

# Over-the-Counter Enzyme Supplements: What a Clinician Needs to Know

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**Learning Objectives:** On completion of this article, you should be able to (1) identify common over-the-counter (OTC) enzymes being used by consumers in the United States, (2) develop a practical approach to reviewing current research on the efficacy of OTC enzymes for various conditions, and (3) communicate with patients regarding the risks and benefits of OTC enzymes.

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## Abstract

Over-the-counter (OTC) enzyme use is increasing in frequency in the United States. The numerous health benefit claims by manufacturers are leading to a surge in enzyme use for various conditions and symptoms. Clinicians need to help patients navigate this complex realm and make informed decisions about the use of OTC enzymes. This review focuses on key concepts for health care providers to understand the current evidence, risks, and benefits of OTC enzymes.

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During clinical encounters, patients often inquire about the use of dietary enzyme supplements (also termed over-the-counter [OTC] enzymes) to relieve symptoms. The Dietary Supplement Health and Education Act of 1994 classified OTC enzymes as dietary supplements, which specifically exempts manufacturers from having to prove the safety or efficacy of a product as long as it does not claim to prevent, treat, or cure a specific disease.<sup>1</sup> Despite these restrictions, manufacturers market OTC enzymes as

being effective for inflammatory disorders, multiple sclerosis, pancreatic insufficiency, allergies, burns, infections, and cancer. The popularity of these OTC enzymes is demonstrated by increased US sales in the past few years.<sup>2</sup> Nevertheless, the quality of dietary supplements has been a cause for concern and has led to the dismissal of these supplements by physicians. The purpose of this review was to summarize the current evidence for the use of OTC enzymes in various disease states, equipping clinicians to have the conversation with the patient.



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## WHAT ARE OTC ENZYMES?

Most clinicians are familiar with prescription pancreatic enzyme products that are used to treat pancreatic insufficiency, such as protease, pancrelipase, and pancreatic amylase. However, some enzymes are sold directly to consumers, including bromelain, papain, trypsin, and chymotrypsin, as well as numerous combination products (Table 1). Bromelain is a group of proteolytic enzymes derived from the stem and fruit of the pineapple (*Ananas comosus*).<sup>3</sup> Taking oral bromelain combined with trypsin and rutin may improve the symptoms of osteoarthritis (OA). The papaya fruit (*Carica papaya*) contains several proteolytic enzymes (papain, chymopapain A, chymopapain B, and papaya peptidase A)<sup>3</sup> and is mainly used in wound débridement. Over-the-counter trypsin is typically produced from bacterial, fungal, or porcine sources.<sup>3</sup> Similar to papain, it is also used conventionally to aid in wound débridement (topical). As a supplement, most chymotrypsin is produced from bovine or porcine sources. Some evidence suggests that chymotrypsin might decrease tissue destruction in burn patients. Oral chymotrypsin seems to be effective for reducing the inflammation and edema associated with hand fractures.<sup>4</sup> Enzymes derived from plant sources are touted as remaining active over a broader pH range, whereas animal-derived enzymes function in a narrower pH range. This wider pH range may protect plant-based enzymes from being degraded in the acidic environment of the stomach. Information about some of the more commonly used OTC enzymes, including dosage and adverse effects, are presented in Table 2.

## MECHANISM OF ACTION OF OTC ENZYMES

The mechanism of action of OTC enzymes is not entirely clear as there are a number of studies demonstrating both pro-inflammatory and anti-inflammatory effects. The constituent of bromelain interferes with the growth of malignant cells and inhibits platelet aggregation. Animal studies suggest that it helps reduce

inflammation and edema and has fibrinolytic activity.<sup>5</sup> Some evidence suggests that papain can increase the release of reactive oxygen species by polymorphonuclear cells.<sup>3</sup> Multi-enzyme preparations also seem to induce tumor necrosis factor (TNF)  $\alpha$ , interleukin (IL)-1 $\beta$ , and IL-6 in a time- and dose-dependent manner.<sup>6</sup> The main mechanism of trypsin is its proteolytic activity, especially in wounds.<sup>3</sup> Chymotrypsin has ingredients with proteolytic, anti-inflammatory, and antioxidant activities that reduce tissue destruction.<sup>3</sup>

## Does Enzyme Production Decrease With Aging and Can OTC Enzymes Help?

One of the main theories advocated by OTC enzyme proponents is that with age, natural enzyme production decreases and enzyme supplementation, therefore, becomes essential. However, enzyme production does not inherently decrease with age. For example, levels of amylin, a peptide hormone released from the endocrine pancreas, decrease in middle age but then increase in older age. Amylin has been implicated in appetite regulation because it is a potent anorectic agent when administered peripherally in rats. Increased amylin levels in older age suggests that it may contribute to anorexia of aging and delayed gastric emptying.<sup>7</sup> No evidence indicates that exocrine pancreatic secretions decrease with age. Evidence supporting OTC enzyme supplementation in older patients is lacking.

## Do OTC Supplements Help Digestion in Healthy Adults?

Although enzyme supplementation for patients with documented pancreatic insufficiency is well established,<sup>8</sup> a recently growing trend is the use of supplemental enzymes to aid digestion in individuals with no obvious pancreatic pathology. Proponents suggest that common symptoms, such as gas and bloating, may indicate a relative deficiency of digestive enzymes that can be overcome with oral supplementation. A commonly cited study describes healthy participants who were given enzyme supplements (containing lipase, protease, and amylase) before and after a fatty meal and reported significantly less gas, bloating, and fullness than controls.<sup>9</sup> However, the pancreatic supplement used (Creon 10; Solvay Pharmaceutical Inc) was a prescription enzyme product. Thus, the

**TABLE 1. Common Claims About Over-the-Counter Enzymes by Their Manufacturers**

- "Enzymes: The Brawn Behind Better Digestion"
- "Proteolytic Enzymes—A Potential Cure for Arthritis"
- "Enzymes for Cancer: Low Enzymes Are Always Found in Cancer ..."
- "How Systemic Enzymes Work to Cure Diseases"

**TABLE 2. Use, Dosage, and Potential Adverse Effects of Common Over-the-Counter Enzymes**

| Name         | Common indication   | Dosage                                       | Potential adverse effects  | Potential drug interactions   |
|--------------|---|--|--|---|
| Bromelain    | Acute postoperative and posttraumatic conditions of swelling, burn débridement, anti-inflammatory action, allergic rhinitis | Up to 400 mg/d PO                            | Gastrointestinal cramping, diarrhea, IgE-mediated allergic reactions | Moderate interaction with amoxicillin and anticoagulant or antiplatelet drugs |
| Papain       | Posttraumatic and postoperative inflammation, digestive aid, pharyngitis, herpes zoster symptoms, chronic diarrhea          | Up to 1500 mg/d PO                           | Esophageal perforation, gastritis, allergic reactions                | None known  |
| Trypsin      | Digestive enzyme supplementation, osteoarthritis, topically for promoting normal wound healing                              | Up to 50 mg, usually combined with bromelain | Localized pain and transient burning                                 | None known  |
| Chymotrypsin | Reducing inflammation and edema associated with abscesses, ulcers, surgery, or traumatic injuries                           | Up to 100,000 U USP, 4 times daily PO        | Anaphylactic reaction (rare)   | None known  |

PO = per os (by mouth); USP = United States Pharmacopeia.

results are not necessarily applicable to the typical OTC enzyme supplements. Current evidence does not permit endorsement of the use of supplemental enzymes to treat common gastrointestinal tract symptoms, such as bloating, gas, and irritable bowel syndrome.

### Do Oral Enzyme Supplements Reach the Bloodstream?

For enzyme supplements to have an effect on systemic symptoms, such as those in OA, rheumatoid arthritis, or muscle soreness, the intact enzyme must reach the joints or muscle tissue after absorption from the gastrointestinal tract. Enzymes (proteins), if not enterically coated or supplemented with a proton pump inhibitor or histamine blocker, would essentially be denatured in the acidic environment of the stomach. However, some evidence suggests that undegraded protein can be detected in the plasma after oral intake. In a study of 19 volunteers, the permeability of the intestinal mucosa for large protein molecules was studied using bromelain as the model enzyme; small amounts of bromelain were detected in the plasma, with part of its enzymatic activity retained.<sup>10</sup> Another double-blind multicenter trial of immunocompetent patients with herpes zoster showed the effectiveness of OTC enzymes in decreasing acute pain after oral ingestion.<sup>11</sup>

### ENZYME SUPPLEMENTS AND INFLAMMATION

The purported ability of OTC enzymes to suppress inflammation and edema may stem from their proteolytic properties. One study reported

a reduction in edema and improved healing with bromelain.<sup>12</sup> In animal models, the combination of oral trypsin and bromelain was shown to be superior to the single enzymes.<sup>13,14</sup> Some evidence suggests that its effects on blood coagulation and prostaglandin levels is vital for decreasing inflammation.<sup>10</sup> In another study, in vitro treatment of human peripheral blood mononuclear cells with bromelain, papain, and amylase resulted in the production of large amounts of TNF- $\alpha$ , IL-1 $\beta$ , and IL-6. Interferon- $\alpha$  and interferon- $\gamma$ , which had no effect alone, synergistically increased TNF- $\alpha$  production when applied together with the enzymes.<sup>6</sup> Further large-scale studies are required before existing treatments can be replaced. Thus, with the current evidence, it is unclear whether OTC enzymes are anti-inflammatory or proinflammatory.

### Do OTC Enzyme Supplements Improve the Symptoms of OA?

In laboratory studies, enzyme supplements seem to have anti-inflammatory properties, making them at least a plausible candidate to help with the symptoms of OA.<sup>14</sup> Recently, a randomized prospective trial compared a commercial enzyme preparation containing bromelain, trypsin, and rutin with diclofenac in the treatment of 73 patients with OA of the knee joint. The commercial enzyme preparation significantly reduced pain indices (80% after 3 weeks' treatment) compared with diclofenac. This effect was sustained for 4 weeks after completion of the drug phase of the study. Furthermore, the commercial enzyme had

lower rates of adverse events and withdrawal and was better tolerated overall compared with diclofenac.<sup>15</sup> In a subsequent study of the same combination product, patients with symptomatic OA of the knee were randomized to receive either an oral enzyme-flavonoid preparation or a nonsteroidal anti-inflammatory drug for 6 weeks.<sup>16</sup> Both groups demonstrated reduced pain and improved joint function, but the enzyme-flavonoid product seemed to be slightly more effective. No serious adverse events were reported. The OTC enzymes may have a clinical role in improving symptoms of OA, but larger studies are needed to confirm these effects.

### **DO OTC ENZYME SUPPLEMENTS IMPROVE MUSCLE SORENESS IN ATHLETES?**

Evidence regarding the effectiveness of OTC enzymes in improving muscle soreness is contradictory. A study of 20 healthy men aged 18 to 29 years showed that protease supplements hasten the recovery of contractile capabilities and attenuate perceived increases in pain after downhill running.<sup>4</sup> Another trial showed effectiveness in reducing the pain and swelling associated with various injuries and hastening of the healing process.<sup>17</sup> However, a double-blind randomized controlled trial with 40 participants showed no difference between bromelain and placebo in treating delayed-onset muscle soreness.<sup>18</sup> A subsequent double-blind trial of 50 individuals with soft-tissue ankle injuries showed, on average, no significant difference in swelling, bruising, and function in the group given oral proteolytic enzymes vs enteric-coated lactose tablets.<sup>19</sup> Currently, evidence of OTC enzymes improving muscle soreness in athletes is insufficient.

### **ENZYME SUPPLEMENTS AND CANCER**

Many OTC enzyme studies related to cancer focus on decreasing the complications of therapy, not on the effects on the disease process itself. Several studies have claimed that OTC enzymes improve the complications associated with chemotherapy, but these studies either were not statistically analyzed or did not show significant improvement with OTC enzymes.<sup>20-22</sup> For example, a retrospective study reported that complementary treatment with OTC enzymes improved quality of life for patients with colorectal cancer by reducing signs and symptoms

of disease and reducing adverse reactions associated with adjuvant antineoplastic therapies.<sup>21</sup> However, a randomized controlled trial of prophylactic treatment with proteolytic enzymes to reduce the acute toxic effects of adjuvant pelvic radiotherapy showed no reduction in acute toxic effects. Furthermore, it did not improve tolerance to adjuvant pelvic radiotherapy.<sup>22</sup> An *in vitro* study investigated the effects of exposing polymorphonuclear cells to a combination product of bromelain and papain and reported a time-dependent and statistically significant increase in the release of reactive oxygen species.<sup>23</sup> In another study, long-term rectal administration of an enzyme mixture containing papain, trypsin, and chymotrypsin in a 1:1:1 ratio was evaluated for antitumor effects in mice inoculated with melanoma cells. Thirty percent of the animals in the test group were reported to be cancer free.<sup>24</sup> One retrospective study reported increased survival of patients recovering from multiple myeloma who were receiving additive therapy with an oral enzyme for more than 6 months.<sup>20</sup> To our knowledge, no published study explains the mechanism of action of OTC enzymes in patients with cancer. Although the effects of OTC enzymes on various cytokines and serine and cysteine proteinases have been proposed by many authors, none have been validated through clinical studies.

### **WHAT ARE THE RISKS OF ENZYME SUPPLEMENTATION?**

The risks associated with enzyme supplement use generally seem to be low. However, because these products are sold as dietary supplements, they may include various contaminants, and the actual amount per dose may vary among different brands. Their interactions with other substances or drugs also are not well understood. Fibrosing colonopathy is a rare but potentially severe complication of prescription enzyme supplementation in children with cystic fibrosis.<sup>25</sup> Oral bromelain may cause gastrointestinal tract disturbances or diarrhea. Immunoglobulin E-mediated allergic reactions to bromelain may occur and include a cross-allergenicity between bromelain and wheat flour. In excessive doses, papain can cause clinically significant adverse effects, such as esophageal perforation. Raw papain or papaya latex is a severe irritant and vesicant. Little is known about the adverse effects of

trypsin, but topical application may cause localized pain and transient burning.<sup>3</sup> Rare reports of anaphylaxis have been associated with oral chymotrypsin. General gastrointestinal tract discomfort has been commonly noted with OTC enzymes, especially with increased dosage. Pregnant and lactating women are advised to consult doctors before taking these products.<sup>3</sup>

### COUNSELING PATIENTS WHO INTEND TO USE ENZYME SUPPLEMENTATION REGARDLESS OF THE EVIDENCE

Despite the absence of robust clinical trial data supporting the use of supplemental enzymes, many patients still want to try them, especially because product marketing seems to be increasing. Given the general safety profile of these products (when used according to manufacturer directions), the overall risk for personal trials is probably low. Health professionals should advise patients who are embarking on a trial of enzyme supplements (or who are currently using them) to be aware of potential adverse effects on the gastrointestinal tract and the need to discontinue use should they occur. For patients who insist on using OTC enzymes, physicians should counsel them on a time-limited personal trial approach. This would encourage discontinuation of the product if there is no significant improvement of their symptoms. In addition, health professionals can advise patients to not give OTC enzymes to children with cystic fibrosis.

### CONCLUSION

The use of enzyme supplements in general seems to be increasing in the United States, both by patients seeking to treat conditions or symptoms and by consumers seeking to enhance general health. The historical and preclinical data on enzymes are intriguing regarding digestion, anti-inflammatory effects, and anticancer properties. Emerging clinical data seem to support many of these purported benefits. However, as with many dietary supplements, the existing research is generally challenged by methodologic weaknesses, small sample sizes, heterogeneity of product, and lack of uniform outcome measures. Thus, well-designed studies with sufficient power are critically needed to further characterize the proper role of enzyme supplements in health promotion and disease treatment.

**Abbreviations and Acronyms:** IL = interleukin; OA = osteoarthritis; OTC = over the counter; TNF = tumor necrosis factor

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