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Plants used as wound healing agents in folk medicines of Pacific Islands: a review of literature

by

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Abstrakt

Cílem této práce bylo identifikovat rostliny používané v tradiční medicíně v oblastech Polynésie, Melanésie a Mikronésie k hojení ran. V odborné literatuře bylo nalezeno celkem 150 druhů používaných k tomuto účelu. Tyto druhy jsou zpracovány ve formě tabulky obsahující údaje o botanickém názvu rostliny, čeledi, výskytu, místním názvu, použitých částech a jejím využití v tamní lidové medicíně. Na základě detailního rozboru literatury bylo identifikováno 88 druhů pacifických rostlin, o kterých zatím neexistují žádné moderní vědecké studie týkající se hojení ran. Dosavadní chemické rozbory ukázaly, že tyto druhy mohou být zdrojem celé řady látek, které jsou účinné při hojení ran, jako jsou například flavonoidy. Z tohoto důvodu se jako perspektivní druhy pro další výzkum jeví např. *Hibiscus tiliaceus, Hernandia ovigera, Premna serratifolia* a někteří zástupci rodu *Piper*. Tyto poznatky mohou pomoci farmaceutickému průmyslu při vývoji léčiv pro hojení ran na rostlinné bázi.

Klíčová slova: Pacifické ostrovy, hojení ran, tradiční medicína, Polynésie, Melanésie, Mikronésie

Abstract

The aim of this thesis was to identify medicinal plants used in folk medicine in Polynesia, Melanesia and Micronesia for wound healing. In the scientific literature, 150 species was found to be used for this purpose. These species are summarised in a table containing its botanical name, family, habitat, local name, parts used and medicinal use in folk medicine. As a result of this literature review, 88 Pacific plant species without any scientific reports on wound healing were identified. Previous reports on their chemical compositions show that these species could be promising sources of compounds effective in wound healing such as flavonoids. For this reason, the perspective species are e.g. *Hibiscus tiliaceus, Hernandia ovigera, Premna serratifolia* and certain representatives of genus *Piper*. These findings can be used by pharmaceutical industry for development of modern herbal-based wound healing preparations.

Key words: Pacific islands, wound healing, traditional medicine, Polynesia, Melanesia, Micronesia

Certification

I, Martin Pazdera, declare that this thesis, submitted in partial fulfilment of the requirements for the degree of Bc, in the Faculty of Tropical Agrisciences on the Czech University of Life Sciences Prague, is wholly my own work unless otherwise referenced or acknowledged.

In Prague 3.4.2017

Martin Pazdera

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Contents

1 Wound healing

Skin is the largest organ of human body creating the protective barrier against the outer environment. It protects us from harmful chemicals, ultraviolet radiation and pathogenic organisms (Sood *et al*., 2014). Wound healing is a dynamic biological process leading to restore skin epithelium after injury. This process involves multiple cell types executed by a number of growth factors and cytokines (Barrientos *et al*., 2014). The wound healing process is achieved through four main precise phases which are represented by hemostasis, inflammation, proliferation and remodelling. For a successful wound healing, all of these phases must occur in the right sequences and right on time. There are some factors which are able to disrupt the phases and lead to improper or impaired healing. These factors include oxygenation, infection, age and sex hormones, stress, diabetes, obesity, medications, alcoholism, smoking, and nutrition (Guo & DiPietro, 2010). Both, acute or chronic wounds have been investigated with aim to find new methods that improve cutaneous wound care. Since the treatment of a small scale acute wounds is effective, the chronic wounds suffering from high protease activity, infection, inflammation and hypoxia still remain a clinical problem. Of course, the wound care is on the rise but still a large scale of wound repair is poorly understood and also have higher financial demands. (Das & Baker, 2016). Most wounds, no matter aetiology, are supposed to heal. The difficulties could be caused by presence of microorganisms leading to infect the wound, which can prolong the time of recovery and also make more demands on financial site of a treatment. The abundance and diversity of microorganisms depends on wound type, depth, location and quality, the level of tissue perfusion, and the antimicrobial efficacy of the host immune response (Bowler *et al*., 2001).

1.1 Wounds: definition, characterization and classification

Wound is defined as a violation of the skin integrity. We distinguish two kinds of wound, acute and chronic ones. In this thesis, the chronic wounds will be described more in details than the acute ones. In cause of an acute wound, there is supposed to be some kind of an external factor that damages the skin and soft tissues. According to an aetiology, the acute wounds are differed to mechanic, thermic, chemical and the radiation ones. In contrast, the chronic wound is described as the secondary healing wound that does not, in spite of suitable treatment, seem to heal in 6-9 weeks. In a treatment of acute wound, we commonly use primary suture. If it is not possible to match the edges of the wound by suture, the most frequent alternative is skin grafting. This kind of the treatment

is usual also in treating chronic wounds. When this occasion happens, we can expect that there is some kind of disruption of reparation process in the wound. The most frequent chronic wounds are leg ulcers of venous aetiology, arterial and neuropathic skin ulcers, decubitus, and skin ulcers in lymphedema (Stryja, 2008). In practice, the chronic wounds are formed firstly by acute wounds but they have potential to move to chronicity due to the affiliated diseases of infections and secondly by microtraumatization of the skin which is predisponed to difficult healing (Sood *et al*., 2014). The third possibility is depression of the skin necrotization based on illness like obliterans atherosclerosis of the lower extremity. Long lasting open wound is a sign of disrupted healing of tissues and becomes a place of possible entrance of microorganisms to a body and can leads to spreading others infectious complications like abscesses, lymphadenopathy and systemic infections. Most of the skin ulcers are very painful and inauspiciously influences medical status of the patient by secretion from the wound that can lead to lose of fluids and proteins. During the time of healing process, there is a presence of bacterial colonization or local infection. Ulcer of the soft tissues is slowly filled with granulation tissue and ephitelize from edges. This process lasts longer period of time and demands sufficient input of nutrients and is ended by formation of perceptible scar.

In the classification of the chronic wound the character of the wound bed should be taken into account. According to presence of clinical marks of infections on the wound bed it is distinguished to infected wounds (deep, flesh) and deep or flesh-wound clean (not infected). Classification of the chronic wounds is shown below (Stryja, 2008).

- phase I: flesh-wound (epidermis, dermis)
- phase II: deep wound (interfering to subcutis)
- phase III: damage of fascia
- phase IV: damage of musculature
- phase V: damage of tendons, ligaments and bones
- phase VI: damage of large cavities

There is also classification by Demidova-Rice *et al.* (2012) categorizing the chronic wound according to its origin. In general, there are vascular (e.g. venous and arterial ulcers), diabetic, and pressure ulcers. Common features of these types are prolonged or excessive inflammatory phase, persistent infections, formation of drug-resistant microbial biofilms, and the inability of dermal and/or epidermal cells to respond to

reparative stimuli (Demidova-Rice *et al.*, 2012). If the reason of bad healing is infection, a paraclinical examination and choice of a proper wound cover is required. Precursor of local infection of chronic wound is critical colonization of the wound. Self-defence capabilities of patient fails and healing process slows down (Stryja, 2008).

1.2 The physiology of healing process

The optimal wound healing should consist of rapid homestasis, appropriate inflammation, mesenchymal cell differentiation, proliferation, migration to the wound site, suitable angiogenesis, prompt re-epithelialization (re-growth of epithelial tissue over the wound surface), proper synthesis, cross-linking and alignment of collagen to provide strength to the healing tissue. Some interruption or prolongation of treatment can lead to delayed wound healing or a non-healing chronic wound (Guo & DiPietro, 2010).

1.2.1 Haemostasis phase

The healing cascade begins right after injury when the platelets come into contact with exposed collagen. During the aggregation of process, the organism releases clotting factors making a fibrin clot at the site of injury. The fibrin clot serves as a matrix and sets surroundings for the next stages of healing, providing a scaffold for the migration of different cell players (Landén *et al*., 2016). This is not the only importance of platelets. They are also providing a sequence of chemical signals, also known as cytokines or growth factors that initiate healing response. The most important ones are platelet-derived growth factor (PDGF) that is released from degranulating platelets upon injury and is present in wound fluid (Barrientos *et al.,* 2014, Diegelmann *et al.*, 2004) and transforming growth factor-beta (TGF-ß). Chemotaxis of neutrophils, macrophages, smooth muscle cells and fibroblasts are results of the PDGF. Also, the mitogenesis of the fibroblasts and smooth muscle cells are stimulated by PDGF.

TGF-β sends signal to initiate the healing process by attracting the macrophages and make them to secrete another cytokines with fibroblast growth factor (FGF), PDGF, tumor necrosis alpha (TNFα) and interleukin-1 (IL-1). FGF, including FGF-2, FGF-7 and FGF-10 have been shown to be integral in cutaneous wound healing and is produces by keratinocytes, fibroblasts, endothelial cells, smooth muscle cells, chondrocytes, and mast cells (Barrientos *et al.,* 2014). TGF-β improves fibroblast and smooth muscle cell chemotaxis and modulates collagen and collagenase expression. As a result, is rapid

deposition of new connective tissue at the injury site during the proliferative phase that follows the inflammatory phase.

1.2.2 Inflammatory phase

Primarily activates immune system, and neutrophils and monocytes rapidly move into injured skin. This phase rivals with haemostasis and is the early stage of wound healing (Landén *et al*., 2016). Neutrophils appear in the injury site within 24 hours. Its major task is to remove foreign material, bacteria and non-functional host cells and also damaged matrix components that may occur in the wound. Bacteria give off chemical signals, attracting neutrophils, which ingest them by the process of phagocytosis. A tripeptid called f-Met-Leu-Phe (formed by methionine, leucine and phenylalanine), which provokes activation and chemotactic migration of neutrophils but show no reaction with lymphocytes (Dixon *et al.*, 1995), is released as a waste product during the bacterial protein synthesis which attracts inflammatory cells. Neutrophils will absorb themselves until they are filled with bacteria and create a formation called laudable pus.

Another marker cell in wound healing is the mast cell. Mast cells release granules which are filled with enzymes, histamine and other active amines that are responsible for the characteristic signs of inflammation around the wound site. They make surrounding vessels leaky and allow speed transfer of the mononuclear cells into the injury area and fluid is accumulated at the wound site. The signs of inflammation are rubor (redness), calor (heat), tumor (swelling) and dolor (pain).

Monocytes tissue is fixed by 48 hours and is activated to become wound macrophages. These macrophages are the most important cells in the normal healing process. Inhibition of macrophage function will delay the healing response. Nowadays, macrophages also release PDGF and TGF-β that are able to bring fibroblasts and smooth muscle cells to the wound site. They are also responsible for removing nonfunctional host cells, bacteria-filled neutrophils, damaged matrix, foreign debris and any other remaining bacteria from the injury area. Fact that macrophages are present in the wound means that the inflammatory phase is near the end and Proliferative phase is beginning. At the later stage, also lymphocytes appear but their precise role in the wound healing remains unclear (Diegelmann *et al.*, 2004). In normal skin wound healing, the inflammation usually lasts

for 2-5 days. The immune system plays the important role the whole wounds healing process (Landén *et al*., 2016).

1.2.3 Proliferative phase

It follows the inflammatory phase and is focused covering the wound surface and restoring the vascular network and forming granulation tissue (Landén *et* al., 2016). During the Proliferative phase, the TGF-β, macrophages and T-lypmhocytes becomes an important signal. TGF-β is supposed to be the most important signal for the regulation of fibroblast function. TGF-ß has a three-pronged effect on extracellular matrix deposition. First, it increases transcription of the genes for collagen, proteoglycans and fibronectin thus increasing the overall production of matrix proteins. At the same time the secretion of proteases that is responsible for the breakdown of the matrix is decreased by TGF-β and it also stimulates the protease inhibitor, tissue inhibitor of metallo-protease (TIMP). Other cytokines considered to be important ones are interleukins, fibroblast growth factors and tumor necrosis factor-alpha (Diegelmann *et al*., 2004).

As the healing cascasde progresses, another important responses are activated. Epidermal growth factor (EGF) and transforming growth factor alpha (TGFα) stimulates epithelization. When the epithelial bridge is complete, the scab is removed by enzymes. There is a high demand for oxygen and nutrients because of the high metabolic activity at the wound site. Local environment is characterized by low pH, reduced oxygen tension and increased lactate actually initiate the release of factors needed to bring in a new blood supply. It is called angiogenesis or neovascularization and is stimulated by vascular endothelial cell growth factor (VEGF), basic fibroblast growth factor (bFGF) and TGF-ß and are produced by epidermal cells, fibroblasts, macrophages and vascular endothelial cells (Diegelmann *et al.,* 2004, Landén *et al*., 2016). Similarly to FGF, VEGF also includes other members, such as VEGF-A, VEGF-B, VEGF-C, VEGF-D, VEGF-E where VEFG-A promotes the early events in angiogenesis, particularly endothelial cell migration and proliferation (Barrientos *et al.,* 2014). One signaling pathway including the role of low oxygen tension that in turn stimulates the expression of a nuclear transcription factor termed "hypoxia-inducible factor" (HIF) by vascular endothelial cells. The HIF fringes to specific sequences of DNA which regulate the expression of VEGF thus stimulating angiogenesis. The HIF activity is blocked by the oxygen when new blood

vessels enter the wound repair area and the oxygen tension is back at a normal level. This leads to a decreased synthesis of VEGF.

During the Proliferative phase the prevailing cell in the injury area is fibroblast. This cell produces the new matrix that is needed for restoring and structure and function of the injured tissue. Fibroblasts attach to the cables of the provisional fibrin matrix and begin to produce collagen. There have been identified at least 23 types of collagen but only type I is predominant for cicatrization. After transcription and processing of the collagen messenger ribonucleic acid, it is attached to polyribosomes on the endoplasmic reticulum and there are produced new chains of collagen. In this process is important part involving hydroxylation of proline and lysine residues. During the process of glycosylation, the collagen molecule begins to form its typical triple helical structure. After that, the procollagen molecule is secreted to into the extracellular spaces to the further processing. Hydroproline in collagen gives the molecule its stable conformation. When hydroxyproline is absent, the collagen has an altered structure and can undergo denaturation much more quickly and at a lower temperature. Collagen released into the extracellular space undergoes further processing by cleavage of the procollagen N and C-terminal peptide. In the extracellular spaces an important enzyme called lysyl oxidase, acts on the collagen to create stable cross-links. As the collagen matures and becomes older, more of these intramolecular and intermolecular cross-links are placed in the molecules. This important cross-linking step gives collagen its strength and stability later (Diegelmann *et al*., 2004, Landén *et al*., 2016).

1.2.4 Remodelling phase

This phase starts right after the end of granulation tissue development. Collagen in normal tissue is a very strong and highly organized molecule. Vice versa, collagen fibres in scar tissue are smaller, have a random appearance and tends to break apart faster than the surrounding skin. Maximum tensile strength of scar tissue is 80 % of normal skin. Also collagen degradation occurs during the process of collagen remodelling. For degradation are responsible specific collagenase enzymes and break it down to collagen fragments that undergo further denaturation.

Normal healing cascade begins with hemostasis and fibrin deposition leading to an inflammatory cell cascade, characterized by neutrophils, macrophages and lymphocytes within the tissue. This process is followed by attraction and proliferation

of fibroblasts and collagen deposition and after that follows final remodelling of collagen forming a scar tissue. Sometimes pathologic responses leading to fibrosis or chronic ulcers may appear. This happens when some part of the healing process is altered (Diegelmann *et al*., 2004, Landén *et al*., 2016). Several different cell types are involved in the wound-healing process. The cellular activities of any particular cell type may vary during different stages of repair. The complexity and coordination of the healing process are major struggles to therapeutic approaches, since any therapeutic must effectively be sequenced to the appropriate stage (Guo & DiPietro, 2010). Before application of any exogenous growth factor, the wound site should be debrided because the cells from the non-healing wound edge have reduced responding capacity to wound healing stimuli (Barrientos *et al.*, 2014).

1.3 Chronic wound and burns care

Successful treatment requires understanding of the molecular and cellular components present within each wound bed. Current wound healing use a multistep acronym known as TIME. Firstly, the nonviable tissue (T) formed within and around the wound site is removed by debridement or debriding agents, like bacterial collagenase. Next step is to minimize infection and inflammation (I) with antibiotics and anti-inflammatory agents. Moisture (M) in the wound is treated with appropriately chosen dressing and finally, epithelization (E) and granulation tissue formation a supported by specific therapies, such as growth factors (Demidova-Rice *et al*., 2012). Of course, there is need for complete examination of patient to consider eventual endocrine diseases (e.g. diabetes), hematologic conditions (e.g. anemia), cardiopulmonary problems (e.g. congestive heart failure), gastrointestinal problems that cause malnutrition and vitamin deficiencies, obesity, and peripheral vascular pathology (e.g. lymphedema, atherosclerotic disease) (Daley *et al.*, 2016). Another important aspect is to assess the wound. Examined factors are size, edge and site of the wound, depth, wound bed, necrotic tissue, slough and eschar, surrounding skin, infection and pain (Grey *et al.*, 2006).

Treatment methods depend on the features of the wound. If there is a wound infection, a debridement and appropriate systemic antibiotic therapy is required. Topical antiseptics are avoided due to interference with wound healing because of its toxicity to healing cells. Very important is also removal of foreign materials helps healing of

traumatic wounds. Those foreign materials include road debris and retained fragments of dressing materials or suture material.

1.3.1 Debridement

Debridement has been known for a long time has an undisputable meaning of in removing necrotic tissue although a lot of patients are worried about it. Professor Finn Gottrup defines debridement as a removal of foreign substance or necrotic tissue from the wound and its aim is to discover the healthy tissue on the wound bed and help it to heal.

Appearance of necrosis depends on the air humidity. In the dry conditions, its form is dry, black and solid tissue. This dry gangrene can be found in patients with ischemic disease of legs or in diabetics with neuroischemic ulcer. In the wet conditions, the softening of eschar happens and gets brighter colour – from brown and yellow to grey. If the wet conditions persist, necrosis falls apart and form a substance called slough. Slough is a muddy necrotic tissue of grey yellow colour, slightly adherent to wound bed and often stinky. The process of transition from dry to wet necrosis is called autolysis.

Doing the debridement can be separated into two phases. The first phase includes removal of the necrotic tissue. The most common way is surgical debridement. Other possibilities are hydrosurgery or larvaetherapy. The second phase can be described as a maintenance to keep the wound clean and without necrosis. The debridement range depends on the injury width. Positives of debridement are removal of bacterial burden, removal of necrotic tissue (the source of toxins), reducing of inflammatory reaction of the surrounding, odour reduce, wound secretion reduce, growth factors are more available. Plenty of methods of debridement are available. We have mechanical, autolytic, chemical and enzyme debridement (Stryja, 2008).

1.3.2 Burns

A burn is a type of injury that damages skin which is the barrier with the outer environment. This impaired skin is a possible area for bacterial growth and eventual infection. Burn injuries are one of the most devastating injuries, having a great impact on the patients physically, physiologically and psychologically (Kwang *et al.*, 2014). Seriousness of a burn depends on depth and how much of the body has been burned. The deepest spot of the burn is usually in the middle of the wounded area. The skin has three layers. The deeper the burn injury is, the greater the number of layers that are damaged. From this statement is derived the current classification of burns. Currently are

used four degrees of burn injuries and the degree depends on how deep the injury is, so it is superficial (first degree) burn, which is commonly sunburn. Partial thickness (second degree) burn and usually leaves scars. Full thickness (third degree) burn destroys all three skin layers and fourth degree burns extended through the skin into underlying tissues, such as muscles. Antibiotics is the first treating therapy and is used in less serious cases, based on a penicillin product (Anonymous, 2016 a). Major problem in burns are staphylococcal and streptococcal infections (Kwang *et al.*, 2014). Its purpose is to prevevent from the enter of infection and also reduce the size of scar. Bandages and topical therapies are another posibillity how to treat wounds. Compound of the bandages are silver compounds (silver sulfadiazine) or salts. The purpose is also to prevent the infection, reduce heat and water vapor loss from burned skin, protect the burned skin due to its sensitivity, keep the burned parts (fingers, limbs, etc) in a proper position and to collect the drainage from the wound. Next burn treating way, although in the harder cases, can be raising the limbs due to its swelling and choking off the blood flow. Also surgical cuts are the way for leaving the pressure out of the swollen limb. Important things is to exercise the burned area because of scar formation. If the wound site is not exercised properly, the scar could get tight and limit the movement. Pressure garments also help to treat hypertrophic scarring. These scars form themselves beyond or above the injured area, although this occur is not fully understood. Created pressure helps to form a normal scar a reduces the amount of hypertrophic scarring. Often used method is skin grafting. This technique is used also in the harder cases (partial and full thickness burns) and is often applied after the debridement and it usually reduces the number of days in the hospital. The best skin graft comes from patient (donor) with healthy unburned skin. The transplanted donor´s skin usually comes from less visible parts like buttocks or upper thighs because donor sites will not be normal in appearance after they heal, but it depends on the size and burn location where the grafts will be taken from. (Anonymous, 2016 b).

1.3.3 Recovery

Next important step is to keep the moist but not wet wound bed. The moist saline dressing should be applied after debridement. Optimal wound coverage need wet-to-damp dressings, which support autolytic debridement, absorb exudate and protects surrounding skin. Polyvinyl film dressing is suitable for wounds, which are neither dry nor highly exudative. For dry wounds is a good choice to use hydrocolloid dressings. Absorptive and hydrofiber dressings are appropriate for exudative wounds and for highly

exudative ones are used impregnated gauze dressings. Due to high exudation, twice-daily dressing changes may be needed. Hydrogel sheets and nonadhesive forms are useful for securing a wound dressing when the surrounding skin is fragile (Daley *et al*., 2016). No less important thing in wound healing is a proper nutrition. Nutrition disorder is quite common to patients with chronic wound. Can be result of another disease of states. Healing of tissues is a process that is demanding for energy and proper nutritions. This disorder is called malnutrition. Its symptoms are reducing of body weight, reducing of fat reserves, decreasing of serous proteins (albumin, prealbumin, transferin etc.). Vitamins are essential in lot of processes in organism. Most common disorders are hypovitaminosis C that causes defective collagen, increased fragility of capillaries and is important for creating strong ligament, also is anti-infectious and vitamin C increases biological availability of iron (Fe). Hypovitaminosis B causes disruption of energy metabolism of cells, microcytar anemia and amiss crosslinked of collagen. Hypovitaminosis A causes insufficient creation of proteoglykan, mucopolysaccharides, collagen, and disrupted epihtelization. Vitamin A delivered as a dietary supplement is able to antagonize negative influence of steroids on healing. Hypovitaminosis K leads to disruption of homeostasis. The next problem is a need of tissue oxidation. Transport of oxygen is secured by blood and blood-vessels. Sufficient blood supply is very important for tissue healing. Reducing of oxygen leads to disruption of healing as a result of violation in collagen synthesis. Another consequence is a predisposition to bacterial infection which is caused as a result of violation of bactericidal reaction of macrophages and granulocytes (Stryja, 2008).

1.4 Wound microbiology

Function of normal intact skin is to control microbial population living on the skin surface from getting the underlying tissue into contact with potential pathogens. Disruption of the skin integrity provides a suitable environment and favourable substrate for microbial reproduction. The abundance and diversion of the microbial organisms depends on the wound type, depth, location. Every wounds, despite clean surgical intervention, is at some risk of potential microbial colonization. Since 1960s, the dressings like polyurethane films, polyurethane foams, and hydrocolloids were invented as suitable treatment and to prevent the bacterial multiplication and keeping the optimal wound environment and these types of dressings are more effective than the dry ones. The acute wounds are expected to heal naturally and quickly without any

special surgical interventions. On the other hand, the more serious traumatic injuries like burns with the presence of nonviable tissue and foreign material are supposed to be colonized by microorganisms and require debridement and antimicrobial therapy to enable the healing process. These chronic wounds are commonly caused by endogenous mechanisms associated with a predisposing condition that ultimately compromises the integrity of dermal and epidermal tissue. Wound contaminants are likely to originate from three main sources. The first is the environment (exogenous microorganisms in the air or those introduced by traumatic injury). The second origin is the surrounding skin (involving members of the normal skin microflora such as *Staphylococcus epidermidis*, micrococci, skin diphtheroids, and propionibacteria) and the third type is endogenous sources involving mucous membranes (primarily the gastrointestinal, oropharyngeal, and genitourinary mucosae). So far, widespread opinion is, that aerobic or facultative pathogens like *Staphylococcus aureus, Pseudomonas aeruginosa*, and beta-hemolytic streptococci are the primary causes of delayed healing and infection in both acute and chronic wounds (Bowler *et al.,* 2001). Many of wound bacteria, including *Staphylococcus, Streptococcus* and *Pseudomonas* produce exotoxins and destroy the hosts cells and disrupt normal cellular metabolism (Rhoads *et al.,* 2012). However, anaerobes are often overlooked and led the experts to make a more detailed research and is reported, that anaerobic bacteria were the likely cause of postoperative infections. The struggle in recognizing the prevalence of anaerobic bacteria in wounds can have three reasons. Firstly, Anaerobes are not regarded as being detrimental to normal wound healing. Secondly compared with aerobic and facultative microorganisms, the culture, isolation, and identification of anaerobic bacteria is more time-consuming, labor-intensive, and expensive and is often deemed to be too demanding for many diagnostic microbiology laboratories. The third reason is that anaerobes die quite quickly in the air so the collection and transport to the laboratory is difficult to maintain the vitality of the collected specimen (Bowler *et al.*,2001). Another problem is microbial biofilm, because it presents a natural habit for bacteria and affects every organ system. Biofilms are more resistant to antimicrobial agents and there is also resistance to host immunity defences. Multi-species biofilm is common in chronic wounds due to the moist adherent environment in which bacteria are embedded in a self-secreted exopolysaccharide matrix. The presence of such biofilm is a result of inefficient antibiotic treatment (Han *et al.*, 2011, Rhoads *et al.*, 2012).

Blood perfusion is an important element and provides minimal opportunity for microorganisms to colonize and proliferate because delivers oxygen, nutrients and cells of immune system to the wound site. So with the decreasing level of oxygen in the tissue, the increasing possibility of infection will be. According to this fact, the chronic wounds are poorly blood perfused (Bowler *et al.,* 2001).

1.4.1 Wound infection

Infection occurs when virulence factors of foreign microorganisms initiate an immune response of host organism and are contributing factor in chronic wound development and maintenance. All wounds are colonized to some degree and a major role of the inflammatory phase of wound healing is to bring microbes down to steady-state levels that can be tolerated and cleared by healthy tissues (Bowler *et al.,* 2001, Eming *et al.,* 2014). Great part of acute and chronic wounds is mixed of both, aerobic and anaerobic origin. The first type is a surgical wound infection where the possibility of the infection depends on the susceptibility of the surgical wound to microbial contamination. Postoperative wound infection in the clean surgery is from 1 to 5 %. In contrast, the dirty procedures are more sensitive to microbial contamination and there is a 27 % risk of the infection. Except of clean surgery, surgical wound infections have polymicrobial aetiology, which means that there both, aerobic and anaerobic microorganisms. The most spread microbial organisms in this type of wound infection are *Staphylococcus aureus*, coagulase-negative staphylococci, *Enterococcus* spp., *Escherichia coli, Pseudomonas aeruginosa*, and *Enterobacter* spp. To minimize the possibility of the postoperative infection, there is need of proper asepsis and antisepsis mediums. The second type are acute soft tissue infection. They also include cutaneous abscesses, traumatic wounds, and necrotizing infection. Approximately about 30 % is responsible for cutaneous abscesses *Staphylococcus aureus*. However, some other studies stated, that cutaneous abscess or traumatic wounds are to 50 % and necrotizing soft tissue infections are about to 47 % combined by mixed types of aerobic and anaerobic microflora. Another pathogens are *Streptococcus pyogenes, Peptostreptococcus* spp., *Bacteroides fragilis, Clostridium perfringens*, *Escherichia coli* and *Prevotella* spp. The classification of necrotising soft tissue has five points and those are the assumed causative microorganism(s), the initial clinical findings, the type and level of tissue involved,

the rate of progression, and the type of therapy required. Next infection type is bite wound infection. Rate of the infection is from 10 to 50 % depending on the severity and location of the bite wound. Up to 20 % of dog and from 30 to 50 % cat bites are contaminated. In 74 % are polymicrobial, which means, there is aerobic and anaerobic microflora including *Staphylococcus aureus, Peptostreptococcus* spp. and *Bacteroides* spp. Due to the oral microflora, most pathogens are of anaerobic aetiology, such as *Bacteroides, Prevotella, Porphyromonas,* and *Peptostreptococcus* spp., less common potential pathogens such as *Pasteurella multocida, Capnocytophaga canimorsus, Bartonella henselae,* and *Eikenella corrodens* may also be involved. Another type is burn infections. Most cases of death in burns are from infection. It is to be 75 % of fatal cases. There is a prevalence of aerobic pathogens like *P. aeruginosa, S. aureus, E. coli, Klebsiella* spp., *Enterococcus* spp., and *Candida* spp. Anaerobic microflora includes microbial organisms like *Peptostreptococcus* spp., *Bacteroides* spp., and *Propionibacterium* acnes. (Bowler *et al*., 2001).

Microorganisms that appear in both, acute and chronic wounds are for example *Staphylococcus aureus, Streptococcus* spp., *Corynebacterium* spp., *Escherichia coli, Enterobacter cloacae, Proteus mirabilis, Peptostreptococcus micros, magnus, anaerobius, Clostriudium perfringens, panaveris, Bacteroides fragilis, cadaveris, uniformis, Prevotella oralis, oris*, etc. Acute wound microorganisms are *Escherichia hermanii, Bacillus* spp., *Clostridium septicum, tertium, limosum, Bacteroides ovatus, Prevotella* spp., *Veillonella* spp. etc. Chronic wound microorganisms are for example *Micrococcus* spp., *Corynebacterium xerosis, Enterobacter aerogenes, Citrobacter freundii, Peptostreptococcus indolicus, Streptococcus intermedius, Clostridium ramosum, Eubacterium limosum, Bacteroides stecoris, capillosus, caccae, Fusobacterium necrophorum* etc. (Bowler *et al*., 2001).

There are other types of wound infections, such as diabetic foot ulcer infections and leg and decubitus (pressure) ulcer infections but I will not describe them more in this thesis.

2 Plant-derived natural products

Medicinal plants have been known for a long time for its valuable source of therapeutic agents and many nowadays medicaments are from plant-derived products or their derivatives. However, in the last years, the pharmaceutic industry was focused

primarily on libraries of synthetic compounds. They are easier to produce and resupply, but on the other hand, at the same time there was a declining trend in the number of new drugs reaching the market and rediscovering the drugs from natural sources, because the result of synthetic compound libraries did not meet the expectations. This circumstance revitalized the interest in natural product-based drug discovery, despite its high complexity, which in turn necessitates broad interdisciplinary research approaches (Atanasov *et al.*, 2015).

Medicaments based plant products are still essential in health care but more developed countries rely more on synthetic drugs. Some significant plant-derived compounds like khellin, made from *Ammi visnaga*, from which was developed chromolyn as a bronchodilator. Galegine was a model for metformin, derived from *Galega officinalis* and was used as an antidiabetic drug. As another important substance can be considered capsaicin from *Capsicum* spp. used as a topical analgesic. Cocaine from *Erythroxylum coca*, codeine and morphine from *Papaver somniferum* are used as local anaesthetics and analgesics. Nicotine is extracted from *Nicotiana* spp. has its use in smoking cessation therapy. Verapamil based on papaverine also extracted from *Papaver somniferum* found its usage in treating hypertension. The latter plant is better known as being the source of painkillers such as morphine and codeine, but possibly best known example of ethnomedicine are antimalarial drugs, like quninine and artemisine (Cragg & Newman, 2013, Raskin *et al*., 2002). There are number of plant species producing the bioactive compound with different chemical scaffolds. Only about 6% of existing plant species have been systematically investigated pharmacologically, and only around 15% phytochemically. However, ongoing climate changes and anthropogenic factors are significant agents in decreasing of vegetative species, thus endangering the potential new drugs from the plants (Atanasov *et al.*, 2015). Besides above mentioned compounds, various plant secondary metabolites are important agents in wound healing. Since this is a main focus of my thesis, further, I will describe some more specific plant-derived therapies and substances used in wound healing. They include therapeutic wound covers, flavonoids, enzymatic therapy and curative cosmetics.

2.1 Alginates

Alginates are derived from brown seaweeds *Ascophyllum nodosum* (Fucaceae) and *Macrocystis pyrifera* (Laminariaceae). *A. nodosum* forms single bladders centrally in long, strap-like fronds. The fronds hang downwards, gently draping sheltered intertidal rocks. The species has two meter long fronds with large yellow egg-shaped air bladders at regular intervals A number of fronds grow from each basal holdfast, and the plant generally regenerates new fronds from the base when one of the larger fronds are damaged, so that the stands you see on the shore may be very persistent indeed. This is a very common seaweed on rocky shores in North of Europe and Canada (Guiry, 2017). *Macrocystis pyrifera*, also known as the giant kelp, may exceed 30 metres in length, characterize benthic habitats on many temperate reefs. Blades absorb nutrients from seawater to support rapid growth primarily from their basal (frond producing) and apical (basal producing) meristems Many algae on rocky reefs are harvested for food, fertilizer, and pharmaceuticals (Kingsford, 2016, Manley, 1981).

Therapeutic wound covers include impregnated gauze covers and alginates consist of compression fabric woven from cotton fibres containing other active substances. There are three types of these covers. The first is hypertonic content of NaCl gauze, also known as Mesalt, which is applied on exuding wounds with the debridement need. The second type is iodne impregnated gauze, or hyiodine and iodine-povidone. This gauze is used on the infected skin ulcers. The last type is vaseline impregnated gauze, which performs wound and its surrounding protection. It also supports wound bed hydration. Cover forms are sterile and unsterile cover of random size with nonocclusive, adhesive and absorption features. There are some undesirable effects like wound edges maceration, adhesion and healthy granulation tissue drying. It also the need of frequent rebandages, during which may be damaged wound edges so extra cover is required. As advantages could be considered its cheapness and is suitable those types of patients who requires frequent rebandages due to an early infection.

Alginates are sterile, soft and notwoven wound cover. It is also nonocclusive, nonadhesive, humidity keeping absorption cover. It consists of highly absorption alginate fibres from brown seaweed. Sodium and calcium salts of alginic acid are in a various ratio. Alginate covers are applied on the surface ulcers and have bacteriostatic and hemostatic effect. By releasing of Ca2+ ionts supports local hemostasis and also are

suitable for the afterdebridement bleeding wounds. Ca2+ or K+ ionts replace Na+ gradually in the exudate. Thanks to this process, the alginate fibres fall apart and convert themselves to a hydrophilic viscous gel which covers the wound bed making optimal humidity. Primary cover for flesh and deep wounds including infected ones. Alginates are not suitable for dry wounds and dry necrosis covered wounds. It is not recommended to apply then on the wound with insufficient secretion and to the alginate hypersensitivity patients. Alergy could be undesirable effect but its advantage is large absorption of exudate. The proper use is to apply them only on the wound bed and cannot overlap to the edges. Always remove remains during the rebandage. Requires secondary cover (gauze or film cover in the dry wounds). Rebangades are usually done every 2 or 3 days, depending on the secretion. Specific types of alginates are alginates with additives which provide steril and nonwoven wound cover with a silver and alginate addition. Differs according to specific product.

•SilverCel – alginate fibres, carboxymethylcellulose (CMC) and X-STATIC fibres covered with Ag^0

•Acticoat absorbent – Ca-alginate, nanocrystalline Ag^0 SILCRYST

•Askina Calgitrol Ag – Ca-alginate, Ag^+ ionts and polyurethane foam

Alginate covers for the widespread ulcers, have bacteriostatic, bactericidal and hemostatic effect, and form optimal humidity on the wound bed. Applied on the flesh, deep infected wounds with medium to heavy secretion (except of Askina Calgitrol Ag), and is not suitable for dry wounds. Side effect could be adhesion of cover on the wound bed or wound bed pigmentation with Ag^+ ionts. As an advantage could be considered antibacterial effect with protection against the exudates. Applied only on the wound bed without edges overlap. Requires secondary cover (Stryja, 2008). In medicine, alginates are used as a Ca-alginate covers on post-operative scars, burns, bedsores and chronic ulcers. In food industry can be found as a stabilizer, thickener or as a gellant (E404) (Adams *et al*., 2012).

2.2 *Aloe vera* gel

Aloe vera is a medicinal plant with cactus appearance from the Aloaceae family. It is a succulent herb, reaching from 50-80 cm height. Grows in hot dry climates (Ernst

& Vogler, 1999), has yellow flowers and the leaves are from pale to grey-green arranged in a rosette configuration, covered with white spots up to 50 cm long with branched floral stem (Hoskovec, 2007, Shelton, 1991). Other variety of Aloe is *Aloe ferox*, which is a perennial succulent plant that can be 5 m high. On the top of the straight, woody, 30 cm thick stem grows lanceolate leaves up to 90 cm long. The leaves are dull green and sometimes have bluish or reddish tinge. The fruits are capsules up to 3 cm long (Svobodová, 2012). *Aloe* attracted attention of medical scholars in recent and is known for its medicinal purposes and as a medicinal plant has been used for a long time. Each part of the plant has its special application (Molazem et al., 2015). The *Aloe vera* gel, chemically mannose-6-phosphate, is consists of amino acids, lipids, sterols and polysaccharides, such as pectin and hemicellulose and is stored inside the leaves and is used for healing of different types of wounds. *Aloe vera* gel derived from the leaf pulp of the plant has become a big industry worldwide due to its application in the food industry (Ahlawar & Khatkar, 2011). On the surface of the leaves, there is a yellowish bitter sap that has laxative properties and contains antrakoin compounds.

Several studies have been conducted on the wound healing effect. As a result, it reduces wound and inflammation of the mucous membrane of the mouth and *Aloe vera* mouthwash was effective in healing of the wound and reducing the inflammation. *Aloe vera* gel is effective in healing the first and second degree burning wounds without any side effects and also accelerates the dermic injuries like wounds, frostbites, inflammations, and cutaneous infections. Furthermore supports forming of collagen and epithelial cells and reduces inflammation and desiccation. As a conclusion, it can be said that *Aloe vera* gel is appropriate and economic dressing for a lots of wounds and can be also used in suntan screens, shaving foams, lipbalms and facial masks (Sharma *et al*., 2013, Molazem *et al*., 2015). Another benefit is in the healing of haemorrhoidectomy. In people with chronic wounds, one trial found no statistically significant difference in pressure ulcer healing with *Aloe vera* and in a trial of surgical wounds healing by secondary intention *Aloe vera* significantly delayed healing. Clinical heterogeneity precluded meta-analysis. The poor quality of the included trials indicates that the trial results must be viewed with extreme caution as they have a high risk of bias (Dat *et al*., 2012). *Aloe vera* gel is a beneficial treatment and cost effective for patients with chronic ulcers. The use of *Aloe vera* gel in chronic ulcer is recommended in developing countries

to lessen the financial burden. (Avijgan *et al*., 2016). In contrast, Schmidt & Greenspoon (1991) in one study reported delay in wound healing after the application of *Aloe vera*.

2.3 Flavonoids

Flavonoids consist of a large group of polyphenolic compounds having a benzo-γ-pyrone structure, are ubiquitously present in plants, and commercially extracted from *Citrus limon* and *Citrus sinensis* of Rutaceae family. *C. limon* is a small, evergreen tree grows to 3-6 m high with green branches, oblong leaves and flowers leaves intensely fragrant. The fruit is a berry sizes up to 14 x 8 cm and are harvested 3 times a year. *C. sinensis* is evergreen tree with its height from 8-15 m. Flowers are intensely fragrant as well as *C. limon.* The whole tree is very similar to *C. limon* (Rak, 2009). Available studies show that secondary metabolites of phenolic compounds including flavonoids are responsible for the variety of pharmacological activities. Flavonoids are synthetized by plants as a response to microbial infection. Their function is also to catch free radicals by chelating metal ions what is the prevention of radical generation, which damage target biomolecules. According to these facts, they are important anti-oxidants and induce human protective enzyme system. The number of reports say that flavonoids also have protective effects against degenerative diseases like cardiovascular diseases, cancers and other age-related problems (Kumar & Pandey, 2013). Anti-oxidants like flavonoids are present in number of wild and exotic plants or fruits, though they are underutilized or not known. Many fruits are consume safe and some of them are developed as medicines. Those wild fruits are rich on flavonoids and anthocyanins. However, in recent years there is an increasing attention wild fruit studies. The investigations proved its bioactive impact, such as antioxidant, antimicrobial anti-inflammatory, and anticancer effects and the wild fruit wild fruits could have the potential to prevent and treat some chronic disease (Li *et al*., 2016).

For this thesis is the most important antimicrobial activity of flavonoids. Several flavonoids including apigenin, galangin, flavone and flavonol glycosides, isoflavones, flavanones, and chalcones have been shown to possess potent antibacterial activity and can have multiple cellular targets, but their antimicrobial activity can be related to their ability in inactivation of microbial adhesins, enzymes, cell envelope transport proteins, and so forth. Catechins, neringerin and sophoraflavanone G acts against

Streptococci and *Staphylococci*. Another study demonstrated inhibitory activity of quercetin, apigenin, and 3, 6, 7, 3′,4′-pentahydroxyflavone against *Escherichia coli* DNA gyrase (Kumar & Pandey, 2013). Flavonoids such as diosmin synthetized from hesperidne that can be found in citrus pericarp have positive effect on microcirculation and lymphatic drainage, fragility, permeability or venous tonus and inflammatory process inhibition. They can be also used for reducing vascular resistance. For treating haemorrhoids, varicose ulcers and for wounds or ulcers edema are used in tableted or gel cures (Tong *et al*., 2013).

2.4 Enzymes

Significant enzymes in wound healing are bromelain and papain. Bromelain comes from *Ananas comosus*, which is a tropical herbaceous perennial plant up to 150 cm tall with an edible food from family Bromeliaceae. Stem grows from the centre of the rosette. The stem can be up to 30 long. Flowers are blue and later purple. It is cultivated in several varieties. Its origin is probably in the South America and still grows in this area (Kovář, 2007). Papain comes from latex of *Carica papaya* (Caricaceae), which is large, tree-like perennial herb, up to 10 m tall and up to 75 cm long leaves. The stem is straight and unbranched with greyish cinnamon colour. On the surface, there are visible scars from old leaves petiole. The fruit is a pear-shaped berry weighing 2-10 kg. Originally grew in the Central America, however currently is spread in tropics and subtropics (Kovář, 2008). Bromelain belongs to group of protein digesting enzymes obtained from pineapple stem or fruit and is considerably absorbable in the body without losing its proteolytic activity and without producing any major side effects. It takes part in lot of therapies treatments such as angina pectoris, bronchitis, sinusitis, surgical trauma, and thrombophlebitis, debridement of wounds, and enhanced absorption of drugs, particularly antibiotics. Bromelain also relieves osteoarthritis, diarrhoea, and various cardiovascular disorders and has anticancerous effect. Another feature regarding wound healing is reversible inhibition of platelet aggregation. Clinical studies have shown that bromelain may help in the treatment of several disorders. It has effect on cardiovascular and circulation, on immunogenicity, blood coagulation and fibrinolysis, diarrhoea, cancer cells, relieves osteoarthritis and has role in surgery and in burn debridement. Bromelain influences blood coagulation by increasing the serum fibrinolytic ability and by inhibiting

the synthesis of fibrin, a protein involved in blood clotting. Some studies have been made in rats where the reduction of serum fibrinogen level by bromelain is dose dependent. Bromelain can also reduce the average number of days for disappearance of pain and post-surgery inflammation. Another use of bromelain nowadays is to treat sports injuries, reduce swellings and bruising (Pavan *et al.*, 2012). In injuries, it can heal soft tissue disruption or inflammation and protects muscle against ischemic injuries (Rathnavelu *et al*., 2016). In burns is bromelain applied as a cream and is suitable for debridement of necrotic tissue and acceleration of healing as it contains escharase, which is responsible for this effect. Enzymatic debridement using bromelain is better than surgical debridement as surgical incision is painful, nonselective and exposes the patients to the risk of repeated anaesthesia and significant bleeding. In the future, there is a potential of use for oncology patients from the development of oral enzyme therapies. There can be also used debriding gel dressing (DGD), which is a bromelain-based enzymatic medical grade agent derived from the stems of pineapples that results in rapid and selective debridement of the necrotic eschar. It represents new alternative method to surgical and non-surgical eschar removal strategies and is minimally invasive to organism. This gel is known as Nexobrid® (Pavan *et al.*, 2012, Rosenberg *et al*., 2015).

Papain is a phytotherapeutic agent extracted from the latex of unripe *Carica papaya* that has been using in treating eschars and as a debriding chemical agent to remove or necrotic tissue of pressure ulcers and gangrene. In spite of its widespread use, there is a little known about its mutagenic and toxic properties. Leaves of *Carica papaya* are used as a poultice to treatment of infected wounds and burns, especially the green papaya that is used for dressing ulcers and is recommended to other chronic skin ulcers treatment. In spite of its extensive use, the following disadvantages were described, as problems concerning the availability of green papaya and difficulties in preparing and storing papaya. Papain is the similar enzyme to human pepsin. The literature states that the proteolytic enzyme papain interacts with partially degraded collagen in the necrotic tissue of carious lesions, causing additional softening of this tissue. This proteolytic action likely occurs only in the necrotic tissue. (Júnior *et al*., 2015, da Silva *et al*., 2010). Papain ointment is used for enzymatic debridement and together with bromelain, are used in treatment of arthritis and arthrosis and is being studied for topical applications on burns, irritations, and wounds. It has also been used for ulcers and bedsores. Traditional cultures in Hawaii and Tahiti made poultices out of the skins of papaya, as this part of the fruit is

particularly concentrated in papain. They applied it to the skin to heal wounds, burns, rashes and bug stings and it also is a powerful antioxidant (Edward, 2011, Sharma *et al*., 2013).

2.5 Benzoic acid

Can be extracted from tree *Styrax benzoin* (Styracaceae), also known as Gum benjamin tree, Kemenyan, Onycha or from a tree called *Myroxylon balsamun* (Fabaceae). *Styrax benzoin* is an evergreen tree that can grow up to 10 meters tall. The bark is gray or brown and the leaves are pointed, oval, around 14 cm long and 5 cm wide with fine gray hairs on the lower surface. The flowers form small clusters and are white, bell-shaped and fragrant (Storluson, 2017). *Myroxylum balsamum* a large and beautiful tree with a valuable wood like mahogany, and a straight smooth trunk; the last is coarse grey, compact, heavy granulated and a pale straw colour, containing a resin which changes from citron to dark brown; smell and taste balsamic and aromatic. Leaves alternately, abruptly pinnate, leaflets two pairs mostly opposite, ovate, lanceolate with the end blunt emarginate; every part of the tree including the leaves abounds in a resinous juice. The mesocarp of the fruit is fibrous, and the balsamic juice, which is abundant, is contained in two distinct receptacles, one on each side. The flowers have very intensive fragrance (Grieve, 2017). Benzoic acid occurs in a pure form as a colorless or needles of leaflets and is one of the oldest chemical preservative used in the cosmetic, drug and food industries. Naturally is present in several foods and commodities like fruit, spices, milk and fermented products, such as beer, black teas and wines. Benzoic acid is responsible for antimicrobial activity as the undissociated molecule. It is reported that antimicrobial effect is efficient in a strongly acidic solution than in the neutral one. It inhibits microorganisms like *Bacillus cereus, Escherichia coli, Staphyloccocus aureus, Pseudomonas* spp., *Aspergillus* spp. *Penicillium* spp. etc. Benzoic acid could be combined with other chemical compounds like sorbic acid and with physical environment changes like temperature and pH to get better antimicrobial results (Davidson *et al*., 2005). In medicine is used in chemical debridement as a cream and solutions in combination with other compounds like malic, salicylic acid and propylene glycol through chemical degradation of necrotic tissue and wound disinfection. In food industry serves as

a preservative (E210) and is added to drinks, fruit products, mustard, chemically yeast dough and spices with pH lower than 4, 5 (Rosen *et al*., 2015).

2.6 Extract of *Centella asiatica*

Centella asiatica, also known as Asiatic pennywort or Indian pennywort is a small, herbaceous, frost-tender perennial plant from Apiaceae family and grows in tropical swampy areas (Sri Lanka, Madagarscar, India). It is a thin perennial with long internode. Leaves are simple and heart-shaped at the base with long petioles. The brownish flowers are small and fruit contains two seeds. Extract from this plant is a rich source of natural bioactive substances, triterpenoid saponins, flavonoids, phenolic acids, triterpenic steroids, amino acids and sugars. *Centella´*s free radicals show anti-inflammatory activity and affect S*tratum corneum*, which is the outermost layer of the epidermis, consisting of dead cells, by hydration and epidermal barrier function. The most important isolated constituents are terpenoids like asiaticoside, centelloside, madecassoside, moside, thankuniside, sceffoleoside, centellose, as well as triterpenic acids such as asiatic, centellic, madecassic and terminolic acids. Among the various chemicals the most important chemicals due to their dermatological and pharmacological activity are, asiaticoside, madecasosside, asiatic acid and madecassic acid. *Centella asiatica* also contains other compounds like flavonoids, phenolic acids, amino acids, sugars, vitamins and essential oils and other volatile constituents in about 0.1% concentration. It has been known, that most important therapeutic activity of this plant are antioxidant, anti-inflammatory, antimicrobial and anti-carcinogenic and in dermatology is used for treating small wounds, hypertrophic wounds as well as burns, psoriasis and scleroderma. The constituents of *Centella asiatica* are able to increase the blood microcirculation in the skin and prevent excessive accumulation of fat in cells (Ratz-Lyko *et al*., 2016). Next important fact is that it supports the formation of collagen and decreases formation of stretch marks and inflammatory reactions in curative medicine by ointments and has been reported that 1% *C. asiatica* extract cream improves wound healing of chronic ulcer in width, length and depth after 7, 14 and 21 days of use of the product. In addition, an oral *C. asiatica* extract capsule has been proved to be effective in promotion of wound healing and scar suppression in patients with diabetes-related wounds, with no serious side effects (Somboonwong *et al*., 2012). *Centella asiatica* could also affect the human nervous

system consisting of the brain, spinal cord, and peripheral nerves because as its antioxidant function reduces oxidative *in vivo* and *in vitro* stress. At the *in vitro* level, *C. asiatica* promotes dendrite arborisation and elongation, and protects the neurons from apoptosis. *In vivo* studies have shown that the whole extract and individual compounds of *C. asiatica* have a protective effect against various neurological diseases. Most of the *in vivo* studies on neuroprotective effects have focused on Alzheimer's disease, Parkinson's disease, learning and memory enhancement, neurotoxicity and other mental illnesses such as depression and anxiety, and epilepsy (Lokanathan *et al*., 2016).

2.7 Tea tree oil

Also known as Melaleuca or Ti tree oil is extracted from an evergreen tree or a tall shrub *Melaleuca alternifolia*, family Myrtaceae, as terpene hydrocarbons, mainly monoterpenes, sesquiterpenes, and their associated alcohols. *M. alternifolia* originates in Australia. It is up to 5 meters tall with leaves 2-5 cm long and blooms with white flowers. The tree is very durable deep rooted tree. It became popular in recent decades for its antiseptic and anti-inflammatory actions. Tea tree oil is produced by steam distillation of the leaves and terminal branches of *M. alternifolia*. Once condensed, the clear to pale yellow oil is separated from the aqueous distillate. The yield of oil is typically 1 to 2% of wet plant material weight. Alternative extraction methods such as the use of microwave technology have been considered, but none has been utilized on a commercial scale. As an antimicrobial agent, the crushed leaves were inhaled to treat coughs and cold or were sprinkled on wounds, after which a poultice was applied (Carson *et al*., 2006). Tea tree oil also has abilities to inhibit bacteria like *Staphylococcus aureus* and *Escherichia coli*. Clinical studies with tea tree oil products have shown efficacy for a range of superficial infections, including acne, cold sores, tinea, and oral candidiasis. It has antiviral and antifungal activity too (Hammer *et al*., 2012). Tea tree oil is used in curative cosmetics such as creams, gels, body milks and shampoos for treating small wounds, burns, acne, insect bites and also as a disinfection (Thomas *et al*., 2016).

3 Traditional medicine on the Pacific islands

Traditional medicine (TM) describes a group of health care practices and products with a long history of use referring to medical knowledge developed by indigenous cultures that incorporates plant, animal and mineral-based medicines, spiritual therapies and manual techniques designed to treat illness or maintain wellbeing. The major herbal medicines used are ointments and dressings applied to surface wounds and to treat skin problems. The World Health Organization (WHO) defines traditional medicine as the sum total of the knowledge, skills and practices based on the theories, beliefs and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health, as well as in the prevention, diagnosis, improvement or treatment of physical and mental illnesses. TM is practiced sometimes outside of allopathic medicine, which is known as biomedicine or Western medicine that is mainly used in developed world. In many cultures, TM functions as a comprehensive system of health care refined over hundreds or thousands of years. Some of the best-known TM systems include traditional Indian (Ayurveda) medicine, traditional Chinese medicine, and traditional Arabic (Unani) medicine. In the Pacific regions, such as, Melanesia, Micronesia and Polynesia, TM is primarily used for wound healnig and treating ghost sicknesses. However, folk remedies are also used for treating classic ailments, such as diarrhea, cough, fever etc. (Abbott, 2014, WHO, 1998).

3.1 Geography and ethnology

Pacific islands are located in the Pacific Ocean and consists of three ethnogeographic groupings – Micronesia, Melanesia and Polynesia. However conventionally excludes the neighbouring island continent of Australia, the Asia-related Indonesian, Philippine, and Japanese archipelagoes, and the Ryukyu, Bonin, Volcano, and Kuril island arcs that project seaward from Japan. It also does not include the Aleutian chain or such isolated islands of the Pacific Ocean as the Juan Fernández group off the coast of South America. However, Micronesia, Melanesia and Polynesia will be described in the next chapter. The more inclusive term Oceania, in its broadest definition, encompasses all the foregoing. The Pacific Islands region covers more than 800.000 km^2 containing combination of independent states, associated states, integral parts of non-Pacific Island countries, and dependent states (Foster & West, 2016). Oceania can be also divided into four different sub-regions based on the geologic processes playing a role in their physical development. Those sub-regions are Australia because it is located in the

middle of the Indo-Australian Plate in separation, islands found on collision boundaries between the Earth's crustal plates, especially in the South Pacific. The third region are volcanic islands, also known as high islands (McDaniel *et al.*, 2012), such as Fiji, typically rising from the seafloor through hotspots in the Pacific Ocean basin. Major part of these areas consist of very small islands with high mountain ranges. The last type of landscape are coral reef islands and atolls, also known as low islands like Tuvalu. These islands are made of the skeletons and living bodies of small marine animals, which are called corals (McDaniel *et al.*, 2012, Rosenberg, 2016).

Climate in Oceania is divided into two climate zones. The first of these is temperate and the second is tropical. Most of Australia and all of New Zealand are within the temperate zone and most of the island areas in the Pacific are considered as tropical. Oceania's temperate regions features cold winters and warm to hot summers. The tropical regions in Oceania are hot and wet year round. The climate is also impacted by trade winds and hurricanes called cyclones in Oceania. Cyclones have caused catastrophic damage to countries and islands in the region. Australia and New Zealand concentrate the majority (about 75 %) of the Oceania population. The remaining population of Oceania is scattered around the various islands making up the region. Like the distribution of population, the urbanization and industrialization also vary. Australia and New Zealand have 89 % of urbanization and industrialization and well established infrastructure. Very important part of incomes is from agriculture, fishing and tourism (Rosenberg, 2016).

Ethnicity is perceived to be grounded in differences of descent and origin. The total membership of other ethnic groups of Pacific Islanders is about 7300. Colonialism and economic transformation play a significant role in shaping structural and behavioural dimension of cultural identity. Oceania was colonized by waves of migration emanating from Southeast Asia. The first waves, which occurred during the Paleolithic, colonized Melanesia and Australia. These migrants could easily reach Melanesia and Australia due to the lower sea level during the Paleolithic. Later waves, which occurred during antiquity, colonized Micronesia and Polynesia, however, the origin of Polynesians is still remains a mystery. The native peoples of Melanesia and Australia are quite dark-skinned, while the peoples of Micronesia and Polynesia are generally lighter in complexion (Anonymous, 2010, Gale, 2008). In Oceania, there are some specific ethnic groups, such as on Fiji, there is a community of people called Rotumans (from Rotuma island),

Calcuttas (from northern India) and Madrassis (from southern India). Maori people occupies New Zealand, Cook Islands and Tahiti. In Melanesia can be found numerous self-defined, distinct groups in a small area, such as Kainatu and Mandok. In Micronesia, there are Banabanas. (Linnekin & Poyer, 1990, Unesco, 1979). However, a very limited amount of information about ethnic groups in Oceania is available.

From the northwest to southeast, forming of Melanesia begins with New Guinea (the western half of which is called Papua and is part of Indonesia, and the eastern half of which comprises the independent country of Papua New Guinea) and continues through the Solomon Islands, Vanuatu (formerly New Hebrides), New Caledonia, Fiji, Maluku Islands and numerous smaller islands. The Andesite Line, a geological feature of extreme volcanic and earthquake activity. It separates Melanesia from Polynesia in the east and from Micronesia in the north, along the Equator. In the south, Melanesia is bounded by the Tropic of Capricorn and Australia. The name Melanesia was derived from the Greek *melas* 'black' and *nesoi* 'islands' because of the dark skin of its inhabitants. In the early 21st century, the population of Melanesia was approximately 10 million (Kahn & Keesing, 2011).

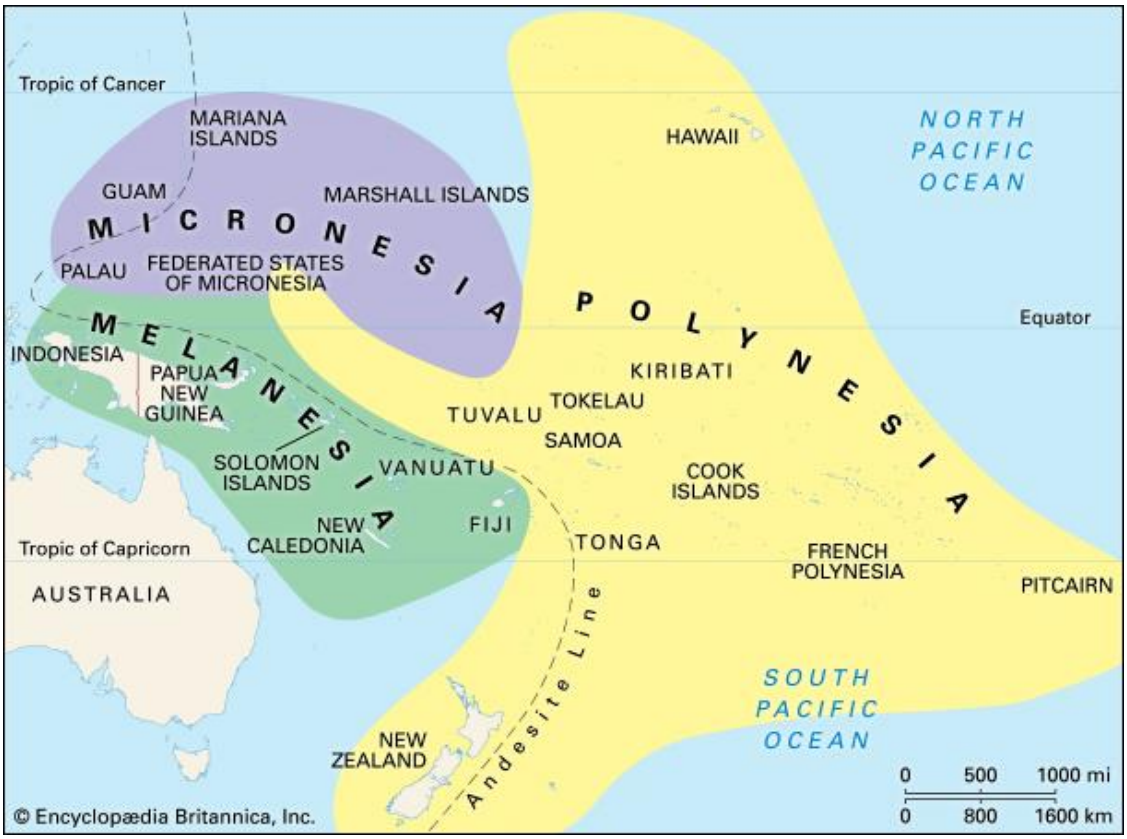
Micronesia lies between the Philippines and Hawaii and includes more than 2,000 islands. The most of the islands are small and many of them are found in clusters. The region includes, from west to east, Palau (also known as Belau), Guam, the Northern Mariana Islands (which include Saipan), the Federated States of Micronesia (which include Yap, Chuuk, Pohnpei, and Kosrae), the Marshall Islands (which include Enewetak, Bikini, Rongelap, Kwajalein, and Majuro), Nauru, and Kiribati (formerly the Gilbert Islands, and which includes Banaba, formerly Ocean Island). Micronesia is located for the most part north of the Equator, includes the westernmost of the Pacific Islands. Micronesia comes from Greek and means *mikros* 'small' and *nēsoi* 'islands' (Fischer *et al.,* 2011). Polynesia unfolds in a huge triangular area of the east-central Pacific Ocean. The edge lies at the Hawaiian Islands in the north and its base angles at New Zealand (Aotearoa) in the west and Easter Island (Rapa Nui) in the east. It also includes (from northwest to southeast) Tuvalu, Tokelau, Wallis and Futuna, Samoa (formerly Western Samoa), American Samoa, Tonga, Niue, the Cook Islands, French Polynesia (Tahiti and the other Society Islands, the Marquesas Islands, the Austral Islands, and the Tuamotu Archipelago, including the Gambier Islands), and Pitcairn

Island. In the beginning of the 21st century, about 70 % of population of Polynesia lives in Hawaii. The name Polynesia is from Greek and means *poly* 'many' and *nēsoi* 'islands' (Suggs *et al.*, 2011). For seeing placement of the single islands in Oceania, see the map below.

3.1.1 Melanesian folk medicine

In comparison with another Pacific regions, not much information is available about folk medicine in Melanesia, whereas Fiji, Vanuatu and New Caledonia are regions

Figure 1. Map of Melanesia, Micronesia and Polynesia (Foster & West, 2016)



were the folk medicine is described more in details. From the little information, it can be said that most of the healers live and operate in the rural area, the knowledge is given from generation to generation and very few of the healers can be found in the cities.

In Fiji, the healers are middle-aged males or females who gained their knowledge from their parents. This family tradition begun in India. A majority of them consult on a part-time basis only on certain days of the week, e.g. Mondays, Thursdays and Saturdays. Since their services is free, they earn their living by small-scale farming and sometimes by gainful employment. However, most patients bring unsolicited donations of money, food and clothing. There are identified two types of specialist healers

– the herbalist and the spiritualist. Herbalists treat almost entirely by prescribing herbal remedies which he himself provide or which are prepared by the patient by following the healer's instructions. The necessary ingredients are usually obtained from plants growing in the vicinity of the healer's or patient's dwelling or some distance from it (Singh, 1986). In cases where bark or root bark is used, the cork layer that might contain foreign matter is removed by scraping. The inner bark is then removed and utilized in medicines. The "squeeze method" consists of wrapping the plant part in a clean cloth and then dipping and squeezing the whole repeatedly into a coconut shell cup of fresh water (Weiner, 1970). The method of diagnosis use by the herbalist is in many ways same to those of the medical doctor. As in Western medicine, the herbalist listens to the patient's descriptions of the symptoms and he also make observations and examinations of his own. Depending on the complaint, this involves watching the patient's gestures, enquiries into the health history of the patient's relations and status of his biological functions, and visual examination of various parts of the body, e.g. eyes, skin, tongue, muscle tone, etc. Sometimes, the healer provided remedies based on the diagnosis made by the Western doctor. On the other hand, the spiritualist usually make their diagnose by listening to the patient's complaints and then by other maneuvers, such as holding the patient's head (around the forehead) or hands or by placing the palm of his hand on the patient's head. Some rather unusual techniques were encountered. In one case, a block of clear camphor resin was held in a closed fist by the patient while the healer (a female) chanted an incantation. The camphor was then held up to the light to reveal silhouettes of various shapes which then were used by the healer to interpret the affliction. The prescribed cure can take several forms: wearing of the *dora* (yellow or black thread) around the neck or waist, rubbing of coconut oil on part or whole of the body, tasting and sprinkling over self or in the house of water of *bhabut* (ash). A *trzbigh* (a miniature copper container fill with blessed materials and sealed waterproof) is worn on a thread around the neck or waist. These cures sometimes involve the chanting of *mantras* (mystic incantations) and the blessing of the curing agent (*doru*, water, *bhabut*, etc.). Observance of certain taboos and restrictions can be necessary for the prescribe cure to be effective like eating of meat or other foodstuffs, drinking alcohol, engaging in certain activities, etc. Further, the prescribed regimen may need to be followed for a fixed (usually odd) number of days at the end of which period a prayer session and offering was required (Singh, 1986).

In Vanuatu most people consider western “hospital medicine” (Bislama: *hospitel meresin*) or “white man’s medicine” (*meresin blong waetman*) and “leaf medicine” (*lif meresin*) or “traditional medicine” (*kastom meresin*) as elements, which create one comprehensive medicinal system. Most common illnesses throughout the country are dermatological and gastrointestinal complaints, followed by respiratory ailments and diseases related to the urogenital system. While diarrheal diseases and pneumonia are still common mortality causes in children under five, cerebrovascular and ischemic heart disease, as well as diabetes mellitus, increase among the adults. Ethnobotanical studies of Vanuatu report that local people are generally familiar with medicinal plants and everyone knows at least a few recipes. Individuals experienced in therapies are called *kleva*s and most often are from *Kastom* high ranks. Some inhabitants, especially those on Loh island, strongly rely of tradition medicine, as western medicine is barely accessible. Medicinal plant knowledge is transmitted from mother to daughter and father to son in a strict “same-gender manner” and is conserved within families. On the Ambrym Island, traditional medicine is used to cure minor troubles and diseases caused by magic, since western doctors are now within reach for everyone. In southwest Ambrym, every member of a village was an expert for a specific sickness. Knowledge on plants and traditional medicine is usually inherited from generation to generation, from mother to daughter and father to son. However, these rules can be modified and knowledge can be passed on intersexually from father to daughter or mother to son or even to third parties. On the Aneytium Island, everyone knows at least some plants and recipes and a few elders were especially experienced in more complicated rituals as well as secret knowledge of special plants and sophisticated potions. Nowadays, traditional medicine is only used for the treatment of diseases, which are not curable by western medicine, e.g. those with a magical origin. Dominating families are Euphorbiaceae and Fabaceae, followed by Asteraceae, Convolvulaceae, Moraceae and Zingiberaceae. Most remedies are taken internally, followed by those for the treatment of skin diseases as well as washing solutions for eyes, mouth, hair or body, which were applied externally. Four species, mainly use for magical purposes have to be planted in special places in order to be effective. Ashes from dry leaves or bark and cataplasms, generally prepare from leaves or fresh inner bark, are used to treat or seal wounds. (Billo *et al*., 2005, Bradacs *et al*., 2011).

Traditional remedies in New Caledonia contain natural antimicrobials, which are ingested by patients when New Caledonian healers recommend medicinal plants in curing Tuberculosis-related symptoms such as blood in the sputum, cough or fever (Billo *et al*., 2005). Microbial infections are an important health problem throughout the world, and plants are a possible source of antimicrobial agents. Some members of the Cunoniaceae family are reputed to have medicinal and antimicrobial properties and are used in some cultures to treat various diseases. These are treatment of symptoms of ciguatera (foodborne illness caused by eating certain reef fish whose flesh is contaminated with a toxin made by dinoflagellates such as *Gambierdiscus toxicus* which live in tropical and subtropical waters), treatment of tiredness, headaches and fever or treatment of infected wounds (Fogliani *et al*., 2002). Annonaceae are known to contain polyphenols, terpenes, acetogenins, and alkaloids. They are also frequently described in folk medicines and numerous species show strong bioactivities, such as insecticidal or antitumoral activities. *Celastrus paniculatus* of Celastraceae is a traditional ayurvedic medicinal plant used because of its various neuroactive properties, especially for its oil content. However, most of the New Caledonian members of this family remain unexplored (Coulerie & Poullain, 2016).

In Maluku Islands, there is a tree called nutmeg (*Myristica fragrans).* In the Maluku Province, nutmeg oil is used for various medicinal purposes. In the past it was used to treat stomach and kidney disorders. Nowadays it is used to cure a condition called 'masuk angin,' which includes most flu symptoms, the Maluku people rub the oil all over their body to get a warm, strengthening feeling. The oil is specifically rubbed on the abdomen to relieve stomach aches and on the forehead to alleviate headaches (Vangils & Cox, 1994).

Several traditional practices including herbal treatment and other types of folk medicine are still in widespread use in Solomon Islands. Christian missions initially introduced Western biomedicine and other services, and the government later took over the supply and support of these services. However, their availability is still limited in rural communities. Despite this fact, many people use modern drug medicine followed by herbal medicine and massages. Modern drugs are usually used to treat fever, headaches and muscle aches. It should be noted that the study village also has a tradition of treatment using shells and other faunal resources. Folk medicine is commonly used in an absence

of nurses or in less serious cases. One of the most important use is that folk medicine is used for the treatment of *putuputu,* an illness with an indigenous name and aetiology. In summary, most of the folk medical practices will likely be switched for effective Western-biomedical alternatives, but others, although limited in number, persist as culturally indispensable treatments for indigenous illnesses (Furusawa, 2006).

This is a brief review of Melanesian folk medicine but as I said before, a lack of information about this topic is available.

3.1.2 Micronesian folk medicine

As well as in previous chapter, Micronesian folk medicine is not widely explored. It is probably the least explored region of the Oceania. Areas that has been investigated somehow are Marshall Islands and Guam. The inhabitants of Micronesia gained their about native species over many centuries of experience. This knowledge is inherited from generation to generation. Traditional medicine contains materials from one or more species and several of them in use as medicinal preparations are common knowledge. The healing mixtures can contain earth, coral or other non-plant materials, so it seems that there is a lack of specificity of a plant being used for a particular illness.

In the Marshall Islands, the most of the traditional medicinal practise is focused on mothers and their babies. For example, after the childbirth, mother drinks a beverage made from coconuts, to relieve stomach cramps and eliminate discharge of fluids associated with childbirth. To recover from childbirth and relive a constant hunger and to smooth skin and restore body strength, it is recommended to steep green and healthy *Konnat (Scaevola sericea)* leaves in a gallon of water and drink it slowly. In the Marshall Islands, there are many plants that are used in daily medicine and which can be prepared by Marshallese people only but they are not licensed to be sold in the pharmacy. *Vitex trifolia* can be used as a mosquito repellent. Typical plant on the Marshall Islands are *Cocos nucifera, Colocasia esculenta, Tacca leontopetaloides, Crinum asiaticum, Artocarpus altilis, Tournefortia argentea, Morinda citrifolia, Premna serratifolia, Scaevola sericea* and *Turnera ulmifolia* (Nandwani & Dasilva, 2003).

In Guam, herb doctors are called *suruhanos* (males) or *suruhanas* (females). These healers are commonly middle-aged and every village has its own healer, although some of them achieved island-wide fame. The people who utilize their services carefully guard their names and activities. Some evidence indicates that it is a common belief

among the people who use the herb doctors that most *suruhanos(-as)* are supposed to have been born by breech birth and that to be a *suruhano(a)* one must renounce his Christian beliefs so as not to offend ancestral spirits. Persons from one area are not generally accepted by a *suruhano(-a)* from another area inasmuch as the ancestral spirits involved may not be known by the *suruhano(-a)* from the other district. This helps to account for the number of "local" practitioners found in each village. However, a *suruhano (-a)* will accept a patient from another area if the affliction is believed to have been caused by an ancestral spirit from his area. In general, most of the sicknesses are blamed on an offense by the victim against the ancestral spirits or *taotaomona* (Chamorros who have been killed and are believed to inhabit their old districts, not as ghosts or gods, but as men of supernatural strength). Most of the medicines include a variety of plant parts (leaves, stems, and roots) and occasionally less socially desirable material such as urine, ash of fire, and bumed chicken feathers. Often medications are accompanied by a massage, generally with coconut oil. Many herb medicines are very simple in both preparation and applications. Breadfruit flower (*Artocarpus altilis*) is used to dry the eyes. Intestinal parasitism is treated by having the afflicted chew and swallow seeds of a ripe papaya (*Carica papaya*). Many of the herbs and their uses are common knowledge, but each year fewer people actually use the medicines (Fletcher, 1971).

Due to the lack of available information, data about Palau, Northern Mariana Islands, Nauru and Federated States of Micronesia were not collected.

3.1.3 Polynesian folk medicine

Traditional medicine from Polynesia is probably the largest and most explored traditional medicine in Oceania. First mentions about Polynesian medicine were brought to Europe by seafarers. In the past, local healers usually used combination of plant material and prayers. In Western Polynesia, the treatment of external ailments such as weapon wounds, cuts, fractures, sprains, scratches, rashes, skin infections and burns were a major concern of Polynesian healers. They preferred traditional folk medicine rather than supernatural remedies. The healers relied on the power of the herbs so there was no need for the priests. However, the surgeons of Eastern Polynesia were very often priests, but this do not have to been the case in Western Polynesia (Whistler, 1992). William Mariner is probably the best-known source of information regarding healing practices in

early Tonga (McGrath, 1999). In Tonga, the most important operations were projectile wounds caused by spears, arrows and lances. In Europe, these kinds of wounds were fatal very often, due to the following infection. Once the arrow was extricated, a folded and oiled piece of banana leaf was inserted into the wound for drainage leading to patient full recovery. Surgeon´s instruments consisted of bamboo knives, bits of broken shell, coconut leaf midribs serving as a probe and for amputations served a stone axe. An early wound dressing, described by Captain Cook, consisted of chewed sugar cane pulp applied to a gunshot wound. In Tokelau, wounds were washed and covered with a wad of *maile* (*Phymatosorus scolopendria*) leaves. Skin diseases was treated by rubbing off body scabs with a coconut husk and applying an ointment made from bread fruit pulp. Bamboo ash was used on burns and the smoke of *Incocarpus fagifer* on war wounds (Whistler, 1992). The leaves, heated over a fire, were formerly applied to superincision (the technical term for the Polynesian form of circumcision) wounds. This was also reported in both, Tonga and Samoa (Whistler, 1988). Strong tradition of surgery and treatment of wounds was in Tuvalu. In spite of very primitive but effective instruments, local healers were able to operate subcutaneous tumors, leprous tissue and the massive accumulation of scrotal tissue resulting from elephantiasis (Whistler, 1992).

Eastern Polynesia consists of islands, such as New Zealand, Hawaii, Tahiti etc., which are not included in this thesis, so this part will be described very briefly. Description of the treatment of injuries in Eastern Polynesia date back to the discovery of Tahiti by Captain Wallis in 1767. There were also used saps from trees, leaves and leaves themselves to treat wide scale of wounds. In surgery, the instruments used by healers were very primitive, such as shark´s-tooth lancelets and probes made of bone in the Marquesas. Similar like in Western Polynesia, shark´s teeth were used in Tahiti to lance abscesses and boils. Blood-letting (withdrawal of blood from a patient to cure or prevent illness and disease) is widespread throughout Polynesia. Both projectile wounds and broken limbs were also successfully treated. In Tahiti, Bamboo splints were used for broken arms, similar to the current practice in Tonga. As with blood-letting, European medical practices may have inspired the use of splints on broken arms. Another feature of Polynesian medicine is massage. Unlike surgery or treatment of disease, it belonged to the realm of folk medicine and is commonly practiced by women or young girls, not by priests or surgeons. Massage was and still is used to treat fractures and dislocations. Also servers to relieve fatigue of muscles, headaches, and general aches and pains, and to shape

the body features of young children. In summary, native surgeons often skilfully treated injuries like broken limbs and war wounds. They were perhaps more successful than the European ones. Treatment included massages and steam baths. The major herbal medicine used in Polynesia were cathartics (possibly emetics), ointments and dressings applied onto the surface of the wounds and skin problems. Fetid herbal preparations used externally or internally were believed to have the power to repulse malicious spirits and to thereby heal and are widely used today (Whistler, 1992).

Nowadays, despite the long exposure to Western culture, most Polynesians still retain a faith in the indigenous methods of treatment performed by native healers. However, the Western medicine is also utilized for many health problems. Simultaneous using of traditional and Western medicine does not produce any contradiction, because people believe that some ailments are treated better with folk medicine, while the others by Western one. Some specific cures have been used for as long as anyone can remember, but new remedies are tried all the time. Polynesians share common cultural origin with Melanesia so the concepts of illness are very similar and is difficult to compare them. In this thesis, Western Polynesia folk medicine is represented by Tonga and Samoa meanwhile Eastern by Cook Islands (McGrath, 1999, Whistler, 1992).

Tongan medical practices can be divided into two types: those employed by the general population (folk medicine) and those employed by medical specialists called *kau faito´o*. Most Tongans know certain number of folk remedies for treating simple ailments. For example a wad of chewed *talatala* (lantana) leaves is applied to cuts and guava leaves are chewed to treat stomachache. Traditional and biomedical healing may on occasion use the same substance or.device, such as a pharmaceutical tablet or an orthopedic splint, but the rationale behind their use is not shared (McGrath, 1999). The ailments can be divided into three categories – *fasi, hangatamaki, ´avanga*. *Fasi* can be something that is broken ruptured in the body, such as broken bone, strained ligament or improperly healed injury. *Hangatamaki* includes boils, rashes, skin diseases, many types of swellings and tumors. For skin ailments, such as boils and sores, the juice form plant is spread (*vali*) or dabbed (*popokahi*) onto the skin as an ointment. Soft plant material can be chewed and spit out (*puhi*) onto the ailment.or macerated by rubbing between the hands (*milimili*). The third type *´avanga*, also called *fakamahaki*, represents ailments caused by spirit. Spirit-caused illnesses belonged to the priest who conveyed divine directives (Whistler,

1992). If the priest's particular god had nothing to say about a particular case, after one or two days another priest would be consulted (McGrath, 1999). Most Tongan medicines are infusions, but boiling is required in the preparation of a few of them. Medicines taken orally are called *vai*. One particular specialist healer is able to heal a broken limb with a coconut spathe (*toume*) to immobilize the arm. This woody spathe can be easily removed, so the patient can receive a regular massage and application of medicine, like infusions and Tongan oil.

As well as in Tonga, Samoa has two different systems of medical care – Samoan and the Western one, however, the Western medical care is officially sanctioned and in the recent years, there has been an effort to combine these two medical cares to improve the health practices. Despite the recent improvements, major part of the medical care is still handled by folk healers, because most Samoans still believe that many indigenous diseases cannot be successfully treated with Western medicine, so there are some remedies which date to the pre-European times; some of these were widely used in Polynesia and can even be traced to Southeast Asia. These include *Achyranthes aspera* (circumcision wounds), *Terminalia catappa* (stomatitis), *Sigesbeckia orientalis* (wounds), *Wollastonia biflora* (wounds), *Calophyllum inophyllum* (eye ailments), *Hibiscus rosa-sinensis* (easing childbirth), *Syzygium maluccense* (stomatitis), *Oxalis corniculata* (childhood ailments), *Morinda citrifolia* (boils and stomatitis), *Centella asiatica* (childhood ailments), *Curcuma Zonga* (sores) and *Zingiber zerumbet* (enteritis). Several other plants, such as *Vigna marina* and *Euodia hortensis*, are widely used in Polynesia for treating "ghost sicknesses" (*fakemahaki*), but evaluation of these would be difficult because of the vague and unscientific nature of the target ailments (Whistler, 1991). Minor, not life-threatening injuries, are healed by local healers. Most of the healers are middle-aged or elder women but men commonly treat injuries like broken bones (Whistler, 1992). To summarize, except for a group of basic remedies known to nearly all Samoans, the practice of Samoan herbalism is carried on by a subspeciality of healer called *taulasea*. Samoan *taulasea* are usually women who learned their craft from their mothers or other female relative. There are very few remaining Samoan herbalists. Those who still offer their service are very old and seldom have apprentices who are learning their knowledge. Samoan ethnomedicine differs significantly from Western medicine in its descriptions of disease aetiology. As a result many Samoan diseases are not directly translatable into Western terminology. When a healer diagnoses a disease requiring herbal

treatment, she will immediately begin to collect the necessary plant materials, since only fresh plants are used. (Cox, 1993). Not every injury requires visiting the healer, because it is commonly known, that bleeding cut can be treated by rubbing it with the leaves of *fue saina* (*Mikania micrantha*). *Hernandia* spp is quite popular medicinal plant in Samoa used onto boils, abdominal pains, to ease menstrual etc. (Dittmar, 1991). Child´s mouth infection can (*pala*) be treated with the bark of *mago* (mango) and ringworm (*lafa*) with the leaves of *la´au fai lafa* (*Senna alata*). Ailments in Samoa are divided into three classes called *mumu, ma´i* or *ila*. *Mumu* refers to swellings and inflammations (Whistler, 1992). These external ailments like wounds, swellings and sores were probably treated in a more scientific way. The affliction was clearly visible, as was the effectiveness of the treatment (Uhe, 1974). *Ma´i* is the general word for sickness and *ila* includes number of unrelated childhood ailments and has no precise medical definition. As well as in the other Polynesian states, the concept of ´´ghost sickness´´ is very similar in Samoa too. As well as Tongan medicine, Samoan also appears to be weak on diagnosis. A diagnosis is usually made retrospectively based upon the medicine judged to have affected the cure. Sometimes the patient can be taken to the hospital until the cure is found, but it is not usual for the patient to undergo treatment at the hospital meanwhile receiving traditional medicine. Many Samoan plants grows also in Tonga, but they have different usage in the most of the cases. Sometimes the inhibition of bacteria growth do not correlate with the effect of the same plant in Tonga. Samoan and Tongan medicines are prepared similarly. Massages are practiced for strains, soreness and fracture and are important part in bone setting, as well as in the rest of Polynesia (Whistler, 1992).

The Cook Islands were inhabited by Tahitians years before Captain Cook discovered them, so Tahiti and Cook Islands show similarities in culture including many in their medical practices. Inhabitants of the Cook Islands and New Zealand are called Maoris. Maori medicine can be divided into two categories. The first simple cures known to and practiced by all (folk medicine), and the other involving semi-specialists broadly known as *ta´unga*. However this term means and expertise in some traditional practice like boat building, carving, or healing. Maori medicine is based on treating simple and easily understood ailments, such as chewed leaves of *piripiri* (*Bidens pilosa*) which is applied to cuts (Whistler, 1985) and *poroporo* (*Solanum americanum*) to boils and carbuncles. The more complicated ailments are left to the curative powers of the *ta´unga*. The *ta´unga*s involved in massages or diagnoses practice very little herbal

medicine. Those who use native remedies are called *ta´unga vai rakau* just to be distinguished from the others. Some of them specialize in certain kind of ailments, such as cancer, diseases of infants, or digestive maladies, but many have remedies for a wide variety of ailments. Most of the healers are older women and the knowledge is learned from older relatives. It is believed that the power of *ta´unga* is an unsolicited gift from God and it is considered to be proprietary of an individual or family and the remedy is not effective for those who use it without permission. The healers do not receive money for their service. Their reward is prestige and satisfaction. There is one exception in non-commercialize use. It is the recent appearance of a remedy called ´´Ma´uke miracle oil´´, which is comprised mainly of coconut oil and *pi´euna* (*Talinium paniculatum*). It is sold in local stores and has curative properties for cuts and other minor ailments. Maori ailments have two categories. The first is *maki tangata* including all natural illnesses and injuries, and *maki tupapaku*, which includes diseases caused by ancestral spirits known as *tupapaku* (Whistler, 1985). In the possession of an ancestral spirit, the sufferer´s behaviour is irrational and disoriented and can include incredible strength when resisting physical restraint. Recovering from possession is talking trough the possessed person. The *ta´unga tupapaku* who is treating the ailment sometimes go into a trance and speaks in the voice of an ancestor to explain the cause of the ailment. If the treatment is not effective, the patient can be taken to another healer or even to hospital, until the proper cure is found. Local healers believe that on rainy day the efficiency of the herbs decreases. The most commonly used parts of the plant are bark (*kiri*), leaves (*rau*), leaf buds (*kao*), and rhizomes or roots (*aka* or *kiko*). Bark is usually cut in strips and the other parts are crushed with a mortar and pestle. A crushed plant material is placed in a piece of cloth or the mesh from base of a coconut frond (*kaka*) and squeezed into a vessel of water or into coconut cream oil. Most of the medicines are infusions, but some require boiling. Major part of Maori remedies consists of one to three ingredients. Maori *vai rakau* (medicine) distinguished two type – external and internal. External are rubbed and spread onto boils, carbuncles, burns, sores and rashes. Fractures and sprains (*´ati*) are soaked in cold *vai rakau ´ati* and massaged. Steam baths are occasionally given for *maki tupapaku*. Internal medicines are taken as potions. They are often given in a five-day cycle. The potion is taken three days in a row, followed by day off and on the fifth day a purgative is administered to rid the body of the harmful residue (*repo kino*) of the medicine or illness. Much of the medicine is practiced for the infants, because it is believed, that those are

untreatable with Western medicine. There are also some treatments used on a wounds of a stonefish or ´´sting´´ of the poisonous spines. The healers have remedies for these wounds, but there is a little uniformity in the herbs used in wound healing. Some of them are applied to the area of puncture, but others are put on the top of the head, or in case of a hand puncture, onto the uninjured hand. Because of wide diversity of herbs used in treatment of this kind of wound, it is doubtful whether the medicine have much therapeutic value (Whistler, 1992).

In spite the Polynesia is the most explored area in Oceania, there are islands, such as Kiribati, Pitcairn Islands, Easter Islands and Wallis and Futuna, which remain unexplored in local traditions and medicine.

4 Aims

The aim of this study is analysis of literature data on plants used in folk medicine of Melanesian, Micronesian and Polynesian Pacific islands for wound healing. The identification of the plant species that are the most prospective for further pharmacological and phytochemical research is specific goal of this analysis. Ethnobotanical data such as scientific names, synonyms, families, origins, local names, parts used and traditional way of application of selected plants are summarised as the main output of the work. In addition, the thesis provide overview of the wound treatment and physiology of wound healing process.

5 Materials and Methods

A systematic literature review was performed using databases, such as Web of Knowledge, PubMed, and Google Scholar from their inception until March 2017, and due to manual search of relevant journals, textbooks, and bibliographies. No language restriction was applied. Primary search terms used were ‘folk medicine’ ‘wound healing’ ‘Melanesia’ ‘Micronesia’ and ‘Polynesia’. The web-based database of International Plant Name Index was used to determine the correct scientific names of the selected plants. In this thesis, as a wound are mainly defined cuts, burns, sores, boils, sprains, fractures, bites and swellings.

6 Results and Discussion

Through a literature review, 150 plant species belonging to 66 families, which are distributed and used in traditional medicine for wound healing in Pacific islands, were identified. The scientific names of selected plant species (in alphabetical order), local names, location, parts used and traditional medicinal uses are shown in the Table 1.

The most abundant families used for wound healing in folk medicine of Pacific islands are Euphorbiaceae (13), Rutaceae (6), Malvaceae (6), Piperaceae (6) and Solanaceae (6). The most common genera are *Piper* (4), *Ficus* (3), *Ipomoea* (3), *Macaranga* (3), *Stachytarpheta* (3) and *Solanum* (3). At the present time, several species that are of worldwide industrial importance frequently used as foods and medicines. These species are *Aloe vera, Carica papaya, Citrus* spp., *Cocos nucifera, Morinda citrifolia, Piper* spp., *etc*. In contrast, there is relatively high number of endemic species used in Pacific folk medicine. For example *Piper graeffei* is an endemic specie of Samoa and Fiji (Smith, 1943). Waldren *et al.* (1995) claims, that *Santalum insulare* is indigenous specie to Pitcairn Islands but Butaud *et al*. (2007) said that it can be found on French Polynesia either. The most explored area is Polynesia, which is, also the largest, then is Melanesia and the least explored is Micronesia.

The most widespread plant on Pacific islands used in wound healing is *Calophyllum inophyllum*, which can be found on Vanuatu, New Caledonia, Fiji, Cook Islands, French Polynesia, Kiribati, Marshall Islands, Samoa, Salomon Islands, Tonga, Tokelau and Futuna and is used on skin injuries from burns and infected wounds. *Carica papaya* is a cosmopolitan fruit, which grows on Cook Islands, Samoa, Tokelau, Marshall Islands, Tuvalu and Niue and is used on cuts and boils, skin infections and as a vermifuge (an agent that destroys or expels parasitic worms). Another plant is *Morinda citrifolia*, which grows on Cook Islands, Tokelau, Samoa, Marshall Islands, Fiji, Futuna and Niue and in folk medicine, is used on sting of the stonefish (applied on the head), boils, sprains, fractures, skin infections, and abscess or as a wound dressing. *Capsicum annuum*, commonly known as pepper, is considered as another quite expanded plant growing on Fiji, Cook Islands, Samoa, Tokelau, Tuvalu, Niue and Tonga and traditional healers use it onto swellings, circle around a boil, infected cuts or wounds and abscess. *Artocarpus altilis* is a staple crop, which can be found on Samoa, American Samoa, Tonga, Futuna, Cook Islands and Tokelau and treats ailments such as sprains, fractures, eye wounds, sores and boils.

Table 1. Wound healing medicinal plants of Pacific islands								
No.	**Scientific name**	**Synonymus (IPNI, Plant list)**	**Family**	**Country**	**Local name**	**Part used**	**Use**	**Reference**
1	*Achyranthes aspera*	*Centrostachys aspera, Stachyarpagophora aspera, Achyranthes velutina*	Amaranthaceae	Samoa, Tonga, Tokelau, Niue, Cook Islands	Lau tamatama, Vao tuitui (Tok., S.),La ´au latatala (S.), Tamatama (To., Fut.,Tuv.), Talamoa fisi (Ni.), Piripiri (CI.)	leaves, juice from leaves	healing of wounds, snake and insect bites, circumcision	Castro et al (2001), Whistler (1996), Sotheeswaran et Sotheeswaran (1999), Uhe (1974),Whistler (1992), Whistler (1991), Whistler (1988)
2	*Acronychia laevis*		Rutaceae	Vanuatu, New Caledonia	Nengone (NC.)	wood and leaves	cicatrization	Billo et al (2005)
3	*Ageratum conyzoides*	*Carelia conyzoides, Eupatorium conyzoides*	Asteraceae	Vanuatu, Fiji	Noragidi (V.), Botebotekoro (F.)	juice from leaves	squeezed from leaves to healwounds	Bradacs et al (2011), Singh (1986)
4	*Aglaia samoensis*		Meliaceae	Samoa	Laga´ali (S.)	inner bark	infected sores	Uhe (1974)
5	*Aleurites moluccana*	*Aleurites moluccanus*	Euphorbiaceae	Samoa, Tonga, Niue, Futuna, Cook Islands	Lama (S.), Tuitui (Ton., Ni., Fut., CI.)	bark, seed, roots	skin and head sores, skin fungi, healing of wounds	WHO (1998), Whistler (2000), Whistler (1992), Uhe (1974)
6	*Allium sativum*		Alliaceae	Fiji	Lesun, Lahsun (F.)	juice of crushed bulbs	sores	Singh (1986)
7	*Aloe vera*	*Aloe perfoliata*	Aloaceae	Tonga, Cook Islands, Samoa	Aloe (Ton.), Cactus (CI.)	broken leaves,	cuts, burns, wounds	Whistler (1992)
8	*Alphitonia zizyphoides*		Rhamnaceae	Western Samoa			swellings	Dunstan et al (1997)
9	*Alpinia purpurata*		Zingiberaceae	Samoa	Teuila (S.)	fruits	sores	Uhe (1974)

Table 1. Continues

10	*Amaranthus gracilis*	*Chenopodium caudatum*	Amaranthaceae	Cook Islands	Va´ine´ara (CI.)	crushed plant	burns	Whistler (1985)
11	*Artocarpus altilis*	*Sitodium altile*	Moraceae	Samoa, American Samoa, Tonga, Futuna, Cook Islands, Tokelau	Ulu (S., Tok.), Mei (Ton., Ni., Tuv., Fut.), Kuru (CI.)	milky latex, leaves, sap	healing of wounds, sprains, fractures, eye wounds, sores, boils,	Whistler (1992), Whistler (1985), Whistler (1988), Dunstan et al (1997)
12	*Artocarpus communis*		Moraceae	Samoa	Ulu (S.)	petiole	eye wounds, sores	Uhe (1974)
13	*Azadirachta indica*	*Melia azadirachta*	Meliaceae	Fiji	Nim, Neem (F.)	leaves	boils, burns	Singh (1986)
14	*Bambusa vulgaris*		Poaceae	Samoa	Ofe, Ofe Fiti (S.)	leaves	burns, wounds	Uhe (1974)
15	*Barringtonia asiatica*		Lecythidaceae	Samoa, Cook Islands, Tuvalu, Tokelau	Futu (S.), Utu (CI.)	seed, fruit, roots, grated seeds	skin sores, wounds, vermifuge, burns	Whistler (2000), Uhe (1974), Whistler (1985), Whistler (1988)
16	*Bidens pilosa*	*Bidens leucantha, Ceratocephalus pilosus, Kerneria pilosa, Kerneria tetragona*	Compositae	Cook Islands, Tonga, Niue	Piripiri (CI.), Fisi´uli (Ton.), kofe Tonga (Ni.)	leaves	cuts, boils	Whistler (1985), Whistler (1992)
17	*Bischofia javanica*		Euphorbiaceae	Western Samoa Samoa, Tonga, Futuna, Niue, Cook Islands	O´a (S.), Koka (To., Fu., Ni,. CI.)	leaves	boils, sores, burns, cracks on feet	Dunstan et al (1997), Uhe (1974), Whistler (1992)
18	*Brassica campestris*	*Brassica sativa, brassica rapa, gorinkia campestris*	Brassicaceae	Fiji	Sarson (F.)	powdered seeds with castor oil	burns, insect bites	Singh (1986)

Table 1. Continues								
19	*Bryophyllum pinnatum*	*Cotyledon pinnata*	Crassulaceae	Fiji	Motta patti (F.)	toasted leaves	sprains, bruises, swellings	Singh (1986)
20	*Cajanus cajan*	*Cytisus cajan*	Fabaceae	Fiji	Arhar (F.)	boiled leaves	wounds	Singh (1986)
21	*Calophyllum inophyllum*		Calophyllaceae, Guttiferae, Clusiaceae	Vanuatu, New Caledonia, Fiji, Cook Islands, French Polynesia, Kiribati, Marshall Islands, Samoa, Salomon Islands, Tonga, Tokelau, Futuna	Tamanu (Cl), Pua (?), Fetau (S., Ni., Tu.), Feta´u (To.), Silo (Fu.)	Bark, fruit, latex, leaves	skin injuries from burn, scar and infected wounds	Leguillier et al (2015), Whistler (1988), Uhe (1974)
22	*Canavalia rosea*	*Canavalia apiculata (Piper), Canavalia arenicola (Piper), Canavalia obtusifolia (Lam.), Canavalia maritima (Aubl.), Dolichos emarginatus (Jacq.), Dolichos roseus (Sw.), and Dolichos maritimus*	Fabaceae	Solomon Islands, New Caledonia	Awikiwiki? (SI., NC.?)	leaf extracts	treat burns, stop bleeding	Mendoza-Gonzáles et al (2014)
23	*Capsicum annuum*	*Capsicum futescens*	Solanaceae	Fiji, Cook Islands, Samoa, Tokelau, Tuvalu, Niue, Tonga	Mircha (F.), ´Oporo (Cl.), Polo, Polo feu (S.), Polo fifisi (To.), Polo mangiho (Ni.)	poultice of ground fruit, mashed leaves, leaves, fruit,	swellings, circle around a boil, infected cut or wound, abscess	Singh (1986), Whistler (1985), Whistler (1988), Uhe (1974), Whistler (1992)
24	*Carica papaya*	*Papaya carica*	Caricaceae	Cook Islands, Samoa, Tokelau, Marshall Islands, Tuvalu, Niue,	Nita, Vi nita, Vi puaka (Cl), ´Ehi (Tok.), Olesi (Tu.) Keinabbu, Kainapu (Ml.), Lesi (To.), Loku (Ni.) Papaya (?), Paw Paw, Esi (S.)	green fruit, sap, roots, leaves, seeds	cuts and boils, skin infections, vermifuge	Whistler (1985), Whistler (1988), Nandwani (2003),Uhe (1974), Whistler (1992)
25	*Cassia alata*	*Senna alata*	Caesalpiniaceae	Samoa	La´au Fai Lafa (S.)	leaves	snakebite	Uhe (1974)

Table 1. Continues

26	*Cayratia trifolia*	*Vitis trifolia*	Vitaceae	Vanuatu	Awur (V.)	juice from stalk	wounds, severe wounds	Bradacs et al (2011)
27	*Centella asiatica*	*Hydrocotyle asiatica*	Apiaceae, Umbelliferae	Samoa, Tonga, Niue, Futuna, Cook Islands, Fiji	Tono (S., To., Ni.), Togo (S.), Tona (Fu. ?), Kapukapu, To´etupou (CI.), Brahmi (F.)	leaves, leaves juice	boils, swellings, eye injuries, bone fractures	Uhe (1974), Whistler (1992), Singh (1986)
28	*Cerbera manghas*	*Tanghinia manghas*	Apocynaceae	Samoa	Leva (S.)	leaves	skin sores and skin infections	Whistler (2000), Uhe (1974)
29	*Citrus spp.*		Rutaceae	Samoa	Moli (S.)	bark	bone fractures	Uhe (1974)
30	*Clerodendron inerme*		Verbenaceae	Samoa	Alo Alo Tai (S.)	plant	wounds	Uhe (1974)
31	*Clitorea ternatea*		Leguminosae	Fiji	Koyal booty (F.)	crushed leaves, juice of leaves	sprains, sores, stop bleeding	Singh (1986)
32	*Cocos nucifera*	*Calappa nucifera (L.)*	Arecaceae, Palmae	Vanuatu, Cook Islands, Tokelau, Marshall Islands, Samoa	Lihol, Natora, Kav(u)ra, Navara, Samsam, Kokonas (V.), Nu (CI.), Niu (S., Tok.), Ni (MI.)	outer bark, crushed husk, sheath, endosperm, root, juice, pounded leaves and fruits, oil	ash to heal wounds, fractures, sprains, broken limbs (support), open sores, cut from poisonous fish, abcess, burns	Bradacs et al (2011) Whistler (1985), Whistler (1988), Nandwani (2003), Uhe (1974)
33	*Colocasia esculenta*	*Arum esculentum*	Araceae	Samoa	Taro, Talo (S.)	leaves	boils	Uhe (1974)
34	*Colubrin asiatica*	*Ceanothus asiatica*	Rhamnaceae	Samoa	Fisoa (S.)	leaves	bone fractures	Uhe (1974)
35	*Commelina diffusa*		Commellinaceae	Samoa	Mauutoga (S.)	leaves	to staunch bleeding of cuts	Whistler (2000)
36	*Cordyline fruticosa*	*Convallariafruticosa*	Agavaceae	Samoa, Tonga, Futuna, Niue, Cook Islands	Ti (S., Fu.), Si (To, Ni)	leaves, juice	swellings, burns	Whistler (1992)
37	*Cordyline terminalis*		Agavaceae	Cook Islands, Samoa, Tokelau	Rau Ti (CI.), Lau Ti (Tok.), Ti (S.)	young leaves, leaf and root juice	burns, cuts	Whistler (1985), Whistler (1988), Uhe (1974)

Table 1. Continues

38	*Crinum asiaticum*		Amaryllidaceae	Samoa, Tokelau, Marshall Islands	Lau talotalo (Tok.), Kieb (MI.)	membrane at the base of the leaves, leaves, trunk	boils, splintered limbs (support)	Whistler (1988), Nandwani (2003)
39	*Curcuma longa*		Zingiberaceae	Cook Islands, Samoa, Tonga, Futuna, Niue, Fiji	Renga (CI), Ago (S., To., Fu., Ni.), Hardi, Haldi (F.)	grated, powdered rhizome	treating septic puncture wounds, sores, sprains, bruises	Whistler (1985), Uhe (1974), Whistler (1992), Singh (1986)
40	*Cyanthillium cinereum*	*Conyza cinerea*	Asteraceae	Vanuatu		juice from leaves	healing of wounds	Bradacs et al (2011)
41	*Cynodon dactylon*	*Panicum dactylon*	Poaceae	Fiji	Doob (F.)	rubbed leaves	cuts, bruises	Singh (1986)
42	*Cyperus rotundus*		Cyperaceae	Samoa	Mumuka (S.)	bulbs	wounds	Uhe (1974)
43	*Datura spp*		Solanaceae	Fiji	Dhatur, Dhatura (F.)	juice of leaves	boils, sores	Singh (1986)
44	*Diplazium latifolium*		Woodsiaceae	Vanuatu	Libarr (V.)	frond	cataplasm for wounds	Bradacs et al (2011)
45	*Eucalyptus spp.*		Myrtaceae	Tonga	Pulukamu (To.)	decoction from leaves	cuts	Whistler (1992)
46	*Eugenia corynocarpa*		Myrtaceae	Samoa	Sea Sea (S.)	leaves	boils, wounds, body blows	Uhe (1974)
47	*Euodia hortensis*		Rutaceae	Futuna, Tonga	Usi (F.), Uhi (To.)	leaf infusion, leaves	swellings, boils	Whistler (1992)
48	*Euphorbia atoto*	*Chamaesyce atoto*	Euphorbiaceae	Samoa	A´atasi, Pulutai ufi tamaite (S.)	leaves, whole plant	boils, wounds, abcess	Uhe (1974)
49	*Evodia hortensis*		Rutaceae	Samoa	Usi, Fuapini, Lalatai (S.)	bark	bone fractures	Uhe (1974)
50	*Ficus obliqua*	*Urostigma obliquu, Ficus graeffii*	Moraceae	Tonga, Niue, Futuna, Samoa	´Ovava (To.), Aoa (S.)	bark, leaves	treating wounds, boils	Whistler (1991), Uhe (1974)
51	*Ficus prolixa*		Moraceae	Tonga, Samoa, Futuna	Aoa (S., F.), ´ovava (To.)	chewed leaves, infusion of the bark	boils, wounds	Whistler (1992)
52	*Ficus scabra*		Moraceae	Samoa	Mati (S.)	roots, leaves, inner bark	swellings, burns, injured eye	Uhe (1974)

Table 1. Continues

53	*Fagraea berteriana*		Loganiaceae	Vanuatu, New Caledonia	Bois tabou (NC.)	leaves, heated roots maceration	cicatrization	Billo et al (2005)
54	*Fimbristylis cymosa*	*Iria cymosa*	Cyperaceae	Marshall Islands	Padalijmaan (MI.)	grass	balm for the wounds of diabetic patients	Nandwani (2003)
55	*Flacourtia rukam*		Flacourtiaceae	Samoa	Filimoto (S.)	bark, plant	fractures, swelling	Uhe (1974)
56	*Fleurya interrupta*		Urticaceae	Samoa	Ogo ogo (S.)	young shoots	wounds or infection	Uhe (1974)
57	*Guettarda speciosa*	*Matthiola speciosa, Guettarda hirsuta*	Rubiaceae	Tokelau	Puapua (Tok.)	leaves	boils	Whistler (1988)
58	*Glochidion billardierei*	*Phyllanthus billardierei*	Euphorbiaceae	Vanuatu, New Caledonia	Hmana (?)	leaves	cicatrization	Billo et al (2005)
59	*Glochidion ramiflorum*		Euphorbiaceae	Samoa	Masame (S.)	leaves	wounds	Uhe (1974)
60	*Gossypium arboreum*		Malvaceae	Fiji	Kapas (F.)	burned cotton	wounds	Singh (1986)
61	*Gossypium barbadense*	*Hibiscus barbadensis*	Malvaceae	Tonga	Vavae (To.)	juice from leaves	wounds, abcesses	Whistler (1992)
62	*Heliotropium anomalum*		Boraginaceae	Niue	Toihune fifine (Ni.)	leaves pounded in salt	sprains, fractures, bites	Whistler (1992)
63	*Hernandia ovigera*		Hernandiaceae	Samoa	Ku´a, Pu´a (S.)	bark	boils	Dittmar (1991), Uhe (1974)
64	*Hibiscus rosa-sinensis*		Malvaceae	Samoa, Tuvalu	Aute (S., Tu.)	leaves, flowers	wounds caused by bite ghost, boils, sores, stop bleeding	Whistler (2000), Uhe (1974), Whistler (1992)
65	*Hibiscus tiliaceus*		Malvaceae	Samoa, Cook Islands, Vanuatu	Fau (S.), ´au (CI.), Brao, Burao, Nevar, Lipolwar (V.)	sap from inner bark, young leaves,root, juice	cuts, burns, injuries, sores, fractures,wounds, stop bleeding, anti-hemorrhage, remains to cover the wound	Whistler (2000), Cox (1993), Uhe (1974), Whistler (1992), Bradacs et al (2011)

Table 1. Continues

66	*Homolanthus nutans*		Euphorbiaceae	Samoa	Mamala, Fanuamamala, Fongamamala (S.)	leaves, roots, bark	wounds, sores, cuts	Uhe (1974)
67	*Hoya australis*		Asclepiadaceae	Samoa	Fue selela,´olive vao, Suni (S.)	infusion of the crushed leaves	swellings	Whistler (1992)
68	*Hoya upoluensis*		Asclepiadaceae	Samoa	Fue magoni (S.)	leaves	swellings	Uhe (1974)
69	*Inocarpus fagifer*		Fabaceae	Samoa, Tonga	Ifi (S., To.)	wood and leaves, bark	wounds, burns	WHO (1998), Whistler (1992)
70	*Ipomoea alba*	*Ipomoea grandiflora,Convulvulus grandiflorus*	Convulvulaceae	Samoa	Fue Sina (S.)	leaves	boils, wounds, stings from local nettle	Uhe (1974)
71	*Ipomoea macrantha*	*Convulvulus macranthus, Ipomoea longiflora*	Convulvulaceae	Tuvalu, Tokelau	Fue (Tok.), Fui (Tu.?)	sap from the stems	sores	Whistler (1988)
72	*Ipomoea pes-caprae*		Convulvulaceae	Cook Islands, Samoa	Po´ue, Papati (CI.), Fue fue tai (S.)	leaves	fractures and sprains, swellings, boils, stop bleeding	Whistler (1985), Uhe (1974)
73	*Jatropha curcas*		Euphorbiaceae	Fiji	Wiriwiri (F.)	leaf juice	stop bleeding from cuts and bruises	Singh (1986)
74	*Kleinhovia hospita*		Sterculiaceae	Samoa	Fuafua (S.)	sap from inner bark	cuts and wounds to staunch bleeding	Whistler (2000), Whistler (1996), Uhe (1974)
75	*Lantana camara*		Verbenaceae	Vanuatu, Tonga	Talatala (To.), Latana (S.), Blakvari, Blakberi	juice	healing of wounds, cuts, stop bleeding	Whistler (1992)
76	*Lycopersicon esculentum*	*Solanum lycopersicum*	Solanaceae	Fiji	Tamatar (F.)	juice of fruit	stop bleeding	Singh (1986)
77	*Macaranga dioica*		Euphorbiaceae	Vanuatu	Nafenua, Navenu(e), Nahawanatschill, Nahivaing/Nihivai, Leviunu, Brata blong, Burao, Livinu hanlala, Nafanuha (V.)	juice, young leaves, inner bark, leaf	squeezed from leaves to healwounds, bath in cold infusion, heated leaf to heal wound as a dress	Bradacs et al (2011)

Table 1. Continues

78	*Macaranga harveyana*		Euphorbiaceae	Samoa	Lau pata (S.)	roots	wound healing	Cox (1993)
79	*Macaranga tanarius*		Euphorbiaceae	Vanuatu	Navenu, Livinu, Leviunu tahor, Nehivaing, Nevingne (V.)	juice	as an anti-hemorrhage, juice heated over fire to heal wounds	Bradacs et al (2011)
80	*Macropiper puberulum*		Piperaceae	Samoa, Tonga, Futuna	´ava´ava aitu (S.), Kavakava´ulie (To.), Kavakava atua (Fu.)	leaves, bark	wounds, boil, swellings	Whistler (1992)
81	*Mangifera indica*		Anacardiaceae	Fiji	Aam (F.)	juice of leaves	burns	Singh (1986)
82	*Melastoma denticulatum*		Melastomataceae	Fiji	Kaunisiga, Vidikoso (F.)	chewed leaves	for bad wounds that won´t heal	Weiner (1970)
83	*Messerschmidia argentea*	*Tournefortia argentea*	Boraginaceae	Samoa	Tau suni (S.)	leaves	wounds	Uhe (1974)
84	*Merremia peltata*		Convulvulaceae	Samoa	Fue vao (S.)	roots	bone fractures, bruises	Uhe (1974)
85	*Micromelum minutum*		rutaceae	Samoa	Talafalu (S.)	bark	bone fracture	Uhe (1974)
86	*Miscanthus japonicus*		Poaceae	Samoa	U, Fiso (S.)	leaf juice	eye injuries	Uhe (1974)
87	*Mikania micrantha*	*Willoughbya micrantha*	Asteraceae	Samoa, Niue, Fiji, Vanuatu	Fue saina (S., Ni.), Amerikan rop, Amerika maelminit, Wandei, Tudei (V., F.)	juice from leaves, leaves	wounds to staunch bleeding and prevent infection, stop bleeding, wasp and bees stings, rubbed in hands to heal wounds, heated as cataplasm	Whistler (2000), Whistler (1996), Uhe (1974), Whsitler (1992), Bradacs et al (2011), Weiner (1970),
88	*Mimosa pudica*		Mimosaceae, Leguminosae	Fiji	Lajwania (F.)	leaves decoction	Insect bites	Singh (1986)

Table 1. Continues								
89	*Morinda citrifolia*		Rubiaceae	Cook Islands, Tokelau, Samoa, Marshall Islands, Fiji, Futuna, Niue	Nono (Cl.), Nonu (Tok., Fu., Ni), Nen, Gogu (?), Nonu Vao (S.), Achi (F.)	grated roots, leaves, juice, fruit	sting of the stonefish (on the head), boils, sprains, fractures, skin infections, abscess, wound dressing	Whistler (1985), Whistler (1988), Nandwani (2003),Uhe (1974), Singh (1986), Whistler (1992)
90	*Moringa oleifera*	*Guilandina moringa, Moringa pterygosperma*	Moringaceae	Fiji	Saijan (F.)	leaves ground	dog bite	Singh (1986)
91	*Mosses sp.*			Samoa	Limu Sa (S.)		wounds	Uhe (1974)
92	*Musa paradisiaca*		Musaceae	Samoa, Fiji	Fa´i pata (S.), Kera, Kela (F.)	meristems, green fruit, crushed sucker, dry burnt leaves, green leaves	wounds, burns, injured arms, centipede bites	Cox (1993), Uhe (1974), Singh (1986)
93	*Myristica fragrans*		Myristicaceae	Maluku Islands	Nutmeg (MlkI.)	seeds,oil	sprains	Vangils (1994)
94	*Nerium oleander*		Apocynaceae	Fiji	Kaner (F.)	infusion of leaves	bruises	Singh (1986)
95	*Nothopanax guifoylei*		Araliaceae	Samoa	Tagi Tagi (S.)	roots	wound lotion	Uhe (1974)
96	*Ocimum basilicum*		Lamiaceae	Futuna	Pea, ´ukaki (Fu.)	lotion from leaves	painful swellings	Whistler (1992)
97	*Ocimum sanctum*		Lamiaceae	Fiji	Tulsi (F.)	ground seeds in ghee	sores	Singh (1986)
98	*Omalanthus nutans*	*Homalanthus populifolius*	Euphorbiaceae	Samoa	Mamala, Fanuamamala, Fongamamala (S.)	leaves	circumcision wounds	WHO (1998),Whistler (2000), Whistler (1996)

Table 1. Continues								
99	*Oxalis corniculata*	*Xanthoxalis corniculata, Acetosella corniculata*	Oxalidaceae	Fiji	Amrul (F.)	juice of leaves	open wounds	Singh (1986)
100	*Pandanus tectorius*		Pandanaceae	Tonga	Fa (To.)	juice from the root tips	sores	Whistler (1992)
101	*Peperomia pellucida*	*Piper pellucidum*	Piperaceae	Samoa	Vao vai (S.)	leaves and stems	boils	Whistler (2000)
102	*Phyllanthus niruri*	*Diasperus niruri*	Euphorbiaceae	Fiji	Jar-amla (F.)	juice of leaves	cuts, bruises	Singh (1986)
103	*Phymatosorus scolopendria*	*P. grossus?, Polypodium scolopendria, Polypodium indium, scolopendriae facie, polyphodium phymatodes ??*	Polypodiaceae	Samoa, Niue, Tuvalu, Tokelau	Lau maga maga, Lau auta (S.), Mamanu (Ni.), Maile (Tu., Tok.)	frond, rhizome, leaves, crushed leaves	hard-to-cure wounds, boils, septic wounds, abscess, swellings, cuts, infections, sores	WHO (1998),Whistler (2000), Whistler (1992), Whistler (1988), Uhe (1974)
104	*Plumeria rubra*		Apocynaceae	Cook Islands, Tokelau, Samoa	Tipani (CI.), Pua fiti (Tok.)	sap, scraped bark	sting of the stonefish, wasps, bees and bites of centipedes	Whistler (1985), Whistler (1988)
105	*Piper graeffei*		Piperaceae	Samoa	Fue mangoi (S.)	leaves	infected wounds	Whistler (2000)
106	*Piper methysticum*		Piperaceae	Samoa, Tonga	´Ava (S.), Kava (To.)	leaves	wound dressing, stings and bites	Uhe (1974), Whistler (1992)
107	*Piper puberulum*		Piperaceae	Fiji	Yaqoyaqona, Mavoa, Bibi (F.)	chewed leaves	stop bleeding from serious wounds	Weiner (1970)
108	*Piper tutuilae*		Piperaceae	Samoa	´Ava ´Ava aitu (S.)	stem, leaves, roots	wounds, boils, abcess	Uhe (1974)
109	*Pipturus argenteus*		Urticaceae	Marshall Islands	Armwe (MI.)	leaves, branch	skin infections	Nandwani (2003)
110	*Plantago major*		Plantaginaceae	Tonga	Filo (To.)	leaves	cuts	Whistler (1992)
111	*Plectronia merrillii*	*Psydrax merrillii*	Oliniaceae	Samoa	Olavai (S.)	bark, leaves	bone fractures, burns, sores	Uhe (1974)
112	*Premna taitensis*		Lamiaceae	Samoa	Alo Alo (S.)	bark, leaves	wounds, sores, boils	Uhe (1974)
113	*Premna serratifolia*	*Premna barbata*	Lamiaceae	Samoa, New Caledonia	Aloalo (S.), Hat, Khama, Khamio, Alchadscha, Al, Ari, Veek (NC.)	crushed leaves, bark, leaves	wounds, internal injuries, sores, cicatrization	Whistler (2000), Castro et al (2001), Whistler (1992), Desrivot et al (2007)

Table 1. Continues								
114	*Psidium guajava*	*Psidium pyriferum, Myrtus guajava*	Myrtaceae	Cook Islands, Samoa	Tuava (CI.), Ku´ava (S.)	leaves, tender shoots	cuts, sores, boils, sprains	Whistler (1985), Whistler (1992)
115	*Psychotria insularum*		Rubiaceae	Samoa, American Samoa	Matalafi, Lau matifati, Laumafatifati, Fati Fati (S.)	leaves, meristems	infected wounds, injuries, boils, swellings, abscess, bone fractures	Whistler (2000), Cox (1993), Dunstan et al (1997), Uhe (1974), Whistler (1992)
116	*Rhizophora mangle*		Rhizophoraceae	Samoa	Togo togo (S.)	leaves	wounds, sores, boils	Uhe (1974)
117	*Ricinus communis*		Euphorbiaceae	Fiji	Redh, Redhi (F.)	seed oil	burns	Singh (1986)
118	*Rorippa sarmentosa*	*Cardamien sarmentosa, Rorippa wolgensis*	Brassicaceae	Samoa, American Samoa	Aatasi (S.)	leaves	infected wounds	Whistler (2000),Castro et al (2001), Dunstan et al (1997)
119	*Santalum austrocaledonicum*		Santalaceae	Vanuatu, New Caledonia	Santal, Tapaka (V., NC.)	leaves	vulnerary	Billo et al (2005)
120	*Santalum insulare*		Santalaceae	French Polynesia	A´i, Maramia? (FP.)	Oil	small wounds	Butaud et al (2007)
121	*Scaevola frutescens*	*Scaevola sericea*	Goodeniaceae	Samoa, Tuvalu, Tokelau	To´i to´i (S.), Gahu (Tok.)	bark, fruits	fractures, skin sores	Uhe (1974), Whistler (1988)
122	*Schizostachyum glaucifolium*		Poaceae	Samoa	Ofe (S.)	leaves	burns	Whistler (2000)
123	*Sida rhombifolia*	Malva rhombifolia, Napea rhombifolia	Malvaceae	Samoa, Western Samoa	Matofu (S.)	leaves	cuts, especially infested ones, boils, wounds, burns, deep wounds	Whistler (2000), Whistler (1996), Dunstan et al (1997), Uhe (1974), Whistler (1992)
124	*Siegesbeckia orientalis*		Asteraceae	Samoa, Tonga, Futuna, Cook Islands	´a´ami´a (S.), Kakamika (To., Fu?.), Kamika (CI)	leaves, flowers	wounds, sores	Whistler (1992)
125	*Smilax orbiculata*		Smilacaceae	Vanuatu, New Caledonia	Salsepareille (NC, V.)	leaves	cicatrization	Billo et al (2005)

Table 1. Continues

126	*Solanum nigrum*	Solanum americanum	Solanaceae	Cook Islands	Poro, Poroporo, Poro puaka (CI.)	mashed leaves	circle around a boil, boils	Whistler (1985), Whistler (1992)
127	*Solanum uporo*		Solanaceae	Cook Islands	Poro´Iti (CI.)	leaves	circle around a boil	Whistler (1985)
128	*Solanum viride*		Solanaceae	Tonga	polo Tonga (To.)	crushed leaves	boils	Whistler (1992)
129	*Solenostemon scutellarioides*		Lamiaceae	Samoa	Pate (S.)	leaves	skin sores	Whistler (2000)
130	*Stachytarpheta cayennensis*	*Verbena cayenennsis*	Verbenaceae	Vanuatu	Inchai, Unasuandan, Bluflaoa, Suga (V.)	juice	wounds	Bradacs et al (2011)
131	*Stachytarpheta jamaicensis*	*Verbena jamaicensis*	Verbenaceae	Samoa	Mautofu Vao, Mautofu Tala, Samoaga (S.)	leaves	boils	Uhe (1974)
132	*Stachytarpheta urticifolia*	*Verbena salisburi, Cymburus urticifolius, Zappania urticifolia*	Verbenaceae	Fiji	Lilaiyah (F.)	leaf tea	boils	Singh (1986)
133	*Stephania forsteri*		Menispermaceae	Samoa	Lau latolo (S.)	plant, leaves	boils	Uhe (1974)
134	*Syzygium aromaticum*		Myrtaceae	Fiji	Laung, Lawang (F.)	clove oil	Insect bites	Singh (1986)
135	*Syzygium corynocarpum*	Syzygium corynocarpa, Eugenia corynocarpa	Myrtaceae	Samoa, Tonga, Western Samoa, Futuna	Seasea (S., Fu.), Hehea (To.)	young leaves, chewed and rubbed leaves	skin sores, boils, wounds, severe body blows, swellings	Whistler (2000), Dunstan et al (1997), Whistler (1992)
136	*Tabernaemontana pandacaqui*		Apocynaceae	Vanuatu	Newawedäl, Litschi, Inmathethil (V.)	latex, leaf	wounds, severe wounds?	Bradacs et al (2011)
137	*Tacca leontopetaloides*	*Leontice leontopetaloides*	Taccaceae	Cook Islands, Niue	Pia (Ni., CI.)	strach, crushed leaf stalk	sores, burns, bee and wasp stings	Whistler (1992)
138	*Tamarindus indica*		Leguminosae	Fiji	Imli (F.)	leaves	sprains	Singh (1986)
139	*Tarenna sambucina*	Coffea sambucina	Rubiaceae	Samoa	Ma´anunu (S.)	bark, leaves	bone fractures, wounds, sores	Uhe (1974)
140	*Tectaria latifolia*		Dryopteridaceae	Vanuatu	Rababa-gongon (V.)	frond	as a cataplasm	Bradacs et al (2011)
141	*Tephrosia piscatoria*		Leguminosae	Samoa	Avasa (S.)	stem, leaves, plant	wounds, swellings, sores	Uhe (1974)

Table 1. Continues								
142	*Terminalia catappa*	Buceras catappa	Combretaceae	Cook Islands, Tuvalu, Tokelau, Samoa	Kauariki (CI.), Talie (S., Tu.)	crushed leaves	sprains, fractures, sores, wounds	Whistler (1985), Whistler (1988), Dunstan et al (1997), Whistler (1992)
143	*Thespesia populnea*		Malvaceae	Samoa	Milo (S.)	inner bark, dry wood, leaf infusion	sores, injuries, stop bleeding, eye injuries	Uhe (1974), Whistler (1992)
144	*Trachyspermum ammi*		Appiaceae	Fiji	Ajwain (F.)	seeds ground	boils	Singh (1986)
145	*Triumfetta procumbens*		Tiliaceae	Marshall Islands	Atat, Beach bur (MI.)	Leaves, stem	cuts, open wounds	Nandwani (2003)
146	*Vigna marina*		Fabaceae	Cook Islands, Samoa, Tonga	Pipi, Po´ue, Ka´eta, Keketa (CI.), Fue(fue) sina (S.), Lautolu tahi (To.)	crushed leaves, leaf infusion	sprains, fractures, deep abscesses	Whistler (1985), Whistler (1992)
147	*Wollastonia biflora*		Asteraceae	Tonga	Ate (To.)	juice from leaves	prevent infection, cuts	Whistler (1991), Whistler (1992)
148	*Xylocarpus granatum*		Meliaceae	Tonga	Lekileki (To.)	decoction of the bark	internal injuries	Whistler (1992)
149	*Zieridium melicopaefolium*		Rutaceae	Vanuatu, New Caledonia	Whoo, Wayiü, Sopio (NC., V.)	bark	vulnerary	Billo et al (2005)
150	*Zingiber zerumbet*	Amonum zerumbet	Zingiberaceae	Futuna	Kavapui (Fu.)	rhizome	wounds	Whistler (1992)

Abbreviations: CI – Cook Islands, F – Fiji, FP – French Polynesia, Fu – Futuna, MI – Marshall Islands, MlkI – Maluku Islands, NC – New Caledonia, Ni – Niue, S – Samoa, SI – Solomon Islands, To – Tonga, Tok – Tokelau, Tu – Tuvalu, V – Vanuatu

It is generally known, that Oceania have rich tradition in folk medicine. Despite this fact, the medicinal plants of Melanesia, Micronesia and Polynesia are poorly explored. It can be summarised from available literature, that traditional pacific medicine uses a number of plant species for wound healing purposes. Further pharmacological and phytochemical investigation of these plants could be helpful in the development of new pharmaceutical preparations.

Until present time, several plant species used in traditional medicine of Pacific islands for wound healing have systematically been studied for their pharmacological effects and chemical composition. Several of them are even used in common pharmacological praxis. Typical example is *Aloe vera*. In one of the newest studies, Jahandideh *et al.* (2017) evaluated the healing effect of a poly herbal paste, retrieved from Iranian traditional medicine, containing *Aloe vera*, *Commiphora myrrha* and *Boswellia carteri* using rat excision wound model. In another study on papain gel, derived from *Carica papaya*, noticeably reduce the healing time when applied to dogs with necrotic tissue wounds (Porsani *et al.*, 2016). Possibly the newest report on wound healing effect of *Centella asiatica* is from Azis *et al.* (2017), in which they evaluate the wound healing efficacy via *in vitro* scratch assay and *in vivo* circular wound excision model. According to Dua *et al.* (2016), *Curcuma longa* with combination with norfloxacin is suitable treatment for bacterial infection and burns. *Ricinus communis* was tested for its antibacterial, anti-inflammatory and mutagenic effects in wounds and retained placenta (Luseba *et al.*, 2007).

In contrast to previously mentioned species, there are no modern pharmacological studies on wound healing properties of *Acronychia laevis, Aglaia samoensis, Alphitonia zizyphoides, Amaranthus gracilis, Artocarpus communis, Bambusa vulgaris, Barringtonia asiatica, Bischofia javanica, Canavalia rosea, Cayratia trifolia, Cerbera manghas, Clerodendron inerme, Clitorea ternatea, Colubrin asiatica, Cordyline fruticose, Cordyline terminalis, Crinum asiaticum, Cyanthillium cinereum, Datura* spp.*, Diplazium latifolium, Eugenia corynocarpa, Euodia hortensis, Euphorbia atoto, Evodia hortensis, Ficus obliqua, Ficus prolixa, Ficus scabra, Fagraea berteriana, Fimbristylis cymosa, Flacourtia rukam, Fleurya interrupta, Guettarda speciosa, Glochidion billardierei, Glochidion ramiflorum, Heliotropium anomalum, Hernandia ovigera, Hibiscus tiliaceus, Homolanthus nutans, Hoya australis, Hoya upoluensis, Inocarpus fagifer, Ipomoea alba, Ipomoea macrantha, Kleinhovia hospital, Macaranga dioica, Macaranga harveyana, Macropiper puberulum, Melastoma*

denticulatum, Messerschmidia argentea, Merremia peltata, Micromelum minutum, Miscanthus japonicas, Nothopanax guifoylei, Omalanthus nutans, Oxalis corniculata, Pandanus tectorius, Phymatosorus scolopendria, Piper graeffei, Piper methysticum, Piper puberulum, Piper tutuilae, Pipturus argenteus, Plectronia merrillii, Premna taitensis, Premna serratifolia, Psychotria insularum, Rorippa sarmentosa, Santalum austrocaledonicum, Santalum insulare, Scaevola frutescens, Schizostachyum glaucifolium, Stachytarpheta cayennensis, Stachytarpheta urticifolia, Stephania forsteri, Tacca leontopetaloides, Tabernaemontana pandacaqui, Tarenna sambucina, Tectaria latifolia, Tephrosia piscatoria, Triumfetta procumbens, Smilax orbiculata, Solanum uporo, Solanum viride, Syzygium corynocarpum, Vigna marina, Wollastonia biflora, Xylocarpus granatum, Zieridium melicopaefolium. All of these species has promising potential for further research on their wound healing properties.

Some of these species have already been phytochemically investigated and the results of their analyses show that they can contain compounds with wound healing properties. For example, tetracyclic triterpenoids, compounds present in *Hibiscus tiliaceus*, are possible candidates for study of wound healing properties because of their anti-inflammatory, antioxidant, anti-mutagenic and antidepressant effects (Cheng *et al.,* 2013). In the recent study of Sabandar *et al.* (2017), reported that plant triterpenoids are effective in wound healing. Another example is *Hernandia ovigera* that has been found to contain flavonoids (Novelo *et al.,* 1993). In previous studies, flavonoids exhibited significant *in vivo* wound healing action (Lodhi *et al*., 2016). Besides the alkaloids, *Piper* species contain chalcones, flavonoids and kava-pyrones (Xiang *et al.,* 2016). Because Correa *et al.* (2017) presented in her recent study that chalcones together with flavonols were effective in treatment of wounds using mice as model, it is possible to suppose that these compounds are prospective for further studies. In *Premna serratifolia,* there is a fungi called *Hypocrea virens*, which is known for its antimicrobial activity and which can be useful agent in treating wounds (Ratnaweera *et al.,* 2016). The *Hypocrea* genus also protects the plant against diseases (Hirpara *et al.,* 2017) and due to the content of alkaloids in *Premna serratifolia* there is a possibility for wound healing potential (Rajendran *et al.,* 2008). Photographs of certain species mentioned above are shown in the Appendix.

7 Conclusion

There is a rich tradition in wound healing practices in folk medicine of Pacific islands. In this work based on literature analysis of ethnobotanical data, 150 species of plants used in folk medicine of Melanesian, Micronesian and Polynesian Pacific islands for wound healing have been identified. The results showed that 88 of these species have not previously been investigated by modern pharmacological methods for their wound healing properties. All of these plants are therefore prospective for further pharmacological and phytochemical research focused on identification compounds responsible for their potential effect. These findings can be used by pharmaceutical industry for development of modern herbal-based wound healing preparations.

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9 Appendix of photos of potential species

Figure 2. *Hibiscus tiliaceus*: (College of Natural & Applied Sciences, 2017)

Figure 3.*Hernandia ovigera:* (Stuart GU Jr., 2017)

Figure 4. *Piper graeffei:* (Anonymous, 2016 c)

Figure 5. *Premna serratifolia:* (CSIRO, 2010)