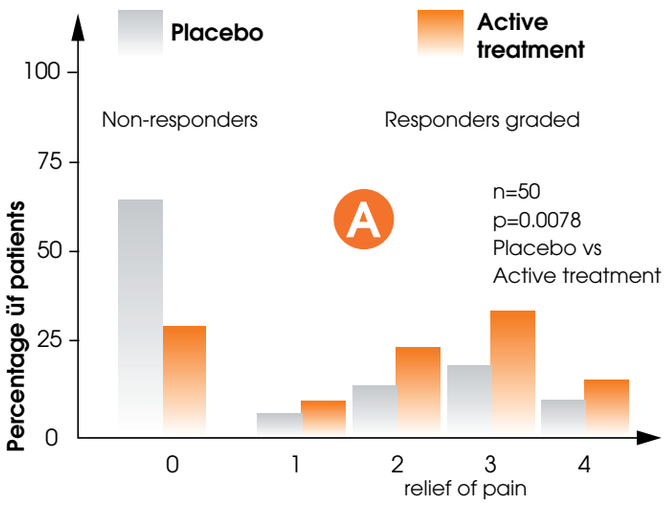
Table 2. Pain given on a scale from 0 (no reduction) to 4 (almost total relief of pain), consumption of rescue medication given as paracetamol equivalents (g)

	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			
	Placebo	Active treatment	p-value
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. Twentyfive patients handed in medical diaries adequate for ITT analysis of their daily use of paracetamol 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.



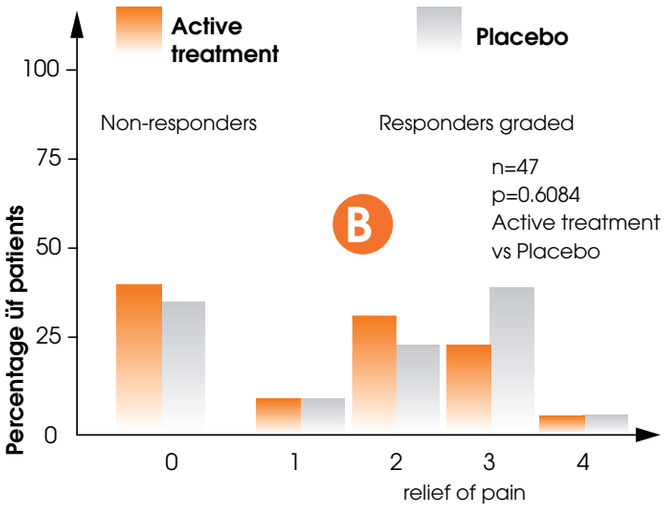


Fig. 2. (A) Histograms comparing, in group A subjects (placebo first then Hyben Vital), the degree of improvement in pain relief from placebo (white columns) as compared with Hyben Vital (shaded columns). The height of each column indicates the percentage of patients who experienced pain relief of category 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.

Acknowledgements

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References

Altman, R.D., Markussen, K.C., 2001. Effect of a ginger extract on knee pain in patients with osteoarthritis. Arthritis Rheum. 44 (11), 2531–2538.

Altman, R.D., Brandt, K., Hochenberg, M., Moskowitz, R.D., 1996. Conduct of clinical trials in patients with osteoarthritis. Osteoarthr. Cartilage 4, 217–243.

Brandt, K., A(kesson, B., 2002. Health promoting compounds in vegetables and fruit. Plant Prod. 29, 43–44.

Brewer's Dictionary of Phrase and Fable (Revised edition, 1981) 346. In: Evans, I.H. (Ed.), Cassell, London. p. 1213.

Harris Jr., E.D., 1988. Pathogenesis of rheumatoid arthritis: a disorder associated with dysfunctional immunoregulation. In: Gallin, J.H., Goldstein, I.M. (Eds.), Snyderman, R. (Eds), Inflammation. Basic Principles and Clinical Correlates. Raven Press, New York, pp. 751–773.

Hochberg, M.C., Altman, R.D., Brandt, K.D., Clarck, B.M., Dieppe, P.A., Griffin, M.R., Moskowitz, W., Schnitzer, T.J., 1995. Guidelines for the medical management of osteoarthritis (Part 1 and 2). Arthritis Rheum. 38 (11), 1535–1546.

Kharazmi, A., Winther, K., 1999. Rose-hip inhibits chemotaxis and chemiluminescence of human blood neutrophils in vitro and reduces certain inflammatory parameters in vivo. Inflammopharmacology 7 (4), 377–386.

Larsen, E., Kharazmi, A., Christensen, L.P., Christensen, S.B., 2003. An antiinflammatory galactolipid from rose-hip (Rosa canina) that inhibits chemotaxis of human peripheral blood neutrophils in vitro. J. Nat. Prod. 66, 994–995.

Lægemiddelkataloget, 2002. Dansk Lægemiddel Information A/S: ISSN 0105-287X.

McAlindon, T.E., Jacques, P., Zhang, Y., Hannan, M.T., Aliabadi, P., Weissman, B., Rush, D., Levy, D., Felson, D.T., 1996. Do antioxidant micronutrients protect against the development and progression of knee osteoarthritis? Arthritis Rheum. 39 (4), 648–656.

Mukherjee, D., Nissen, S.E., Topol, E.J., 2001. Risk of cardiovascular events associated with selective Cox-2 Inhibitors. JAMA 286 (8), 954–959.

The Older Pliny, 1966. Natural History VII: books XXIVXXVII, 149. William Heinemann, London (ISBN: 0-434-99419-7).

Rodrigues, L.A.C., Hernandes-Diaz, S., 2001. Relative risk of upper gastrointestinal complications among users of acetaminophen and non-steroidal anti-inflammatory drugs. Epidemiology 12, 570–576.

Vane, J.R., Botting, R.M., 1998. Anti-inflammatory drugs and their mechanism of action. Inflamm. Res. 47 (2) 578–587.

Winther, K., 2000. Rose-hip, in the form of HybenVital, has no impact on coagulation, platelet function and fibrinolysis. In: Proceedings of the Third International Exhibition and Conference on Nutraceuticals and Food for Vitality, Palexpo Exhibition and Conference Centre, Geneva, Switzerland, May 2–3.

Winther, K., Rein, E., Kharazmi, A., 1999. The antiinflammatory properties of Rose-hip. Immunopharmacology 7, 63–68.

THE EFFECTS OF A STANDARDIZED HERBAL REMEDYMADE 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 osteoarthritis. 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, calculated 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 categoric 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 4months 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 amean (SD) improvement of 2.71 (4.42°) (P=0.012); this value improvementwas 3.75° (5.32°) in the placebo group (P=0.005). Asimilar pattern occurredwhen flexionwas 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 1month 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 (<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 (=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 activetreatment 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 indicated 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 ofNSAIDs, 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 parace amol. 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).

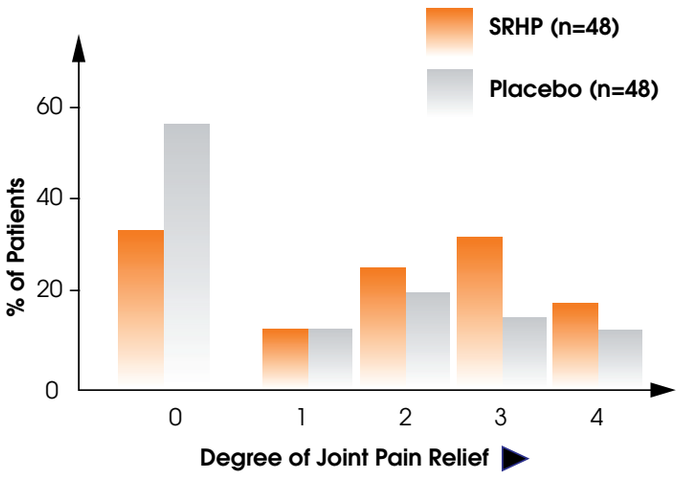

Figure. Degree of joint pain relief on a scale from 0 (no impact) to 4 (almost total relief of pain) after 4 months of treatment with standardized rose-hip powder (SRHP) or placebo. P=0.035 for SRHP versus placebo (Mann-Whitney test).

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 trial[8] of avocado/ 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 study[12]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.

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References

1. Hochberg MC, Altman RD, Brandt KD, et al. Guidelines for the medical management of osteoarthritis. Part 1. American College of Rheumatology. Arthritis Rheum. 1995;38:1535–1540.
2. Simon LS, Lanza FL, Lipsky PE, et al. Preliminary study of the safety and efficacy of SC-58635, a novel cyclooxygenase 2 inhibitor: Efficacy and safety in two placebocontrolled trials in osteoarthritis and rheumatoid arthritis, and studies of gastrointestinal and platelet effects. Arthritis Rheum. 1998;41:1591–1602.
3. Winther K, Rein E, Kharazmi A. The anti-inflammatory properties of rose-hip. Inflammopharmacology. 1999;7:63–68.
4. Kharazmi A, Winther K. Rose hip inhibits chemotaxis and chemiluminescence of human peripheral blood neutrophils in vitro and reduces certain inflammatory parameters in vivo. Inflammopharmacology. 1999;7:377–386.
5. Kendall FP, McCreary EK. Muscles: Testing and Function. 3rd ed. Baltimore: Williams & Wilkins; 1983.
6. Bliddal H, Rosetzsky A, Schlichting P, et al. A randomized, placebo-controlled, crossover study of ginger extracts and ibuprofen in osteoarthritis. Osteoarthritis Cartilage. 2000;8:9–12.
7. Altman RD, Markussen KC. Effects of a ginger extract on knee pain in patients with osteoarthritis. Arthritis Rheum. 2001;44:2531–2538.
8. Blotman F, Maheu E, Wulwik A, et al. Efficacy and safety of avocado/soybean unsaponifiables in the treatment of symptomatic osteoarthritis of the knee and hip. A progressive, multicenter, three-month, randomised, double-blind, placebo-controlled trial. Rev Rhum Engl Ed. 1997;64:825–834.
9. Endres S, Ghorbani R, Kelley VE, et al. The effect of dietary supplementation with n-3 polyunsaturated fatty acids on the synthesis of interleukin-l and tumor necrosis factor by mononuclear cells. N Engl J Med. 1989;320:265–271.
10. Mustafa T, Srivastava KC, Jensen KB. Drug development report (9): Pharmacology of ginger, Zingiber officinale. J Drug Dev. 1993;6:25–39.
11. Kiuchi F, Iwakami S, Shibuya M, et al. Inhibition of prostaglandin and leukotriene biosynthesis by gingerols and diarylheptanoids. Chem Pharm Bull (Tokyo). 1992; 40:387–391.
12. Winther K. Impact on coagulation, platelet function and fibrinolysis. In: Proceedings of the 3rd International Exhibition and Conference on Nutraceuticals and Food for Vitality; May 3–5, 2000; Geneva, Switzerland. Abstract.
13. Winther K, Kharazmi A, Rein E. Rose-hip, given as a standardised dry powder, exerts anti-inflammatory and cell preserving properties in humans. Presented at the 2nd International Congress on Coronary Artery Disease; October 18–21, 1998; Florence, Italy.
14. Brand C, Snaddon J, Bailey M, Cicuttini F. Vitamin E is ineffective for symptomatic relief of knee osteoarthritis: A six month double blind, randomised, placebo controlled study. Ann Rheum Dis. 2001;60:946–949.
15. Brandt K, A° kesson B. Health promoting compounds in vegetables and fruit. Plant Production. 2002;29:43–44.

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/1.

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 rain at 37°C Following preincubation, chemotaxis of the cells towards the chemotactic peptide f-Met-Leu-Phe (tMLP) 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 ceils 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 ± SEM. p values of ≤ 0.05 were considered significant.

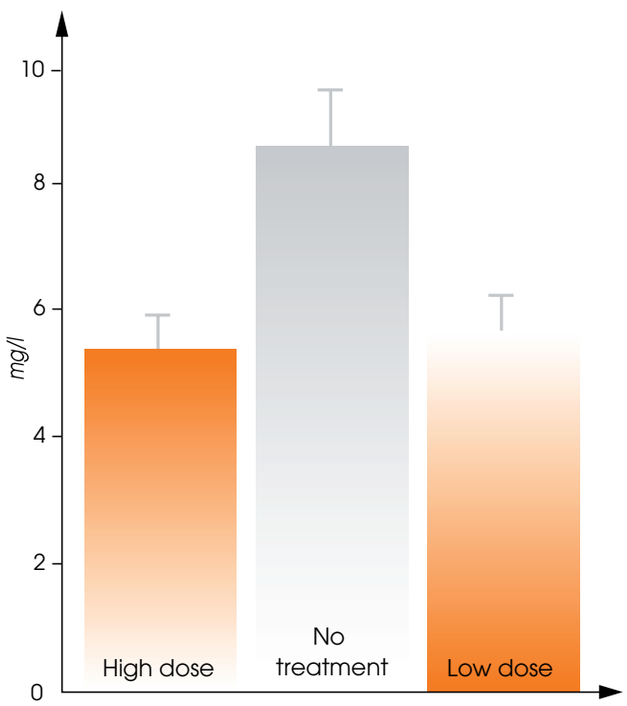

Figure 1. C-reactive protein levels in the serum of eight volunteers given high dose, low dose or no treatment. The values are given as mean ± SEM in rag/1. There were statistically significant differences between CRP levels from the high dose group and no treatment (p ≤ 0.02) and low dose group and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

3. Results and discussion

Rose-hip extract at concentrations as low as 100 µg/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 ≤ 0.02) and in the low-dose groups (p ≤ 0.05) as compared to the no-therapy group. The CRP levels (mean ± SEM) in the patient group were 5.75 ± 2.95, 6.67 ± 2.67 and 8.25 ± 4.98 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 ≤ 0.01) and in the low dose groups (p ≤ 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 ± 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 ± SEM response to fMLP was 101 ± 45 as compared to 308 ± 22 and to ZAS 272 ± 125 as compared to 600 4- 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 neutropbil 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 CRE 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 ± SEM

	High dose	No therapy	Low dose
Chemotaxis (fMLP)	144 ± 38.7[a]	339 ± 24.0	172 ± 18.0[b]
Chemotaxis (ZAS)	343 ± 89.7[a]	637 ± 29.3	432 ± 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 rosehip, 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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References

1. K. Winther, A. Kharazmi and B. Rangaard (1997). Cell preserving and antiinflammatory property of rose-hip (Hyben Vital). Possible clinical implication, 1st. Int. Congress on Coronary Artery Diseases: From prevention to intervention, p. 68. Prague, Czech Republic.
2. E Jensen and A. Kharazmi (1991). Computer-assisted image analysis assay of human neutrophil chemotaxis in vitro, J. Immunol. Method 144, 43-48.
3. A. Leung and S. Foster (1996). Encyclopedia of Common Natural Ingredients. John Wiley, New York.
4. E M. Ridker, M. Cushman, M. J. Stampfer, R. E Tracey and C. H. Hennekens (1997). Inflammation, aspirin and the risk of cardiovascular diseases in apparently healthy men, New Eng. J. Med. 336, 973-979.
5. E. D. Harris, Jr. (1988). Pathogenesis of rheumatoid arthritis: A disorder associated with dysfunctional immunoregulation, in: Inflammation: Basic principles and clinical correlates, J. H. Gallin, I. M. Goldstein and R. Snyderman (Eds), pp. 751-773. Raven Press, New York.
6. M. C. Hochberger, R. D. Altman, K. D. Brandt, B. M. Clarck, R A. Dieppe, M. R. Griffin, R. W. Moskowitz and T. J. Schnitzer (1995). Guidelines for the medical management of osteoarthritis (part one), Arthritis Rheum. 38, 1535-1540.
7. M. C. Hochberger, R. D. Altman, K. D. Brandt, B. M. Clarck, E A. Dieppe, M. R. Griffin, R. W. Moskowitz and T. J. Schnitzer (1995). Guidelines for the medical management of osteoarthritis (part two), Arthritis Rheum. 38, 1541 - 1546.

8. Y. Matzner, R. Drexler and M. Levy (1984). Effect of dipyrone, acetylsalicylic acid and acetaminophen on human neutrophil chemotaxis, Eur. J. Clin. Invest. 14, 440-443.
9. A. Kemp and J. Smith (1987). The effect of salicylate on human leukocyte migration, Clin. Exp. Immunol. 49, 233-238.
10. I. Rivkin, V. Foschi and C. H. Rosen (1976). Inhibition of in vitro neutrophil chemotaxis and spontaneous motility by anti-inflammatory agents (39518), Ptvc. Soe. Exp. Biol. Med. 153, 236- 240.
11. H. B. Kaplan, H. S. Edelson, H. M. Korchak, W. R Given, S. Abramson and G. Weismann (1984). Effect of non-steroidal anti-inflammatory agents on human neutrophil functions in vitro and in vivo, Biochem. Pharmacol. 33, 371-378.
12. E. G. Maderazo, S. E Breaux and C. L. Woronick (1984). Inhibition of human polymorphonuclear leukocyte cell response by ibuprofen, J. Pharm. Sci. 73, 1403-1406.

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 µg/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: RThese 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 imuune 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 methodes

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 500µg/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 1000µg/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 500µg/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-tochopherol) was also used as a known antioxidant control. Vitamin E at a concentration of over 1µg/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

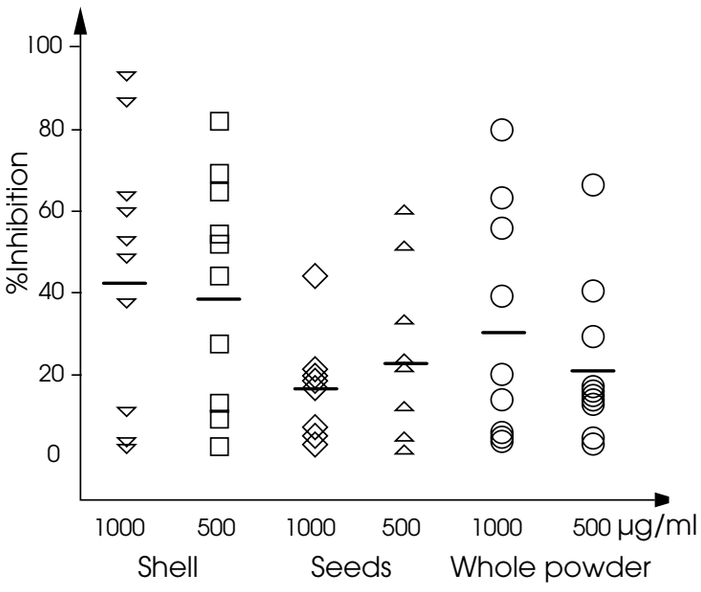

Figure 1. Effect of rose hip extract on polymorphonuclear leukocytes (PMN) chemotaxis in vitro. Cells were preincubated with various concentrations of rose hip powder as given in the X-axis for 30 min. The data are presented as percent inhibition of PMN chemotaxis for each subject tested.

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 occured 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 ± SEM (90.0 ± 2.1 µmol/1) to values obtained after 10 days: (87.4 ± 1.8 µmol/1) and 28 days (84.9 4 ± 1.9 µmol/1) of intake, respectively 3 ($p < 0.001$). When treatment had been stopped for 28 days the serum creatinine levels significantly increased (93.2 ± 1.9µmol/1) ($p < 0.001$) 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 ± SEM values of CRP were 5.38 ± 0.4 mg/l and declined to 3.31 ± 0.49 mg/ and 4.31 ± 0.47 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 ± 0.54 mg/l ($p < 0.051$ as compared with that previously.

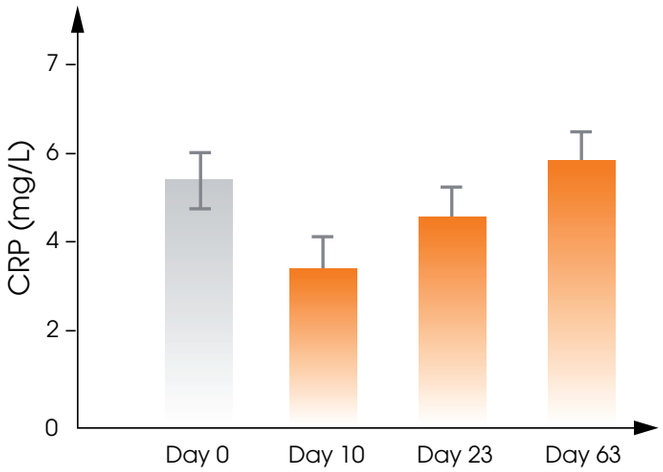

Figure 2. Levels of serum C-reactive protein (CRP) as given in mg/l from subjects on the start (Day 0), 10 days and 28 days during intake of rose hip and 35 days after cessation of treatment (Day 63) with 45 g daily intake of rose hip. The results are given as mean 4 ± SEM values from 13 subjects. The 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 preceeding 28 days (Figs 3 and 4). The mean ± 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 ± 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.

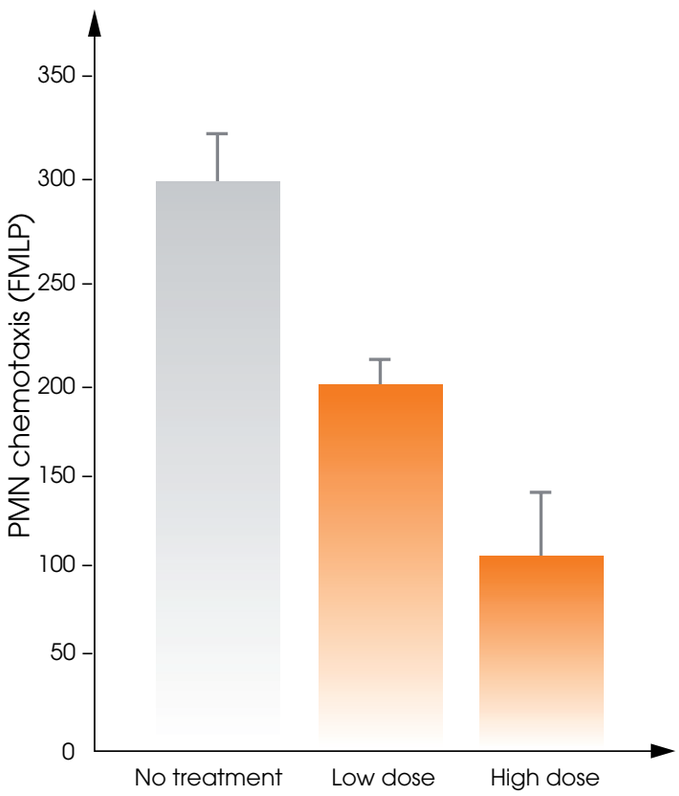

Figure 3. Chemotaxis of peripheral blood polymorphonuclear leukocytes (PMN) from subjects during and 28 days after cessation of treatment with 45 g (high dose) or 10 g (low dose) daily intake of rose hip for 28 days or no treatment. The chemotaxis is determined towards the chemotactic petide FMLP. The results are given as mean ± SEM number of ceils 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.

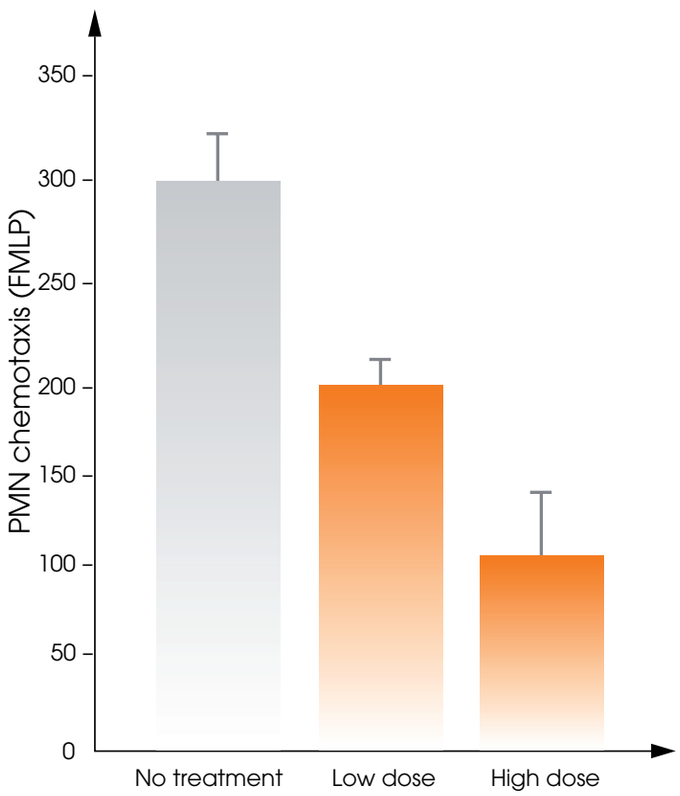

Figure 4. Chemotaxis of peripheral blood polymorphonuclear leukocytes (PMN) from subjects during and 28 days after cessation of treatment with 45 g (high dose) or 10 g (low dose) daily intake of rose hip for 28 days or no treatment. The chemotaxis is determined towards zymosan activated serurm (ZAS). The results are given as mean ± SEM number of cells migrated from 13 subjects. The mear chemotaxis value for high dose was significantly lower than that for no treatment group ($p \leq 0.00l$),

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 leucocytes, 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 55-125 and females 45-100 µmol/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 livei 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 pHadjusted rose hip extarct 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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References

Harris, Jr., E. D. (1988). Pathogenesis of rheumatoid arthritis: A disorder associated with dysfunctional immunoregulation. In: Inflammation. Basic Principles and Clinical Correlates, Gallin, J. H., Goldstein, I. M. and Snyderman, R. (Eds), pp. 751-773. Raven Press, New York.

Hochberger, M. C., Altman, R. D., Brandt, K. D., Clarck, B. M., Dieppe, E A., Griffin, M. R., Moskowitz, R. W. and Schnitzer, T. J. (1995). Guidelines for the medical management of osteoarthritis (Part 1), Arthritis Rheum. 38, 1535-1540.

Hochberger, M. C., Altman, R. D., Brandt, K. D., Clarck, B. M., Dieppe, E A., Griffin, M. R., Moskowitz, R. W. and Schnitzer, T. J. (1995). Guidelines for the medical management of oseteoarthritis (Part 2), Arthritis Rheum. 38, 1541 - 1546.

Jensen, E and Kharazmi, A. (1991). Computer-assisted image analysis assay of human neutrophil chemotaxis in vitro, J. Immunol. Methods 144, 43-48.

Kaplan, H. B., Edelson, H. S., Korchak, H. M., Given, W. E, Abramson, S. and Weismann, G. (1984) Effect of non-steroidal anti-inflammatory agents on human neutrophil functions in vitro and in vivo Biochem. Pharmacol. 33, 371-378.

Kemp, A. and Smith, J. (1982). The effect of salicylate on human leukocyte migration, Clin. Exp. Immunol. 49, 233-238.

Kharazmi, A., HØiby, N., Döing, G. and Valerius, N. H. (1986). Pseudomonas aeruginosa exopro teases inhibit human neutrophil chemiluminescence, Infect. Immun. 44, 587-591.

Maderazo, E. G., Breaux, S. P. and Woronick, C. L. (1986). Inhibition of human polymorphonuclear leukocyte cell response by ibuprofen, J. Pharm. Sci. 73, 1403-1406.

Matzner, Y., Drexler, R. and Levy, M. (1984). Effect of dipyrone, acetylsalicylic acid and aceta minophen on human neutropbAl chemotaxis, Eur. J. Clin. Invest. 14, 440-443.

Ridker, P. M., Cushman, M., Stampfer, M. J., Tracey, R. P. and Hennekens, C. H. (1997) Inflammation, aspirin and the risk of cardiovascular diseases in apparently healthy men, N. Eng. J. Med. 336, 973-979.

Rivkin, I., Foschi, V. and Rosen, C. H. (1976). Inhibition of in vitro neutrophil chemotaxis and spontaneous motility by anti-inflammatory agents (39518), Proc. Soc. Exp. Biol. Med. 153 236-240.

Winther, K., Rein, E. and Kharazmi, A. (1999). The anti-inflammatory properties of rose-hip Inflammopharmacol. 7, 63-68.

OVERVIEW ON **ABSTRACTS**

Rein E., Kharazmi A., Thamsborg G., Winther K. (2004): A herbal remedy, made from a subspecies of rose-hip rosa canina, reduces symptoms of knee and hip osteoarthritis. Abstract. 9th World Congress of the Osteoarthritis Research Society International, Chicago.

Warmholm O., Skaar S., Hedman E., Molmer H., Eik L. (2001): Alternative Therapies in health and medicine. First International Conference on Complementary Alternative & Integrative Medicine Research, San Francisco.

Winther K., Kharazmi A., Rein E. (2005): A powder made from a subspecies of rose hip (rosa canina), reduces WOMAC symptoms score as well as cholesterol level in patients suffering from osteoarthritis. Abstract. 10th World Congress on Osteoarthritis, Boston.

Winther K., Kharazmi A. (2004): A powder prepared from seeds and shells of a subtype of rose-hip rose canina reduces pain in patients with osteoarthritis of the hand – a double-blind, place-controlled, randomized study. Abstract. 9th World Congress of the Osteoarthritis Research Society International, Chicago.

Winther K., Kharazmi A. (2004): A subtype of rosa canina exerts anti-inflammatory properties. Abstract. The XXIX Nordic Congress in Clinical Chemistry, Malmö.

Winther K. (2006): Breakthroughs in Reducing Inflammation. Abstract. NUTRACON Conference, Anaheim.

Winther, K. (2000): Impact on coagulation, platelet function and fibrinolysis. Abstract. Copenhagen.

Rein E., Winther K. (2001): LDL-cholesterol and C-reactive protein is influenced by Rose-hip, a randomized, double blind, placebo controlled trial. Abstract. XIV. International Symposium on Drugs Affecting Metabolism, New York.

Kharazmi A., Song J., Winther K., Hoiby N. (2000): Natural Medicine and the Immune System: Immunomodulatory properties of ginseng and antiinflammatory properties of rose-hip. Abstract. Vitafoods International Conference 2000, Geneva.

Winther K., Kharazmi A., Rein E. (1998): Rose-hip, given as a standardised dry powder, exerts anti-inflammatory and cell preserving properties in humans. Abstract. 2nd International Congress on Coronary Artery Disease, Florence.

Rein E., Kharazmi A., Winther K. (1999): 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.

Bütner S., Jacobsen O., Andersen J.R., Winther K. (2004): The impact of a standardized powder made from a subtype of Rose-hip on IBDQ symptom score in patients with Crohn's Disease or Ulcerative Colitis. Abstract. Scandinavian Journal of Gastroenterology, Oslo.

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