

Review

Bromelain as a Treatment for Osteoarthritis: a Review of Clinical Studies

Sarah Brien¹, George Lewith¹, Ann Walker², Stephen M. Hicks² and Dick Middleton³

¹University of Southampton, Southampton, ²University of Reading, Reading and ³Medic Herb UK Ltd, UK

Bromelain, an extract from the pineapple plant, has been demonstrated to show anti-inflammatory and analgesic properties and may provide a safer alternative or adjunctive treatment for osteoarthritis. All previous trials, which have been uncontrolled or comparative studies, indicate its potential use for the treatment of osteoarthritis. This paper reviews the mechanism of its putative therapeutic actions, those clinical trials that have assessed its use in osteoarthritis to date, as well as considering the safety implications of this supplement for osteoarthritis and reviewing the evidence to date regarding the dosage for treating this condition. The data available at present indicate the need for trials to establish the efficacy and optimum dosage for bromelain and the need for adequate prospective adverse event monitoring in such chronic conditions as osteoarthritis.

Keywords: bromelain – herbal – osteoarthritis – proteolytic enzymes – review

Introduction

In recent years, a number of clinical studies have appeared to substantiate one of the traditional therapeutic uses of extracts of bromelain, namely, in the treatment of inflammatory disorders of the musculoskeletal system. This paper sets out to review the clinical evidence for the use of bromelain in osteoarthritis.

Osteoarthritis is the most common form of arthritis in Western countries; in the USA prevalence of osteoarthritis ranges from 3.2% to 33% dependent on the joint (1). Its prevalence increases with age, and sex differences are evident (2). It can also create substantial disability (2). The risk of disability attributable to knee osteoarthritis alone is greater than any other medical disorder in the elderly (3), apart from cardiac diseases. Risk factors associated with both the development (e.g. heredity, age, female sex, obesity, trauma) and progression of the disease [e.g. obesity, low bone density, non steroidal anti-inflammatory drug (NSAID) use] have been identified (4); obesity is considered a major risk factor for both the development and progression of osteoarthritis (5,6). As allopathic medicine is unable to halt this progression

conventional medical treatment is aimed at decreasing pain and improving function by the use of NSAIDs, other analgesics, steroidal joint injections and, as a last resort, joint replacement. Because the high incidence of adverse events, especially gastrointestinal, associated with both non-selective and COX-2-selective NSAID use is high (7–9), effective but safer alternative treatments would be of benefit to osteoarthritis sufferers.

Bromelain

Bromelain is a food supplement that may provide an alternative treatment to NSAIDs for patients with osteoarthritis. Bromelain is a crude, aqueous extract obtained from both the stem and fruit of the pineapple plant, which contains a number of proteolytic enzymes (10,11) and has shown potentially beneficial effects due to its anti-inflammatory and analgesic properties. Currently, bromelain is used for acute inflammation and sports injuries. It is not a licensed medical product and is freely available to the general public in health food stores and pharmacies in the USA and Europe.

Mechanism of Action

The mechanisms of action have been reviewed (10–12). Bromelain has been shown to have a number of beneficial

For reprints and all correspondence: Dr Sarah Brien, Complementary Medicine Research, Primary Medical Care, Aldermoor Health Centre, Aldermoor Close, Southampton, Hampshire, S016 5ST. Tel. +44 2380 241068; Fax: +44 2380 8070 1125; E-mail: sbb@soton.ac.uk

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properties including anti-inflammatory and analgesic actions in addition to its anti-oedematous, antithrombotic and fibrinolytic effects (11). Experimental evidence suggests that bromelain's action as an anti-inflammatory is mediated via the following factors: (i) by increasing serum fibrinolytic activity (13), reducing plasma fibrinogen levels (14) and decreasing bradykinin levels (which results in reduced vascular permeability) and hence reducing oedema and pain (15); (ii) by mediating prostaglandin levels (by decreasing levels of PGE₂ and thromboxane A₂); and (iii) through modulation of certain immune cell surface adhesion molecules (16–20), which play a role in the pathogenesis of arthritis (21). However, many of these studies are of poor quality and further data is needed to clarify definitive mechanisms of its action.

Data have also indicated that bromelain has analgesic properties, for example in inflammatory pain in humans (22), human urogenital inflammation (23), and in various animal inflammatory models (13,23). Its analgesic properties are thought to be a result of its direct influence on pain mediators such as bradykinin (15), as well as its indirect effects through its anti-inflammatory actions (e.g. reduction in oedema, debris and immune complexes), which reduce pain.

Clinical Studies

Bromelain was first reported to be of value as an analgesic/anti-inflammatory for use in both rheumatoid arthritis and osteoarthritic patients in 1964 (24). Clinical trials have assessed the effectiveness of bromelain most frequently using preparations containing differing complexes of proteolytic enzymes and differing concentrations of bromelain. Three complexes have been used: (i) PhlogenzymeTM (PHL), which contains the proteolytic enzymes bromelain (90 mg/tab), trypsin and rutin; (ii) WobenzymeTM (WOB) which contains bromelain (45 mg/tab), papain, trypsin, chymotrypsin, pancreatin, lipase and amylase; and (iii) Wobenzym NTM (WOB-N) which contains bromelain (45 mg/tab), trypsin, papain, chymotrypsin, pancreatin and rutin. Bromelain has been assessed in the treatment of osteoarthritis of two joints, i.e. the knee (24–30) and the shoulder (as assessed under the global term peri-arthritis humeroscapularis) (31,32). Tables 1 and 2 summarise those studies that have investigated the effect of bromelain in knee and shoulder osteoarthritis, respectively.

The majority of studies assessing bromelain for osteoarthritis have been either open studies (24,30) or equivalence studies designed to assess comparative effectiveness and safety against standard NSAIDs treatment (25–29, Klein, 1994, unpublished data.). A number of these studies are unpublished [as reviewed by Leipner *et al.* (25)], including two placebo controlled studies designed to assess the efficacy of bromelain in knee osteoarthritis. The following sections will review the studies that have been carried out to date. Direct comparison between these trials is difficult as different dosages or preparations of bromelain have been administered. The majority of the studies have methodological issues that make it difficult to draw definite conclusions.

Bromelain for Knee Osteoarthritis

Ten studies have been identified that have assessed bromelain in osteoarthritis of the knee (Table 1). The earliest reported studies investigating bromelain were a series of case reports on 28 patients, with moderate or severe rheumatoid or osteoarthritis, described by Cohen and Goldman (24). The studies reported indicated that the use of bromelain, at varying doses (these doses were relatively low as compared to subsequent studies) and differing duration, had positive clinical effects in 18 patients (as measured by assessment of reduction in soft tissue swelling, pain and/or joint stiffness) and no adverse events associated with the medication were reported in any of these case reports. This data therefore provided a plausible basis for the further assessment of bromelain in musculoskeletal disorders.

Four unpublished studies: two placebo-controlled, randomised trials and two controlled and randomised studies were reported in the review by Leipner *et al.* (25). These studies were designed to assess the comparative effectiveness of bromelain with a standard treatment, the NSAID diclofenac (DF). No significant improvement in outcome was observed in either of the two placebo-controlled trials but both are of poor methodological quality. The outcome measure for one of the unpublished trials may have been inappropriate and both studies may have been inadequately powered (sample size in both studies was $n = 60$). In addition, in common with the majority of studies assessing bromelain for this indication, the treatment period was short (3 weeks duration) as compared to normal herbal practice where this preparation may be prescribed for 2–3 months in the first instance. Definitive conclusions cannot therefore be drawn from these two efficacy studies. However the safety and tolerability in both these studies appeared adequate as only minor (mainly gastrointestinal) adverse events were reported and dropout rates were low (5% in both studies). Klein and Kullich's (27) double blind, randomised, controlled trial of 73 patients with osteoarthritis of the knee compared a commercial proteolytic enzyme preparation (Phlogenzym®) containing bromelain (among other proteolytic enzymes) with a dose of DF (100–150 mg/day) (24). They report an equivalent reduction in pain indices of 80% for the two treatments during 3 weeks of therapy and 4 weeks of follow-up with few adverse reactions to either treatment. The two unpublished comparative trials identified that treatment with bromelain (540 mg/day as part of the complexes PHL or WOB) reduced osteoarthritis symptoms and that the reduction was comparable to standard treatment. However, again the treatment period in both these studies was short and it is not possible to identify if the study was adequately powered as no sample size calculations are available. Tolerability was good with both PHL and WOB; however, a high rate of adverse drug reactions (none serious) was reported in the WOB study, with a rate of reporting of 50% of subjects in the WOB and the DF treatment groups. These unpublished reports therefore show equivocal evidence in support of bromelain in osteoarthritis, but highlight the potential safety issue.

Table 1. Summary of studies assessing the effectiveness of bromelain as a treatment for osteoarthritis of the knee

Authors	Study design	n ⁺	Dosage	Condition	Treatment period	Follow up	Adverse events	Primary outcome	Conclusion
Cohen & Goldman (24)	Uncontrolled series of case reports	29	60–160 mg/day bromelain	Moderate to severe arthritis (25 RA; 2 OA; 10 A and RA; and 1 gout)	3 weeks to 13 months	When soft tissue swelling	None reported	Soft tissue swelling and pain	Reduction in soft tissue swelling in 72.4%
Leipner <i>et al.</i> (25). Series of unpublished studies in OA involving Phlogenzym™ (PHL), Wobenzym™ (WOB), Wobenzym N™ (WOB-N). Studies investigating OA of knee are reported	(i) placebo controlled DB RCT	(ii) 60 (ref. 31)	PHL 3 × 2 tabs/day (540 mg/day bromelain) versus placebo	Arthrosis of the knee (57%) or hip (43%)	3 weeks	NK	No SAE reported. Two ADR reported in PHL group	Sum score of various pain (active, pressure, rest, night) and dysfunction (four point category scale) measures	Similar reduction in primary outcome for both groups. NS group differences. Drop out n = (1 PHL)
	(ii) placebo controlled DB RCT	(ii) 60 (ref 32)	PHL 3 × 2 tabs/day (540 mg/day bromelain) versus placebo	OA of the knee joint	3 weeks	NK	No SAE reported. Two ADR reported in PHL group	Lequesne index	Reduction in primary outcome for both groups; NS group differences. Drop out n = 3 (1 PHL)
	(iii) Comparative DB, RCT	(ii) 60 (ref 38)	PHL 3 × 2 tabs/day (540 mg/day bromelain) versus DF (100–150 mg/day)	OA of the knee joint	3 weeks	NK	No SAE reported. One ADR (0 PHL; 1 DF)	Lequesne index	Similar reduction in primary outcome for both groups. NS group differences. Drop out n = 1 (0 PHL)
	(iv) Comparative DB, RCT	(iv) 60 (ref 45)	WOB 3 × 4 tabs/day (540 mg/day bromelain) versus DF (100–150 mg/day)	OA of the knee joint	3 weeks	NK	No SAE reported but 30 ADR (15 WOB; 15 DF)	Lequesne index	Similar reduction in primary outcome for both groups. NS group differences. Drop out n = 2 (1 WOB)
Singer and Oberleitner (26)	Comparative DB, RCT	80	WOB 4 × 7 tabs/day (945 mg/day bromelain) versus DF (100 mg)	OA of the knee joint	4 weeks	4 weeks	No SAE reported. 22 ADR (13 WOB) Mainly GI but allergic skin reaction in n = 1	Mobility and pain (five point scale) in morning	Equivalence not tested but similar reductions in primary outcome for both groups. NS group differences. Drop outs n = 12 (8 WOB; 4 DF)
Klein & Kullich (27)	Comparative DB, RCT	73	PHL 3 × 2 tabs/day (540 mg/day bromelain) versus DF (100–150 mg/day)	Knee OA	3 weeks	4 weeks	1 in 36 (2.8%) (headache probably not related)	Lequesne index (pain and function)	Reduction in pain indices by 80% sustained at 4 weeks post treatment. Equivalence was identified at week 3 (Mann Whitney = 0.47) and week 7 (Mann Whitney = 0.55)
Singer <i>et al.</i> (28)	Comparative DB, RCT	68 (ref 37)	PHL 3 × 2 tabs/day (540 mg/day bromelain) versus DF (100–150 mg/day)	OA of the knee joint	3 weeks	4 weeks	No SAE reported. 14 ADR (7 PHL; 7 DF)	Lequesne index and sum of pain scores	PHL group showed significant > reduction compared to DF for both Lequesne (P = 0.017) and sum of pain scores (P = 0.047). Drop out n = 5 (3 PHL)

Table 1. Continued

Authors	Study design	<i>n</i> ⁺	Dosage	Condition	Treatment period	Follow up	Adverse events	Primary outcome	Conclusion
Tilwe <i>et al.</i> 2001 (29)	Comparative SB, RCT	50	PHL 4 × 7 tabs/day (1890 mg/day bromelain) versus DF (100–150 mg/day)	Arthritis of the knee	3 weeks	4 weeks	'well tolerated'; specific AE not reported.	Likert scale to assess pain	Equivalence not tested. Reduction in pain (NS), tenderness ($P < 0.05$) and swelling (NS) in both groups. Joint tenderness was significantly greater ($P < 0.05$) in PHL group than DF group
Walker <i>et al.</i> (30)	Open. Dose ranging	77	Bromelin™ 200 or 400 mg/day	Mild, acute knee pain	4 weeks	4 weeks	No SAE. Minor AE ($n = 19$) mainly GI	WOMAC i.e. total score, pain, stiffness and function	Significant WOMAC total score at both doses ($P = 0.0001$ for 200 mg; $P = 0.000001$ for 400 mg). Significant difference between groups for total score [$(P = 0.036)$, stiffness (0.026), physical function (0.021), well-being.]

⁺Citations quoted in this column refer to references contained within publications listed in the first column.

PHL, Phlogenzym; WOB, Wobenzym; DF, diclofenac; DB, double blind; SB, single blind; RCT, randomised controlled trial; AE, adverse event; SAE, serious adverse event; ADR, adverse drug reaction; GI, gastrointestinal; WOMAC, Western Ontario McMaster University Arthritis Index; NK, not known; NS, not significant.

Bromelin™ contains bromelain 200 mg per tablet. Phlogenzym™ each tablet contains proteolytic enzymes in the following doses: bromelain (90 mg), trypsin (48 mg), rutin (100 mg). Wobenzym™, each tablet contains: bromelain (45 mg), papain (60 mg) trypsin (24 mg), chymotrypsin (1 mg), pancreatin (100 mg), lipase (100 mg), amylase (100 mg), rutin (50 mg).

Four published studies reported trials to assess the effectiveness of bromelain for knee osteoarthritis (26–29). These studies used similar treatment periods (3 or 4 weeks) and similar daily doses of a standard treatment, DF (150–100 mg/day); however, different doses of bromelain were tested (range from 540 to 1890 mg/day). The first study reported by Singer and Oberleitner (26) assessed bromelain at a dose of 945 mg/day (which is higher than that used in most studies) versus DF after 4 weeks of treatment, and although assessment of equivalence was not reported, both groups showed similar reductions in the primary outcome. However, there were more adverse drug reactions (mainly gastrointestinal: 13 in the WOB group versus nine in the DF group) and drop-outs (20% WOB versus 10% DF) as compared to the standard treatment group, which raises concerns about the safety and tolerability of bromelain at this higher dose. These safety and tolerability issues were not replicated in the study by Tilwe *et al.* (29) who administered a daily bromelain dose of 1890 mg/day (in the form of the complex PHL) against the DF comparative group. Equivalence was not tested in this study, but both groups showed reduced symptoms of pain and swelling (comparable across groups), and also joint tenderness (the improvement was significantly better in the PHL group). Tolerability was deemed good (there were no drop-outs), and no significant safety issues were raised in this study despite the high dose employed. The final comparative study was reported by Singer *et al.* (28) who compared bromelain (in the complex PHL) at a dose of 540 mg/day against DF in 68 subjects. This study demonstrated that bromelain showed significantly better improvement in both the primary outcome (Lequesne index, $P = 0.017$) and summary pain scores ($P = 0.047$) as compared to DF. Tolerability and safety were acceptable and levels were similar in both treatment groups. In summary, the four comparative trials indicate that bromelain appears to be as effective as the standard treatment in osteoarthritis of the knee, but higher doses may be associated with safety concerns.

Finally, Walker *et al.* (30) recently described an open study of one month treatment intervention of bromelain using two dose regimes (200 and 400 mg) in otherwise healthy adults ($n = 77$) with acute knee pain with no medical diagnosis. The data identified a significant clinical improvement compared to baseline in both the primary outcome [symptoms assessed by the Western Ontario McMaster University Arthritis Index, WOMAC (32)] and in the secondary outcomes (overall psychological wellbeing), at both doses. Furthermore, mean improvements in total symptom score, stiffness and physical function and psychological well-being were significantly greater in the high-dose compared with the low-dose group. However, definitive conclusions cannot be drawn from this study since there are a number of methodological shortcomings. These include the issue of power, which was not addressed: there was no control group (and therefore bias cannot be eliminated) and these patients did not have a formal diagnosis of their knee pain.

In conclusion, bromelain appears to have potential for the treatment of knee osteoarthritis. However it is important to

note that there are a number of methodological issues that are common to the studies reported, including the possibility of inadequate power, inadequate treatment periods, inadequate or non-existent follow-up to monitor possible adverse drug reactions. Furthermore, the optimum dosage for this condition remains unclear. A phase II clinical trial would be beneficial to identify the optimal dosage and to systematically monitor safety issues before a definitive efficacy study could be completed.

Bromelain for Osteoarthritis of the Shoulder

Two studies have assessed the use of bromelain in osteoarthritis of the shoulder (31, Klein, 1994, unpublished data) (Table 2). Both studies have assessed the complex PHL, which has been used at the same daily dose (equivalent of 540 mg bromelain per day) and for the same treatment period of 3 weeks with no follow-up. The first study (by Klein, 1994) is an unpublished report of a double blind placebo controlled trial assessing PHL in 60 patients. No significant difference in treatment groups was observed after treatment. The level of adverse drug reactions and rate of drop out was low. However, there are a number of methodological caveats. It is unclear if the study was adequately powered to detect treatment group differences and, as with the knee osteoarthritis studies, the treatment period and lack of follow-up period are inadequate and the optimum dosage is not clear. The second study by Klein *et al.* (31) was designed to compare PHL against the standard DF treatment (100 mg/day) in $n = 40$ patients with this condition. No group differences in the primary outcome measures (summary pain score) were observed and safety and tolerability were adequate at this dose. However, this study also suffers from possibly being inadequately powered, a brief treatment period and limited follow up.

In conclusion the data from these two studies do not provide support for the effectiveness and safety of bromelain in osteoarthritis of the shoulder; further studies are needed that are adequately powered to identify the optimal dose and optimal treatment period for this condition.

Summary of Clinical Trials Assessing Bromelain for Osteoarthritis

The use of bromelain for the treatment of osteoarthritis looks promising. However, a number of methodological caveats indicate that further studies are warranted, in particular phase II clinical trials to identify the optimum dosage, followed by a definitive randomised placebo-controlled trial to confirm its efficacy in the treatment of osteoarthritis.

Bromelain and Adverse Events

Bromelain has been used as treatment for a number of disease conditions, in addition to osteoarthritis of the knee and shoulder joints (Table 1). No serious adverse events have been reported with the consumption of either bromelain or pineapples in these studies. Adverse events that have been reported are

Table 2. Summary of studies assessing the effectiveness of bromelain as a treatment for osteoarthritis of the shoulder (periarthritis humero scapularis)

Authors	Study design	n	Dosage	Condition	Treatment period	Follow up	Adverse events	Primary outcome	Conclusion
Klein <i>et al.</i> (33) Unpublished	DB, placebo controlled RCT	60	PHL 3 × 2 tabs/day (540 mg/day bromelain) versus placebo	Peri arthritis humero scapularis	3 weeks	N/A	No SAE reported. Three ADR (1 PHL)	Sum score of various pain (active, pressure, rest, night) and dysfunction (four point category scale) measures	No significant group difference in primary outcome after 3 weeks treatment. n = 4 drop outs (2 PHL)
Klein <i>et al.</i> (31)	Comparative DB, RCT	40	PHL 3 × 2 tabs/day (540 mg/day bromelain) DF (100 mg/day)	Peri arthritis humero scapularis tendopathica	3 weeks	N/A	No SAE reported. Three ADR (2 PHL)	Sum score of various pain (active, pressure, rest, night) and dysfunction (four point category scale) measures	No significant group difference at outcome after 3 weeks treatment (P = 0.14). n = 5 drop outs (3 PHL)

PHL, Phlogenzym; DF, diclofenac; DB, double blind; RCT, randomised controlled trial; SAE, serious adverse event; ADR, adverse drug reaction; N/A, not applicable. Phlogenzym™ each tablet contains proteolytic enzymes in the following doses: bromelain (90 mg), trypsin (48 mg), rutin (100 mg).

mainly gastrointestinal (i.e. diarrhoea, nausea and flatulence), but have also included headache, tiredness, dry mouth, skin rash and allergic reactions (not specified).

The trials assessing bromelain in osteoarthritis have used doses of bromelain in the range 540–1890 mg/day. Safety and tolerability for bromelain at the lower dose appears good with similar if not better safety profiles as compared to standard treatment. However, the studies that have used a higher daily dose of bromelain [945 mg/day (26); 1890 mg/day (29)] appear to be conflicting. The authors employing the highest dose reported that the medication was well tolerated; the dose of 945 mg/day, however, showed a higher incidence of adverse drug reactions and drop-outs as compared to the profiles from the standard NSAID treatment group. A formal phase II study is needed to identify safety and efficacy/effectiveness of bromelain. In addition, it is conceivable that patients would clinically receive bromelain for longer treatment periods than have been assessed by the current osteoarthritis studies. Further work is therefore needed to evaluate the long-term safety of this supplement. Finally, there are also a number of other potential safety issues that need to be addressed. These include investigating the possibility of renal effects (because of modulation of biosynthesis of prostaglandins), potentiating effects on the action of anticoagulants [e.g. warfarin (33)] and enhanced absorption of antibiotics (11).

Dosage in human studies

The review by Maurer (11) identified that bromelain has been used in the daily dosage range of 200–2000 mg, with therapeutic action shown at 160 mg/day. The trials assessing bromelain in osteoarthritis have used bromelain at a higher therapeutic dose, in the range of 540–1890 mg/day. Safety and tolerability at the lower dose appears to be good; the data indicates that bromelain at this dose appears to be as effective as standard treatment with at least similar safety and tolerability profiles. The two studies employing a higher daily dose [945 mg/day (26) and 1890 mg/day (29), both comparative trials] showed that the dose of 945 mg/day showed similar outcomes to DF, whereas 1890 mg/day appeared to be superior to DF in one of the primary outcome measures (joint swelling). As yet there have been no formal phase II studies to assess the optimal dose. However, the recent study by Walker *et al.* (30) in acute knee pain showed a significant dose-dependent effect between the two doses of 200 and 400 mg per day, over a period of one-month therapy. Further study is needed to identify the optimal dose for the treatment of chronic joint inflammation over longer periods of time (e.g. 3–4 months) within a blinded and randomised trial.

Summary

The currently available data do indicate the potential of bromelain in treating osteoarthritis. However, further studies are needed before a definitive conclusion can be drawn. Specifically, there is a need for trials to establish efficacy, and dose ranging studies to identify the optimum dosage (with

adequate prospective adverse event monitoring). Finally, future work should focus on the dose–response parameters and efficacy of long-term bromelain use in chronic conditions such as osteoarthritis.

Conflict of Interest

Dick Middleton is consultant to Lichtwer Pharma UK Ltd who manufacture bromelain. Steven Hicks was funded by Lichtwer for a post-graduate fellowship from 1998 to 2002.

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References

- Lawrence RC, Helmich CG, Arnett F, et al. Estimates of prevalence of arthritis and selected musculoskeletal disorders in the United States. *Arthritis Rheum* 1998;41:778–99.
- Felson DT, Lawrence RC, Dieppe PR, et al. Osteoarthritis: New Insights. Part 1. The disease and its risk factors. *Ann Intern Med* 2000;133:635–46.
- Guccione AA, Felson DT, Anderson JJ, et al. The effects of specific medical conditions on the functional limitations of elders in the Framingham study. *Am J Public Health* 1994;84:351–8.
- Doherty M. Risk factors for the progression of knee osteoarthritis. *Lancet* 2001;358:775–6.
- Anderson JJ, Felson DT. Factors associated with osteoarthritis of the knee in the first national Health and Nutrition Examination Survey (HANES I). Evidence for an association with overweight, race, and physical demands of work. *Am J Epidemiol* 1988;128:179–89.
- Minor MA, Hewitt JE, Weibel RR, Anderson SK, Kay DR. Efficacy physical conditioning exercise in patients with rheumatoid arthritis and osteoarthritis. *Arthritis Rheum* 1989;32:1396–1405.
- Singh G. Recent considerations in nonsteroidal anti-inflammatory drug gastropathy. *Am J Med* 1998;105(16):315–85.
- Griffin MR. Epidemiology of nonsteroidal anti-inflammatory drug-associated gastrointestinal injury. *Am J Med* 1998;104 (3A):23S–29S.
- Wright JM. The double-edged sword of COX-2 selective NSAIDs. *Can Med Assoc J* 2002;167:1131–7.
- Cooreman WM, Scharpe S, Demeester J, Lauwers A. Bromelain, biochemical and pharmacological properties. *Pharm Acta Helv* 1976;51:73–97.
- Maurer HR. Bromelain: biochemistry, pharmacology and medical use. *Cell Mol Life Sci* 2001;58:1234–45.
- Taussig SJ, Batkin S. Bromelain, the enzyme complex of Pineapple (*Ananas comosus*) and its clinical application. An update. *J Ethnopharmacol* 1988;22:191–230.
- Pirotta F, de Giuli-Morghen C. Bromelain: anti-inflammatory and serum fibronolytic activity after oral administration in the rat. *Drugs Exp Clin Res* 1978;4:1–20.
- Livio M, Bertoni MP, De Gaetano G, Donati MB. Effects of bromelain on fibrinogen level, prothrombin complex and platelet aggregation in the rat—a preliminary report. *Drugs Exp Clin Res* 1978;4:49–53.
- Kumakura S, Yamashita M, Tsurufuji S. Effect of Bromelain or kaolin-induced inflammation in rats. *Eur J Pharmacol* 1988;150:295–301.
- Hale LP, Hayes BF. Bromelain treatment of human T cells removes CD44, CD45RA, E2/MIC2, CD6, CD7, CD8 and Leu 8/LAM1 surface molecules and markedly enhances CD-2Mediated T cell activation. *J Immunol* 1992;149:3809–16.
- Kleef R, Delohery TM, Bovbjerg DH. Selective modulation of cell adhesion molecules on lymphocytes by Bromelain protease 5. *Pathobiology* 1996;64:339–46.
- Mynott T, Ladhams A, Scarmato P, Engwerda C. Bromelain from pineapple stems, proteolytically blocks activation of extracellular regulated kinase-2 in T cells. *J Immunol* 1999;163:2568–75.
- Hale LP, Greer PK, Sempowski GD. Bromelain treatment alters leukocyte expression of cell surface molecules involved in cellular adhesion and activation. *Clin Immunol* 2002;104:183–90.
- Hale LP. Proteolytic activity and immunogenicity of oral bromelain within the gastrointestinal tract of mice. *Int Immunopharm* 2004;4:255–64.
- Mojcik C, Shevach E. Adhesion molecules: a rheumatologic perspective. *Arthritis Rheum* 1997;40:991–1004.
- Bodi T. The effects of oral bromelains on tissue permeability to antibiotics and pain response to bradykinin: double blind studies on human subjects. *Clin Med* 1966;73:61–5.
- Uhlig G, Seifert J. Die Wirkung proteolytischer Enzyme auf das posttraumatische Syndrom. *Fortschritte der Medizin* 1981;15:554–6.
- Cohen A, Goldman J. Bromelain therapy in rheumatoid arthritis. *Penn Med J* 1964;67:27–30.
- Leipner J, Iten F, Saller R. Therapy with proteolytic enzymes in rheumatic disorders. *Biodrugs* 2001;15:779–89.
- Singer F, Oberleitner H. Drug therapy of activated arthrosis. On the effectiveness of an enzyme mixture versus diclofenac. *Wien Med Wochenschr* 1996;146:55–8.
- Klein G, Kullich W. Short-term treatment of painful osteoarthritis of the knee with oral enzymes: a randomised, double-blind study versus Diclofenac. *Clin Drug Invest* 2000;19:15–23.
- Singer F, Singer C, Oberleitner H. Phyloenzym versus diclofenac in the treatment of activated osteoarthritis of the knee. *Int J Immunother* 2001;17:135–41.
- Tilwe GH, Beria S, Turakhia NH, Daftary GV, Schiess W. Efficacy and tolerability of oral enzyme therapy as compared to diclofenac in active osteoarthritis of the knee joint: an open randomised controlled clinical trial. *Journal of the Association of Physicians of India. JAPI* 2001;49:621.
- Walker AF, Bundy R, Hicks SM, Middleton RW. Bromelain reduces mild acute knee pain and improves well being in a dose dependant fashion in an open study of otherwise healthy adults. *Phytomedicine* 2002;9:681–6.
- Klein G, Kullich W, Brugger A. Phlogenzym in der Behandlung der Periarthropathia humeroscapularis tendopathica simplex. *Arzt Praxis* 1997;51:879–85.
- Bellamy N, Buchanan W, Goldsmith C, Campbell J, Stitt L. Validation study of WOMAC: a health status instrument for measuring clinically important patient relevant outcomes to anti-rheumatic drug therapy in patients with osteoarthritis of the hip or knee. *Rheumatology* 1988;15:1833–40.
- Stenton SB, Bungard TJ, Ackman ML. Interactions between warfarin and herbal products, minerals, and vitamins: A pharmacist's guide. *Can J Hosp Pharm* 2001;54:184–90.

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