ABSTRACT:
Millions of patients worldwide with chronic musculoskeletal symptoms are on long term therapy with non-sterooidal anti-inflammatory drugs (NSAIDs). But the unfortunate fact is that these drugs have common and potentially severe adverse effects, including renal impairment, gastrointestinal complications and cardiotoxicity. The cardiotoxic effect produced by these drugs is particularly worrying because many patients have both cardiovascular disease and musculoskeletal disease. Clinicians and medical researchers worldwide are in general agreement that pharmacologic pain treatment for musculoskeletal conditions is unsatisfactory and the irrational use of NSAIDs in such conditions is adding the agony of the patients. Thus new drugs are needed to replace NSAIDs to treat musculoskeletal diseases. Newer natural and safer alternatives identified in recent past are Bromelain, Trypsin and Rutoside. Their combination to treat inflammatory diseases is a coming out with promising results.

Key-Words: Trypsin, Rutoside, Bromelain, Anti-Inflammatory

INTRODUCTION:
The most common reason for people seeking the advice of health professionals is that they are in some sort of pain. In general, pain is symptom of some form of dysfunction and resultant inflammatory processes in the body.

Many drugs are available that help to reduce inflammation and relieve pain. They act by interfering with the body’s natural inflammatory response mechanisms; however their chronic use may lead to side effects.

Over the past few years research suggest role for more natural and safe alternatives for the management of pain and inflammation. Some areas of research include supplemental essential fatty acids, herbs such as ginger, turmeric, and boswellia, proteases (trypsin, bromelain) and bioflavonoids (rutoside).

Recent clinical studies show that the Bromelain, Trypsin and Rutoside fixed dose combination to be a very potent and safe in relieving oedema, inflammation and promoting wound healing.

The individual therapeutic role of these natural substances was established long back in 1960s but in recent years further clinical studies were done to prove this role more substantially and now there is sufficient evidence that the combination of Bromelain, Trypsin and Rutoside has a significant implication in alleviate oedema and inflammation.

In this article the anti-inflammatory activity of Bromelain, Trypsin and Rutoside as individual drugs and their fixed dose combination has been discussed.

TRYPsin:
Trypsin is produced in the pancreas in the form of the inactive zymogen trypsinogen. When the pancreas is stimulated by cholecystokinin, it is then secreted into the duodenum via the pancreatic duct. Once in the duodenum, the enzyme enteropeptidase activates it into trypsin by proteolytic cleavage. Trypsin in the duodenum catalyses the hydrolysis of peptide bonds so that proteins can be broken down into smaller peptides.

Clinical studies exhibit that the anti-inflammatory effect of trypsin is possibly due to inhibitory action on the vascular permeability and its ability to inhibit the rise in C-reactive protein and enhance the rise in alpha 1-antitrypsin, alpha 2-macroglobulin. Trypsin-chymotrypsin has also been shown to modulate cytokine levels in burns.

BROMELAIN
Bromelain is a crude extract from the pineapple that contains, among other components, various closely
related proteinases, demonstrating, in vitro and in vivo, antiedematous, antiinflammatory, antithrombotic and fibrinolytic activities.\textsuperscript{12}

Bromelain when applied topically as a cream (35% bromelain in a lipid base) is beneficial in the elimination of burn debris and in acceleration of healing.\textsuperscript{13} Several groups have provided significant evidence for both the edema-protective and edema-reducing efficacy of bromelain in various animal experiments.\textsuperscript{14}

Bromelain is used as an anti-inflammatory and analgesic agent in treating the symptoms of arthritis.\textsuperscript{31-33} The analgesic and anti-inflammatory effects are reportedly due to inhibition of the arachidonic acid pathway of inflammation by selectively decreasing thromboxane generation, changing the ratio of thromboxane/prostacyclin (in favor of prostacyclin), and inhibiting PGE2 in addition to the direct effects on the nociceptors.\textsuperscript{15,16} Other reported anti-inflammatory mechanisms of action of bromelain include inhibition of bradykinin at the site of inflammation via depletion of the plasma kallikrein system, and limiting the formation of fibrin by reduction of clotting cascade intermediates.\textsuperscript{17,18} A few clinical trials in patients with arthritis reported statistical equivalence of pain reduction, whether they were treated with bromelain or diclofenac.\textsuperscript{19}

**Rutoside**

Rutoside is a natural flavone derivative. It has anti-inflammatory, anti-allergy and immunomodulating activity.\textsuperscript{20} Rutoside inhibits platelet aggregation, as well as decreasing capillary permeability, making the blood thinner and improving circulation. Rutin also strengthens the capillaries. It helps to prevent venous edema of the legs. Thus, rutoside is useful in the management of venous edema and capillary fragility.\textsuperscript{21}

Rutoside is a powerful anti-oxidants and effectively combat the harmful free radicals such as nitric oxide, released during the inflammatory process.\textsuperscript{22,23}

Rutoside also suppresses the major inflammatory and proarthritic mediators of macrophages.\textsuperscript{24} The ability of Rutoside to decrease MCP-1 levels in vivo and in vitro may add to its beneficial effects because this cytokine is a potent stimulator of monocyte recruitment into the site of inflammation.\textsuperscript{25} Rutoside also inhibit the phosphorylation and activation of Jun N-terminal kinase/stress-activated protein kinase, leading to the suppression of AP-1 activation. They also decrease the activation of NF-κB in both human and experimental models.\textsuperscript{26,27}

**COMBINATION OF TRYSPIN, RUTOSIDE AND BROMELAIN**

Combination of Trypsin, Rutoside and Bromelain has shown to have significant anti-inflammatory effects in several clinical studies. However, the combined mechanism of action of these agents is not clear and need to be explored further.

In a clinical study conducted in 2004, the efficacy of an enzyme-flavonoid mixture was compared with diclofenac, a prescription NSAID.\textsuperscript{28} The proteolytic enzymes used were bromelain and trypsin. These three agents were used in the form of an enteric-coated tablet (to prevent the enzymes from being destroyed by stomach acid) that contained 90 mg of bromelain, 48 mg of trypsin, and 100 mg of rutoside.

For the 6-week trial, the researchers recruited 103 middle-aged patients who had painful osteoarthritis of the knee with a disease flare in one knee joint. The results showed that diclofenac and the bromelain/trypsin/rutoside mixture were about equally effective in relieving the patients’ pain and improving their mobility, with no serious adverse events in either case.\textsuperscript{28}

In another clinical study conducted in 2006, the Phloenzym- (PE-fixed dose combination of trypsin, bromelain and rutoside) was compared to the non-steroidal anti-inflammatory drug (NSAID) diclofenac in patients with osteoarthritis of the hip. After six weeks of observation this trial showed significant non-inferiority from 6 weeks treatment with PE in patients with osteoarthritis of the hip and with regard to drug tolerability some tendencies in favour of PE. Thus, PE may well be recommended for the treatment of patients with osteoarthritis of the hip with signs of inflammation as indicated by a high pain level.

**CONCLUSION**

Over the past many decades anti inflammatory drugs NSAIDs are being used very extensively all over the world but their chronic use may lead to side effects such as gastric ulcers and liver- kidney damage. After bitter experiences with NSAIDs like Rofecoxib and Valdecoxib, virtually all NSAIDs come with a warning about potential increased risks of heart attack and stroke with their use. A recent study on the cardiovascular safety of NSAIDs has highlighted further evidence that diclofenac is associated with cardiovascular risks that are higher than the other non-selective NSAIDs, and similar to the selective COX-2 inhibitors.\textsuperscript{30} Thus their frequent use is not recommended. Another group of drugs used in severe inflammatory conditions are steroids that contribute to even more severe and serious adverse effects on long-term use.

Considering these facts, the use of drugs of natural origin with lesser hazards is a positive alternative. Bromelain, Rutoside and Trypsin are known to have a very promising role in relieving inflammation and promote wound healing and based on the clinical studies performed on their combination, the Bromelain, Rutoside and Trypsin combination might be a safer alternative in comparison to other drugs used for these conditions. Although further studies need to be done to determine how each individual drug affects the activity of another two ingredients in this combination.
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