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Bromelain reduces mild acute knee pain and improves well-being in a dose-dependent fashion in an open study of otherwise healthy adults

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Summary

There is preliminary clinical evidence to support the contention that the anti-inflammatory and analgesic properties of bromelain help to reduce symptoms of osteo- and rheumatoid arthritis. However, there have been no controlled studies of its effects on joint health in healthy subjects who lack such diagnosis. The current study investigated the effects of bromelain on mild acute knee pain of less than 3 months duration in otherwise healthy adults. The study was an open, dose-ranging postal study in volunteers who had been recruited through newspaper and magazine articles. Two validated questionnaires (WOMAC knee health Index and the Psychological Well-Being Index) were completed at baseline and after one month's intervention with bromelain, randomly allocated to volunteers as either 200 mg or 400 mg per day. Seventy seven subjects completed the study. In both treatment groups, all WOMAC symptom dimension scores were significantly reduced compared with baseline, with reductions in the final battery (total symptom score) of 41 and 59% ($P = 0.0001$ and < 0.0001) in the low and high dose groups respectively. In addition, improvements in total symptom score ($P = 0.036$) and the stiffness ($P = 0.026$) and physical function ($P = 0.021$) dimensions were significantly greater in the high-dose (400 mg per day) compared with the low-dose group. Compared to baseline, overall psychological well-being was significantly improved in both groups after treatment ($P = 0.015$ and $P = 0.0003$ in the low and high dose groups respectively), and again, a significant dose-response relationship was observed. We conclude that bromelain may be effective in ameliorating physical symptoms and improving general well-being in otherwise healthy adults suffering from mild knee pain in a dose-dependant manner. Double blind, placebo-controlled studies are now warranted to confirm these results.

Key words: bromelain, pineapple extract, knee pain, arthritis, well-being

Introduction

Knee pain is a very common complaint. Apart from those diagnosed with osteo-, rheumatoid, and other forms of arthritis, large numbers of otherwise healthy individuals suffer pain and inflammation brought on by injury. The knee is vulnerable to twisting or shearing forces, and twisting suddenly whilst walking or even crouching can be sufficient to traumatize the knee, whereas overuse injuries are typically associated with activities such as walking, running, and cycling (Grisogono, 1988).

Since inflammation is a pathogenic factor in these types of knee pain, NSAIDS (non-steroidal anti-inflammatory drugs) are often prescribed to reduce swelling and pain. However, the risk of serious side-effects with these drugs, especially gastrointestinal damage, is well known (Singh, 1998). Hence, a natural, ef-

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fective, and safe remedy which lacks undesired side-effects would offer a welcome alternative treatment for knee pain. Bromelain may offer such an alternative (Maurer, 2001).

Bromelain is the name given to the crude aqueous extract obtained from the stem and fruit of the pineapple plant (*Ananas comosus* Merr.). Its main active components include a number of enzymes showing proteolytic activity (Cooreman et al., 1976; Maurer, 2001), which were first shown to be anti-inflammatory by Uhlig (1981). Bromelain has been shown to demonstrate many potentially beneficial properties, both *in vitro* and *in vivo*, including those which are anti-edematous, anti-thrombotic, fibrinolytic and, importantly for the current study, anti-inflammatory and analgesic (Maurer, 2001). Evidence for intact absorption of these proteases in animals comes from a study of ^{125}I-labelled bromelain by Seifert et al. (1979).

Bromelain's mode of action as an anti-inflammatory and analgesic agent is thought to be multifaceted. There is experimental evidence to suggest that its effects on blood coagulation (through increasing serum fibrinolytic activity) and prostaglandin levels (by decreasing levels of PGE_2 and thromboxane A_2) may be important in reducing inflammation (Maurer, 2001). Its action as an analgesic is thought to be both as a secondary effect of reducing pain-inducing factors, such as oedema, debris and immune complexes (Klein and Kullich, 2000), and through a direct influence on pain mediators such as bradykinin. For example, bromelain was shown to significantly reduce pain response to a high degree when bradykinin was applied directly onto surgically denuded blisters in healthy male subjects (Bodi, 1966).

As well as evidence from animal studies, a number of human studies have demonstrated anti-inflammatory and analgesic properties of orally administered bromelain (Maurer, 2001). Early evidence came from Cohen and Goldman (1964), who administered bromelain (60 to 160 mg per day) to patients with moderate or severe arthritis with residual joint swelling following long-term steroid therapy. Nearly three-quarters of the patients reported either complete or near total reduction of swelling after the treatment, with a corresponding reduction in pain and soreness.

Whilst clinical observations or small-scale studies have shown promising anti-inflammatory effects of bromelain for ulcerative colitis (Kane and Goldberg, 2000) and urogenital tract inflammation (Lotti et al. 1993), it is studies of joint inflammation that are particularly relevant here. A small, blinded, multi-centre study conducted in Germany reported a positive outcome compared with placebo for patients with arthritis (Vogler, 1988). Recently, a double-blinded trial compared the oral enzyme preparation Phlogenzym® (which contains bromelain, trypsin, and rutin) with an NSAID (diclofenac) during 3 weeks of treatment of 73 patients suffering osteoarthritis of the knee joint (Klein and Kullich, 2000). It was found that Phlogenzym® was as effective as diclofenac in significantly reducing pain indices (by about 80% after the 3 weeks treatment), and this decrease was sustained for 4 weeks post-treatment. In addition, the oral enzyme therapy was better tolerated with a lower dropout rate than diclofenac. Tilwe and colleagues (2001) also compared Phlogenzym® to diclofenac in 50 patients with arthritis of the knee joint, and likewise found reductions in pain, tenderness and swelling in both groups after 3 weeks, and 4 weeks post-treatment. Furthermore, the reduction in joint tenderness was significantly greater in the group receiving Phlogenzym®. Despite these promising studies on bromelain as part of an enzyme complex, there are currently no well-controlled human studies on the effects of bromelain alone.

The study reported here was aimed at investigating, in an open manner, the effect of daily bromelain supplementation for 30 days at two doses on acute mild knee pain in otherwise healthy adults. Primary outcome was assessed through the use of a validated knee health questionnaire (WOMAC). A secondary outcome was the estimation of wellbeing.

Materials and Methods

Volunteers

One hundred and twenty six volunteers were recruited through national newspaper and magazine articles in the UK, following a press release. Recruitment criteria for the study included adults aged 25 to 50 years who had suffered knee pain on a regular basis for no longer than three months, but were otherwise in good health. Respondents excluded from the trial included those who currently suffered a serious medical condition, those taking anti-thrombotic, anti-inflammatory or analgesic drugs, and those who had undergone knee surgery, even of an exploratory nature. Pregnant and lactating women were also excluded. All subjects gave informed consent prior to participation, and understood that they could withdraw at any time without reason. A letter was also sent out to each subject's General Practitioner for information. The study was allowed by the University of Reading Ethics and Research Committee and the West Berkshire Local Research Ethics Committee.

Study design

The design of the study was open, parallel, and dose ranging, and conducted by means of postal questionnaires. Initially, a general questionnaire was used to

screen volunteers, and those suitable for study were randomly assigned equally and by accession into the study to receive either 200 or 400 mg (ie 1 or 2 tablets per day) of bromelain (Bromelin™, Lichtwer Pharma (UK) Ltd., Marlow, UK) daily for 30 days. The tablets were posted to each subject along with two copies of each of two validated self-assessment questionnaires, to be completed on the day before commencement of the study (baseline), and then again at the end of the study. Volunteers were requested to avoid reference to their baseline responses when completing the questionnaires at the end of the study. All completed questionnaires were returned to the researchers by post at the end of the study.

The primary outcome questionnaire was the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC; Bellamy et al., 1988), which comprised 24 individual symptom questions relating to three dimensions (pain, stiffness, and physical function). Each question required a response on a 10 cm horizontal visual analogue scale (VAS) with terminal descriptors (0 = no pain/stiffness/difficulty, 10 = extreme pain/stiffness/difficulty respectively). The secondary outcome questionnaire was the Psychological General Well-Being Index (PGWB; Dupuy, 1984), which comprised 22 individual questions relating to six dimensions (anxiety, depressed mood, positive well-being, self-control, general health, and vitality). Each question was scored on a scale of 0 to 5 (0 = the most negative response, 5 = the most positive response). In addition, a post-study questionnaire allowed subjects to comment on the perceived benefit of the intervention on knee pain, and any side-effects experienced during the course of the study.

Statistical Analysis

Unless otherwise stated, results are expressed as means ± SEM. WOMAC Index dimension scores were calculated by summing the individual symptom values relevant to each dimension, with the final battery (total symptom score) calculated as the sum of these, and PGWB dimension values were similarly calculated, as previously described (Bowling, 1997, 2001). On rare occasions where individual symptom questions were not answered, the relevant dimension score was calculated as a proportion of the completed questions for that dimension. Higher scores indicated worse symptoms in the WOMAC index, but better symptoms in the PGWB Index. A two-sample t-test was used to confirm lack of baseline differences in mean WOMAC and PGWB dimensions and overall scores between the two treatment groups. A paired t-test was then applied to test for differences in mean values of these scores before and after treatment for the two groups. Lastly, the differences in overall and dimension scores for each volunteer from baseline were calculated, and mean group difference values were then subjected to an unpaired t-test to detect any differences in efficacy between the two doses. Statistical analyses were performed using Excel 2000 (Microsoft Corporation).

Results

Study population characteristics

Three hundred and eighteen volunteers were screened and 126 were found to be suitable for the study and entered into it. Seventy-seven volunteers completed the study: 43 had taken the lower and 34 the higher dose. The personal characteristics of those who completed the study were generally similar between the two treatment groups (Table 1).

Most dropouts gave no reason for lack of completion of the study, although one volunteer dropped out because of perceived weight gain, another because knee pain ceased spontaneously.

The majority of volunteers completing the study had been suffering from recurrent knee pain, and over half reported that the onset of the current episode was more than one month before the trial commenced. Additionally, nearly 50% of volunteers in the high dose group reported pain in both knees. Only four volunteers were taking over-the-counter dietary supplements for their knee pain at the start of the study (one cod liver oil, two glucosamine sulphate, and one both of these plus methylsulfonylmethane). None reported taking any conventional anti-inflammatory or analgesic medications.

Table 1. Personal characteristics of volunteers by intervention group.

	200 mg per day	400 mg per day
n	*43*	*34*
Male	32.6%	24.2%
Female	67.4%	75.8%
Mean Age (range)	37.1 (25–50) y	38.0 (26–50) y
Recurrent knee pain	71.4%	72.7%
Current knee pain duration		
<1 week	20.9%	12.1%
>1week <1 month	18.6%	30.3%
>1 month < 3 months	60.5%	57.6%
Both knees affected	27.3%	45.5%

Primary Outcome – WOMAC Index

A summary of WOMAC Index data is shown in Table 2. There were no significant differences in any baseline values between the two groups. However, after intervention for one month, both groups reported highly significant reductions in scores for all dimensions. Pain decreased by 44.6 and 58.2% ($P < 0.0001$) in the lower and higher dose groups respectively, and there were similar reductions of 41 and 59% ($P < 0.0001$) in the final battery scores. When the difference between final and baseline dimension scores were compared between groups, mean values for the 400 mg per day group showed significant improvements in stiffness, physical function, and the final battery ($P = 0.026$, 0.021 and 0.036 respectively) over and above those of the 200 mg per day group (Fig. 1).

Secondary Outcome – General Well-Being

There were no significant differences in mean baseline PGWB Index values between groups. The overall PGWB scores were significantly increased after treatment with both 200 mg and 400 mg per day bromelain ($P = 0.016$ and 0.0003 respectively). Additionally, all six dimension scores were significantly higher compared with baseline in the higher dose group ($P = 0.023$ to <0.0001), while only anxiety, well-being and general health showed significant improvement in the lower dose group ($P = 0.017$, 0.013, and 0.009 respectively). It is worth noting that the 19.2% improvement in overall PGWB score in the higher dose group was more than double that observed when volunteers received half this dose.

When the two groups were compared after adjusting for baseline, the difference in scores for two individual dimensions, self-control and vitality, were significantly improved in the high dose group compared with the low dose group ($P = 0.004$ and 0.026 respectively; Fig. 2). In addition, the difference between overall PGWB scores tended toward significance ($P = 0.068$).

In a post-study questionnaire, 59.5 and 67.6% of volunteers reported a definite overall improvement in

Table 2. WOMAC Knee Health Index dimension scores at baseline and after intervention with bromelain for one month.

	200 mg per day		400 mg per day	
	Baseline	Final	Baseline	Final
Pain	130 (13)	72 (12)[1]	121 (16)	50 (10)[2]
Stiffness	59 (8)	33 (7)[1]	67 (9)	23 (5)[2]
Physical function	290 (39)	176 (27)[1]	380 (51)	159 (37)[2]
Final Battery	*479 (54)*	*281 (42)*[1]	*568 (72)*	*232 (50)*[2]

Data are means (SEM)
[1] $P < 0.001$ for final value vs. baseline value
[2] $P < 0.0001$ for final value vs. baseline value

Table 3. PGWB Index dimension scores at baseline and after intervention with bromelain for one month.

	200 mg per day		400 mg per day	
	Baseline	Final	Baseline	Final
Anxiety	17.4 (0.7)	18.6 (0.7)[1]	16.8 (0.7)	18.3 (0.8)[1]
Depressed	12.2 (0.4)	12.6 (0.4)	12.6 (0.4)	13.4 (0.3)[1]
Well Being	12.0 (0.6)	12.9 (0.5)[1]	12.2 (0.6)	13.6 (0.5)[2]
Self Control	12.4 (0.4)	12.3 (0.4)	11.6 (0.5)	12.9 (0.4)[2]
General Health	10.2 (0.4)	11.1 (0.4)[2]	9.3 (0.4)	10.7 (0.4)[3]
Vitality	11.9 (0.6)	12.2 (0.6)	11.9 (0.5)	13.6 (0.4)[3]
Overall Score	*76.0 (2.4)*	*83.0 (3.1)*[1]	*74.5 (2.3)*	*88.8 (3.4)*[3]

Data are means (SEM)
[1] $P < 0.03$ for final value vs. baseline value
[2] $P < 0.01$ for final value vs. baseline value
[3] $P < 0.001$ for final value vs. baseline value

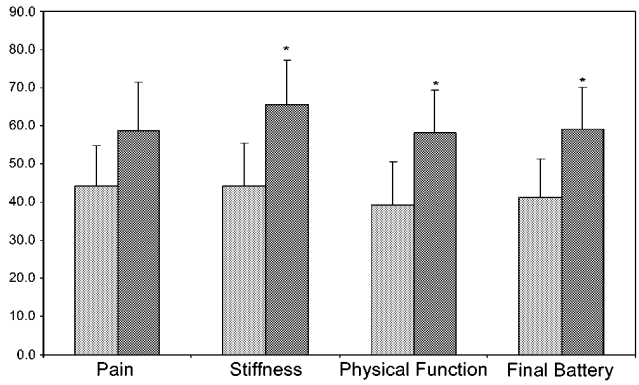

Fig. 1. WOMAC Index dimensions scores in healthy adults with acute mild knee pain before and after treatment with either 200 or 400 mg bromelain per day for one month. Values are expressed as the mean (SEM) percentage improvement over baseline (* $P < 0.05$ high dose vs. low dose group). ■ 200 mg; ■ 400 mg.

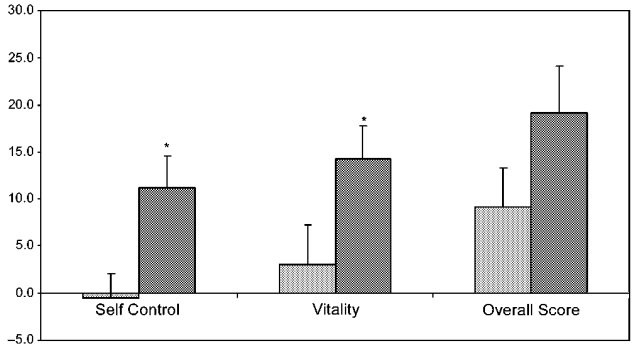

Fig. 2. PGWB Index dimension scores in healthy adults suffering acute mild knee pain after treatment with either 200 or 400 mg bromelain per day for one month. Data are expressed as the percentage mean (SEM) improvement over baseline (* $P < 0.03$ high dose vs. low dose group). ■ 200 mg; ■ 400 mg.

knee pain in the low and high dose groups respectively, whereas 35.7 and 29.4% reported no change, and 4.8 and 3.9% reported a deterioration in symptoms. Serious adverse side effects were not reported. Stated incidences of minor side effects were of flatulence (6 cases), headache (5 cases), nausea and tiredness (3 each), and dry mouth and skin rash (1 each).

Discussion

Bromelain has been the subject of scientific research since it became commercially available over 50 years ago (Taussig and Batkin, 1988). Although anti-inflammatory and analgesic properties have been demonstrated *in vitro* and through animal studies (Lotz-Winter, 1990), studies in humans have generally been confined to patients suffering major trauma or chronic diseases (Maurer, 2001). In the current pilot study, the effect of bromelain was investigated on mild acute knee pain, a condition that is common in the healthy adult population. Data obtained using the WOMAC knee health Index showed that all self reports of physical symptoms were significantly improved after intervention for one month, as were indices of psychological well-being which were measured as a secondary outcome. In addition, dose-response effects of supplementation were observed in both physical symptoms and reported well-being.

Although originally developed and validated as an index of hip and knee osteoarthritis (Bellamy et al., 1988), WOMAC has recently been used to effectively assess anterior knee pain before and after physiotherapy in otherwise healthy adults (Clark et al., 2000). The improvements in all symptom dimensions observed in the current study are consistent with reports of other studies of bromelain supplementation, although it is difficult to compare results directly. For example, Cohen and Goldman (1964) used physical measurements to show bromelain was effective in reducing swelling in patients with rheumatoid arthritis, duration of treatment varied widely between the individuals (3 weeks to 13 months), and various doses of bromelain were employed.

In the current study, a 59% decrease in the WOMAC final battery (a sum of pain, stiffness, and physical function scores) was observed in the higher dose group after one month of intervention. Klein and Kullich (2000) in a randomised double-blind clinical trial reported a 77.1% decrease in symptoms of knee pain and function in 73 adults suffering painful knee osteoarthritis after 3 weeks of daily treatment with a Phlogenzym® dietary supplement containing bromelain along with trypsin and rutin. The difference in response compared with our study may be due to the higher dose of bromelain given in Klein and Kullich's study (540 vs. 400 mg per day), the enhancement of actions of bromelain in co-administration with the other components of Phlogenzym®, and the greater severity of patient symptoms. Tilwe and colleagues (2001) also noted a significant reduction in knee pain (at rest or during movement) in 25 patients with similar symptoms treated with Phlogenzym® daily for 3 weeks in a single-blind study. Both studies noted that the enzyme preparation was as effective as diclofenac, an NSAID, in treating symptoms of osteoarthritis of the knee, while being generally better tolerated. Good toleration and lack of significant side-effects were also a characteristic of bromelain intervention in the present study.

Improved well-being is an important goal in any therapy, and this is the first time that it has been measured using a validated questionnaire in any study of bromelain in humans. The results showed, compared to baseline, a significant improvement in well-being in both groups after intervention. In particular, there was a significant dose-response improvement in both the self-control and vitality dimensions, with the overall well-being score tending toward significance.

There was no control group in this study, and it is expected that outcomes would have been influenced by the placebo effect. It is probable that volunteer motivation upon joining the study would have had some positive effects on perception of health. Indeed, it has been shown recently that a pessimistic outlook may increase perceived knee pain in patients with arthritis (Brenes et al., 2002). However, the present study was carried out by post with no direct contact with the investigators, therefore it was anticipated that the placebo effect would be minimised. Of particular importance in the present study is the finding of an enhanced benefit to knee health and well-being of the higher dose of bromelain. Volunteers (but not researchers) were unaware that they had been randomised to one of two possible dosages. Hence the significant improvements observed in the higher dose group are strong indications of the efficacy of bromelain in promoting knee health and general well-being over and above just a placebo effect.

This open study has shown a significant effect of bromelain on reducing symptoms of knee pain and improving well-being in otherwise healthy adults. In addition, improvements were significantly higher in a number of physical and well-being dimensions in the group receiving the higher dose. On the basis of these results, a larger placebo-controlled trial is justified to further strengthen these findings.

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