Effects of mix herbs topical and oral therapies on diabetic foot ulcers: a case report
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Background: Indonesia is a tropical country with lots of potential-therapy resource plants, including those for wound care like honey, sea cucumber, black seed and aloe vera. There are other complementaries used by oral such as Radix Rehmanniae Preparata, Panax Ginseng and Gypsum Florosum.

Case presentation: This study case reported the effectiveness of complementary herbs by topical and oral for two patients with diabetic foot given on the wound area.

Conclusion: The result revealed that mix herbs (radix rhamanniae, panax ginseng and gypsum florosum) by oral and topical (natural honey, black seed and sea cucumber) could heal diabetic foot ulcers.

INTRODUCTION
At present, the use of herbs and botanical in medicine have been increasingly widespread. Botanicals and herbs could be used for wound healing, both topically and orally. They always are used as an alternative and complementary therapy. Many studies revealed that botanicals and herbs have therapeutic effects. Aloe vera is a medicinal plant well known for its therapeutic benefits and has been used for medical purposes for a long time. The therapeutic effect of Aloe vera is caused by its contains, namely vitamins, minerals, enzymes, amino acids, natural sugars. In addition, Aloe vera also has bioactive compounds such as antimicrobial, anti-inflammatory, antioxidant, antifungal, and antiseptic. Numerous studies revealed that this plant was effective to be topical for burns.

A similar effect is also found in honey. Numerous studies have been proven that it has a therapeutic effect. The liquid has been used in wound care as a topical treatment. It could stimulate tissue regeneration, debriding necrotic, reducing edema, and promoting wound healing. In addition, it has many advantages for wound healing, such as angiogenesis, decreasing wound area, and re-epithelization on acute and chronic.

Another herb is Black Seed. The Black Seed in Arabic has long been used as an alternative therapy. It has antioxidant, antimicrobial, anti-diabetic, and antibacterial effects. Sea cucumber, or was known as gamat. In vivo studies using animals, it was reported that sea cucumber has antibacterial, angiogenesis, antioxidant, and anti-inflammatory effects.

Other herbs commonly used for traditional Chinese medicinal herb is Radix Rehmanniae Preparata (Shu Dihuang). Radix Remanniae Preparata is produced from the root of Rehmannia glutinosa Libosch (Dihuang). Its already has known and widely used by some countries such as China, Japan, Korea, and other Asian countries. Due to radix contains various compounds such as polysaccharides, iridoid glycoside, phenol glycoside ionone, flavonoid, amino acid, inorganic ions, and microelement, so it has an anti-fatigue effect. Other herbs is Panax ginseng C. A. Meyer (ginseng). Panax ginseng contains 15% water-soluble polysaccharides (WGP). As a result, ginseng has pharmaco-
logical effects, such as anti-tumor, antioxidant, and hypoglycaemic activities\textsuperscript{12-14}. Also, in Chinese traditional medicine, ginseng is used for the development of physical strength, particularly severe fatigue patients\textsuperscript{15}. The last herb in this report is \textit{Gypsum fibrosum}. It is always administered with radix for a cough with a high temperature\textsuperscript{16}. It has anti-hypertensive effect\textsuperscript{17} and asthma\textsuperscript{18}.

The herb could be applied by both topical and oral. However, no clinical trial has been reported combining between topical and oral on diabetic foot ulcer (DFU’s). In this study, we will report combining herbs application by topical and oral on two cases, diabetic foot ulcer in the clinical setting.

**CASE PRESENTATION**

**Case 1**

Mrs. L, 52 years old, female, government employee, living in Parit. H. Husin 2, Pontianak, is a diabetic patient (blood glucose value: 435 mg/dl), treated at the Kitamura clinic, and reported suffering from necrotic wounds, edema, and infection of the dorsal at the left foot (Figure 1). Based on the medical record, it is found that the physical assessment recorded a good general condition and consciousness. The first wound assessment was on April 2, 2019, DFUS=16, and BWAT=36, and the wound area was 11.09 cm x 13.09 cm. The treatment was with saline solution at 0.9%, followed by the application of the modern dressing (duoderm gel, alginate, cutisorb, and allevin) and complimentary dressing (natural honey, black seed, and sea cucumber). The wound was debrided based on the wound bed. Changing the dressing was done on a regular daily basis. Besides, the care was given for the affected area by the systematic use of medication to control glucose levels, antibiotic, and herbal via oral. Interestingly after 29 weeks, the wound was healed, indicated by DFUS=0 and BWAT=11 (Figure 2).

**Case 2**

Mrs. W, 58 year old, female, living in Darma putra, Pontianak, is a diabetic type II patient (blood glucose: 424 mg/dl), treated at the Kitamura clinic, and reported to suffer from sleepy, fatigue. He had a wound on the dorsal left foot 3 months ago with slough and necrotic (Figure 3). Based on the medical record, it is reported that the mechanism of injury was traumatic. No data was found about pain, previous amputation, monofilament test, vibration sensation, and temperature perception. The first wound assessment was on June 5, 2019, DFUS=21 and BWAT=34, and the wound area was 24.39 cm x 18.91 cm. The treatment was done using the saline solution at 0.9%, followed by the application of the modern dressing (ribbon gauze, intrasite gel, stomahesive, duoderm gel) and complimentary dressing (natural honey and sea cucumber). The changing of dressing was every 3-day and debrided based on wound bed condition. Besides, the care was also provided for the affected area, such as the systematic use of medication to control glucose levels, antibiotic, and herbal via oral. After 24 weeks, the wound was healed, showing DFUS=0 and BWAT=12 (Figure 4).

**DISCUSSION**

The wound infection is caused by the existence of bacteria, particularly on chronic wound\textsuperscript{19}. There are two factors influencing wound healing namely local factors (oxygenation, infection, foreign body, and venous insufficiency) and systemic factors (age and gender, sex, hormones, stress, ischemia, diseases, uremia, obesity medications, chemotherapy, alcoholism, smoking, and Immunocompromised conditions), and nutrition. DFUs were a common complication of diabetes. Of 84% of all diabetes done lower-leg amputations\textsuperscript{19, 20}. There are complex pathophysiology mechanisms in diabetes patients, so influencing the wound healing process of both DFUs and acute wounds. Hypoxia is one of a cause of nonhealing injuries such as DFUs, venous, and pressure ulcer wounds\textsuperscript{21}. This condition may be caused by both insufficient perfusion and insufficient angiogenesis. In addition, it will be increasing the levels of oxygen radical-related to an increased inflammatory response by hypoxia\textsuperscript{21}.

All patients were controlled by antibiotics. One of the nutrients that the most influencing wound healing was protein. The capillary formation, fibroblast proliferation, proteoglycan synthesis, collagen synthesis, and wound remodeling will be inhibited related to protein deficiency. Besides, the inadequacy of protein also affected the immune system, with resultant decreased leukocyte phagocytosis and increased susceptibility to infection\textsuperscript{22}. The major protein component of connective tissue was collagen. Compounds of collagen are composed essentially of glycine, proline, and hydroxyproline. Lysine, proline, and co-factors such as ferrous iron and vitamin C are required to collagen synthesis. Deficiencies of these co-factors will result in delayed wound healing\textsuperscript{23}.

In this present study, we evaluated the wound healing process using BWAT and DFUS. Patient 1 (total score of DFUS 16 to 0 and BWAT 36 to 11) and Patient 2 (total score of DFUS 21 to 0 and BWAT 34 to 12). The result has shown that wounds were significantly healed. This healing is reached because all patients used complementary therapies, both topical (natural honey, black seed, and sea cucumber) and oral. Many studies show that natural honey does accelerate wound healing. This could be due to the varying pH of different types of honey, unusual composition, and floral source of the honey used\textsuperscript{24}. 
Using the mixture of black seed oil, honey on wound healing could enhance the healing in the experiment in rabbit\textsuperscript{25}, but clinically no data was recorded. Meanwhile, using sea cucumber on wound healing for two weeks has been proven to reduce wound area, but no data was recorded about the healing time\textsuperscript{26}.

In this case, all patients got complementary therapy (a combination of \textit{radix rehmanniae}, \textit{panax ginseng}, and \textit{gypsum florosum}) via oral. \textit{Panax ginseng} promotes vitality and stamina and maintains general well being. It contains constituents (the ginsenosides) that are structurally related to the corticosteroids. Corticosteroids have main functions in regulating the immune and endocrine systems that are mediated by the HPA axis\textsuperscript{27}. The actions of \textit{radix rehmanniae} root include regulating blood sugar, blood pressure and immune functions\textsuperscript{28} and the last \textit{gypsum florosum} has actions of clearing the excess heat and good for stomach.\textsuperscript{29}

**CONCLUSIONS AND RECOMMENDATION**

In this study case, the wound areas have been healed well, and they are much smaller than the initial condition. The wound area treated is different from the previous studies. However, this study has revealed that mix herbs both by oral (\textit{radix rehmanniae}, \textit{panax ginseng} and \textit{gypsum florosum}) and topical (natural honey, black seed, and sea cucumber) could successfully heal diabetic foot ulcers. Surely, this study has certain limitations and other studies involving larger samples and a more extended period to make sure the effectiveness of the treatment for diabetic ulcers.

**REFERENCES**

5. Haryanto, Sugama J, Nakatani T. Effectiveness of Indonesian Honey on the Acceleration of Cutaneous


