Enzymes have aptly been called the “Fountains of Life”. They are biological catalysts that are ubiquitously found in nature and are responsible for the myriad reactions taking place in our bodies. Not only do they orchestrate the break down of complex molecules into simple molecules useful to our body, but they also regulate and control each and every process that keeps the body functioning harmoniously.

Consequently, their therapeutic applications are equally varied and as far-reaching, from digestive aids and nutritional supplements to treatment of pancreatic insufficiency in diseases such as chronic pancreatitis and even for the lysis of blood clots especially for treating cardio vascular diseases (streptokinase, tissue plasminogen activator, urokinase).

The following article takes a look at some of the varied applications of enzymes as therapeutic molecules.

Enzyme therapy is not new to us. Several evidences show that it has been in practice since times ancient. Enzyme Therapy began with using enzymes from plants for curing certain ailments. The enzymes papain, from the papaya plant *Carica papaya* and bromelain from the pineapple plant *Ananas comosus* have been put to multiple uses: as a digestive aid, as a cleansing agent to improve the texture of the skin and even to promote the healing of wounds (Kelly et al 1996). The enzyme ficin obtained from the fig plant has been employed for treating cancer for several years. This has been documented in the Bible (Second book of Kings, Chapter 20, Verse 7). In Europe, during the Middle Ages, early forms of enzyme therapy were practiced, in which topical enzyme preparations were used to heal ulcers and warts.

After plant based enzymes, people turned to enzymes of animal origin. Beginning in the 1900s, proteolytic enzyme extracts of pancreas (pancreatin) were used systemically with some success for treating certain cancers. In the early 1950s it was discovered that intravenous trypsin was capable of relieving the symptoms of many different inflammatory conditions.

Later on combination of enzymes came into use. Pancreatic enzymes were added to mixtures of enzymes from plant origin. Initially enzyme therapy was followed empirically but over the years systematic scientific work has lead to elucidation of mode of action so as to support applications (Kelly 1965).

Since non-invasive routes of administration of drugs are preferred over invasive routes, soon, the possibility of developing oral formulations of proteolytic enzymes was explored. It is essential that any enzyme preparation be properly enterically coated so as to release the enzymes in the intestines, where they can be absorbed and not in the stomach where they can be degraded. Around 35 years ago it was shown that enterically coated enzymes are equally useful.

What evolved was the Modern Day Systemic Enzyme Therapy, which involves oral administration of high doses of mixtures of enzymes from plant, animal and microbial origin. Some of these enzyme blends include other constituents such as anti-oxidants as well.
Effects of enzymes shown by Dr Wolf and Dr Benitez, pioneers in Enzyme Therapy

- Reduced swelling and inflammation
- Enhanced immune function
- Improved circulation
- Reduction in pain
- Strengthen connective tissue
- More rapid recovery from traumatic injury
- Minimal scar formation
- Prevention of serious consequences of injury
- Management of rheumatic diseases, such as rheumatoid arthritis, soft tissue rheumatism and ankylosing spondylitis

Enzymes as digestive aids and dietary supplements:

The natural production of enzymes slows down as the body ages. Hence, enzymes such as trypsin and chymotrypsin or pancreatin are given as digestive aids or supplements to boost up the enzyme levels and consequently metabolism and repair. They are also given in case of diseased conditions such as chronic pancreatitis.

Enzymes for cardiovascular disease

Conventionally, streptokinase and tissue plasminogen activator or urokinase are being used as fibrinolytic agents following heart attack. The ability of other proteolytic enzymes such as serratiopeptidase and bromelain (Kelly et al 1996) to bring about fibrinolysis and digest arterial plaque makes them attractive molecules for cardiovascular disease. The enzyme serratiopeptidase is also anti-inflammatory. It acts as a blood thinning agent without the side effects of conventional drug thinning agents like Aspirin. Bromelain is also a blood thinning agent and has been found useful for cardiovascular disease such as angina pectoris and coronary heart disease. Bromelain is known to influence blood pressure and heart rate (Gutfreund A E et al 1978; Nieper et al 1978).

Enzymes as mucolytic agents:

Proteolytic enzymes like bromelain and serratiopeptidase have shown mucolytic activity and thus have found use in treating respiratory tract diseases such as asthma, sinusitis and bronchitis. (Kase et al 1982)

Enzymes as NSAIDS (non steroidal anti inflammatory drugs), as healing agents:

The anti-inflammatory activity of proteolytic enzymes such as bromelain and serratiopeptidase has been attributed to several mechanisms. They can reduce the swelling on mucous membranes, decrease capillary permeability, dissolve blood clot-forming fibrin deposits and microthrombi. Enzymes reduce the viscosity of the blood and thus improve circulation. This consequently increases the supply of oxygen and nutrients to traumatized tissue, at the same time transporting harmful waste products away from it. Bromelain has been shown to inhibit platelet aggregation by using in vitro and in vivo models (Kelly 1996). Proteolytic enzymes also help break down plasma proteins and cellular debris at the site of an injury into smaller fragments facilitating their passage through the lymphatic system and resulting in
more rapid resolution of swelling. The net result is relief of pain and discomfort. Comparative studies in animal models for anti-inflammatory action of proteolytic enzymes with standard drugs such as phenylbutazone, hydrocortisone, indomethacin, and acetylsalicylic acid (aspirin) revealed that the enzymes were on par with the standard drugs and at times even superior (Netti et al 1972).

Due to the above properties, enzymes act as excellent healing agents for minor musculoskeletal injuries, and accelerate recovery in surgeries and burns. This has been proven especially in case of bromelain (Levenson S 1979; Masson M 1995). Proteolytic enzymes have been of particular use to sportsmen for reducing bruising, swelling, pain and discomfort and improving healing thereby putting athletes back in action. Studies were conducted in Germany on hockey players and skiers to prove this and the enzyme formulations proved to be far more effective than non-steroidal anti-inflammatory drugs (NSAIDS) like ibuprofen and aspirin (Muller-Hepburn 1979).

**Enzymes as analgesic agents:**
It is also thought that the analgesic effect of the above proteolytic enzymes is due to their cleavage of bradykinin, a messenger molecule involved in pain signaling. However, according to another theory, peptidases such as trypsin may be acting not as anti-inflammatory agents but rather as accelerants of the inflammatory process, thereby shortening its duration (Kelly et al 1996).

**Enzymes as novel antimicrobial agents:**
Overuse and misuse of antibiotics is leading us towards a world in which there would be no effective treatment available for the very infections that were once upon a time curable. Besides, the steadily emerging antibiotic resistance, antibiotics have other limitations such as numerous side effects and toxicities. Therefore, there is a constant need for looking for new antimicrobials to combat these limitations.

Proteolytic enzymes are indeed quite amazing. They have been found to be useful against certain bacterial infections. Bromelain (Chandler et al, 1998; Mynott et al 1997), papain and trypsin inhibit the growth of pathogens. Also, bromelain (Taussig et al 1988), serratiopeptidase (Aratani et al 1980), trypsin and chymotrypsin are known to increase the bioavailability of antibiotics: when combined with antibiotics enzymes can increase the concentration of the drug at the site of infection leading to rapid control of infection (Kelly et al 1996). Synergistic action of enzyme – antibiotic mixtures could be an answer to the several problems associated with antibiotic therapy (Selan et al 1993). This was proved using proteolytic enzymes in conjunction with different antibiotics such as Ampicillin, Tetracyclines, Trimethoprim etc. Enzyme – antibiotic combinations have proved to be of particular use for treatment of urinary tract infections (Mori et al 1972). Proteolytic enzymes also have activity against the otherwise difficult to treat fungi. Antiviral activity of different enzymes has been recorded.

At last, do we have an answer to the escalating drug resistance problems associated with bacteria, fungi and viruses?

**Enzymes as immunomodulators:**
Enzymes are an indispensable part of the regulatory mechanisms involved in the Immune System of our body. It has been found that enzymes can act as wonderful
immunomodulators. They play a significant role in inflammation and other processes of the Immune System. They are known to induce or enhance the production of cytokines such as tumour necrosis factor, interferon (IFN-γ), interleukins such as IL-1, IL-6 (Desser et al 1994). They are known to bring about an increase in the phagocytic activity of macrophages and in the potency of NK cells. Enzymes bring about proteolytic modification of cell-surface adhesion molecules, which play an important role in auto-immune diseases such as arthritis and guide inflammatory cells to their targets (Kelly 1996).

Circulating immune complexes are the primary causes of auto-immune diseases such as rheumatoid arthritis, glomerulonephritis, type 1 diabetes, multiple sclerosis etc. Proteolytic enzymes such as bromelain, trypsin, chymotrypsin and papain are capable of preventing the formation of such complexes, facilitate the breaking up these complexes enhancing their lymphatic drainage (Roep et al 2002; Leipner et al 2001).

**Enzymes as novel anticancer agents:**

Studies have shown that enzyme therapy can reduce the adverse effects caused by radiotherapy and chemotherapy. The survival of patients with certain types of tumours may be prolonged with systemic enzyme therapy along with quality of life. Although, the exact role of enzymes is not clear, the beneficial role of enzymes has been attributed to the anti-inflammatory property of enzymes. Other possibilities include digestion of adhesion molecules present on tumour cells and a possible role in differentiation of tumour cells. In general, proteolytic enzymes have been suggested as complementary therapy with the usual chemotherapeutic practices. (Batkin et al 1988; Leipner et al 2000)

**Safety issues and enzymes:**

The long-term safety of enzyme supplements has been explored in great details. The result is that enzymes are generally found to be highly safe and no toxic limit no matter how much you take or how long you take them. It is the lack of enzymes that causes problems, not taking too many. Enzyme action is highly specific and is well known and well characterized. Each enzyme has its own specific role and activity and has typical biochemical properties. Therefore there are few side effects. Healthy tissues and cells have natural mechanisms protecting them from enzyme action. The body is full of checks and balances including plenty of enzyme inhibitors, which allow the enzymes to function properly without self-digestion. Enzymes are used for wound healing because they selectively degrade dead tissue and infected tissue while leaving the healing tissue growing. Enzymes are used to remove tumours: they attack the cancerous tissue and remove it while facilitating growth of healthy tissue. This built-in natural selective property of enzymes can be seen on surface wounds and tumours (Enzyme Therapy, Max Wolf). No known toxicity at any level of enzyme dosing in animal / human studies has been recorded. Animals survived large quantities of enzymes without damage so it has been impossible to find LD 50. Rats fed with human doses have shown no ill effects (Taussig and Batkin 1988; Kelly 1996).
Novel enzyme based formulations:

Industrial Enzymes are being manufactured in India for a long time. The size of the Industrial enzymes market in 2003-2004 was approximately Rs 250 crore and was growing at a rate of 20-25% (BioSpectrum, 3 (5), May 2005). Advanced Enzyme Technologies Ltd. (ABL), Thane is a leading manufacturer of enzymes in India manufacturing enzymes from different sources viz., animal, plant and those obtained by microbial fermentation. These include papain, bromelain, serratiopeptidase, trypsin, chymotrypsin, fungal proteases and many more. Amongst the wide array of enzymes made by ABL, digestive and anti-inflammatory enzymes are the main types of enzymes that find their way into the formulations made by different pharmaceutical companies in India. ABL has hence largely been a bulk supplier of these two categories of enzymes to Pharma companies.

ABL is now all set to broaden its horizons.

Currently, in ABL’s R&D cauldron, work is on at a heady level to bring out novel polyenzyme blended herbal products that can boast of much greater efficacy than conventional enzyme blended allopathic products. In fact, nine products are ready and have been going through extensive testing. These products are novel anti-inflammatory, antipyretic, analgesic, immunomodulatory formulations, broad-spectrum antimicrobials including antibacterial, antifungal and antitubercular formulations and anticancer agents with no toxicities or side effects.

The result would be the development of remedies that are closer to nature, which overcome the problems posed by conventional therapy and yet are equally effective and safer; leading us to the betterment of human life.

References:


