An Overview of Systemic Enzyme Therapy and Serrapeptase

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Abstract
The reliance on prescription medication has increased over the past few decades. There currently exists a widespread use of prescription pain medication such as opioids along with an increase in opioid related deaths. Patients and physicians are seeking safe, non-addictive methods to reduce the reliance on prescription medication. Systemic enzyme therapy may present a potential alternative to prescription pain medications. The purpose of this review was to discuss the effectiveness of systemic enzyme therapy as a natural method of therapy. The method used was a systematic review from a database including CINAHL, PubMed, Science Citation Index, resulting in relevant peer-reviewed journal articles pertaining to the effectiveness of systemic enzymes for therapeutic effects in the body. The study eligibility criteria included placebo controlled, double-blind, and randomized controlled trials with a statistically significant samples size. The research question focused on the effectiveness of the systemic enzyme serrapeptase as therapy for natural healing effects in the body. Results of the review assessed the use of systemic enzymes for anti-inflammatory and fibrinolytic properties with demonstrated validity of the serrapeptase enzyme as therapy for natural healing. Conclusions determined the benefits of enzyme therapy were examined in the context of anti-inflammatory and fibrinolytic effects and conclusions reached determining the healing effects of the body. Primary sources had Institutional Review Boards or Independent Ethics Committees which reviewed the methods and followed best practices.

Keywords: anticoagulant, anti-inflammatory, enzyme therapy, fibrinolytic, serrapeptase, serrati peptidase
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An Overview of Systemic Enzyme Therapy and Serrapeptase

Chapter 1

Introduction

Statement of the Problem

The reliance on prescription medication has increased dramatically over the past decades (Kallivayalil, 2008). For example, there exists widespread use of prescription pain medication such as opioids. Opioid pain medication related deaths have also been increasing rapidly. Records show a four-fold increase in the number of deaths due to opioids overdose in a 15 year period (CDC, 2016). Patients and physicians are seeking safe, non-addictive methods to reduce the reliance on prescription medication (Davuluri & Dharmarajan, 2014). It seems that as a result of opioid deaths, patients are simply desiring a safer method for pain relief such as provided by some contemporary alternative medicines (Barry, Savant, Beitel, Cutter, Moore, Schottenfeld, & Fiellin, 2012). Similarly, physicians are also trying to avoid the potential liability of deaths caused by opiate analgesics. The opiate analgesic class of drugs are the most likely to cause prescription medication abuse and addiction (Fields, 2011). In addition, patients are looking into enzyme therapy as alternative medicine and literature shows there are benefits of enzyme therapy (Chandanwale, Langade, Sonawane, & Gavai, 2016).

Systemic enzyme therapy is the therapeutic use of natural enzymes for their desired healing effects in the body (Noriega, Yang, Alvarez, & Rathi, 2015). Evidence in the form of research and clinical study exists for the benefits of enzyme therapy (Kotb, 2014). The difference between traditional use of opioids and alternative medicine such as enzyme therapy is that enzyme therapy uses a protein-based approach that will not cross the Blood Brain Barrier (BBB). Opioids use small-molecule compounds that cross the BBB and reach the central
nervous system (Zheng & Zhan, 2011). If a small-molecule compound crosses the BBB, neuroanatomical progression reaches to areas in the brain including the nucleus accumbens and dorsal striatal. These areas are the reward pathways of drug-seeking behavior. When the reward pathways can be reached, the propensity for abuse and addiction is increased (Gardner, 2011). Initiating a single day’s supply of opioids can result in 6 percent of the opioid initiating patients being on an opioid a year later, and the rate of long-term opioid use increases to about 13% for patients who used opioids for more than eight days (Hooten et al., 2015).

**Purpose of this Review**

The purpose of this systematic review is to discuss the effectiveness of systemic enzyme therapy with a focus on the anti-inflammatory benefits of the serrapeptase enzyme. This review also discusses the misuse of opioids for inflammatory conditions. There are many people suffering from the conditions of pain associated with chronic inflammation. Approximately 20% of the U.S. population is affected by pain lasting at least 6 months (Edlund et al., 2010). Also, approximately 19.3 million patients in the United States show incidents of chronic inflammation (El-Gabalawy, Guenther & Bernstein 2010). The symptoms of inflammation present as pain, redness, heat, and swelling. One of the most common symptoms of inflammation is pain. Many people attempt to relieve chronic pain with opioids and often become addicted. In comparison, there exists evidence of a natural, non-addictive alternative to relieving pain associated with chronic inflammation that is not harmful to the organs. This review discusses such an alternative, specifically the effectiveness of the enzyme serrapeptase as an anti-inflammatory that may also relieve chronic pain.

Disease related topics covered in this paper include the symptoms, conditions, and disorders affected by inflammation. Chronic inflammation is the leading cause of many
diseases, and results in excess fibrin buildup (Cooper, 2000). One of the symptoms of chronic inflammation is pain resolved with the use of opioids and natural methods such as the use of enzyme therapy and serrapeptase. The use of opioids for pain may be effective, but they do not treat inflammation. In a 10-year study, despite long-term opioid use, inflammation in patients persisted. This is evidenced by the increased inflammatory markers called C-reactive proteins (CRP) and erythrocyte sedimentation rate (ESR), in the patients (Tennant, 2013).

The inflammatory disease conditions and disorders also covered in this paper include excessive mucus production, breast tenderness, edema, carpal tunnel, superficial thrombophlebitis, cancer, and diabetes. Other topics discussed will include existing anti-inflammatory and fibrinolytic medications, anti-coagulation and anti-scarring properties and anti-inflammatory and fibrinolytic activity of the serrapeptase enzyme.

**Background**

**Enzymes.** This chapter discusses what enzymes are, the main types of enzymes and the enzyme relationship to the research review study. Enzymes are a substance produced by a living organism acting as a catalyst to bring about a specific biochemical reaction. The enzyme structure is a protein acting as a catalyst to increase the rate of most chemical reactions within cells. Most biochemical reactions are so slow that without the catalytic action of enzymes, they would not occur to support life. Enzymes accelerate the rates of such reactions over a million times. With the right enzymes, reactions that would take years can occur in fractions of seconds. Biological cell activity determines which of the chemical reactions take place inside the cells containing of different enzymes (Cooper, 2000).

Enzymes are molecular catalysts of biological systems determine the patterns of chemical transformations. Most reactions in biological systems do not take place in the absence of
enzymes. Enzymes also regulate energy transformation in the cells (Kamerlin & Warshel, 2010). A unique characteristic of enzymes are their catalytic power that increase the rate of a chemical reaction with a specific active site of a protein. The enzyme may be part of a complex or may interact with a Cofactor. Catalysis of biochemical reactions in the cell is vital because of the very low reaction rates of the un-catalyzed reactions (Berg, 2002).

**Types of Enzymes.** There are two types of enzymes, digestive and systemic enzymes. Digestive enzymes differ from Systemic Enzymes in that the main catalytic activity occurs in the gastrointestinal (GI) system, rather than absorbed into the bloodstream. Digestive enzymes are able to break down proteins, carbohydrates and lipids. Digestive enzyme supplementation may assist in the management of digestive disorders. Digestive enzymes are produced by the GI system to degrade and absorb fats, proteins, and carbohydrates as nutrients. Digestive enzymes are found in different areas of the body including the saliva, linings of the stomach, and in pancreas secretions. Digestive enzymes of the pancreas can be further subdivided into three groups, according to their respective function: proteolytic enzymes, such as trypsin and chymotrypsin, amylolytic enzymes such as amylase, and lipolytic enzymes such as lipase. Sources of digestive pancreatic enzymes can be found both endogenously (in the body) and exogenously, for example, extracted from bovine sources. Lipase may also be synthesized from microbial sources. The advantages of microbial enzymes are the requirement of a lower dosage to be effective and a broader pH range of activity than animal-based enzymes (Ianiro, 2016).

Systemic enzymes are consumed orally, absorbed through the small intestine, and go into the bloodstream. Systemic enzymes are enteric coated in order to bypass the acidity of the stomach. Through the small intestines, systemic enzymes travel throughout the circulatory system targeting tissues and organs. Systemic enzymes are metabolized in the liver and kidney
for excretion. Systemic enzymes work by targeting areas of inflammation in the body to help in the healing process. The therapeutic use of natural enzymes for their healing effects in the body describes systemic enzyme therapy. There are several systemic enzymes such as bromelain, papain, nattokinase and lumbrokinase, however this research paper focuses on serrapeptase because of the numerous clinical studies of the effect of serrapeptase on inflammation (Viswanatha & Patil, 2008). Serrapeptase is a proteolytic enzyme that breaks down protein, targeting areas of inflammation to help in the therapeutic effects of healing.

**Serrapeptase Enzyme.** For purposes of this review, Serrapeptase will also be referred to by names the enzymes is also known by such as Serratiopeptidase, Serratia E-15 protease, and chemical names such as serrati peptidase, serrati E-1 protease, serralysin, serratiapetase, serratia peptidase, serratio peptidase, or serrapeptidase. Serrapeptase is an enzyme that acts on inflammation by thinning the fluids in the body that collect around injured areas and increases fluid drainage. This thinning and drainage effect enhances tissue repair and reduces pain. Pain is also reduced by the ability to block amines. Fibrinolytic properties of serrapeptase include the ability to dissolve the dead and damaged tissue without harming living tissue. This process is part of the healing response. Serrapeptase also works by modifying cell-surface adhesion molecules that are known to affect the development of arthritis and other autoimmune diseases. Modifying the cell-surface adhesion guides inflammatory cells to their targets to mitigate the development of such diseases (Klein & Kullich, 2000).

In various areas of clinical research, the role and benefits of serrapeptase includes enhancing blood circulation, removing cellular debris, and modulating inflammatory cytokines. (Mazzone et al., 1990). There are health benefits to serrapeptase modulating inflammation. When inflammatory cytokines are not controlled, it can increase inflammation in isolated parts of
the body that increases pain and disrupts the quality of life. Inflammatory cytokines can also increase chronic inflammation and may cause the onset of disease. An increasing amount of clinical evidence shows chronic inflammation causes and advances many common diseases (Hunter, 2012). This is an important area in enzyme therapy, in that orally administered proteolytic enzymes can be utilized to control the inflammatory cytokines, prevent further damage, and prevent the onset of chronic inflammation related disease.

**Statement of the Hypotheses**

If the systemic enzyme serrapeptase is effective for natural healing effects in the body, then it may provide an alternative to the abuse and addiction of prescription pain and reduce the amount of pain medication related deaths. This alternative may also alleviate the total overall costs of substance abuse including health costs and loss in productivity which amounts to more than five hundred billion dollars per year (Zheng & Zhan, 2011).

**Questions to be answered by the Literature Review**

What is the effectiveness of the systemic enzyme serrapeptase as therapy for natural healing effects in the body? What are the anti-inflammatory and fibrinolytic properties of serrapeptase? What is the mechanism of action of the serrapeptase proteolytic enzyme? What extent is serrapeptase used in Europe and Asia compared to the United States?

**Definition of Terms**

1. Anti-Inflammatory. Counteracting or suppressing inflammation, or an agent that so acts. ("Anti-Inflammatory", 2017)

2. Anticoagulant. An agent serving to prevent the coagulation of blood in the formation of a clot. ("Anticoagulation", 2017)
3. **Fibrinolytic.** Adjective of Fibrinolysis, that is the dissolution of fibrin by enzymatic action. (“Fibrinolytic”, 2017)

4. **Inflammation.** The response of body tissues to pathogens, damaged cells, or other harmful stimuli (Ferrero-Miliani L et al., 2007)

5. **Serrapeptase.** Serratiopeptidase (Serratia E-15 protease, also known as serralysin, serrapeptase, serratiapetase, serratia peptidase, serratio peptidase, or serrapeptidase) is a proteolytic enzyme (protease) produced by enterobacterium Serratia sp. E-15 (Nakahama, K., Et Al., 1986)

6. **Systemic Enzyme.** Systemic enzymes work by targeting areas of inflammation in the body to help in the healing process (Janeway et al., 2001).

7. **Systemic Enzyme Therapy.** Systemic enzyme therapy is the therapeutic use of natural enzymes for their desired healing effects in the body (Noriega, Yang, Alvarez, & Rathi, 2015).

8. **Blood Brain Barrier (BBB).** The blood-brain barrier (BBB) is a diffusion barrier, which impedes influx of most compounds from blood to brain. Three cellular elements of the brain microvasculature compose the BBB-endothelial cells, astrocyte end-feet, and pericytes (PCs). Tight junctions (TJs), present between the cerebral endothelial cells, form a diffusion barrier, which selectively excludes most blood-borne substances from entering the brain. (Ballabh P, Braun A & Nedergaard, 2004).

9. **Central Nervous System (CNS).** The nervous system has two parts, called the central nervous system and the peripheral nervous system due to their location in the body. The central nervous system (CNS) includes the nerves in the brain and spinal cord. It is safely contained within the skull and vertebral canal of the spine (National Library of Medicine, 2017).
10. Median Lethal Dose (LD50). The dose of a poison that kills half the subjects exposed to it. Used as a measure of the toxicity of drugs and other substances. (Collins Dictionary of Medicine (2004)).

11. Contemporary Alternative Medicine (CAM). Complementary and alternative medicine is a group of diverse medical and health care systems, practices, and products that are not presently considered to be part of conventional medicine (National Center for Complementary and Integrative Health, U.S. Department of Health and Human Services (2017)).


**Significance of the Study**

This study adds to scholarly research and literature in the contemporary alternative medicine field by contributing a current systematic review of evidence based, double-blind, placebo-controlled studies that have evaluated serrapeptase in a broad spectrum of inflammatory and immunologic conditions. Existing reviews evaluating the efficacy of serratiopeptidase have small sample population, are of poor methodological quality, and are outdated (Chopra, Rehan, Mehra, & Kakkar, 2009). This review provides a more current comprehensive overview of enzyme therapy and serrapeptase in relation to a broad spectrum of conditions including those affecting third molar pain, breast engorgement, mucus biofilm, ear/nose/throat (ENT) pain secretions, edema, knee/ankle, carpal tunnel, and superficial blood clots.

The study may help to improve the practice and policy of health professionals and health educators to gain an understanding of natural therapy available to the patient population, particularly with respect to chronic conditions. Understanding natural methods of therapy would allow health care professionals to assist in dispelling myths, disseminate health care information,
and where necessary, counteract misinformation individuals may have obtained. Natural systemic enzymes may be a useful therapy for health promotion by practitioners to reach an audience of patients seeking natural methods of health care. Health care professionals can gain the opportunity to assist and educate patients with a comprehensive solution to their well-being. Also, if health educators want to be the primary purveyor of health information, they must understand the increasing choices of health care therapy.

This review may also be beneficial to researchers who are currently exploring the potential benefits of integrative health in a variety of situations. These situations include pain management for veterans, relief of symptoms in cancer patient, and programs to promote healthy behaviors (Complementary, Alternative, Integrative, 2017). This review may also be beneficial to health care practitioners using supplements, recommending supplements, and in some cases dispensing supplements in their offices. A recent survey of primary-care physicians, nurses, and naturopathic doctors revealed that many are currently recommending or contemplating dispensing supplements, nutraceuticals, or natural products to their patients (Kingsley & Grebow, 2014).
Chapter 2

Review of Literature

Widespread use of Opioid Pain Medications

Opioid abuse and addiction are a major global medical and social problem. In the United States, President Donald Trump recently declared widespread opioid use, a public health emergency (Talev, Hopkins, & Edney, 2017). The most abused substances are psychoactive drugs, such as cocaine, illicit opiates (opium, morphine and heroin), amphetamine-type stimulants, ecstasy-group substances and cannabinoids (United Nations Office of Drugs and Crime, 2010).

As researched by Zheng and Zhan (2011), the financial burdens in the USA alone, including health- and crime-related costs as well as loss in productivity, are more than $500 billion dollars per year. Additional social burdens include danger to public health and safety, including loss of lives, family deterioration increased un-employment, higher school dropout rates, domestic violence, and other crimes (Zheng & Zhan, 2011).

Drug overdose deaths and opioid-involved deaths continue to increase in the United States. Reports show a four-fold increase in opioid related drug overdose deaths since 1999 (CDC, 2016). According to one report, opioids are currently the main cause of drug overdose deaths (Rudd, 2016). There have been more than 500,000 opioid related deaths between the years 2000 to 2015. This amounts to over 93 Americans dying from an opioid overdose every day.

The increase in opioid related deaths shows a positive correlation with the number of prescriptions written by physicians. In a ten year period from 1999-2010, the number of opioids sold with a prescription in pharmacies and hospitals has had a four-fold increase (Paulozzi,
There may be a correlation between the four-fold increase of opioid prescriptions and the number of deaths from prescription opioids (Center for Disease Control, 2016). What is contradictory is that the four fold increase in opioid use in this 10 year period occurred despite the fact there has not been an overall change in the amount of pain diagnoses reported (Chang, Daubresse, Alexander, & Kruszewski, 2014).

The disastrous effects of drug abuse and addiction have caused an increase in focus in the development of drug free alternatives.

**Non-Addictive Evidence of Enzymes**

Recent progress in the study of enzymes demonstrates enzyme-therapy approaches using enzymes show promise for the treatment of drug overdose and addiction (Zheng & Zhan, 2011). The use of a protein-based approach, such as an enzyme, has a potential advantage over traditional approaches using a small-molecule compound, such as opioids, since a protein-based agent will not usually be expected to cross the BBB and reach the CNS (Zheng & Zhan, 2011).

Opioid dependence and addiction are results of brain changes caused by the long-term use of opioids (Kosten & George, 2002). When a small-molecule compound can cross the BBB, neuroanatomical progression to areas in the brain including the nucleus accumbens and dorsal striatal. These areas are the reward pathways of drug-seeking behavior and when these areas are reached, the propensity for abuse and addiction is increased (Gardner, 2011).

Small molecule drugs may cross the BBB through lipid-mediated free diffusion if the drug has a molecular weight less than 400 Daltons (Pardridge, 2012). The molecular weight of the popular prescription opioid pain medication, Oxycodone, is 315 Daltons (Karch, 2008). The molecular weight of Serrapeptase is approximately 52,000 Daltons (Mohankumar & Raj, 2011). A study of 27 substances found the four drugs in this group study, with molecular weights over
400 Daltons, had no measurable brain uptake. The largest substance found to date to cross the BBB by the mechanism of transmembrane diffusion is a cytokine-induced neutrophil chemoattractant-1 (CINC-1) at 7,800 Daltons (Banks, 2009). The large molecule structure of Serrapeptase will not cross the BBB and not be subject to addictive and abusive effects of small molecule drugs such as Oxycodone. Small molecule drugs have can have a psychoactive effect on the CNS.

According to the American Addiction Centers (2017), drugs interact with the brain and body to alter emotions and behaviors by changing the brain chemistry and a person’s perceptions. The more often drugs are used, the more they will impact brain chemicals and physiology. This can lead to drug dependence when the drugs are metabolized out of the body. Psychoactive drugs are able to cross the BBB and act primarily on the CNS to alter brain functions. This results in changes in perception, mood, consciousness, cognition and behavior. Drug cravings, dependence, and withdrawal symptoms are signs of addiction. The American Society of Addiction Medicine defines addiction as a disease affecting brain chemistry and circuitry that can lead to compulsive drug-seeking and using behaviors (American Addiction Centers (2017).

**Median Lethal Dose (LD50) Levels of Opioids, NSAIDs, and Serrapeptase**

The median lethal dose (LD50) is the dose of a substance that kills half the subjects exposed to it, and is used as a measure of the toxicity of drugs and other substances (Collins Dictionary of Medicine, 2004). The following presents the LD50 of various pain medication and anti-inflammatory substances.

Hydrocodone is an opioid medication widely used as an analgesic. Since 2004, hydrocodone is one of the most commonly prescribed drugs in the United States. Hydrocodone is
often found in the postmortem analysis as a cause of death in drug overdose. The median lethal dose of hydrocodone concentration in cases where the hydrocodone caused death, is 0.47 mg/L. Hydrocodone has a volume of distribution of 3.3 to 4.7 L/kg (Molina, 2010). The following calculations are taking into account the oral bioavailability of oxycodone hydrochloride 5 mg, 15 mg, and 30 mg tablets of 96% and 101%, respectively (Oxycodone, 2017). For a user who weighs 150 lbs. = 68 kg, multiplied by the volume of distribution of 3.3 to 4.7 L/kg, relative to the LD50 of 0.47 mg/L, results in a median lethal dose of 30 tablets of the lowest potency dose, or 3 tablets of the highest potency dose of Oxycodone at one time (Molina, 2010).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a drug class that reduce pain, decrease fever and decrease inflammation. Aspirin, also known as acetylsalicylic acid (ASA), is a medication used to treat pain, fever, or inflammation. The median lethal dose of ASA is 200 mg/kg. (MSDS, 2017). The following calculations are taking into account the oral bioavailability of ASA of 325 mg tablets of 80% to 100%, respectively (Aspirin, 2016). For a user who weighs 150 lbs. = 68 kg, relative to the LD50 of 200 mg/kg, results in a median lethal dose of 41 of the 325 mg tablets at one time.

Serrapeptase is a proteolytic enzyme that has a pharmacological classification as an anti-inflammatory agent that is non-steroidal in nature. In addition to anti-inflammatory actions, serrapeptase has analgesic, antipyretic, and platelet-inhibitory actions (Pubchem, 2017). Large quantities of enzymes have been consumed in clinical studies without damage and there is no LD50 resulting in a toxic dose (Lopez, 1994).

**Damage to Organs with Chronic use of Opioids, NSAIDs, and Serrapeptase**

Through a variety of mechanisms, opioids can cause adverse events in several organ systems. Chronic opioid therapy is associated with constipation, sleep-disordered breathing.
fractures, hypothalamic-pituitary-adrenal dysregulation, and overdose. Overdosing on opioid painkillers can lead to respiratory depression. This slows down breathing. The median lethal dose (LD50) of opioids can cause respiratory arrest that reduces the amount of oxygen to the brain and body tissues, resulting in debilitating organ system injury (Baldini, 2012).

Nonsteroidal anti-inflammatory drugs (NSAIDs) are effective anti-inflammatory and analgesic agents and are among the most commonly used classes of medications worldwide. However, NSAIDs, such as ibuprofen, aspirin and acetaminophen, have several side effects. The most frequently affected organ systems are the kidneys and gastrointestinal (GI) systems, with increasing evidence of heart attacks (Aspirin, 2016). Kidney damage can result from chronic ingestion of NSAIDs (Lewis, 2013). GI damage, such as upper and lower GI complications can result from the dose-dependent ingestion of NSAIDs (Goldstein, 2015). The symptoms of respiratory reactions and hypersensitivity reactions to NSAIDs can damage respiratory organs. NSAIDS such as Acetyl Salicylic Acid, can cause aspirin-induced asthma, also known as Samter's triad. Samter’s triad is an aspirin-exacerbated respiratory disease. NSAID-exacerbated respiratory disease (N-ERD) is a medical condition with three key features: asthma, respiratory symptoms exacerbated by aspirin, and nasal/ethmoidal polyposis (Wohrl, 2013).

There is very little evidence that enzyme therapies cause organ damage. Minor, elevations in liver serum enzymes occur with some agents. However, none of the current enzyme therapies have been associated with severe liver test abnormalities or clinically apparent liver injury. None of the enzyme therapies have been linked to cases of acute liver failure, chronic hepatitis or vanishing bile duct syndrome. No instances of acute liver failure, chronic hepatitis or vanishing bile duct syndrome due to enzymes have been reported (Lewis & Stine,
Although the enzyme proteins do not cause liver disease, a hypersensitivity reaction is a rare occurrence.

Serrapeptase may contribute to indirect damage to organs during the preparation of surgery as well as during post-operative procedures (Baghat et al., 2013). The fibrinolytic properties of serrapeptase can increase bleeding recovery because of the anti-platelet effects. The fibrinolytic properties can cause anticoagulation that may be contraindicated for surgery. However, the use of serrapeptase during post-operative recovery as an anti-inflammatory agent has been supported in literature (Baghat et al., 2013). The pre and postoperative risk of the use of serrapeptase as an anti-inflammatory agent must be weighed against the benefits.

Table 1 shows a comparison of safety in the various therapies: Systemic Enzyme, Opioids, and Aspirin (NSAID)

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Opioid</th>
<th>NSAID (Aspirin)</th>
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<tbody>
<tr>
<td><strong>Short Term</strong></td>
<td></td>
<td></td>
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<tr>
<td>Acute Risk (Overdose)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LD50 = No known Toxicity</td>
<td>LD50 = 6 capsules*</td>
<td>LD 50 = 35 tablets*</td>
</tr>
<tr>
<td><strong>Long Term</strong></td>
<td></td>
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<tr>
<td>Chronic Risk</td>
<td></td>
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<tr>
<td>(Addiction &lt; 400 kDA, crosses BBB, potential psychoactive substance)</td>
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<td></td>
</tr>
<tr>
<td>None = Large protein</td>
<td>Major = small molecule</td>
<td>Minor = small molecule</td>
</tr>
<tr>
<td>52,000 kDA</td>
<td>325 kDA</td>
<td>179 kDA</td>
</tr>
<tr>
<td>Acts Locally</td>
<td>Acts on CNS</td>
<td>Acts Locally and on CNS</td>
</tr>
<tr>
<td>(Organ Irritation and Damage)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal Liver Metabolism, Normal GI Absorption and Excretion</td>
<td>Increase in Liver Metabolism and Toxicity</td>
<td>Gastrointestinal Irritation via Cox 1 and Cox 2 inhibition</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increase in Liver Metabolism and Toxicity</td>
</tr>
</tbody>
</table>

* Based on 150 lbs. = 68 kg user
**Background**

**Serrapeptase proteolytic enzyme.** Proteolytic enzymes break down protein (Purves et al., 2014). Serrapeptase is a proteolytic enzyme, which means it breaks down proteins. Serrapeptase was originally discovered in the secretions of bacteria in silkworm intestines. It is Serrapeptase the enzyme responsible for dissolving a silkworm’s cocoon while leaving its biological inhabitant intact (Nakahama et al., 1986).

The anti-inflammatory properties of the serrapeptase enzyme was discovered 40 years ago as serretia peptidase (Bhagat et al., 2013). Serrapeptase is used in clinics throughout Europe and Asia as an alternative to aspirin, ibuprofen, and NSAIDs. Serrapeptase is an anti-inflammatory, proteolytic enzyme and has no gastrointestinal side effects (Bhagat et al., 2013).

Serrapeptase is processed through modern fermentation and microfiltration (Noriega et al., 2015). However, serrapeptase was originally found in the intestine of the silkworm. Enzymes secreted by the bacteria in silkworm intestines can dissolve non-living tissue but have no effect on vital cells. The silkworm secretes the serrapeptase enzyme through the saliva which dissolves an exit hole from the nonliving material of the cocoon and the silkworm emerges as a moth and is able to fly away (Noriega et al., 2015).

**Enzymes and enzyme therapy.** Enzymes are proteins acting as catalysts and help accelerate biological reactions in the body (Purves, Sadava, Orians,, & Heller, 2014). Enzymes are found ubiquitously in every living cell and support important systems, including digestive, cardiovascular, and immune systems. Enzymes initiate, accelerate and regulate chemical reactions that control functions such as metabolism, heart rate, and breathing. Although aging is not a disease, aging may affect pathways of maintenance, repair and defense that may cause age related disease (Rattan, 2014). Biological changes, such as the lower production of enzymes,
occurs as the body ages (Greenberg & Holt, 1986). The decrease of effectiveness in the aging body’s enzymes can be supported with enzyme therapy. Enzyme therapy improves the maintenance of a balanced metabolism using plant and animal enzymes supplements (Noriega et al., 2015).

Biological reactions require energy and enzymes act as a catalyst to lower energy needed to move the reaction forward. See Appendix, Figure 3, for an illustration of the effects of an enzyme catalyzed and non-enzyme catalyzed reaction. The energy reaction balance is necessary for proper function of systems in body to support health maintenance (Purves et al., 2014). The immune system depends on proper enzyme function for regulating inflammation and protecting cells from damage. For example, the clearance of inflammatory cytokines activity is regulated by enzymes that degrade proteins called protease. A protease is any proteolytic enzyme that performs proteolysis (Purves et al., 2014). Proteolysis is protein cleavage by catabolism through the mechanism of hydrolysis of peptide bonds. Serrapeptase is a type of proteolytic enzyme that acts as a catalyst to support health maintenance of the immune system (Noriega et al., 2015).

A large number of complement proteins are activated by proteolytic enzyme cleavage, such as the cleavage properties of serrapeptase (Janeway, Travers, & Walport, 2001). The complement system is contained in the immune system enhancing the ability to clear damaged cells from an organism, promotes inflammation, and attacks pathogens (Purves et al., 2014). The complement system helps clear out pathogens by allowing antibodies to kill bacteria. This activity complements the antibacterial activity of antibody. The complement system is made up proteins that react with the pathogens and initiate inflammation to help to fight infection.

**Systemic enzymes.** Systemic enzymes work by targeting areas of inflammation in the body to help in the healing process (Janeway et al., 2001). Systemic enzymes are consumed
orally, absorbed through the small intestine, and go into the bloodstream. Systemic enzymes are enteric coated in order to bypass the acidity of the stomach. Enteric coating protects enzymes in low pH and are activated in the higher pH of the small intestine. Through the small intestines, systemic enzymes travel throughout the circulatory system for up to 12 hours, targeting tissues and organs. Systemic enzymes are metabolized in the liver and kidney for excretion (Noriega et al., 2015).

**History of the serrapeptase enzyme.** Serrapeptase is has been used as an anti-inflammatory agent in Europe and Asia for more than 25 years, with growing interest in the United States (Bhagat, Agarwal, & Roy, 2013). In the 1920s, Dr. Max Wolf noticed that cancer patients lacked proteolytic enzymes in their digestive tracts because the enzymes were diverted to fighting the cancer. Seventy-three years later proteolytic enzymes would obtain a grant for a clinical trial. In the 1990s, the National Cancer Center funded a Columbia University cancer specialist to test enzymes. Dr. Nicholas Gonzales uncovered selective anticancer cell activity, causing cancer cells to lose their nuclei and progress to complete cell destruction or cytolysis (Gonzalez, 2014). The mechanisms of action of oral hydrolytic enzymes as fibrinolytic, anti-edematous, anti-inflammatory, and analgesic are cited in pharmacological and medical literature (Grabs, Nieman, Haller, Halle, & Scherr, 2014). The serrapeptase enzyme is utilized in many countries around the world for various illnesses and health disorders (Bhagat et al., 2013).

Serrapeptase is categorized as a dietary supplement by the Federal Drug Administration (FDA) and was first made available in the United States in 2002. Dietary supplements are products that are not drugs, food additives, or conventional food, and supplement a person’s diet. The FDA monitors dietary supplements, and regulates supplements as a type of food rather than a type of drug. The Dietary Supplement Health and Education Act of 1994 (DSHEA), is a United
States’ statute regulating dietary supplements. Under the DSHEA, supplements are effectively regulated by the FDA for Good Manufacturing Practices (Center, 2017). Similar to the food industry, government approval is not required to make or sell dietary supplements, however the manufacturer is responsible for the safety of dietary supplements (Committee, 2004).

**Effectiveness**

**Reduces inflammation and swelling.** Serrapeptase is shown to reduce inflammation and swelling without causing harm to healthy tissue, thus providing a safe alternative to anti-inflammatory drugs (Moriya et al., 1994). Serrapeptase has better anti-inflammatory activity than both animal based enzymes and NSAIDS (Viswanatha-Swamy & Patil, 2008). The animal based enzymes compared in the study was trypsin and chymotrypsin. The aspirin used in the study was administered in doses of 200 mg/kg and 54 mg/kg.

Serrapeptase is absorbed through the intestines and released into the body through the bloodstream systemically. The enzyme degrades cellular waste, that helps drain harmful accumulations near the site of inflammation. Serrapeptase decreases the symptoms of inflammation and speeds up tissue repair (Kakinuma, Moriya, Kawahara, & Sugino, 1982).

**Antibacterial activity.** *Listeria monocytogenes* is an invasive bacteria associated with life-threatening food-borne diseases in humans (Longhi et al., 2008). Several surface proteins called biofilms have been shown to be essential in the adhesion of *L. monocytogenes*. Serrapeptase has the ability to break down the biofilms that cause bacteria to attach to the cell. The decrease in the amount of attachment to cells reduces the entry of the bacteria into host cells in the human gut (Longhi et al., 2008).

Serrapeptase added to antibiotics also works synergistically better than antibiotics alone at decreasing the number of biofilm-forming bacteria that cause infections (Mecikoglu et al.,
2006). The effectiveness of serrapeptase is shown to inhibit biofilm-bacteria in infections related to prosthetic devices (Selan, Berlutti, Passariello, Comodiballanti, & Thaller, 1993). Serrapeptase was also effective at helping with the absorption of antibiotics into tissues (Koyama et al., 1986).

**Reduce antibiotic resistance.** The use of enzyme therapy may help reduce the amount of antibiotic resistance. The overuse of antibiotics may increase the mechanism of antibiotic resistance. The biochemical and physiological mechanism of action response of bacteria to the overuse of antibiotics may be the cause of antibiotic resistance. The biochemical modes of resistance of bacteria to penicillin include hydrolysis and efflux on peptidoglycan synthesis (Depardieu, Podglajen, Leclercq, Collatz, & Courvalin, 2007). These modes of resistance were discovered during patient treatment. Bacterial conjugation and horizontal gene transfer are the methods that bacteria affect mutations to confer resistance (Depardieu, et al., 2007). The *Staphylococcus aureus* bacterium can also produce enzymes called penicillinase to destroy the penicillin antibiotic (Nikaido, 2009). However, an antibiotic called methicillin was created to destroy *S. aureus*. The bacterium, *S. aureus* would develop a biochemical mechanism to resist methicillin. Another way bacteria become resistant to antibiotics is by making use of alternate metabolic pathways. For example, the bacteria may accelerate the mechanism for transporting antibiotics out of cells by increasing the activity of efflux pumps (Soto, 2013). The use of enzyme therapy may help reduce the amount of antibiotic resistance by providing a complimentary alternative with a different mechanism of action.

**Existing Anti-Inflammatory and Anti-Fibrinolytic Medications**

**Inflammatory response.** The purpose of the inflammatory response is to protect the body from attack by pathogens, injury, and cells that have mutated (Purves et al., 2014).
However, the immune system can become impaired and not distinguish between non-threatening and threatening substances (Ferrero-Miliani, Nielsen, Andersen, & Girardin, 2007). This impairment can lead to a variety of diseases, such as allergies, rheumatoid arthritis, psoriasis, multiple sclerosis, and cancer (Ferrero-Miliani et al., 2007). The traditional therapy for inflammatory associated disease and trauma are drugs and non-steroidal anti-inflammatory agents (NSAIDs). Drugs cannot treat the condition, however, can temporarily alleviate swelling, inflammation, and pain (Kristova, Fackovcova, Kriska, & Kurtansky, 2005).

**Anti-inflammatory drugs.** The drugs used in mediating inflammation can suppress the immune system and cause dangerous side effects (Purves et al., 2014). The long-term risks may out weight the benefits of using of NSAID for chronic conditions. For example, the suppression of the inflammatory process can cause limited of joint function, bone, cartilage, and articular deterioration (Kristova et al., 2005). As noted by Leipner, Iten & Saller, 2001, placebo-controlled studies demonstrated proteolytic enzymes produced anti-inflammatory, analgesic effects. Compared with NSAIDs, enzyme therapy is well tolerated and shows fewer adverse drug reactions. Enzyme therapy can be beneficial for patients who cannot tolerate NSAIDs (Leipner, Iten, & Saller, 2001).

**NSAID side effects.** NSAIDs are commonly prescribed for rheumatoid arthritis and other inflammatory joint conditions (Kristova et al., 2005). NSAIDs inhibit the production prostaglandins by blocking an enzyme called cyclooxygenase (COX). Aspirin-intolerant asthma (AIA) is a clinically distinct syndrome characterized by a series of asthma attacks following the consumption of aspirin and other NSAIDs. The prevalence of respiratory symptoms triggered by aspirin/NSAID use was found to be 10% to 11% in patients with asthma and 2.5% in non-
asthmatic patients. Aspirin sensitivity appears to be a significant problem (Vally, Taylor, & Thompson, 2002).

The detrimental effects of NSAIDs have been studied by Vally, Taylor and Thompson, 2002, and have been reported to cause neurological and gastrointestinal side effects. NSAIDs inhibit a chemical hormone called prostaglandin that protects gastric mucosal cells (Vally, Taylor, & Thompson, 2002). The long-terms use of NSAIDS can cause gastric ulcers, cardiovascular, and kidney damage. The most frequently used individual traditional NSAIDs and selective COX 2 inhibitors are associated with an increased risk of hospital admission for heart failure (Arfè et al., 2016). The problem increases when one type of NSAID causes side effects or stops working, and a physician simply changes it for a different brand of NSAIDS (Kristova et al., 2005).

**Common prescriptions.** Doctors have long prescribed NSAIDs to ease the pain and inflammation of arthritis and other types of pain (Matsui et al., 2011). The mechanism of action in NSAIDs is to inhibit prostaglandins that mediate inflammation in the joints. When prostaglandin production is unregulated, it can cause inflammation. An enzyme in the body called Cyclooxygenase (COX) blocks prostaglandin production. NSAIDs inhibit COX-1 and COX-2, which increase prostaglandins production. However, COX-1 plays an important role in protecting the stomach lining, and its inhibition can lead to stomach irritation and ulcers (Matsui et al., 2011).

**Synergy and interactions.** Systemic enzymes can be taken with other enzyme supplements (Noriega et al., 2015). However, there are interactions with some over-the-counter and prescriptions drugs. Systemic enzymes carry out multi-purpose functions and could lead to
enhanced effects. For example, serrapeptase has demonstrated synergistic effects with aspirin and other anticoagulants (Viswanatha-Swamy & Patil, 2008).

**Anti-Inflammatory Activity of Serrapeptase Enzyme Therapy**

**Background.** Inflammation is the natural response of the body’s immune system to invading pathogens, toxins, irritants, and trauma (Viswanatha-Swamy & Patil, 2008). Inflammation is the process recruiting immune cells to tissues in the body for immunity and cell defense. However, excessive levels can cause joint pain and accelerate signs of aging and disease, such as cancer or obesity. The inflammatory process is initiated when damaged cells release chemical signals that controls fibrinolytic activity and causes nearby blood vessels to become wider. The inflammatory process allows the release of immune cells from the bloodstream into the site of damage (Miller & Keane, 2003).

Inflammation is regulated by cell-signaling proteins called cytokines (Purves et al., 2014). During the inflammatory response, cytokines are released from the bloodstream to the site of damage along with clotting factors. Not only do cytokines directly promote inflammation, but they also recruit other inflammatory molecules to the injured area. Clotting factors help with recovery process by triggering fibrin buildup to separate infected cells from healthy cells (Miller & Keane, 2003).

**Effectiveness of serrapeptase on inflammation.** Systemic enzymes work by clearing dead tissue and debris from the blood, controlling inflammatory signals and immune cell mitigation, and breaking down scar tissue (Purves et al., 2014). Inflammation associated with pain and swelling is reported to be more effective than placebo for patients before surgery. Inflammation and swelling has also been reduced in patients given serrapeptase after surgery (Tachibana, Mizukoshi, Harada, Kawamoto, & Nakai, 1984).
Anti-inflammatory Mechanism of Action of Serrapeptase. Low enzyme concentration in a person’s diet leads to enzyme deficiency. This favors the development of diseases like chronic infection, fibrosis (formation of excess fibrous connective tissue in an organ or tissue), sclerosis (abnormal hardening of body tissue), immune dysfunction, and chronic inflammation.

Proteolytic enzymes are required in the blood to reduce the excess cytokine production during inflammation. Systemic enzymes elevates the concentration of enzymes in the blood and subsequently the concentration of activated alpha 2 macroglobulin (α2M) in the blood also rises. According to LaMarre et al., 1991, this shows how enzyme-activated alpha-2 macroglobulin (α2M) supports the clearance of cytokines during inflammation. The anti-inflammatory mechanism of action of the serrapeptase proteolytic enzymes is to activate and increase [α2M], reducing excess cytokine production that reduces excess inflammation, subsequently reducing chronic excess scarring, and concluding with a reduction in chronic fibrosis, cirrhosis, and sclerosis (LaMarre et al., 1991).

Anti-Fibrinolytic Activity of Serrapeptase Enzyme Therapy

**Background.** Inflammation is necessary to control cellular damage and initiate the healing process, normally subsiding when the source of the injury is healed (Guyton, 1974). Sometimes, individuals experience chronic inflammation that results in excessive accumulation of fibrin over a long period of time. In chronic inflammation, cytokine signaling and fibrin accumulation are uncontrolled, that can form scar tissue. Scarring of tissues and organs can make them rigid and unable to function properly (Guyton, 1974).

**Evidence of the effectiveness of serrapeptase on excess fibrin accumulation.** Many health conditions are the result of abnormal thickening or scarring of fibrous connective tissue or
fibrosis (Kakinuma et al., 1982). Serrapeptase was given to subjects with induced fibrin activity due to scalding, who presented abnormal thickening of connective tissue, a risk factor in scalding cases. The abnormal thickening of connective tissue is a risk factor in scalding cases. The serrapeptase was shown to repress the fibrosis. The repressive effect of serrapeptase is dependent on its proteolytic activity and was stronger than the other proteases tested (Kakinuma et al., 1982).

**Surgical and Primary Care Perspective**

Serrapeptase is limited in use for preparation of surgery as well as limited in use for post-operative procedures (Baghat et al., 2013). The fibrinolytic properties of serrapeptase can increase bleeding. The fibrinolytic properties can cause anticoagulant effects, which may be contraindicated for surgery. However, the use of serrapeptase during post-operative recovery as an anti-inflammatory agent has support in the literature (Baghat et al., 2013). Evidence of the effectiveness of serrapeptase from a primary care perspective broadens its use (Mecikoglu et al., 2006).

**Inflammation Affects Many Aspects of Health**

**Disorders, conditions, and illnesses.** Inflammation affects many aspects of health. When inflammation is reduced, it can have a wide range of applications in managing disease and conditions (Guyton, 1974). Serrapeptase is effective in reducing inflammation. The inclusion of serrapeptase in therapy is effective at reducing inflammation affecting pain, mucus production, breast tenderness, edema, carpal tunnel, superficial thrombophlebitis, cancer, and diabetes.

**Pain and inflammation.** Pain is the sensation associated with injury, arthritis, and nerve impingement that impairs well-being and day-to-day living (Chopra, Rehan, Mehra, & Kakkar, 2009). Supplements may reduce or alleviate the pain associated with inflammation.
When comparing serrapeptase with a relative drug called Protease S, pain was reduced in both cases. When compared with a placebo, serrapeptase was reported to be more effective for pain associated with swallowing (Chopra et al., 2009).

**Mucus production.** Nasal congestion may cause excessive mucus production in the sinus cavity, that reduces the area for breathing (Mazzone et al., 1990). The use of serrapeptase decreases the thickness of excessive mucus. The mucolytic property of serrapeptase is useful for both nasal congestion and lung sputum experience with cystic fibrosis patients (Mazzone et al., 1990). To study efficacy, serrapeptase was given to subjects suffering from ear, nose and throat (ENT) related symptoms. When compared with placebo, serrapeptase was reported to have greater efficacy for all symptoms. The results have shown positive localized anti-inflammatory and fibrinolytic activity (Mazzone et al., 1990).

**Breast tenderness.** Breast tenderness refers to the actual physical tenderness of breast tissue associated with a minor pain (Kee, Tan, Lee, & Salmon, 1989). Breast tenderness can be a symptom of pre-menstruation or menopause. A decrease in breast tenderness and soreness is noted with treatment of serrapeptase (Kim et al., 1989).

**Edema.** Edema is the retention of water in tissue, resulting in weight gain, bloating, and may cause the leg to swell (Esch, Gerngross, & Fabian, 1989). Anti-inflammatory effects related to the swelling and edema were reduced in patients after knee surgery when given serrapeptase. Edema related to inflammation and swelling and edema after surgery were reduced with serrapeptase enzyme treatment (Esch et al., 1989).

**Carpal tunnel syndrome.** A combination of serrapeptase and non-steroidal anti-inflammatory drug was able to reduce symptoms in patients with carpal tunnel syndrome.
Serrapeptase may be a useful alternative for conservative treatment for carpal tunnel syndrome (Panagariya & Sharma, 1999).

**Superficial thrombophlebitis.** Superficial thrombophlebitis is a thrombosis and inflammation of superficial veins (James, Berger, & Timothy, 2006). Symptoms include a hardened mass due to fibrous accumulations with reddening of the skin associated with excessive inflammation (James et al., 2006). Due to the fibrinolytic properties of serrapeptase, there was a decrease in symptoms. Patients with superficial thrombophlebitis given serrapeptase were able to reduce pain and symptoms of thrombophlebitis by 65%. The reduced symptoms included pain on pressure, edema, erythema, and nighttime cramps. Serrapeptase was effective for patients with inflammatory venous diseases (Bracale & Selvetella, 1996).

**Cancer.** Pancreatic cancer is an especially debilitating disease because there is limited effectiveness of conventional medication (Gonzales & Isaacs, 1999). Pancreatic cancer patients have a prognosis of 95% mortality in 5 years after diagnosis with 76% mortality within the first year (Kaur, Baine, Jain, Sasson, & Batra, 2013). Patients on enzyme therapy lived 81% longer than 1 year compared with 24% with conventional treatment (Gonzales & Isaacs, 1999).

**Diabetes.** Some conditions diabetic patients experience are characterized by edema as a result of excessive inflammation (Wiest-Ladenburger, Richter, Moeller, & Boehm, 1997). Patients with Type 1 diabetes have had positive results with systemic enzymes for reducing inflammation. Systemic enzymes such as serrapeptase, can positively affect the immune response. Serrapeptase is shown to reduce the production of chemicals called cytokines to a non-inflammatory level by regulating T-cell activity and moderating the cell surface molecules expression (Roep et al., 2002). Protease enzyme treatment resulted in prevention or delay of Type I diabetes (Wiest-Ladenburger et al., 1997).
Blood thickness is important when assessing blood pressure that may increase during the progression of through the five stages of diabetes (Pais, Alexy, Holsworth, & Meiselman, 2006). Enzymes can help reduce red blood cell aggregation and improve flow rates (Pais et al., 2006). Serrapeptase can reduce the aggregation of blood and excess fibrin from the circulation, that lowers the risk of blood clot formation. Serrapeptase can improve kidney filtration by degrading undigested food particles and toxic fragments (Mecikoglu et al., 2006).

Increased infection and impaired wound healing are risk factors for diabetic patients (Mecikoglu et al., 2006). The effectiveness of serrapeptase in helping with wound healing was shown in research of an infection in an implanted orthopedic device. Risk factors can increase because of the complication of slime forming bacteria, such as *Staphylococcus epidermidis* which form at these implanted sites. Serrapeptase has shown to be effective at reducing infection and improving wound healing (Mecikoglu et al., 2006).
Chapter 3

Methods and Procedures

Methodology

The methodology used for this paper to collect data was a systematic review. The literature review included a comprehensive search organized with folders of the articles to keep track of data. Analysis for the review was chronologically categorized and segmented by themed concepts such as the safety of various therapies, study characteristics, the past and current effectiveness of serrapeptase. Conversion metrics were utilized to calculate potency from milligrams to mg/kg. Tables were used to compare the effectiveness of serrapeptase versus placebo administration. The review drew conclusions about enzyme therapy and serrapeptase. The review focused on the research question of the effectiveness of systemic enzymes for therapeutic use in desired healing effects in the body. Elements of the systematic review were utilized to conduct a meta-analysis to provide current evidence for the effectiveness of the serrapeptase enzyme for therapeutic purposes.

Procedures

Assumptions. For the systematic review it was assumed the current clinical evidence of the effectiveness of serrapeptase studies were published within the last 10 years. For the past clinical evidence, literature used was published within the last 28 years, with the exception of historical references. Second, it was assumed health experts and health professionals had adequate knowledge of the symptoms, conditions, and illnesses mentioned.

Limitations. This paper has a limited methodology that influenced the interpretation of the findings from the research. The scope of this paper is limited to health professionals with a naturopathic focus, working with a patient population presenting with the symptoms, conditions, and aforementioned illnesses. The second limitation was that the data utilized was collected from
secondary sources. Search limitations include English language publications that were peer reviewed. Search limitations for the current evidence from clinical studies of serrapeptase, were between the years 2008-2017, and limited only to human-based interventions. Search limitations for the past studies of the effectiveness of serrapeptase were between the years 1980-2006.

**Delimitations.** The topic of enzyme therapy can be quite vast, but the scope of this paper is confined to the enzyme, serrapeptase. The focus in this paper was to establish the effectiveness of serrapeptase as therapy for natural healing effects with demonstrated anti-inflammatory and fibrinolytic activity. Boundaries were also set to exclude the effectiveness of digestive enzymes as the topic of this paper is an overview of systemic enzyme therapy. The Harriet K. and Philip Pumerantz library at Western University of Health Sciences was used for the literature search. Search engines that were not used include the Cochrane Library which is subscription-based with limited public access. The Global Health search engine was not used because the intended audience of the review is based in the United States. The SPRESI Database was not used in the search because the scope of the review did not require specific details such as chemical structure and mechanism of action. Years of data that were not included other than for historical reference were those before the year 2009 as to obtain contemporary viewpoints of alternative medicine.

**Search procedures.**

**Libraries used.** The Pumerantz Library at Western University of Health Sciences was used in the writing of this paper.

**Search engines and/or databases used.** Several databases were used to search for the literature. The following databases were used: CINAHL, PubMed, Science Citation Index, and Google Scholar.
Search terms. Several search terms were considered for the literature search. The following search terms were used: anticoagulant, anti-inflammatory, fibrinolytic, serrapeptase, serratiopeptidase, Serratia E-15 protease, serrati peptidase, serretia E-1 protease, serralysin, serratiapase, serratia peptidase, serratio peptidase, and serrapeptidase.

Boolean strings. Boolean strings were considered for the literature search. The following Boolean strings were used: serrapeptase AND inflammation, serrapeptase AND anticoagulant, fibrinolytic AND anti-inflammatory, serrapeptase AND serratiopeptidase.

Inclusion criteria. There were five criteria included in the search. The following were included in the inclusion criteria: (a) literature published after 2009 for current evidence, literature published after 1989 for past evidence; (b) peer-reviewed journals; (c) full-text articles; (d) English language; and (e) reputable Websites about serrapeptase, enzyme therapy, and inflammation.

Exclusion criteria. There were seven criteria for the exclusions used in identifying secondary data: (a) literature published before 1989, except for historical sources; (b) literature unavailable through Pumerantz Library; (c) literature that needed to be purchased; (d) literature that was not peer reviewed; (e) articles that were not full text; (f) literature that was not published in the English language; and (g) Web sites that were not related to serrapeptase.

Ethical consideration. The primary sources had Institutional Review Boards or Independent Ethics Committees that reviewed the methods and followed best practices in their recruitment of subjects.

Statistical analysis performed. The clinical studies in the review utilized ANOVA, Bonferroni, Chi-square, independent sample tests and nonparametric tests. ANOVA, and Bonferroni corrective measurements were used for pain and swelling. Chi-square and
independent sample tests were used to identify variance in treatment methods and outcome. P-value of < 0.05 was set as the level to determine statistical significance, and nonparametric tests were used to determine statistical significance.
Chapter 4

Findings

Evidence acquisition. A systematic review of all the published articles of serrapeptase using CINAHL, PubMed, Science Citation Index and Google Scholar was conducted and included studies from 1989-2006 (Figure 1 and Table 3), and studies from 2008-2017 (Figure 2 and Table 6). All studies related to serrapeptase included placebo-controlled, double-blind, and prospective trials, were screened and analyzed.

Evidence synthesis. A search of serrapeptase on CINAHL, PubMed, Science Citation Index and Google Scholar revealed 267 records on the past efficacy of serrapeptase. After duplicates were removed, 258 records remained of which 166 were excluded due to non-clinical significance, resulting in 92 records screened. Eighty-three full-text articles were excluded because they were animal or manufacturing processes. Nine full-text articles were included in the qualitative synthesis and 6 studies were included in the quantitative synthesis for the meta-analysis.

Figure 1.

Diagram of past studies included in the review of effectiveness of serrapeptase
The evidence supporting the efficacy of serrapeptase as an anti-inflammatory, fibrinolytic and analgesic is based on clinical studies with relevant methodology. All the clinical studies were placebo controlled, double-blind with a statistically significant sample size. Figure 1 shows the reporting items for systematic reviews flow diagram.

Table 2 shows the Study Selection that utilized 4 databases, with a total of 267 articles screened. A total of 175 articles were excluded in the review due duplicates, a high risk of bias, and some articles not having been peer-reviewed. A total of 92 articles were included in the review of literature and narrowed down to 6 clinical studies for the systematic review of past evidence due to moderate to low risk of bias and having been peer reviewed.

Table 2

<table>
<thead>
<tr>
<th>Database</th>
<th># of articles</th>
<th># of articles included in Past Studies</th>
<th># article included in Literature Review</th>
<th># of articles excluded in Literature Review</th>
<th>Reasons/comments for inclusion and exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>CINAHL</td>
<td>34</td>
<td>2</td>
<td>11</td>
<td>23</td>
<td>Studies included due to a low risk of bias, and have been Peer reviewed</td>
</tr>
<tr>
<td>PubMed</td>
<td>82</td>
<td>3</td>
<td>33</td>
<td>49</td>
<td>Studies excluded due to high risk of bias</td>
</tr>
<tr>
<td>Science Citation Index</td>
<td>44</td>
<td>2</td>
<td>23</td>
<td>21</td>
<td>Studies included due to a low risk of bias</td>
</tr>
<tr>
<td>Google Scholar</td>
<td>107</td>
<td>0</td>
<td>25</td>
<td>82</td>
<td>Non-peer reviewed articles and manufacturing processes were excluded</td>
</tr>
</tbody>
</table>
Table 3 shows the Study Characteristics with study design that was predominantly randomized (83.3%), double-blind (66.7%), and placebo controlled (83.3%). Two of the studies were single blind (33.3%), one study was preliminary (16.7%) and one was a prospective study (16.7%). The studies were statistically significant to highly statistically significant with p-values ranging from 0.001 to 0.05. The studies were conducted globally and reported in English. The objectives of most of the studies assessed symptoms of pain, inflammation, fibrinolysis, and swelling.

**Table 3**  
*Study Characteristics*

<table>
<thead>
<tr>
<th>Author/year</th>
<th>Location</th>
<th>Language</th>
<th>Study design/ follow-up</th>
<th>Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mecikoglu et al.,</td>
<td>US</td>
<td>English</td>
<td>RCT, Double-blind placebo-controlled, Lab experiment. Chi-square &amp; Independent samples t-tests</td>
<td>Assessed symptoms of inflammation and fibrinolysis</td>
</tr>
<tr>
<td>(2006)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mazzone et al.,</td>
<td>Italy</td>
<td>English</td>
<td>Multi-center, double-blind, RCT trial versus placebo $X^2$-test, t-test ($p &lt; 0.001$)</td>
<td>Assessed symptoms of pain, mucus secretions and fragmentation of fibrin exudate viscosity</td>
</tr>
<tr>
<td>(1990)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kee et al.,</td>
<td>Singapore</td>
<td>English</td>
<td>RCT, Double-blind placebo-controlled, trial. ($p &lt; 0.05$)</td>
<td>Assessed symptoms of pain and inflammation</td>
</tr>
<tr>
<td>(1989)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Panagariya &amp;</td>
<td>India</td>
<td>English</td>
<td>Preliminary, single-blind clinical study ($p &lt; 0.01$)</td>
<td>Assessed symptoms of pain and paresthesia</td>
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<tr>
<td>Sharma (1999)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Esch et al.,</td>
<td>Germany</td>
<td>English</td>
<td>Prospective, single-blind RCT Placebo controlled study. ($p &lt; 0.013$)</td>
<td>Assessed symptoms of swelling and inflammation</td>
</tr>
<tr>
<td>(1989)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bracale &amp; Selvetella</td>
<td>Italy</td>
<td>English</td>
<td>RCT, Double-blind placebo-controlled, Experimental design</td>
<td>Assessed symptoms of inflammation, pain, erythema, and edema</td>
</tr>
<tr>
<td>(1996)</td>
<td></td>
<td></td>
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</table>

*Note: RCT= Randomized Controlled Trial*
Table 4 shows the Risk of Bias and may explain variation of the results of the past clinical studies included in the review. In the preliminary trial conducted by Panagariya and Sharma (1999), 15% of patients had a worsening condition that required intervention and it is unknown if this was included in the results. The Esch et al., (1989) study is susceptible to detection bias because of the single-blind method that may have revealed knowledge of which intervention was utilized. The Bracale and Selvetella, (1996) study may have a risk of reporting bias due to an absent p-value. The remainder of the past clinical studies showed low risk of bias.

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Risk of Bias</th>
</tr>
</thead>
<tbody>
<tr>
<td>Author/year</td>
<td>Risk of bias</td>
</tr>
<tr>
<td>Panagariya &amp; Sharma (1999)</td>
<td>moderate risk of Attrition bias due to 15% of patients, requiring intervention, and unknown if included in results</td>
</tr>
<tr>
<td>Esch et al., (1989)</td>
<td>moderate risk of Detection bias due to single-blind study design</td>
</tr>
<tr>
<td>Bracale &amp; Selvetella, (1996)</td>
<td>moderate risk of Reporting bias due to absent p-value</td>
</tr>
</tbody>
</table>

Results

Results of the review assessed the use of systemic enzymes for anti-inflammatory and fibrinolytic properties with demonstrated validity of the serrapeptase enzyme as therapy for natural healing. Novel evidence was reported about the benefits of enzyme therapy (Chandanwale et al., 2016). Systemic enzyme therapy was shown to have therapeutic use of natural enzymes for their desired healing effects in the body (Noriega et al., 2015). The effectiveness of serrapeptase enzyme due to the anti-inflammatory and fibrinolytic properties of
the therapy was demonstrated. Research and clinical study exists for the benefits of enzyme therapy (Kotb, 2014).

Randomized, double-blind, placebo-controlled clinical trials in medical classification of immunology, neurology and inflammatory conditions were summarized comparing the efficacy of serrapeptase. Of the total patient study group ($N = 563$), 367 had shown 100% effectiveness versus placebo, the majority of which were in the ENT Secretion Study Mucus biofilm study ($n = 193$) and the remaining in the $3^{rd}$ Molar inflammation study ($n = 174$). Seventy had shown 85.7% effectiveness vs. placebo in the Breast pain study. Sixty-six had shown 50% effectiveness vs. placebo in the Knee/Ankle Edema study. Sixty had shown 65% effectiveness versus placebo, mostly in the Superficial Blood Clot study ($n = 40$) and the remaining in the Carpal Tunnel study ($n = 20$).

Table 5 presents a visual summary of the data from randomized clinical trials.

<table>
<thead>
<tr>
<th>Medical Classification</th>
<th>Condition</th>
<th>Subsection</th>
<th>Patients in the Study</th>
<th>Percentage better with Serrapeptase vs. Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunology</td>
<td>Inflammation</td>
<td>$3^{rd}$ Molar</td>
<td>174</td>
<td>100</td>
</tr>
<tr>
<td>Neurology</td>
<td>Pain</td>
<td>Breast</td>
<td>70</td>
<td>85.7</td>
</tr>
<tr>
<td>Immunology</td>
<td>Mucus Biofilm</td>
<td>ENT Pain Secretions</td>
<td>193</td>
<td>100</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Edema</td>
<td>Knee/Ankle</td>
<td>66</td>
<td>50</td>
</tr>
<tr>
<td>Inflammatory</td>
<td>Carpal Tunnel</td>
<td>Wrist</td>
<td>20</td>
<td>65</td>
</tr>
<tr>
<td>Immunology</td>
<td>Superficial Blood Clot</td>
<td>Legs and Lower Extremity</td>
<td>40</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Total</td>
<td>563</td>
</tr>
</tbody>
</table>


Table 6 presents a visual summary of the data from current randomized clinical trials.
Table 6
*Current evidence from clinical studies of Serrapeptase*

<table>
<thead>
<tr>
<th>Clinical trial</th>
<th>No. of patients</th>
<th>Study design</th>
<th>Treatment</th>
<th>Control</th>
<th>Duration</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evidence of serrapeptase as anti-inflammatory agent</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Al-Khateeb &amp; Nusair, (2008)</td>
<td>24</td>
<td>Prospective, intra-individual, randomized, double-blind, crossover study (P &lt; 0.05)</td>
<td>Serrapeptase 5mg</td>
<td>Placebo</td>
<td>7 days</td>
<td>Significant reduction in the extent of cheek swelling and pain intensity in the serrapeptase group at the 2nd, 3rd and 7th postoperative days</td>
</tr>
<tr>
<td>Chopra et al., (2009)</td>
<td>150</td>
<td>Randomized, double blind, placebo-controlled study (P &lt; 0.05)</td>
<td>Serrapeptase 20 mg 3 time per day 0.5 mg</td>
<td>Placebo, ibuprofen 600 mg, betamethasone paracetamol 1 g</td>
<td>7 days</td>
<td>Serrapeptase group showed less mean pain score and swelling than</td>
</tr>
<tr>
<td>Passariello et al., (2012)</td>
<td>64</td>
<td>Randomized, double-blind controlled study (P &lt; 0.01)</td>
<td>Serrapeptase and Antibiotic</td>
<td>Antibiotic alone</td>
<td>15 days</td>
<td>Addition of serrapeptase to Antibiotic protocol improves outcome</td>
</tr>
<tr>
<td>Evidence for fibrinolytic efficacy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chandanwale et al., (2016)</td>
<td>75</td>
<td>Randomized double-blind controlled clinical trial (P &lt; 0.01)</td>
<td>Serrapeptase 5 mg</td>
<td>Trypsin 48 mg Bromelain 90 mg Rutoside 100 mg</td>
<td>10 days</td>
<td>Efficacy and tolerability, and VAS pain scale reduction reported</td>
</tr>
<tr>
<td>Mangesi &amp; Zakarija-Grkovic, (2016)</td>
<td>70</td>
<td>Randomized double-blind (P &lt; 0.001)</td>
<td>Serrapeptase 10 mg 3 times day (30 mg/day)</td>
<td>Placebo</td>
<td>3 days</td>
<td>Moderate to marked improvement in breast pain</td>
</tr>
</tbody>
</table>
Current evidence from randomized, double-blind, placebo-controlled clinical trials of inflammatory and anti-fibrinolytic conditions were also summarized comparing the efficacy of serrapeptase. Of the total patient study group ($N = 383$), 24 had shown 100% effectiveness versus placebo post status surgical extraction, 150 had shown 100% efficacy vs. placebo in dental pain, 64 had shown 96.9% effectiveness in the treatment of periimplantitis, 75 had shown better 56% effectiveness versus no treatment in wound management, and 70 had shown 85.5% better improvement in breast pain versus the placebo.

**Current evidence acquisition.** A systematic review of all the published articles of serrapeptase using CINAHL, PubMed, Science Citation Index and Google Scholar was conducted from September 2016 until December 2017. All studies related to serrapeptase included Randomized controlled trials (RCTs), placebo-controlled, double-blind, and prospective trials that were screened and analyzed. One of studies that met the inclusion criteria was also a prospective cross-over study. A total of 5 studies on the clinical efficacy of the current evidence of serrapeptase met inclusion criteria.

**Current evidence synthesis.** A serrapeptase search on CINAHL, PubMed, Science Citation Index and Google Scholar revealed 114 Database Search Results on the efficacy of serrapeptase. There were 87 results after duplicates were removed. Fifty-nine studies were excluded due to their non-clinical significance, resulting in 28 full-text articles assessed for eligibility. Twenty-one full text articles were excluded because they were animal or manufacturing processes. Seven studies were included in the qualitative synthesis and 5 studies were included for the quantitative synthesis of the meta-analysis. The evidence supporting the efficacy of serrapeptase as an anti-inflammatory, fibrinolytic and analgesic is based on clinical studies with relevant methodology. All the clinical studies were RCTs, placebo controlled,
double-blind with a statistically significant sample size. The dose and the duration of treatment was specified in the studies, and outcome of the studies clearly defined.

Figure 2. shows the reporting items for systematic reviews flow diagram

**Figure 2.**
*Diagram of current studies included in the review of effectiveness of serrapeptase*

Evaluation of Findings

This review only begins the investigation for the benefits of enzyme therapy and the anti-inflammatory/anti-fibrinolytic activities of serrapeptase. More research into the current body of knowledge of serrapeptase published and unpublished research studies, would be beneficial. A meta-analysis report to aggregate the existing body of evidence of serrapeptase versus placebo with statistical methods is also recommended.
Chapter 5

Discussion, Implications, Recommendations, Conclusions

Restatement of Hypothesis

The purpose of the review was to discuss the effectiveness of systemic enzyme therapy with a focus on the anti-inflammatory benefits of the serrapeptase enzyme. The study has shown that the systemic enzyme serrapeptase is effective for natural healing effects in the body. The review further demonstrated systemic enzymes and serrapeptase may provide an alternative to current anti-inflammatory and pain medications.

Implications of the Findings

The review appears to support a potential alternative to traditional anti-inflammatory and pain medications. The findings are consistent with current theories in the field evaluating the efficacy of serrapeptase. The study helps to advance research methodology by providing a review of evidence based on double-blind, placebo-controlled studies that evaluate serrapeptase in a broad spectrum of inflammatory and immunologic conditions. The research findings improve the understanding by providing a comprehensive overview of enzyme therapy and serrapeptase in relation to a broad spectrum of conditions.

Current evidence from clinical studies of serrapeptase. Improvements in both study design and efficacy have been shown in current clinical studies within the last 10 years. For example, the current clinical studies included in this review are all randomized controlled versus only 85.7% the randomized controlled trials prior to 2008. Improvements in the efficacy of serrapeptase versus the placebo were also improved from 77.62% prior to 2008, increasing to 87.7% in the last 10 years.
Translation to health education practice. This review is applicable to the work of health professionals and educators by gaining an understanding of natural therapy available to the patient population, particularly with respect to chronic conditions. Understanding natural methods of therapy would allow health care professionals to assist in disseminating health care information, especially in areas that have few alternatives. Natural systemic enzymes may be a useful therapy for health promotion by practitioners to reach an audience of patients seeking natural methods of health care. Health care professionals have any opportunity to assist and educate patients of a comprehensive solution to their well-being. Also, if health educators want to be the primary purveyor of health information, they must understand the increasing choices of health care therapy.

Recommendations

Conducting genetic studies about the pharmacogenetics aspect of non-responders of enzyme therapy who may be carriers of a gene mutation that metabolizes the serrapeptase enzyme may be advantageous. In addition, studies into the efficacy of serrapeptase vs. other microbial, plant and animal based enzymes would add to the existing body of knowledge of enzyme therapy. Finally, exploration into the social science, public health and global impact of serrapeptase usage may also reveal possibly beneficial correlations.

Combined probiotic and enzyme therapy. Possible areas of further research would be the use of a combined probiotic and enzyme therapy may help to reduce the amount of antibiotic resistance. Enzyme supplementation therapy may have a role in several digestive and malabsorption issues where antibiotics are being currently being used. Probiotic and enzyme combinations are being evaluated in treatment that may be used to supplement antibiotic treatment and become a therapeutic option in the future (Ianiro et al. 2016).
Antibiotic resistance reduction. Antibiotic Resistance (AR) challenges include the increasing number of cases and prevalence rates of AR as high as 34% (Ventola, 2015). Risk factors include the frequent use of antibiotics as a popular treatment in the healthcare setting. The frequency of use of antibiotics has created resistant strains such as methicillin-resistant *Staphylococcus aureus* (MRSA). Antibiotic Resistance affects the quality of care, health-care costs and admission protocol (Ventola, 2015). As reported by Conley and Johnson (2004), there is increasing evidence that selected probiotic strains can provide health benefits to their human hosts. For example, the Food and Agriculture Organization of the United Nations and the World Health Organization have stated there is adequate scientific evidence to indicate that there is potential for probiotics to provide health benefits (Conley & Johnson, 2004).

Publish current systematic review and meta-analysis. No published, systematic review of current evidence based double-blind, placebo-controlled studies have evaluated serrapeptase in broad spectrum of inflammatory and immunologic conditions. Published reviews evaluating the efficacy of serratiopeptidase are small, are of generally of poor methodological quality, and outdated (Chopra, Rehan, Mehra, & Kakkar, 2009). This review provides a comprehensive overview of enzyme therapy and serrapeptase in relation to a broad spectrum of conditions including those affecting third molar pain, breast engorgement, mucus biofilm, ENT pain secretions, edema, knee/ankle, carpal tunnel, and superficial blood clots. The meta-analysis reveals current evidence of the effectiveness of serrapeptase and publication is recommended.

Further support for the use of natural supplements. To further support the use of natural supplement in private practice, reference is made to a recent survey of the use of alternative medicine conducted by Erik Goldman, editor of Holistic Primary Care (Kingsley & Grebow, 2014). As discovered by Kingsley and Grebow (2014), the findings of the survey
revealed evidence that there are a lot more practitioners using supplements, recommending supplements, and in some cases dispensing supplements in their offices than there were just a few years ago. The survey revealed 91% of the 643 respondents, including primary-care physicians, nurses, and naturopathic doctors, are currently recommending supplements, nutraceuticals, or natural products to their patients. In addition, 45% of respondents are contemplating dispensing supplements and natural products out of their offices directly to patients (Kingsley & Grebow, 2014). Despite the large amount of pharmaceutical medication prescribed to patients, physicians tend to use vitamins and supplement for their own health. In a recent survey of 900 physicians and 277 nurses, 72% of the physicians and 89% of nurses used dietary supplements (Dickson, 2009).

**Demographic and economic impact of natural supplements.** Addition support for the use of natural supplements from a financial perspective can also be compelling. For example, Consumer-Driven Health Plans (CDHPs) have increased usage with employers, individuals, and policy makers because of the potential to reduce health care costs. Thirteen percent of employers offered a CDHP in 2008, which is an increase from seven percent from 2006, and 8 percent of employees were enrolled in CDHPs in 2008 that is an increase from 4 percent in 2006 (Lo Sasso et al., 2010). One study revealed that CHDP enrollees not only had lower initial health spending than traditional managed plans such as HMO (Health Maintenance Organizations) and PPO (Preferred Provider Organization), but that CDHP enrollees were also reported to be healthier (Parente et al., 2004).

The most common type of CDHP is the health savings accounts (HSAs). HSAs combine a low premium, high-deductible health insurance plan with tax-deductible account that is used to pay for health expenditures, including supplements. Since 2003, dietary supplements prescribed
by doctors for the general wellness of medical condition have been covered under HSAs. If a physician determines a patient’s overall health can benefit from nutritional supplements, the physician can prescribe a supplement regimen (BodyLogicMD, 2017). There is evidence that HSAs are associated with a decrease in spending when compared with individuals who remained in traditional plans (Lo Sasso et al., 2010). Proper nutrition and dietary supplements can prevent or delay the progression of certain diseases. One study of the actual cost savings from the use of dietary supplements (Calcium, Vitamin D, Omega-3 Fatty Acids, Lutein) over a five year period (2008-2012) revealed potential savings of over $24 billion (DaVanzo & Freeman, 2007). Further discussion into the demographic and economic impact of natural supplements such as serrapeptase may provide insight to potential alleviation in the healthcare industry.

Table 7 show an example of proposed cost-benefit analysis from the use of the serrapeptase dietary supplement.

**Table 7**

*Proposed Step of a Cost-Benefit Analysis from the use of Dietary Supplements: Serrapeptase*

<table>
<thead>
<tr>
<th>Cost of Dietary supplements (serrapeptase) in millions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cost for new users (not currently taking supplement)</td>
</tr>
<tr>
<td>Cost Offsets from Reduced Hospitalizations, Skilled Nursing Facilities (SNF), and Physician Visits</td>
</tr>
<tr>
<td>Cost offset due to avoided hospitalizations, SNF stays, and physician visits</td>
</tr>
<tr>
<td>Net Cost (in millions)</td>
</tr>
<tr>
<td>Net costs (savings)</td>
</tr>
<tr>
<td>Premium offset (in millions)</td>
</tr>
<tr>
<td>Potential Savings to Medicaid and Medicare in millions</td>
</tr>
</tbody>
</table>
Conclusions

In this therapeutic overview of systemic enzymes, the effectiveness of serrapeptase was demonstrated. Novel evidence was reported about the benefits of enzyme therapy (Chandanwale et al., 2016). Systemic enzyme therapy was shown to have therapeutic use of natural enzymes for their desired healing effects in the body (Noriega et al., 2015). Research and clinical study exists for the benefits of enzyme therapy (Kotb, 2014).

Serrapeptase is evaluated in numerous studies for its effectiveness in reducing signs of inflammation throughout the body. The use of the systemic enzyme serrapeptase is successfully demonstrated to provide a potential natural alternative for conservative health maintenance. Limitations addressed the added costs of measurement, objective interpretation of subjective values and funding sources of analysis.
References


Chapter 8, Enzymes: Basic Concepts and Kinetics.

doi:10.1016/j.ijsu.2013.01.010


Center for Disease Control and Prevention. (2016). *Wide-ranging online data for epidemiologic research (WONDER)*. Atlanta, GA: CDC, National Center for Health Statistics.

Retrieved from https://www.healthdata.gov/dataset/wide-ranging-online-data-epidemiologic-research-wonder


doi:10.1002/btpr.1918


Oxycodone Hydrochloride Tablets, USP5 mg, 10 mg, 15 mg, 20 mg and 30 mg. U.S. National Library of Medicine, National Institutes of Health, dailymed.nlm.nih.gov/dailymed/archives/fdaDrugInfo.cfm?archiveid=58871.


Appendix

Figure 3.
Effects of an Enzyme Catalyzed and Non-Enzyme Catalyzed Reaction

![Diagram showing the effects of enzyme catalysis on reaction energy]

*Figure 1.* This figure shows the use of enzymes can lower the activation energy of a reaction (Ea). Thus the rate of the reaction is increased because more activated complexes can form. The graph shows the changes in energy through the transition state during conversion of reactants to product (Purves et al., 2014)