Introduction
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CHAPTER 1  
INTRODUCTION

Since mediaeval times plants played an important role in the life of human beings, as the major source of food, as well as for the maintenance and improvement of health and the elimination of enemies. The World Health Organization (WHO) estimated that about 80% of the world's population still relies on plant-based medicines for their primary health care. It is a clear indication for the role of medicinal plants in the maintenance of health and treatment of diseases as therapeutic alternatives throughout the world, still in the late 20th and early 21st century (WHO, 2002).

Ayurveda, the Indian traditional system of medicine, is based on empirical knowledge of the observations and the experience over millennia. More than 1200 diseases are mentioned in different classical Ayurvedic texts. Management in various forms of these diseases is made with more than 1000 medicinal plants (89.93%); 58 minerals, metals, or ores (5.24%); and 54 animal and marine products (4.86%) (Sharma, 2003). Healing of wound is an important area of clinical medicine explained in most of the Ayurvedic texts since about 5000 BC under the heading “Vranaropaka.” The wound as a medical problem was first discussed by Maharshi Agnibesha in Agnibesha Samhita (later known as Charaka Samhita) as “Vrana” (Dutta, 1941). Maharshi Sushruta in Sushruta Samhita elaborated on the subject.

The translated works of Hippocrates (circa 30 BC) state that nutrition is important for maintaining health (Hippocrates, 1939). Thompson et al., 1938 demonstrated a tendency for wound dehiscence associated with diet-induced hypoproteinemia using a dog model of surgical wound repair. Among the many advances that came during this period, the story pertaining to vitamin C is probably the most remarkable, as briefly outlined below.

Among the first descriptions of vitamin C deficiency, scurvy came from the Portuguese sailor Vasco da Gama while traveling around the trip of Africa in 1498. Vasco da Gama observed swelling of the hands, feet, and gums among many of the sailors. The illness disappeared rapidly after the ship came ashore and the crew was able to consume fruits, including oranges. However, upon sailing again, the sickness
reappeared after ten weeks, this time causing old wounds to reopen, eventually leading to death. Vasco da Gama wrote down that the ill sailors requested oranges. Indeed, Sir James Lancaster took bottles of lemon juice to prevent scurvy during his voyage to the East Indies in 1601.

In 1747, the Scottish physician James Lind conducted the first clinical trial among patients with scurvy and observed the rapid and dramatic effects of citrus fruit. Lind concluded that citrus fruits were the “most effectual remedies for distemper at sea”. Despite this and the efforts of Sir Gilbert Blane, it took the Admiralty until 1795 to approve taking citrus fruits for long sea voyages. The incidence of scurvy declined dramatically, flaring occasionally during the Great Potato Famine and the First World War.

Attempts to reproduce scurvy in an animal model were successful in 1907, when Axel Holst and Theodor Frolich developed the guinea pig model and showed that scurvy was a disorder of dietary deficiency. In 1912, the Polish Chemist Casimir Funk described the importance of certain nitrogen-containing compounds with an amine structure, which he called “vitamins” short for vital amines. Although the name vitamins have persisted, not all vitamins proved to be amines. In 1927, the Hungarian scientist Albert Szent-Gyorgyi unknowingly isolated vitamin C from oranges and cabbages. He later proved that the substance was in fact vitamin C and reported its effectiveness in preventing scurvy in guinea pigs (Jukes, 1988).

In 1939, John Crandon investigated the effects of vitamin C deficiency unwound healing on himself. After 182 days abstaining from vitamin C, an old appendectomy scar began to disintegrate and a newly formed wound failed to heal, thus confirming the importance of vitamin C deficiency in wound healing (Crandon et al., 1940; Crandon and Lund, 1940). It is now known that vitamin C is a specific co substrate for the enzymes 4-hydroxylase and lysyl hydroxylase, which are important in collagen synthesis (Kivirikko et al., 1990). In addition to the vitamins, a number of inorganic compounds are essential for maintaining skin integrity and are potential therapeutics for lower extremity
wounds. Often very small amounts are required for homeostasis, in addition to the detrimental effects of dietary deficiency, dietary excess can be harmful.

Zinc is one of the oldest medicinal treatments known; it is described in Egyptian papyrus tablets more than 3000 years old for topical treatment of skin disease. In 1934, Todd et al realized zinc was essential for the normal reproduction, development, and growth of rats (Todd et al., 1934). Zinc metalloenzymes, of which there are more than 50 examples in mammals, are involved in synthesis of DNA and RNA. Six zinc-based enzymes are involved in glycolysis. Zinc is essential for the normal maturation of the epidermis, a process referred to as terminal differentiation (Molokhai and Portnoy, 1969; Tucker et al., 1976).

Zinc deficiency is reported to delay wound healing (Prasad, 1988). In original studies on postsurgical wounds following pilonidal sinus excision, patients treated with zinc supplementation healed faster (Pories et al., 1967). However, studies in animals failed to demonstrate improved wound healing with zinc-supplemented diets (Weismann, 1978). Despite this, advocates suggest zinc supplementation should be used preoperatively even in otherwise normal individuals to accelerate wound healing after surgery (Faure et al., 1991). Human studies in lower leg ulceration treated with zinc supplementation have yielded conflicting results (Husain, 1975; Greaves and Skillen, 1970; Haeger and Lanner, 1974).

Magnesium is a cofactor for many enzymatic reactions, including collagen synthesis, an assay that is often used to assess wound healing (Demling and De Biasse, 1995). Similarly, copper is a cofactor in protein synthesis, and it too may be deemed essential for wound healing (Nimni, 1977). Iron is required for hydroxylation of proline and lysine; both amino acids are essential for collagen synthesis. It is likely that many other trace elements are involved in wound healing. However, it remains to be determined if supplemental doses can enhance healing.
1.1. Herbal remedies

In 1996, sales of dietary “herbal” supplements rose by 9% over the previous year and reached over £5 billion (Aarts, 1998). Herbal alternative therapies are common, particularly among patients with chronic painful conditions. It is important to realize that many patients find them helpful, even though there may be a lack of good clinical trials to support their use. For some herbal remedies, there is concordant acceptance, such as the use of carnitine supplementation. A brief description of some herbs is afforded below.

Patients with peripheral arterial disease may be taking hawthorn, garlic, ginger and turmeric, as advised by herbalist. Hawthorn is reported to have antioxidant properties, whereas the others are believed to reduce thrombosis by interfering with platelet function and lowering lipid levels. Extra-virgin olive oil fish oils (Ramirez et al., 1999), vitamins (Langlois et al., 2001; Tornwall et al., 1999; Swain and Kalplan, 1999) have shown in studies to reduce atherogenesis, though the clinical benefit to patient remains to be determined (Pittler and Ernst, 2000; Jepson et al., 2000).

Patients with diabetic foot ulcers and peripheral arterial disease often have coexisting peripheral neuropathy. Neuropathic symptoms are notoriously difficult to control. Progression of peripheral neuropathy may be impeded by improved glycemic control. For existing peripheral neuropathy, alpha-lipoic acid, an endogenously produced sulfur-based antioxidant, if taken for up to 7 months has been shown to improve symptoms (Ziegler et al., 1999).

For the management of venous leg ulcers, herbalists recommend horse chestnut seed extract, which has been proven to reduce edema, pain, and pruritus in a number of clinical studies (Pittler and Ernst, 1998).

Many chemical constituents isolated from plants have been reported to inhibit tissue and bacterial hyaluronidase and display anti-inflammatory activity. Many biologically active compounds isolated from plants are considered as secondary metabolites. Secondary metabolites are by-and-end products of complex biosynthetic pathways. They are usually unimportant for plant metabolism; however, they have
significantly ecological functions for the protection against bacteria and fungal infections (Walton and Brown, 1999). Topical administration of medicinal plants to dermal wounds has been shown in animal models to accelerate the progression of wound healing, reduce epithelization time, and scar area, and increase tensile strength (Nagappa and Cheriyan, 2001). Phytochemical constituents of medicinal plants have anti-inflammatory, astringent, demulcent, emollient, anti-oxidant, and anti-microbial effects, which are beneficial for wound healing (Jerlin et al., 2002; Mensha et al., 2001). Other studies have demonstrated inhibitory effects of medicinal plants on the enzymatic systems involved in the breakdown of extracellular matrix substances (Facino et al., 1995), in vitro stimulation of fibroblast growth, and protection of fibroblasts against oxidative stress (Mensha et al., 2001). For example, caffeoyl derivatives are capable inhibitors of free radical production and lipid peroxidation, which are key processes involved in the events leading to inflammation (Speroni et al., 2002).

1.2. Basics of wound healing and treatment

A wound is the disruption of the anatomic structure and its function in any body part. An example of this would be a simple cut, such as a paper cut on the finger- the skin is disrupted and can no longer protect the underlying structures.

Healing is the restoration of that structure and function. In the example above, the skin will spontaneously close over the cut in the next several days in most cases, protecting the structures underneath by restoring its continuity.

The ideal in wound healing is restoration/regeneration. Unlike many life forms that are phylogenetically lower, humans have lost the ability to regenerate most tissues and heal by scar not regeneration. One of the ultimate goals in wound healing research would be to find ways for humans to heal by regeneration of tissues.

Wounds may be said to be acute if they proceed through the restoration process, achieving a sustained period of anatomic structure and function. An example of this is the above cut closing over a few days as it usually does. They may be called chronic if the result is not sustained or if the restoration process is interrupted and not completed.
Most sources indicate that wound healing is made up of an orderly sequence of events. This, in turn, is characterized by specific infiltration of specialized cells into the wound, accomplishing specific tasks. The movement of the cells and the orderly sequence of events in healing are in part regulated by cytokines or growth factors. These are recently discovered chemicals that act as local "hormones" or communication packets causing events to occur. The cytokines may be secreted and arrive at the wound area through the circulation of blood, they may be secreted by cells in the area and act on nearby cells, and a cell may also secrete a chemical that acts on itself (Bodeker and Hughes, 1998).

1.3. Mechanisms in wound healing

Mechanisms involved in wound healing are epithelialization, contraction, connective tissue (matrix) deposition. The involvement of each varies over a spectrum dependent largely on the type location, milieu factors embracing the wound. Epithelialization is the process where keratinocytes migrate from the lower skin layer and divide. Contraction is the process where the wound contracts, narrowing or closing the wound.

Connective tissue and matrix deposition is the process where fibroblasts come into the area and produce new matrix (the wounds milieu) and collagen is laid down over and amongst this amorphous material. The epithelial tissues may then migrate over this. When formed the matrix, or wound repair milieu, consists of collagen, elastin, fibronectin, laminin, hyaluronic acid, proteoglycans. These structures and chemicals give strength and support, allow expansion and contraction, provide a surface for cell movement, and help necessary chemical reactions to occur (Bodeker and Hughes, 1998).

1.3.1. Wound occurs. The inflammatory phase begins

1. Transient vasoconstriction and coagulation followed by dilation and capillary leak of plasma to the wound area. Coagulation, as mentioned, is often called the first stage of healing because of its primary importance in this process. During vasoconstriction, platelets aggregate and secrete vasoactive substances along the endothelium of injured blood vessels and also promote clotting. Platelets provide the
initial signals to begin the repair process. Platelet derived growth factor attracts fibroblasts to the wound and stimulates them to proliferate and transforming growth factor beta (TGFb) causes them to make collagen.

Vasodilatation is caused by cell (largely platelet) released substances and similar substances cause subsequent changes. Fibroblasts are important sources of inflammatory cytokines early in wound healing. Fibrocytes probably travel from blood to the wound to form fibroblasts but may also arise from adjacent tissue.

2. White cells migrate through vessels especially from venules to the wound. The wound is filled with inflammatory exudates in the next few hours, which consists of red and white cells, soluble plasma proteins and fibrin strands. The white cells seem to scavenge up the area at different rates that appear related to the natural length of survival of that particular type of cell. Polymorphonuclear neutrophils are important cells here for patients own bacterial defense.

3. Neutrophils and macrophages are these scavenger cells and the macrophage seems to be the most important inflammatory cell for wound healing. The latter also release growth factors as well as remove bacteria and debris. These cells also release factors to promote angiogenesis, formation of new blood vessels.

4. Monocytes must be present to create normal fibroblast production and invasion of the wound space.

5. Migration is diminished in the presence of many antiseptics.

1.3.2. Epithelialization. The proliferative phase begins

It is the beginning of the proliferative phase at the edges of wounds, the epidermis immediately begins to thicken and the marginal basal cells begin to migrate across the wound along fibrin strands stopping when they contact each other (contact inhibition). Within the first 48 hours the entire wound is epithelialized. Layering of epithelialization is re-established. The depths of the wound at this point contain inflammatory cells and fibrin strands. Epithelialization is quite an aggressive process
and in a few days it will proceed along sutures and their tracts and in doing so many encircle tissues in inflammatory cysts or sterile abscesses.

1.3.3. Fibroplasia. The maturation phase begins

It is the beginning of the maturation phase. The cellular phase of healing lasts for several weeks, but by the 4th to 5th week the number of fibroblasts in the wound has decreased and the rich capillary network has dwindled to a well-defined capillary system. Collagen fibers now become the dominant feature of wounds. Fiber bundles enlarge and produce a dense collagenous structure, the scar. All scars slowly and progressively change in bulk and form over the years. This is referred to as remodeling of the scar or wound.

Wounds and particularly chronic wounds are major concerns for the patient and clinician alike; chronic wounds affect a large number of patients and seriously reduce their quality of life. Current estimates indicate that nearly 6 million people suffer from chronic wounds worldwide. There are very few Indian studies on the epidemiology of chronic wounds. In one study, the prevalence of chronic wounds in the community was reported as 4.5 per 1000 population whereas that of acute wounds was nearly doubled at 10.5 per 1000 population. The causes for chronic wounds are many, including such systemic conditions as diabetes mellitus, atherosclerosis, tuberculosis, and leprosy. Other major causes include venous ulcers, pressure sores, and trauma vasculitis. Such conditions as tuberculosis and leprosy, which are uncommon in Western societies, are often encountered in India. However, diabetic foot ulcers are an extremely common clinical condition encountered in Varanasi, India, similar to that seen in the Western population, and may be due to the, inadequate and inappropriate treatment of acute wounds was the commonest cause of chronic wounds. The practice of walking and working barefoot especially in the agricultural fields also contributed as causes. In India, the problem of chronic wounds are compounded by other demographic factors such as low literacy rates, poor access to health care, lack of adequate manpower, and inadequate health infrastructure (Shukla et al., 2005). The other major area of concern for wound care Physicians is a limited knowledge of the physiological processes involved in wound healing. The field of wound healing and tissues regeneration
represents a tremendously diverse area of clinical and scientific activity encompassing the most basic of wound care therapies to the most advanced analysis of cellular regulatory mechanisms. Chronic wounds, burns, and scars are complex, they have many causes, and they affect patients in many different ways. As a result, they can only be understood using a broad range of scientific and medical disciplines. Chronic wounds afflict a very large number of patients and seriously reduce their quality of life. The physiology of wound healing should be a major area of focus for ongoing scientific research. At present, there is a multitude of therapeutic approaches for the management of chronic wounds (Shukla et al., 2005). Current efforts in wound healing research are directed towards developing new methods for promoting wound closure to be used alongside the traditional approaches of debridement and infection control.

1.4. Anti-Inflammatory activity

Inflammation is a local response of living mammalian tissues to injury. It is a body defence reaction in order to eliminate or limit the spread of injurious agent. There are various components to an inflammatory reaction that can contribute to the associated symptoms and tissue injury. Oedema formation, leukocyte infiltration and granuloma formation represent such components of inflammation (Mitchell and Cortan, 2000). Oedema formation in the paw is the result of a synergism between various inflammatory mediators that increase vascular permeability and/or the mediators that increase blood flow (Ialenti et al., 1995). Several experimental models of paw oedema have been described. Carrageenan-induced paw oedema is widely used for determining the acute phase inflammation. Histamine, 5-hydroxy tryptamine and bradykinin are the first detectable mediators in the early phase of carrgeenan-induced inflammation (Di Rosa and Willoughby, 1971) whereas prostaglandins are detectable in the late phase of inflammation (Salvemini et al., 1996a) A large number of Indian medicinal plants are attributed with various pharmacological activities because they contain a diversified class of phytochemicals. It is believed that current analgesia inducing drugs as opioids and non-steroidal anti-inflammatory drugs are not useful in all cases, because of their side effects and potency (Ahmadian et al., 1998). As a result, a search for other alternatives seems to be necessary and beneficial. Medicinal plants having a wide variety of chemicals from which novel anti-inflammatory agents could be discovered.
Scientific studies are required to judge their efficacy. Traditional and folklore medicines play an important role in health services around the globe. About three quarters of the world population relies on plants and plant extracts for healthcare. India has an extensive forest cover, enriched with plant diversity. Several plants have been used in folklore medicine (Premanathan et al., 2000). The rational design of novel drugs from traditional medicine offers new prospects in modern healthcare.

Inflammation is characterized by pain, redness, swelling and immobility. Inflammation occurs in three phases viz. acute inflammation, immune response and chronic inflammation. Acute and chronic inflammation is complex processes that can be induced by a variety of means. Anti-inflammatory agents exert their effect through a spectrum of different modes of action (Arrigoni-Martelli, 1977). All the steroidal and non-steroidal anti-inflammatory drugs currently available are probably polycomponent in that they are able to modulate more than one mediator or cellular event concerned with the inflammatory response (White house, 1974). While screening of new anti-inflammatory compounds, carrageenin induced oedema in the rat hind paw (acute inflammation) is widely employed (Billingham and Davies, 1979).

1.5. Analgesic activity

Pain is sensorial modality, which in many cases represents the only symptom for diagnosis of several diseases. It often has a protective function throughout history and man has used several therapies for the management of pain (Ahmadiani et al., 1998). Medical herbs are highly highlighted due to their wide use and less side effects. An example is *Papaver somniferum*, from which morphine was isolated. It is regarded as a prototype of opiate analgesic drugs. For the relief of pain, opiates generally acts on the central nervous system, exercising their effects through three receptors (\(\mu, \kappa, \delta\)); such drugs are specially important for the treatment of chronic pain. Although morphine has reigned for centuries as the king of painkillers, its rule cannot be considered as totally benign. There are concerns regarding the side effects and addictive properties, which include respiratory depression, drowsiness, decreased gastrointestinal motility, nausea and several alterations of endocrine and autonomic nervous system (Almeida et al., 2001).
Therefore, the currently used analgesics such as opiates and non-steroidal anti-inflammatory drugs are not useful in all cases; hence an active medicinal plant is very much required. A large number of Indian medicinal plants are attributed with various pharmacological activities because they contain a diversified class of phytochemicals. Analgesics are drugs, which relieve the pain. Separate methods are available to study peripheral analgesics and central analgesics.

1.6. Anti-pyretic activity

Pyrexia or fever is caused as a secondary impact of infection, malignancy or other diseased states. It is the body’s natural defense to create an environment where infectious agent or damaged tissue cannot survive (Chattopadhyay et al., 2005). Normally the infected or damaged tissue initiates the enhanced formation of pro-inflammatory mediators (Cytokines like interleukin 1β, α, β and TNF-α), which increase the synthesis of prostaglandin E2 (PGE2) near peptic hypothalamus area and thereby triggering the hypothalamus to elevate the body temperature (Spacer and Breder, 1994). As the temperature regulatory system is governed by a nervous feedback mechanism, so when body temperature becomes very high, it dilate the blood vessels and increasing sweating to reduce the temperature; but when the body temperature become very low hypothalamus protect the internal temperature by vasoconstriction. High fever often increases faster disease progression by increasing tissue catabolism, dehydration and existing complaints, as found in HIV (Veugelers et al., 1997). Drugs having anti-inflammatory activity generally possess antipyretic activity (e.g.) non-steroidal anti-inflammatory drugs (NSAIDs). It has been suggested that prostaglandin (PGE) mediates pyrogen fever; the ability of NSAIDs, to inhibit prostaglandin synthesis could help to explain their antipyretic activity.

1.7. Anti-ulcer activity

Ulceration of the stomach is a serious gastrointestinal disorder mainly develops in the antral region due to lesions in the gastric mucosa. Epigastric pain is the common clinical feature and in severe cases blood appears in the vomitus. Since in majority of cases it is aggravated due to pepsin-hydrochloric acid, it is also termed as peptic ulcer. It is considered as one of the major human sufferings today affecting nearly 5% of the
global population. Management of this painful disease, its prevention or cure is one of the challenging problems today.

Gastric ulcer develops when a balance between some aggressive and defensive (cytoprotective) factor is lost. The aggressive factors are either endogenous or exogenous in origin. The endogenous damaging factors are hydrochloric acid, pepsin, refluxed bile, leukotrienes and reactive oxygen species (ROS) such as $O_2^-$, $H_2O_2$ and 'OH. The exogenous damaging factors mainly include alcohol, steroidal nonsteroidal, anti-inflammatory drugs, drugs which stimulate gastric acid pepsin secretion, stress, and tension and *Helicobacter pylori*. The mucosal defense against these aggressive factors are contributed by mucus-bicarbonate barrier, surface active phospholipid, prostaglandin, mucosal blood flow, cell renewal and migration, antioxidants and antioxidant enzymes (Bandyopadhyay *et al*., 2002).

**1.8. Hepatoprotective activity**

The liver is the key organ regulating homeostasis in the body. It is involved with almost all the biochemical pathways related to growth, fight against disease, nutrient supply, energy provision and reproduction (Ward and Daly, 1999). The liver is expected not only to perform physiological functions but also to protect against the hazards of harmful drugs and chemicals. In spite of tremendous scientific advancement in the field of hepatology in recent years, liver problems are on the rise. Jaundice and hepatitis are two major hepatic disorders that account for a high death rate (Pang *et al*., 1992). Presently only a few hepatoprotective drugs and that too from natural sources (there is not a single effective allopathic medication) are available for the treatment of liver disorders.

**1.9. Anti-diabetic activity**

A study of ancient literature indicates that diabetes (Madhumeha/Prameha) was fairly well known and well conceived as an entity in India. The knowledge of the system of diabetes mellitus, as the history reveals, existed with Indians since prehistoric period. “Madhumeha” is a disease in which a patient passes sweet urine and exhibits sweetness all over the body. The practical usage of juices of various plants achieved the
lowering of blood glucose by 10-20\% (Ivorra et al., 1989). Diabetes mellitus occurs throughout the world; however, it is more common in more developed countries. Diabetes is in the top ten, of the most significant diseases in the developed countries and is still gaining significance (WHO, 1999).

Diabetes mellitus is heterogenous primary disorder of carbohydrate metabolism with multiple etiological factors; it generally involves absolute or relative insulin deficiency, or insulin resistance, or both. Whatever be the cause, diabetes ultimately leads to hyperglycemia, which is the landmark of this disease syndrome. Non-insulin dependent diabetes mellitus (NIDDM) has also been associated with an increased risk for premature arteriosclerosis due to increase in triglycerides and low-density lipoprotein levels. About 70-80\% of deaths in diabetic patients are due to vascular disease. An ideal treatment for diabetes would be a drug that not only controls the glycemic level but also prevents the development of arteriosclerosis and other complications of diabetes (Halliwell and Gutteridge, 1985).

Long before the use of insulin became common, indigenous remedies were used for the treatment of diabetes mellitus and hyperlipidemia. There has been an increasing demand from patients for the use of natural products with antidiabetic and antihyperlipidemic activity. This is largely because insulin cannot be used orally and insulin injections are associated with the risk of hypoglycemia and impairment of hepatic and other body functions. The undesirable side effects and contra indications of synthetic drugs, and the fact that they are not suitable for use during pregnancy, have made scientists look towards hypoglycemic agents of plant origin (Berger, 1985). Many herbs and plant products have been shown to have antihyperglycemic and antihyperlipidemic action (Badole et al., 2006; Elder, 2004; Srinivasan 2005).

1.10. Anti-cancer activity

The need for low toxic anticancer compounds with novel antiradical and antioxidative/Prooxidative mechanism of action is in great demand. Consequently, there has been growing interest in a number of phytochemicals, polyphenolics and compounds which have long been recognized to possess many potentially significant
benefits, including anticarcinogenic, antioxidant, antiviral and antiproliferative activities (Grandics, 2003). In recent years, there has been growing evidence that the major flavonoids (Polyphenolics) can inhibit \textit{in vitro} as well as \textit{in vivo} tumour cell growth and induce apoptotic death of cells in different cell lines. Flavonoids, a group of polyphenolics quinoids, are widely distributed in edible plants, edible fruits, leafy vegetables, roots, tubers, bulbs, herbs, spices, legumes, tea, coffee, red wine and beer. Conception of these flavonoids through diet posing potentially detrimental and protective biological characteristics (Doll, 1992). Various antioxidant effects have been ascribed to flavonoids, viz., the scavenging of free radicals, the chelation of transition metals and the inhibition of free radicals producing enzymes (Wiltz and Hornung, 1988).

Flavonoids have been found to have a marked selection against malignant cell types \textit{in vitro}. (Agullo et al., 1996; Bors et al., 1990; Hirano et al., 1994; Kutnz et al., 1999). Worldwide efforts are on to discover new anticancer agents from plants (Cragg and Newman, 2005; Man et al., 2000; Newman et al., 2000). The anticancer activity of certain natural products and their analogs can be enhanced by synthesizing new derivatives based on active pharmacophore models, drug resistance and solubility and metabolic limitations can be overcome by appropriate molecular modifications; and new biological properties or mechanisms of action can be added by combining other functional groups or molecules.

1.11. Anti-venom activity

Snakebite is a major health hazard leading to high mortality rate especially in villages. The venom of \textit{Naja nigricollis} is extremely potent, and antiserum, being the only therapeutic agent, its development from animal source is time consuming and expensive. Although, use of plants against the effects of snakebite has been long recognized, more scientific attention has been given since last two decades. Many Indian medicinal plants are recommended for the treatment of snakebite (Chopra et al., 1956). In almost any part of the world, where venomous snakes occur, numerous plant species are used as folk medicine to treat snakebite (Martz, 1992). Topical application of the
plant or its sap onto the bite area, chewing leaves or bark or drinking plant extracts or decoctions are some procedures intended to counteract snake venom activity.

In most cases the efficacy of this treatment regimen is unproven. Most of the studies dealing with antiscanle bite testing of folk medicines, plant extracts are either mixed with snake venom and injected into mice or are given to the experimental animals before the venom is administered (Akunyili and Akubue, 1987). Due to the fact that most plant extracts failed to show any curative effect when applied after envenoming, necessitates the search for plant constituents, which have supportive effect in antivenom. However, literature review has failed to reveal any scientific studies taken up to screen locally used herbs for neutralizing capacity of *Naja nigricollis* envenomation and hence, the present work aims to find out the antivenom activity in *Azima tetracantha* (*A. tetracantha*) a freely available shrub throughout Tamil Nadu.

1.12. Scope of the present investigation

Wounds remain a huge public health issue, at least in terms of morbidity and long-term disability, throughout the world, especially in the developing countries. Some wounds, which affecting the lower extremities, are slow to heal despite good care; there is a constant need for new and cost-effective therapies. Wound healing is a complex process and does not require much help but still cause discomfort and are prone to develop infection and other complications. Infection is a major complication of injury and is responsible for 50-74% of hospital deaths. Many of the synthetic drugs available pose problems such as allergy, drug resistance, etc, forcing scientists to seek alternative medicines. In India, medicines based on herbal origin have been the basis of treatment and cure for various diseases and physiological abnormalities under practice such as Ayurveda, Siddha and Unani. Further, Indian folk medicine comprises numerous prescriptions for therapeutic purposes, such as healing of wounds, inflammation, ulcers, diabetes, cancer, hepatoprotective, leprosy, diartrhoea, snake bite, etc. More than 80% of the world’s population still depend upon traditional medicines in wound management involving disinfection, debridement and providing a moist environment to encourage the establishment of suitable environment for natural healing process. Since, sufficient validation is not available in the leaves of *A. tetracantha*, hence
it is necessary to validate the potency for phytochemical, pharmacological and pharmacognostical studies. The aim and objectives of the present investigation is to explore the potentials offered by natural (plant) products for pharmacological activities and hence the ethanolic leaf extract of *A. tetracantha* is used to investigate the following parameters:

- Wound healing activity on excision and dead space wound model.
- Anti-inflammatory activity.
- Analgesic activity.
- Anti-pyretic activity.
- Anti-ulcer activity.
- Hepatoprotective activity.
- Anti-diabetic activity.
- Anti-cancer activity.
- Anti-venom activity.