Bromelain Containing Enzyme-Rutosid Combination Therapy is as Effective as Nonsteroidal Antiinflammatory Agents for Treatment of Osteoarthritis

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Recommended Citation
Bradley, Paul, "Bromelain Containing Enzyme-Rutosid Combination Therapy is as Effective as Nonsteroidal Antiinflammatory Agents for Treatment of Osteoarthritis" (2014). School of Physician Assistant Studies. 475.
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Abstract

**Background:** Osteoarthritis (OA) affects 20 million Americans and OA of the knee is the number one disability in the US. OA is due to inflammation and dysfunction of the immune system. One commonly used therapy for OA is nonsteroidal antiinflammatory drugs (NSAIDs) but they have adverse reactions that affect the gastrointestinal, renal, and cardiovascular systems. Combination oral enzyme therapy contains naturally extracted enzymes (bromelain and trypsin) and combines them with the antioxidant rutosid, extracted from buckwheat or the pagoda tree, as an alternative treatment for OA. The combination oral enzyme therapy has antiinflammatory, antiedematous, antihistaminic, antiviral, antithrombotic, and fibrinolytic properties. Is this combination oral enzyme therapy as effective as NSAIDs in the treatment of OA?

**Methods:** An exhaustive search of available medical literature was conducted through Medline-OVID, CINAHL, and Web of Science using the keywords: bromelain, nonsteroidal antiinflammatory agents, and osteoarthritis. Studies were screened for use of the English language and use of randomized controlled trial design. Relevant articles were assessed for quality using GRADE.

**Results:** Four studies met inclusion criteria and were included in the systematic review. Four randomized controlled trials demonstrated that combination oral enzyme therapy was as effective as diclofenac (NSAID) in management of active osteoarthritis. The studies showed no significant differences when comparing NSAIDs to combination oral enzyme therapy where regarding pain at rest, pain with movement, Lequesne's Functional Index, joint stiffness, range of motion, and swelling in the affected joint.

**Conclusion:** Combination enzyme therapy has been shown to be as effective as NSAIDs in treatment of active osteoarthritis. More studies need to be done to evaluate long term efficacy and tolerance. Recommend use of combination oral enzyme therapy in patients that cannot tolerate NSAIDs or have contraindications to NSAID therapy.

**Keywords:** Bromelain, nonsteroidal antiinflammatory agents, osteoarthritis

**Degree Type**
Capstone Project

**Degree Name**
Master of Science in Physician Assistant Studies

**Keywords**
Bromelain, nonsteroidal antiinflammatory agents, osteoarthritis

**Subject Categories**
Medicine and Health Sciences

This capstone project is available at CommonKnowledge: https://commons.pacificu.edu/pa/475
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Bromelain Containing Enzyme-Rutosid Combination Therapy is as Effective as Nonsteroidal Antiinflammatory Agents for Treatment of Osteoarthritis

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A Clinical Graduate Project Submitted to the Faculty of the School of Physician Assistant Studies Pacific University Hillsboro, OR

For the Masters of Science Degree, August 9th 2014

Faculty Advisor: Mark Pedemonte, MD.

Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS
Biography

[Redacted]
Abstract

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Conclusion: Combination enzyme therapy has been shown to be as effective as NSAIDs in treatment of active osteoarthritis. More studies need to be done to evaluate long term efficacy and tolerance. Recommend use of combination oral enzyme therapy in patients that cannot tolerate NSAIDs or have contraindications to NSAID therapy.

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Acknowledgements

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Table 1: Characteristics of Reviewed Studies
Table 2: Summary of Findings

List of Abbreviations

DC  Diclofenac Sodium
ERC  Enzyme-Rutosid Combination
GRADE Grading of Recommendations, Assessment, Development and Evaluation
IFN-γ Interferon Gamma
IL-1 Interleukin-1
LFI Lequesne’s Functional Index
NSAIDs Nonsteroidal Antiinflammatory Drugs
OA Osteoarthritis
PE Phlogenzym
TNF-α Tumor Necrosis Factor Alpha
VAS Visual Analog Scale
VRS Visual Rating Scale
WOMAC Western Ontario and Masters Osteoarthritis Index
Bromelain Containing Enzyme-Rutosid Combination Therapy is as Effective as Nonsteroidal Antiinflammatory Agents for Treatment of Osteoarthritis

BACKGROUND

Osteoarthritis (OA) is the most common type of joint disease, affecting an estimated 27 million individuals in the United States.\(^1\) OA is characterized by non-systemic progressive loss of articular cartilage and bony overgrowth at affected joints. These manifestations lead to joint pain, joint stiffness, and disability of varying severity. There is an established inflammatory component of OA\(^2,3\) and there is increasing evidence that immune system dysfunction contributes to the pathophysiology of OA.\(^4-6\)

A first line treatment for active inflammatory OA is nonsteroidal antiinflammatory drugs\(^7\) (NSAIDs). The primary effect of NSAIDs is to inhibit cyclooxygenase enzyme thus inhibiting prostaglandin synthesis, a mediator in the inflammatory process. Prolonged or repeated use of NSAIDs has been associated with increased risk of gastric and duodenal ulcers resulting in upper gastrointestinal perforation and bleeding.\(^8,9\) According to the American Gastroenterological Association (AGA), each year the side effects of NSAIDs hospitalize over 100,000 people and kill 16,500 in the US, mostly due to bleeding ulcers.\(^10\) A spokesperson for the AGA named Byron Cryer, MD. stated, “More than half of all bleeding ulcers are caused by NSAIDs.”\(^10\) Diclofenac, which was used in each study reviewed in this paper, has been shown to be one of the better tolerated NSAIDs.\(^11\)
Phlogenzym (PE) is an oral enzyme-rutosid combination that combines bromelain 90mg, trypsin 48mg, and rutosid 100mg. All ingredients are absorbed in the upper intestine. Bromelain is a crude extract from pineapple stems and fruit that contains various closely related proteases that have demonstrated in vivo antiedematous, antiinflammatory, antithrombotic, and fibrinolytic activities.\textsuperscript{12,13} Bromelain’s antiinflammatory properties are from inhibiting the production of bradykinin at the inflammatory site via depletion of the plasma kallikrein system.\textsuperscript{14} Bromelain has been associated with diarrhea and stomach and intestinal discomfort.\textsuperscript{15} Trypsin is a hydrolase enzyme secreted by the pancreas and aids in the digestion of food proteins. Trypsin enhances fibrinolysis and together with bromelain lowers the proinflammatory cytokines including: TNF-\textit{\alpha}, IL-1, and IFN-\gamma.\textsuperscript{16} Rutosid is derived from extraction from the seed of the Japanese pagoda tree or buckwheat.\textsuperscript{17} Rutosid is a phenolic antioxidant which accounts for many of its properties, including being antiinflammatory, antihistaminic, and antiviral.\textsuperscript{14}

The goal of this investigational review is to evaluate another option for the treatment of osteoarthritis that has a history of fewer serious side effects than the current available treatment with the same efficacy. What is the efficacy of bromelain containing enzyme-rutosid combination (ERC) therapy compared to nonsteroidal antiinflammatory drugs in the treatment of osteoarthritis?

**METHODS**

An exhaustive search of available medical literature was conducted using Medline-OVID, CINAHL, and Web of Science using the keywords: bromelain, nonsteroidal antiinflammatory agents, and osteoarthritis. Only English language,
randomized controlled trials were included. The bibliographies of each study were further searched for relevant sources. The randomized controlled trials were assessed for quality using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) scale.18

RESULTS

The above search strategy of available medical literature yielded eight articles. After removing duplicates and irrelevant articles, screening for studies in the English language, and including randomized controlled trials four articles remained.16, 19-21 See Table 1.

**Oral Enzyme Combination Versus Diclofenac in the Treatment of Osteoarthritis of the Knee: A Double-Blind Prospective Randomized Study**

This randomized, double blinded, double dummy, active comparator-controlled trial16 compared the effects of Phlogenzym (PE) to diclofenac sodium (DC) for treatment of osteoarthritis with a disease flare in one knee joint. The study took place in Pakistan. The age of the participants ranged from 36-77 years with 70 female participants and 28 male participants. The control group was given diclofenac sodium 50 mg, one tablet twice daily for 6 weeks whereas the test group was given PE one tablet three times daily for 6 weeks. Baseline, 2, 4, and 6 week evaluations were conducted on participants and treatment compliance was measured by pill counting at visits. The primary end points were Lequesne’s Functional Index (LFI) and complaint index using the visual analog scale (VAS) for pain at rest, pain in motion, and restricted function. Secondary endpoints included: pain free range of motion and circumference of affected knee measured in
centimeters at each evaluation. About half of the participants received physical therapy during the study and was equally distributed between the two treatment groups.\textsuperscript{16}

Baseline demographics and other baseline characteristics did not reveal relevant differences between the two treatment groups. Mean value of LFI decreased by 26.3\% in the PE group and 23.6\% in DC group. Pain at rest revealed a median decrease of 41\% for PE group and 22.5\% for DC group; pain in motion median decrease in both groups of 28.6\%, and joint stiffness decreased by 10\% in PE group and 0\% in DC group. There was no change from baseline in range of motion for either group and joint swelling was decreased 1.2\% in PE group and no median decrease in the DC group (see Table 2).\textsuperscript{16} These values were not statistically different when comparing the two study groups.

**Phlogenzym Versus Diclofenac in the Treatment of Activated Osteoarthritis of the Knee: A Double-Blind Prospective Randomized Study**

This prospective, randomized, double blinded, double dummy phase III clinical trial with two parallel groups\textsuperscript{19} compared the effects of Phlogenzym (PE) to diclofenac sodium (DC) for treatment of osteoarthritis with a disease flare in one knee joint. There were a total of 63 patients included in the study, 31 in the PE group and 32 in the DC group. The control group was given diclofenac sodium 50 mg, one tablet three times daily for 1 week and then one tablet twice a day for 2 weeks and the test group was given PE one tablet three times daily for 3 weeks. Baseline, 1, 2, 3, and 7 week evaluations were conducted on participants and treatment compliance was measured by pill counting at visits. The primary end points were Lequesne’s Functional Index (LFI) and complaint index using visual analog scale (VAS) for pain at rest, pain in motion, and restricted
function. Secondary endpoint was circumference of affected knee measured in centimeters at each evaluation.\textsuperscript{19}

At the end of therapy (week 3) mean values for relevant end-points had decreased as follows: pain at rest 57.6\% for the PE group and to 53.9\% for the DC group; pain on movement 55.6\% for PE group and 49.4\% for DC group; joint stiffness 52.5\% for PE group and 52.0\% for DC group and LFI scores decreased 29.1\% in PE group and 31.5\% in DC group from baseline scores. At the follow up period (>7 weeks) mean values for relevant end-points had decreased as follows: pain at rest 66.7\% for PE group and 38.3\% for DC group; pain with movement 67.4\% for PE group and 35.6\% for DC group; joint stiffness 70.0\% for PE group and 45.3\% for DC group and LFI scores decreased 36.6\% in PE group and 19.2\% in DC group from baseline (see Table 2).\textsuperscript{19}

\textbf{Efficacy and Tolerability of Oral Enzyme Therapy as Compared to Diclofenac in Active Osteoarthritis of Knee Joint: An Open Randomized Controlled Clinical Trial}

This randomized, single blinded, active comparator controlled trial\textsuperscript{20} compared the effects of Phlogenzym (PE) to diclofenac sodium (DC) in the treatment of osteoarthritis with an active flare of one knee joint. There were 50 participants consisting of 31 females and 19 males. The control group was given DC 50mg, one tablet twice a day and the test group was given three tablets of PE twice a day for 1 week and then two tablets of PE twice a day for 2 weeks. Evaluations were conducted at baseline, 3, and 7 weeks for follow up. The primary endpoints were pain at rest and pain with movement measured subjectively using VAS. Secondary endpoints were joint swelling measured at
the upper patella margin at full extension of the knee in centimeters and range of motion of the affected knee measured by goniometer at each visit.\textsuperscript{20}

According to study, patients were comparable with respect to their presenting features; however, there is no data given comparing the demographics of each group at the onset of the study. At the end of therapy (3 weeks) the mean scores for the relevant end-points had decreased as follows: pain at rest 42.9\% in PE group and 25.8\% in DC group from baseline; pain with motion 39.6\% in PE group and 36.3\% in DC group from baseline and joint swelling 4.5\% in PE group and 2.1\% in DC group from baseline. At the follow up exam (7 weeks from baseline) mean scores for the relevant end-points decreased as follows: pain at rest 50.0\% in PE group and 32.2\% in DC group compared to baseline; pain with movement 37.5\% in PE group and 41.2\% in DC group and joint swelling 4.6\% for PE group and 1.0\% for DC group compared to baseline. There was no change in range of motion in either group from baseline recordings (see Table 2).\textsuperscript{20} These values were not statistically different when comparing the two study groups.

**Efficacy and Tolerance of an Oral Enzyme Combination in Painful Osteoarthritis of the Hip: A Double-Blind, Randomized Study Comparing Oral Enzymes with Nonsteroidal Antiinflammatory Drugs**

This randomized, double blinded, double dummy, active comparator-controlled trial\textsuperscript{21} compared the effects of Phlogenzym (PE) to diclofenac sodium (DC) for treatment of osteoarthritis with a disease flare in one hip joint. The study took place in Austria. The age of the participants ranged from 35-69 years with 31 female participants and 59 male participants. The control group was given diclofenac sodium 50 mg, one tablet twice
daily for 6 weeks whereas the test group was given PE two tablets three times daily for 6 weeks. The first 3 weeks were as an inpatient and last 3 weeks were as outpatient. Baseline, 3, and 6 week evaluations were conducted on participants and treatment compliance was measured by pill counting at visits. The primary end points were Lequesne’s Functional Index (LFI) and Western Ontario and Masters Osteoarthritis Index (WOMAC) which measures joint pain, stiffness, and physical function via visual rating scale (VRS).21

Comparison of baseline demographics and other baseline characteristics of all patients included into the study did not reveal relevant differences between the two treatment groups. After the 6 weeks observation period the adjusted changes from baseline to the end-point of the target parameters were as follows: WOMAC subscale pain (PE -10.3 ±1.2, DC -9.5 ±1.2); WOMAC joint stiffness (PE -3.9 ±0.5, DC -3.6 ±0.5) and LFI (PE -2.89 ±0.47, DC -2.27 ±0.47)(see Table 2).21

DISCUSSION

Bromelain containing enzyme-rutosid combination therapy is as effective alternative to NSAIDs in the treatment of active OA. The studies included in the review all conclude that combination oral enzyme therapy is as efficacious as NSAIDs in primary and secondary end-points of acute flares of OA (see Table 2). In the studies the two therapies were equally well tolerated, therefore, safety is likely to be equivalent as well. This equivalency is probably due to the lack of sample size in the trials and the probability of having a serious adverse reaction threshold was not reached.

While the studies16,19-21 demonstrated that combination oral enzymes are effective in treatment of OA, they all have limitations. One study,20 the investigators did not blind
the patients to the drug that they were receiving. Three of the studies\textsuperscript{16,19,21} used double dummy design to further ensure concealment of study group allocation. All the studies’ primary outcomes agreed with each other and all the studies came to similar conclusions. All medication in each trial was provided by the manufacturer of Phlogenzym which might have introduced bias. Although precision was not an issue, sample sizes for each trial may be of concern in regards to the strength of any recommendations. Furthermore, in three of the studies\textsuperscript{16,19,20} the participants did have a female predominance. Further research, with larger sample sizes and longer treatment regimens to evaluate the efficacy of long term enzyme-rutosid combination therapy compared to NSAID therapy in the treatment of OA is recommended. In the recommended longer, larger study they could also evaluate adverse side effect profiles and measure which therapy is better tolerated with less complications.

Another consideration is the difference in price of the products. Phlogenzym is twice the amount of a diclofenac 50mg pill and three times the amount of an ibuprofen 400mg pill.\textsuperscript{22, 23} NSAIDs are available at any pharmacy in the US, whereas, Phlogenzym and other bromelain containing enzyme-rutosid combination therapies are only available through online ordering.

\textbf{CONCLUSION}

For the management of OA, bromelain containing oral enzyme combination therapy has been demonstrated to be as effective as the most commonly used therapy, NSAIDs. In some circumstances the enzyme-rutosid combination improved function and decreased pain better than diclofenac, but the difference was not statistically significant. The overall combined quality of the trials reviewed is moderate quality based on GRADE
criteria. An alternative therapy for flares of OA is available and should be considered in patients that do not tolerate NSAIDs well or have contraindications to NSAID therapy. It should also be considered as an alternative to long term NSAID use for OA. Further studies are needed to compare efficacy and tolerance of bromelain containing enzyme-rutosid combination therapy to NSAIDs in the long term treatment of OA.
References


### Table 1. Characteristics of Reviewed Studies

<table>
<thead>
<tr>
<th>Quality Assessment</th>
<th>Downgrade Criteria</th>
<th>Quality</th>
<th>Importance</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Studies</td>
<td>Design</td>
<td>Limitations</td>
<td>Indirectness</td>
</tr>
<tr>
<td>Pain in affected joint at rest and with movement</td>
<td>4</td>
<td>4 RCTs</td>
<td>Serious limitations&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Lequesne’s Functional Index&lt;sup&gt;c&lt;/sup&gt; (LFI)</td>
<td>3</td>
<td>3 RCT</td>
<td>No serious limitations</td>
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<tr>
<td>Stiffness of affected joint</td>
<td>3</td>
<td>3 RCT</td>
<td>No serious limitations</td>
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<tr>
<td>Range of motion of affected joint</td>
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<td>2 RCT</td>
<td>Serious limitations&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td>Swelling of affected joint</td>
<td>3</td>
<td>3 RCT</td>
<td>Serious limitations&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> One study<sup>20</sup> was single blinded.

<sup>b</sup> Three of the studies<sup>16,19,20</sup> had a female predominance enrolled.

<sup>c</sup> Lequesne’s Functional Index- 10 question survey to assess pain, mobility and activities of daily living in patients with osteoarthritis
Table 2. Summary of Findings

<table>
<thead>
<tr>
<th>Study</th>
<th>Duration of study</th>
<th>Number of Patients</th>
<th>Phlogenzym (PE) group (total)</th>
<th>Diclofenac (DC) group (total)</th>
<th>Pain in affected joint (mean % decrease)</th>
<th>Lequesne's Functional Index (Mean % decrease)</th>
<th>Stiffness in affected joint (Mean % increase)</th>
<th>Range of Motion in affected joint</th>
<th>Swelling of affected joint (Mean % decrease)</th>
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<td>Akhtar et al16</td>
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<td>46</td>
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<td>26.3</td>
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<td>Singer et al19</td>
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<td>29.1</td>
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<td>7 weeks (follow-up)</td>
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<td>At rest</td>
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<td>36.6</td>
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<td>At rest</td>
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<td>-1.2(±1.2)</td>
<td>-1.2(±1.2)</td>
<td>-1.3(±0.47)</td>
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</table>

a Statistical significance of difference between the two study groups19. All other values were not statistically significantly different (P-value >0.05).16,20,21