Analysis of Myrmecodia Pendens in Bone Healing Process to Improve the Quality of Life: Literature Review

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Abstract. Myrmecodia pendens is one of the medicinal plants that can provide healing effects, including injuries to the bones. Bone injury can occur due to many things, including injury due to infection, non-infection, degeneration and neoplasm. Bone is the most important part of the body for humans. Decreasing bone function, will affect the human activity, therefore, faster bone healing is needed. The purpose of this article is to study and analyze the role of Myrmecodia pendens on bone wound healing process. Several studies showed that Myrmecodia pendens contains flavonoids, tannins, triterpenoids, saponins, quinones, and glycosides, and anti-inflammatory substances. These materials are markers in the healing process. Myrmecodia pendens was proven to accelerate the healing process. Conclusion showed that Myrmecodia pendens is a medicinal plant that can accelerate the healing process of injury to the bones.

Keywords: Myrmecodia pendens, bone healing.

1. Introduction
Quality of Life (QOL) is the general welfare of individuals and society in general life, where in it contains negative and positive elements of life. To observe the meaning of life satisfaction, it can be seen from many aspects including physical health, family, education, work, wealth, freedom, religious beliefs, and other [1]. QOL has various contexts, including the fields of international development, health, politics and work. In the QOL concept, health factor is an important role, as it can guarantee the failure of other indicators [2].

Bone injury is a case that is quite common in humans. This can occur due to traffic accidents, work accidents, diseases ranging from infections to neoplasm, bones can still get injury. Bone injury must be treated immediately, to ensure optimal health. Bone injury can cause number of complications if not treated properly, for example osteomyelitis or bone necrosis from infection, late healing and more. Economic conditions and insurance rules, make people in Indonesia prefer to get treatment of bone injury in alternative medicine, rather than go to doctors. This often causes many problems for moderate to severe case. For this reason, it is better for people to know natural medicines that are easily available to help accelerate bone wound healing.
Sarang semut (Myrmecodia pendans) is an epiphytic plant from Hydnophytinae (Rubiceae), which is known as natural medicines and has the antioxidant potential. It is believed to heal the wound of several diseases including wound in bones. There are two types of species; Myrmecoda pendens and Myrmecodia tuberosa [3]. Myrmecodia pendans contains bioactive components such as phenolic which include flavonoids, phenylpropanoids, tannins and tocopherols. These antioxidant substances are contained in almost all parts of this plant starting from the stem, twigs to the skin. The active compound contained in the sarang semut is flavonoids, which has antibacterial, anti-inflammatory, antioxidant feature [4,5]. Literature about this plant is still very limited, especially the healing process feature. Therefore, the writer would like to discuss the ability of this medicinal plant of the bone healing process with the aim to provide literature for researchers and readers to get to know about Myrmecodia pendans in the healing process of bone injuries.

2. Method and Material
This article is written with the literature review method, in which we will discuss several studies relating to bone wound healing.

3. Discussion
Myrmecodia pendans is a type of plant that attaches to other plants/parasites which sometimes grow very large and rich with phytochemicals element. Myrmecodia pendans are commonly found in Kalimantan, Sumatra, Papua New Guinea, Philippines, Cambodia, Malaysia, Solomon Islands and Papua [6]. Myrmecodia pendans belongs to the Tracheophyta division of the class Magnoliopsida, subclass Lamiidae, order Rubiales, family Rubiaceae and genus Myrmecodia [8]. Myrmecodia pendans have interactions with ants, where ants make the aisle in the plant tubers as a nest and they make colonies. Eventually there is a natural chemical reaction between the compounds released by ants and the substances contained in the plants themselves. The content of this chemical compound is derived from the flavonoid and tannin groups. Flavonoids act as antibiotics and antiviral, it is also used to treat and prevent several diseases such as asthma, cataracts, diabetes, rheumatism, migraines, hemorrhoids, periodontitis and cancer. Myrmecodia pendans also contains antioxidant compounds, vitamins, minerals and formic acid. Ants antioxidants play a role in the formation of colonies and keep the ants eggs from microorganisms [9].

The process of bone healing --for example bone fractures, principally obtains new bone formation in a short period of time with minimal complications. The healing rate recorded was delayed about 5-10% of cases. The complications causing a delay in healing reported about 18.5% of cases. The acceleration of bone wound healing can also be affected by the presence of biological stimulation. Biological stimulation can significantly accelerate wound healing by stimulating activators and accelerating cell formation [10,11]. The process of bone wounds healing is the same as the healing process in other tissue. The healing process consists of 3 stages. The first phase is the inflammatory phase, this phase begins when injury occurs and there is damage in blood vessels, inducing the hematoma formation and releasing inflammatory mediators. Final result of this phase is callus.
formation of the bone. This phase lasts 5-7 days \([12,13]\). The next stage is the reparative phase. This stage lasts 4-40 days after the first trauma. In this phase callus develops and its growth is 40% of the healing process. Hematoma and callus formed change into mature callus structure caused by the growth of mediators, proteins and calcium so the callus can be seen radiographically \([12,13]\). The last stage is the remodeling phase. This phase makes up about 70% of healing time, occur in 1-2 years. A distinctive feature of this phase is the presence of a continuous bone formation and resorption process. The final result is the formation of a new tissue \([12,13]\).

**Figure 2.** (a) Shows the healing process in the bone from the inflammatory phase where new formation of blood vessel, hematoma and fine callus occur. (b) Reparative phase where there is growth and development of calcium-rich reparative calluses. (c) Finally the resorption phase in which the bone matrix is formed, where the process takes place in the form of resorption and apposition \([14]\).

Bone is an active tissue which will undergo continuous remodeling physiologically. This remodeling process consists of two aspects, the formation of osteoblasts and bone resorption by the activity of osteoclasts. This renewal process lasts a lifetime allowing new bone formation as long as calcium homeostasis remains sufficient for this activity. This activity is achieved and regulated by various systemic hormone actions and local mediators \([15,16]\).

**Figure 3.** Biochemical process of bone remodeling. Describes from 120 days of healing process where several mediators are actively involved in the process \([17]\).
The process of bone remodeling is described as a continuous process, where bone formation and resorption processes continue to occur.[16]

The cycle of bone remodeling takes place starting from the recruitment of osteoclastic precursor cells which will then turn into osteoclasts. Mature osteoclasts will synthesize proteolytic enzymes in charge of digesting the collagen matrix. This bone resorption is the first stage of the renovation cycle. This phase runs very long and under the control of the apoptosis effects carried out by osteoclasts. The next phase of the remodeling cycle is where preosteoblasts from mesenchymal stem cells in the bone marrow to mature osteoblasts which then synthesize bone matrix especially type I collagen and regulate newly formed bone mineralization. Some mature osteoblasts mineralized and turned into osteocytes.[16].

To see the process of bone remodeling, usually by checking the signs of bone remodeling. Examples of bone remodeling biochemical markers, such as in bone resorption processes are hydroxyproline or various cross-links of collagen and telopeptides, whereas markers of bone formation are propeptides from type I collagen, osteocalcin (OC) and alkaline phosphatase (AP).[16]. Biomarkers of bone formation and resorption reflects the overall activity of osteoblasts and osteoclasts in bone.[17]. This marker can also be used as growth and healing marker.[18].

Table 1. Biochemical marker for bone formation [20]

| Marker                                                                 | Tissue origin                      | Analytical sample | Analytical method               |
|-----------------------------------------------------------------------|-----------------------------------|-------------------|---------------------------------|
| Total Alkaline Phosphatase (ALP); specific for bone formation only in patients with no liver or bile duct disease | bone, liver                       | serum             | colorimetry                     |
| Bone alkaline phosphatase (B-ALP); specific osteoblast product; some procedures show cross reactivity with ALP liver isoenzyme | bone                              | serum             | colorimetry, electrophoresis, precipitation, IRMA, EIA |
| Osteocalcin (OC, BGP); specific osteoblast product; there are several reactive forms in blood; some can NASTATI during bone resorption | bone, trophocytes                 | serum             | RIA, ELISA, IRMA, ECLIA         |
| C-terminal propeptide of type I procollagen (PICP); specific proliferating osteoblast and fibroblast product | bone, skin, soft tissues          | serum             | RIA, ELISA                      |
| N-terminal propeptide of type I procollagen (PINP); specific proliferating osteoblast and fibroblast product; partially incorporated into skeletal matrix | bone, skin                        | serum             | RIA, ELISA                      |

IRMA — immunoradiometric assay; EIA — enzyme immunoassay; RIA — radio immuno assay; ELISA — enzyme-linked immunosorbent assay.

ECLIA — electrochemiluminescence immunoassay
Table 2. Biochemical Marker for Bone Resorption [20]

| Marker | Tissue origin | Analytical sample | Analytical method |
|--------|---------------|-------------------|-------------------|
| Hydroxyproline, total and dialyzable (OH-Pro, OHP); specific for all fibrillar collagens and a part of collagen proteins, including C1q and elastin; present in newly synthesized and mature collagen | bone, skin, cartilage, soft tissues | urine | colorimetry, HPLC |
| Pyridinoline (PYD, Pyr); high concentrations in cartilage and bone collagen: not present in skin; present only in mature collagen | bone, tendon, cartilage | urine | HPLC, ELISA |
| Deoxypyridinoline (Dpd, d-Pyr); high concentrations only in bone collagen: not present in cartilage or in skin; present only in mature collagen | bone, dentine | urine | HPLC, ELISA |
| Cross-linked C-terminal telopeptide of type I collagen (ICTP); high proportion from bone collagen in type I collagen; can partly originate from newly synthesized collagen | bone, skin | serum | RIA |
| Cross-linked C-terminal telopeptide of type I collagen (fragments alpha-CTX, beta-CTX); in type I collagen; probably high proportion from bone collagen | all tissue containing type I collagen | urine, serum | ELISA, RIA, ECLIA |
| Cross-linked N-terminal telopeptide of type I collagen (fragments NTX); in type I collagen; big proportion from bone | all tissue containing type I collagen | urine (alpha/beta), serum (only beta) | ELISA, RIA, ICMA |
| Hydroxylysine-glycosides (HyL-Glyc); collagens and collagen proteins; glucogalactosyl-hydroxylysine is highly represented in soft tissue collagens and C1q. Galactosyl-OH-Lys is highly represented in bone collagen | bone, skin, soft tissue, serum complement | urine | HPLC, ELISA |
| Bone sialoprotein (BSP); synthesized by active osteoblasts and lay in extracellular bone matrix; it seems to express osteoclast activity | bone, dentine, hypertrophic cartilage | serum | RIA, ELISA |
| Tartrat-resistant acid phosphatase (TR-ACP); osteoclasts, thrombocytes, erythrocytes | bone, blood | plasma/serum | colorimetry, RIA, ELISA |
| Free gamma carboxyglutamic acid (GLa); resulted from bone proteins (e.g. osteocalcin, matrix Glα protein) and from coagulation factor | blood, bone | serum/urine | HPLC |

Research on the content of Myrmecodia pendans has been studied in several years, especially related to health or prevention and treatment of certain diseases, although research related to bone healing are still rarely found. To find out wheter Myrmecodia pendans has influence, researchers have studied and examined the addition and basic decomposition of certain biochemistry.

Suharyanto and Bambang (2016) conducted a study on experimental animals by adding a liquid extract of Myrmecodia pendans which was administered to several experimental rats. Some mice were given additional DMBA which was believed to cause lung cancer. The results of the study showed that mice given additional infusion of Myrmecodia pendans after suspected lung cancer apparently showed healing with increased appetite [21]. This proved that mice that were sick were able to be cured, but the results of this study could not confirm that intravenous fluids containing Myrmecodia pendans provide a healing effect because no biochemical markers being examined, and the result is only seen based on changes in behavior [22]. A similar study was conducted by Nurul et al (2015), who conducted research on cancer cells in humans where cancer cells were given extracts of active ethanol obtained from Myrmecodia pendans [23]. The results obtained showed that ethanol compounds from Myrmecodia pendans could reduce many cells cancer in humans. In this study, direct examination was carried out on humans where the results were based on histopathological examination; in contrast to the first study the results obtained were more realistic.

Related studies testing the isolation of the Myrmecodia pendans active compound has been carried out by several researchers including: Hertiani et al (2010), who carried out the phytochemical test of the Myrmecodia pendans. In this study immune stimulant tests were conducted which studied
lymphocyte proliferation and phagocytosis of macrophages which were given ethanol extract in n-hexane, ethyl acetate and water fractions with concentrations of 10, 20, 50 and 100 μg/mL. This study provided results where phagocytosis effects of macrophages will be higher when added 50 μg/mL of Myrmecodia pendens extract [24]. Similar studies were also carried out by Muslichah (2013). This study showed the optimal anti-inflammatory activity of 70% ethanol extract, n-hexane fractionation, ethyl acetate fraction, compared with 70% ethanol fraction Myrmecodia pendens. In this study, the results showed that the results of anti-inflammation in the form of 70% total ethanol extract Myrmecodia pendens was better and more optimal when extracted in the form of fractionation [25]. Both of these studies proved that solid healing was accelerated by giving or adding Myrmecodia pendens extracts, this is evidenced by the increase in macrophag activity and anti-inflammation effect.

Satari et al (2012) also examined the phytochemical test of Myrmecodia pendens which carried out the water fraction, n-hexane fraction and ethyl acetate fraction. The fraction carried out contained antibacterial effects on Streptococcus viridans. Similar studies were also conducted by Fatriadi (2014), which showed phytochemical test on the tuber of Myrmecodia pendens which was carried out by the fraction of; water fraction, n-hexane fraction and ethyl acetate fraction [26,27]. The results of research from the same two researchers proved that phenolic, tannin, flavonoid, terpenoid content turned out to have antibacterial effect. These researches proved that Myrmecodia pendens can accelerate the healing process by preventing from microorganisms invasion to the wound.

Research that focuses on the healing process in new bone is carried out by Ismardianita et.al (2017) [28]. This research was conducted by examining the effect of Myrmecodia pendens extracts on healing tooth sockets after extraction, by looking at changes in the expression Transforming Growth Factor-β, Insulin-Like Growth Factors (IGFs) and changes in levels of osteoblasts and osteoclasts. Based on the results of the study, data were obtained that Myrmecodia pendens significantly increased the level of osteoblast, TGF-Factor-β, Growth Factor and decreased levels of osteoclast [26-29]. Although research focused on bone healing is not widely obtained, but in the calculation that Myrmecodia pendens, can be trusted enough to heal bone injuries.

5. Conclusion

The conclusion is the Sarang semut plant (Myrmecodia pendens) contains phenolic, tannins, flavonoids, terpenoids apparently has the ability as antiinflammation, antibacterial, and also has the ability to increase the levels of biochemical markers in the healing process, so that Myrmecodia pendens can be used to accelerate wound healing, especially on the bone so that the Quality of Live of the community can increase.

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