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Review Article

A Review on Wound Healing with Iranian Medicinal Plants and Microbial Flora in Veterinary Medicine

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ABSTRACT

Medicinal plants were used as treatment many years ago, and now the raw materials of most medicines are obtained from plants. Recently, due to the lack of side effects, the variety of effective compounds in plants, the development of industries related to the cultivation of medicinal plants, the recommendations of the World Health Organization to use plants, and several other reasons, the use of medicinal plants has been widespread. Numerous studies have been performed to investigate the effects of medicinal plants and microbial flora on wound healing. Previous studies revealed the positive effects of medicinal plants on wound healing compared to other chemical drugs, and a significant reduction in inflammation, acceleration of the healing process, and reduction of oxidative stress were observed following the use of herbal medicines. In this review, the effects of the most important Iranian medicinal plants and microbial flora on wound healing in veterinary medicine have been investigated.

Introduction

The skin is one of the most significant organs of the body that covers all surfaces of it, and its functions include: temperature regulation, conduction of physical senses, mechanical barrier, synthesis of vitamin D, and protection against ultraviolet rays, erosive and invasive agents. In addition, skin provides an intermediate structure between inside and outside of the body. Morphologically and functionally, the skin is divided in to two layers, the epidermis and the dermis. The epidermis is composed of keratinocytes, Langerhans cells, melanocytes, and Merkel cells. The dermis is a connective tissue, which is rich in collagen that supplies blood and nourishes the epidermis.[1]

Wound is defined as the rupture of a continuous body structure due to injuries caused by physicochemical and biological factors.[2] Wound healing

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is a complex physiological process that involves a series of consecutive stages. The first phase is hemostasis, which occurs within an hour following the damage. The second phase is inflammation, which lasts for 24 to 48 hours after hemostasis. At this phase, damaged tissue cells, capillaries, blood platelets and cytokines are activated. The third phase is the cell proliferation, which begins 1 to 3 weeks after the injury, and the final stage is maturation, which begins 3 weeks after injury. During this phase, complete tissue maturation or scarring is performed.[3] Since open wounds are suitable places for infection, physicians and veterinarians always try to accelerate wound healing. In Iran, disinfectants such as betadine, rinsing with physiological serum, antibiotic ointments and hydrocortisone are currently used to treat infectious wounds.[4] However, studies indicate that many of these solutions are toxic to fibroblasts, lymphocytes, and cells required for wound healing.[5] If appropriate treatment of wounds is not performed or be delayed it causes infection. Therefore, several studies have been conducted in this field and various substances have been investigated such as chemical and herbal agents. Yet, no substance has been introduced as the choice treatment for wound healing.[6] For many years, medicinal plants were utilized as ointments and medicines, and now the main ingredients of most drugs are obtained from plants. Today, due to few side effects, various effective ingredients in plants, the development of industries related to cultivation of medicinal plants, preventing the outflow of currency from the country, the recommendations of the World Health Organization to use plants and several other reasons, there has been increasing interest towards using medicinal herbs.[7]

Probiotics are living microorganisms whose consumption has many beneficial effects. Consumption of probiotics in human was commenced from 1908. Kefir is full of probiotics. The results of study conducted by Camelia Rodriguez *et al*, 2004 on kefir indicated the anti-inflammatory and repairing effects of probiotics on the skin wound healing process.[8] In current study, we reviewed native plant species and probiotics of Iran that have been used for wound healing (Figure 1).

Plants Effective in Wound Healing

Olive Leaf

Olive (*Olea europaea L*) is a small tree of the Oleaceae family with evergreen leaves that in the nature, its height reaches about 5 meters or higher, and if grown in favorable conditions, its height reaches 12 to 15 meters. Olive fruit and leaves are used as therapeutic agents. Its leaves are oppositely arranged on the stem and have the appearance of a long, pointed ellipse, light green, and leathery, towards the top of the leaflet, but the lower surface of the leaflet is darker in color. The beneficial properties of the olive tree include anti-hypertensive, anti-atherosclerotic, antioxidant, laxative, antipyretic, invigorating, headache reliever, and effective in the treatment of urinary tract infections.[9] In a study, the hypoglycemic effect of alcoholic extract of olive leaf in rats was confirmed. There are reports regarding the effects of olive leaf tea in the treatment of malaria. Rubbing olive oil on the scalp prevents hair loss, removes scratches on the scalp and protects it. In a report, the healing effect of olive leaf extract has been attributed to a substance called Oleuropein. Oleuropein supplies hydroxyl groups that directly neutralize and dispose free radicals.[10] Oleuropein reduces blood glucose in diabetes induced rats. Several studies have revealed the analgesic and anti-inflammatory effects,[11] the ability to heal skin wounds,[12] the antibacterial effect and the protective effect against ultraviolet radiation of olive leaf extract.[13] The healing effect of olive leaf extract with 40% concentration on skin wounds in adult male rats has also been demonstrated. Olive leaf extract shortens the phase of chronic and long-term inflammation in diabetic wounds by increasing antioxidant capacity and antibacterial properties.[14] *Olea europaea* in equine has been employed as a gastroprotective agent against equine gastric ulcer syndrome (EGUS).[15] Olive leaf usage in veterinary medicine for wound healing triggered quick epithelialization, contraction, and suppression of inflammation.[16]

Henna Leaves

Henna (*Lawsonia inermis*) is native to the Mediterranean regions, Middle East and India. In Iran, henna is grown in the southern regions, including Baluchistan and Bam. This plant consists of substances including pigments, tannins, resins, volatile oils and fat, and the most functional part of henna is its mature leaves.[17] The red color of Henna is used as a natural color to dye hair and skin. Henna leaf paste is used in cosmetics, decorations, and medicine to treat wounds, burns and some fungal infections. Therapeutic effects

Figure 1: Iranian medicinal plants effective on wound healing in veterinary medicine.

described for this plant are healing infectious wounds triggered by gram-positive bacteria, the treatment of acne and abscess, strong anti-fungal effect, astringent effect and anti-inflammatory effect. The paste of this plant has antimicrobial properties for numerous groups of bacteria.[17] Henna extract possesses chemical components including various phenolic glycosides such as coumarin, xanthon, quinoid, beta-sitosterol glycosides and tannins and alkaloids in the leaves of the plant. Henna leaves, known as the medicinal part of henna plant, has a beneficial effect on wound healing. Anti-inflammatory and antibacterial effects of Henna is related to Lawson, which is considered to be one of the most important ingredients of this plant. Lawson inhibits the activity of macrophages and thus impedes the production of chemical mediators of inflammation and reduces inflammation. The alkaloids in henna also accelerate the healing of skin wounds with their strong physiological effects.[17,18]

Effects of Henna extract with different concentrations (5%, 10%, 15%, and 20%) on wound healing in horses was assessed and results indicated that inflammation of wound edges, bleeding, dryness, abscess and scar tissue formation significantly decreased compared to the control group. Moreover, the extract has cidal effects on Staphylococcus aureus , Streptococcus equi , Pseudomonas aeruginosa.[19]

Myrtle Leaves

Myrtle (*Myrtus communis*) is a small tree or evergreen shrub. The leaves of this plant have an aromatic combination that is reminiscent of eucalyptus.[20] The leaves have a very bitter taste. The plant grows in abundance from the northwest to the eastern Mediterranean region. In traditional medicine, the fruit was used to treat some infectious diseases such as diarrhea.[21] Its leaves are also employed for antiseptic and anti-inflammatory purposes. Many members of this family are effective in lowering blood glucose level.[22]

Ross *et al*. indicated that the ingredients in the leaves of the plant could hinder lipoxygenase and cyclooxygenase, and also inhibit the formation of free oxygen in leukocytes. Moreover, the constituents of this plant can prevent edema and inflammation.[20] The ointment made from Myrtle is effective in escalating the rate of transition from the inflammatory phase to the fibroplasia phase, and ultimately accelerates the wound healing process due to increasing collagen synthesis and induces angiogenesis.[23]

Lavender Extract

Wild lavender plant with the scientific name *Lavandula officinalis* has several medicinal and sedative properties. Lavender is a shrub of the mint family that grows as a small tree in humid regions and has a warm nature and a sharp, bitter taste. This plant with its amazing therapeutic properties relieves headaches, anxiety, neurological disorders and triggers comfortable sleep.[24,25] Lavender is one of the evergreen plants which is resistant to cold and has narrow leaves. Furthermore, it is utilized in the perfume industry due to its pleasant smell. The usable parts of the plant include flowers and flowering branches. This medicinal plant is very effective in relieving fatigue and seizures, eliminating stomach and intestinal worms, loosening cramps, sharpening memory, improving gout and rheumatism, and is used to cure skin diseases such as eczema, acne and burns. It also relieves common cold, flu, angina and bronchitis, and improves liver normal function.[26] It is believed that the use of lavender oil is effective in wound healing and reducing wound infections. Lavender oil affects the wound environment and has antimicrobial, anti-inflammatory and analgesic effects.[26] additionally, the combination of lavender extract and honey improved wound healing.[27] A skin cream for dogs and cats made of herbal extracts, one of the ingredients of which is *Lavandula officinalis* was examined for wound healing in rats and rabbits. A significant increase in tensile strength of wound in the rat model was found and in the rabbit model significant increase in granulation but reduced epithelialisation was confirmed.[28] Beneficial effects of Lavender oil were compared with Black seed oil, Ostrich oil and Cod liver oil on the second intention wound healing in dogs and Lavender oil significantly accelerated wound healing compared to other oils.[29]

Green Tea

Green tea or Ocha, made from *Camellia sinensis* leaves of the Theaceae family, is a plant that may grow up to 9 meters in hot climates. The flowers are white and fragrant. The origin of the tea plant in Asia is mainly east and south China, northern Myanmar and Assam, state of India. Tea cultivation is also common in northern Iran, especially in Lahijan. Green tea was used as a treatment for diabetes in ancient China and East Asia.[30] Green tea is anticoagulant, anti-tumor and anti-AIDS and improves the immune system. Green tea contains caffeine, catechins, polyphenols, vitamins B, C, and E, flavonoids, glycoproteins, fiber, lipids and

carotenoids. General properties of glycoproteins include: anti-tumor, anti-inflammatory, antiviral, anti-coagulation, anti-aging and hypoglycemic.[31] There are 150 studies concerning the effects of green tea on the skin. The primary focus of these studies is on chemical inhibitors against chemical carcinogens or optical carcinogens in rodents.[32] The study conducted by Yaghmayei *et al*. indicated that green tea extract improves wound healing from the seventh day onwards. Reducing the inflammatory phase accelerates the wound healing. Moreover, the antibacterial and antiviral effects of green tea in accelerating wound healing were discerned in previous studies. Polyphenols, catechins, and glycoproteins are ingredients that are involved in accelerating wound healing process. Furthermore, green tea may accelerate healing by preventing infection and sterilizing the wound surface.[33] In a research study, effects of green tea extract on Staphylococcus contaminated wound in dogs was examined. Results of this study revealed Higher wound contraction, bactericidal action, and tensile strength in the treatment groups compared to the control group.[34]

Artemisia

Artemisia is an herbaceous plant that grows in different parts of Iran. Most of its species have a specific smell and taste due to the monoterpene and sesquiterpene compounds. Artemisia has various medicinal uses in complementary medicine and has been utilized as a tonic, appetizer, stimulant, disinfectant, vasodilator and rheumatic pain reliever.[35] This plant contains Santonin, which has long been considered the most famous anti-worm therapy for the gastrointestinal tract. Besides its anti-worm properties, Artemisia species possess antimicrobial, antifungal, antiviral, analgesic, antioxidant and vasodilators effects.[36] *Artemisia aucheri* (Ara) is a species of this plant that grows to about 25 cm high. Based on studies it has flavonoids, santonin, coumarin compounds, bitter substances and volatile essential oils.[35] It is effective in wound healing due to its several biological properties including antimicrobial, anti-inflammatory and vasodilation. The effect of hydroalcoholic extract of *Artemisia aucheri* on skin wound healing was examined in rats, and the results indicated a significant decrease in the wound surface, a significant increase in wound healing percentage and a reduction in the time required for healing in groups for which Artemisia extract was used.[37] Aerial parts of Artemisia laciniata have been utilized topically for wound healing in veterinary medicine.[16]

Teucrium polium

Teucrium polium or felty germander, of Lamiaceae family, is an aromatic, herbaceous and perennial plant that reaches a height of about 40 cm, and has a white cotton appearance that is usually found in the rocky and sandy areas of various parts of Europe, the Mediterranean region, North Africa and Southwest Asia, including Iran. *Teucrium polium* is a plant that contains tannins, terpenoids, saponins, flavonoids, alpha glycosides, sterol, leukoanthocyanin, beta-caryophyllene, Humulene, caryophyllene oxide, diterpenoid, some of which are anti-inflammatory agents.[38,39] According to a report, honey obtained from the flowers of *Teucrium polium* improves the healing process of skin wounds induced by hot metal in rats.[40] Some studies have demonstrated antipyretic, antibacterial, anti-inflammatory, and antihypertensive effects of this plant.[41] Furthermore, in a research, oral administration of aqueous extract of this plant has improved the healing process of gastric ulcers in rats by 85%.[42] Other properties of this plant are as follows: analgesic, antispasmodic and anticonvulsant.[43] In herbal medicine, the plant is used to treat inflammation, rheumatism and ulcers. This plant has several biological properties such as antimicrobial and anti-inflammatory, improves gastric ulcer and its honey accelerates the healing process of burns. In a study, Allah Tavakoli *et al*. investigated the effect of hydroalcoholic extract of Teucrium on rats' skin wound healing, and found a significant increase in wound healing percentage and a reduction in the time required for wound healing.[37] Treatment effects of *Teucrium polium* in acetic acid-induced ulcerative colitis in the dog was examined by Mehrabani et. al (2012) and number of healthy cells in the lumen significantly increased and inflammatory cells reduced. overall, ulcerative colitis was successfully treated using *Teucrium polium* extract.[44]

Milk Thistle

Milk thistle of the family Asteraceae whose scientific name is *Silybum marianum* is also known by the names of Mary thistle, cardus marianus, Akob in Persian and Arabic. Milk thistle is a biennial plant with a matte green color, hairless, thorny and with upright stems.[45] Milk Thistle is found in European, Asian and American countries. In Iran, this plant grows in some areas, namely Gonbad Kavous, Gorgan, Kelardasht, Dasht-e

Moghan, Posht Kooh, Ahvaz, Shush and Kazerun. Among the ingredients in this plant, we can name sylin A and B, Silydianin, Silycresin, Apigenin, Dehydrocylin, Dioxycylin, Cercetin, and Dioxidianine. Silyn is the most effective substance in Silymarin, which has antioxidant and liver protective effects. Besides silymarin, milk thistle has a group of substances called flanoligans, which have anti-inflammatory and antioxidant properties. Due to the existence of important constituents in the extract of milk thistle such as silymarin, this plant has the ability to heal wounds. According to microscopic studies, it is possible that the active ingredients of milk thistle stimulate collagen production, faster wound contraction, angiogenesis, vasodilation, as well as reducing inflammation, bleeding and wound edema.[46] In 2012, a study showed that silymarin had no effect on collagen deposition and hydroxyproline levels in vivo. Silymarin affects inflammation and epithelialization but has no effect on the percentage of wound contraction. The study of Ghorbani Ranjbari *et al*. indicated that due to the use of milk thistle extract, the wound area was significantly reduced compared to the control groups. In the microscopic evaluation, in addition to the formation of epidermis and dermis, fibroblasts and collagen fibers were observed abundantly and inflammatory cells were scarce.[46]

Red Sage or Salvia miltiorrhiza

Salvia miltiorrhiza is derived from a Latin word meaning "healing" and is widely used in cooking and medicine. Many species of sage are native to Mediterranean regions of Europe and are traditionally used to treat a wide range of disorders including digestive diseases, bronchitis, cough, asthma, memory problems, angina, inflammation and excessive sweating. The genus of Salvia has about 900 species, of which 58 species are cultivated in Iran and about 17 species are native.[47] Additionally, in China, Russia and South Korea, a herbal solution called Daneshan is produced, which is used to treat cardiovascular diseases including atherosclerosis, coronary artery disease, vasculitis and cerebral infarction, one of the main ingredients of which is sage.[48] The species of sage are a rich source of polyphenol compounds with more than 160 known polyphenols, including phenolic acids and flavonoids. These phenolic compounds include caffeic acid and its derivatives, rosmarinic acid, salvinolic acids, sagovomarin, lithospermic acids, sagrenic acid and ionaneic acid.[49] Farahpour *et al*. (2020) assessed effects of hydroalcoholic extract of *Salvia miltiorrhiza* to heal infected wounds with Pseudomonas aeruginosa and Staphylococcus aureus and concluded that in the treatment group, the inflammatory phase decreased, cell proliferation increased, perspiration and formation of new epithelium also increased. Furthermore, in the treatment group, the expression of interleukin 6, interleukin 1 beta and TNF α significantly decreased, the level of total antioxidant capacity increased, and the amount of malondialdehyde decreased, which generally revealed wound healing improvement.[50]

Chamomile

Chamomile is an annual, aromatic plant that its height reaches 40 cm. It belongs to the Asteraceae family, and its flowers are generally used for medicinal purposes. Chamomile is native to the Mediterranean region, but its origin has been reported to be Anatolia. The plant is now widely distributed in Europe, West Asia, North Africa, North and South America and Australia. In Iran, different species of the genus Matricarica grow in various regions, including West Azerbaijan, Lorestan, Fars, Andimeshk and Khuzestan. Alpha-bisabolol is one of the main constituents of chamomile, which reduces time of wound healing in laboratory animals. Other ingredients in chamomile include flavonoids, which are effective antioxidants in neutralizing reactive oxygen species.[51] Chamomile has been used in herbal medicine as a pain reliever, antispasmodic and anti-inflammatory. It is also used in the treatment of skin diseases, including psoriasis, eczema, and acne. In some studies, the therapeutic effect of chamomile extract in repairing some types of wounds such as hemorrhoids has been confirmed. Chamomile was also found to be effective in reducing skin inflammation.[52] In another study, chamomile extract did not show a significant therapeutic effect on radiation-induced dermatitis. However, in some studies, positive effects have been reported. The reason for these differences might depend on the type of laboratory animal, the type of wound, the extraction method and other reasons.[53]

Sickle Weed

Falcaria vulgaris or sickleweed of Umbelliferae family grows on the margins of fields and has nutritional consumption in some parts of Iran. This plant contains alkaloids, carotene, vitamin C, saponins. The plant is effective in the treatment of skin wounds,

stomach ulcers, hepatic diseases, kidney stones and gallbladder.[54] Scarce scientific studies have been conducted on the healing properties and constituents of facaria vulgaris. Dry powder of this plant has been traditionally used in Kermanshah region to accelerate wound healing.[55] In a study on the protective effect of hydroalcoholic extract of *Falcaria vulgaris* on aspirin-induced gastric ulcer in rats, the results indicated a significant decrease in wound coefficient and a significant increase in wound healing percentage in experimental groups. This plant increases collagen and the number of fibroblasts and as a result accelerates the healing of skin wounds in rats. Other mechanisms of the plant involved in accelerating the wound healing process include angiogenesis, accelerating the formation of granulation tissue, absorption of edema fluid around the wound, reducing wound inflammation and preventing infection.[55] Shakibaei *et al*. found that using the dried plant leaves, caused significant differences in wound surface area and skin tensile strength between treatment and control groups. However, using 10% alcoholic extract of this plant, did not induce significant difference in the elasticity of the skin.[54] Treatment effects of *Falcaria vulgaris* with 10% enriched diet on experimentally formed epidermis injuries in Cyprinus carpio was evaluated and significant reduction in the wound area was observed.[56]

Verbascum (Mullein)

This plant, which belongs to the Scrophulariaceae family, is native to Asia, Europe and the Mediterranean region. This plant has about 350 species in the world, of which about 40 species grow in Iran. In different regions of Iran this plant is called by other names such as: alaf-e-khargoosh, khargooshak, Gol-e-mahoor and alaf-e-mahoor.[57] In the past, this plant has been used to treat respiratory disorders. Physicians used this plant to relieve coughs. European immigrants took this plant with themselves to the United States. This plant was used in the past to treat coughs, colds, sore throats, tonsillitis, diarrhea, hemorrhoids and infections. The extract of this plant contains bioactive saponins glycosides and phenylethanoid glycosides and verbascoside, which has antiseptic and anti-inflammatory activity and also verbascoside is effective in wound healing.[58] Flavonoids are involved in wound healing process and eliminate free radicals by inhibiting nitric oxide synthesis. In a histochemical study using Trichromacy and van Gieson staining, collagen density increased in experimental groups treated with the extract of this plant. The steroid compounds in the extract of this plant cause angiogenesis, increasing the diameter of blood vessels and accelerating the wound healing process.[59]

Daphne Mucronata

Daphne mucronata is known by Persian names as Mazerion, Turbid, Zagros scent leaf, khoshak, and khish.[60] The bark, leaves, fruits, stems, seeds and roots of this plant are used as therapeutic agents. Betulin is one of the ingredients in this plant, which is a terpenoid compound and has anti-cancer properties.[61] The bark of this plant is used to treat bone diseases. its leaves are used to treat abscesses and the leaf decoction is utilized for inflammatory diseases, arthritis, flu and myositis. Extract of Daphne macronata has antimicrobial, antifungal and biological properties. The cytotoxic effects of its hydroalcoholic extract have been reported on different cell lines.[62] The methanolic extract of leaves, flowers and stems of *Daphne mucronata* was evaluated on skin wound healing in rats and a significant increase in the rate of healing of the skin wounds was observed.[63]

Asclepiadoideae

Asclepiadoideae belongs to the family of Asclepiadaceae and has different species that are known by different local names and in Iran it is called Estabarq. This plant is found in the warm regions of northwestern India, Egypt, Malaysia, South America and in Iran it is found in hot areas from Khuzestan to Baluchistan. The height of this tall shrub reaches 3 to 4 meters. The thick branches of this plant are full of sap, the skin is slightly red and the young branches are covered with white hairs. The leaves and branches of this plant contain calotropin and calotropagine. The sap contains toxins namely osharine, calotoxin and calactin that impairs vision. In India, this plant is used to treat leprosy, stomach ulcers and tumors.[64,65] The leaves, latex and flowers of some species are used in the treatment of toothache and topical cream.[66] Nowadays it is utilized to treat spleen disorders, epilepsy and ulcer. The plant also has antifungal, antimicrobial and anti-cancer activity.[67] The results of a study conducted by Raisi *et al*. revealed that the extract and sap of this plant is effective in reducing the severity of the inflammation in the wound area especially in the early days after wound formation. Moreover, the anti-inflammatory and antimicrobial properties of the extract accelerated the wound healing process.[68]

Oleaster (Russian Olive or Wild Olive)

The scientific name of Russian olive is *Elaeagnus angustifolia*. This plant is found in desert and semi-desert areas and is native to north Asia to the Himalayas and Europe. In Iran, this plant is found in Tehran, Qazvin, and Khorasan, southeastern regions of Iran, Shiraz, Hamedan, Kashan, Isfahan and Azerbaijan. The active ingredients of this plant include flavonoids, tannins, chlorogenic acid, carbohydrates and pigments. The fruit is also edible and has anti-inflammatory effects.[69] In traditional Iranian medicine, this plant is used for treating convulsant, nausea, vomiting, asthma, icterus, bloating, and as an analgesic for joint pain.[70] In a research, the anti-inflammatory and analgesic effects of aqueous extract of oleaster fruit were investigated and its analgesic properties was confirmed in the non-opioid pathway and through the central nervous system.[71] In a study, Moezzi *et al*. compared the effect of oleaster fruit extract and henna paste with silver sulfadiazine on experimental wound healing in rats. The results of this study indicated that wound healing lasted 13 days in the control group, 8 days in the group receiving silver sulfasiazine, 10 days in the group receiving oleaster fruit extract and 12 days in the group receiving henna. Eventually, it was confirmed that speed of wound healing in the oleaster fruit extract treated group was same as silver sulfadiazine group.[72] However, in another study on healing of gastric ulcers the oleaster fruit extract was more effective than misoprostol.[71] *Elaeagnus angustifolia* extract in experimentally induced ulcerative colitis in rats was evaluated and results revealed extract with dosage of 600 mg/kg had the best healing effects.[73]

Lemon Balm

Lemon balm is a medicinal plant with the scientific name of *Melissa officinalis*. Lemon balm is a thick, branched herb with elliptical, heart-shaped, granular, and fibrous leaves which belongs to the Lamiaceae family, and has been known for more than 2000 years. The origin of this plant is mostly in the Mediterranean region, European countries, Central Asia and widely found in Iran in Tehran, Golestan, Azerbaijan, Lorestan, and Kermanshah provinces.[74] Recent studies indicated the antioxidant, hypoglycemic and lipid-lowering, antimicrobial, antitumor, antidepressant, anti-anxiety, analgesic, anti-inflammatory and antispasmodic properties of this plant. The constituents of the plant include terpenes (monoterpene, ciscoterpene, triterpene) and phenolic compounds such as phenolic acids, flavonoids and tannins.[75] The results of the study conducted by Namjoo *et al*. on the effects of ointment and hydroalcoholic extract of lemon balm in wound healing of diabetic rats with alloxan revealed an increase in healing rate, increased wound contraction, and decreased wound area in diabetic rats treated with 5% lemon balm ointment. In histopathological evaluation, epithelial tissue regeneration, granulation tissue maturation, collagen fibers density, and wound contraction were significantly higher in the 5% lemon balm ointment group compared to the control group.[76]

Ajwain, Ajowan

Trachyspermum ammi or Ajwain originates from Asia and grows in Iran, Afghanistan and Egypt.[77] Ajwain is frequently found in eastern Iran and in the region of Baluchistan. Its fruit is rich of thymol and is part of the plant that is used for therapeutic purposes. The fruit is small and oval shaped that has a yellowish-brown color and smells like thymol.[78] Alcoholic extract of ajwain is utilized as an antihistamine. Komeili *et al*. investigated the therapeutic effect of hydroalcoholic extract of the plant seed on ibuprofen-induced gastric ulcer in rats and found that the extract treated groups with doses of 250 mg/kg and 500 mg/kg significantly reduced gastric ulcers.[79]

Yarrow

Yarrow or *Achillea millefolium* is a relatively small plant that grows up to 15-40 cm height. This is herbaceous and perennial plant with leaves lacking petioles and covered with hairs. It possesses white or yellowish flowers.[80] In herbal medicine, this plant is used for improving stomach function, bloating relief, and ameliorating abdominal pain, and indigestion treatment [81]. Previous studies confirmed anticonvulsant, anti-inflammatory, antispasmodic, antibacterial, antifungal, antihypertensive, antioxidant, hepatoprotective, antacid and anti-ulcer effects of Yarrow.[81] Yarrow contains linalool, borneol, camphor, caryophyllene, cineole, carvacrol, alpha and beta-pinene, togen, monoterpenoids and sesquiol, glucoalkaloids, flavonoids, terpenoids, and substances from the wax category.[82] In a study, Niazmandi *et al*. assessed the preventive effects of aqueous-alcoholic extract of Yarrow on indomethacin-induced gastric ulcer and its related biochemical factors in rats. The results indicated a significant decrease in secretion of gastric acids and lipid peroxidation, and remarkable increase in sulfhydryl compounds as antioxidants.[82]

Ferula assa-foetida

Ferula assa-foetida is an herbaceous plant, has a straight and relatively thick root with a strong, rough, fibrous stem. The usable part of this plant is its gum, which is made of resin.[83] The anti-inflammatory properties of *Ferula assa-foetida* gum are attributed to constituents including ferulic acid, coumarins, terzen, terpene coumarins, terpenoids, and sulfur compounds in its oil.[84] The gum accelerates the healing of aspirin-induced gastric ulcer due to its anti-inflammatory and antioxidant properties.[85] In Afghanistan, decoction of the plant gum is used to treat inflammation and gastric ulcers. In India it is utilized topically to heal infectious wounds and reducing inflammation, and in Saudi Arabia to reduce tracheitis and bronchitis. In a study entitled "The effect of aqueous extract of *Ferula assa-foetida* gum on wound healing in streptozotocin-induced diabetic rats", Sadoughi concluded that aqueous extract of *Ferula assa-foetida* gum accelerates the epithelialization process.[86] In another study, Hajhashemi *et al*. indicated the analgesic and anti-inflammatory effects of hydroalcoholic extract of *Ferula assa-foetida* leaves on wounds in mice.[87] Komija *et al*. in a study of topical application of leaves in type 2 burns concluded that the use of this plant improves skin blood flow, reduces the permeability of venules and reduces the permeability of white blood cells. Tam *et al*. Also revealed that sesquiterpenes and coumarins are antioxidant compounds of gum and they reduce time of wound healing in laboratory animals.[88]

Berula angustifolia

Berula angustifolia (L.) Mertens is a species of Fructus lycii. This perennial plant is distributed in humid regions in Europe, Asia, East and South Africa, North America and several parts of Iran. In Iran, this plant is called Khashak.[89] In numerous countries, this plant is used per oral due to its diuretic, antipyretic, sexual enhancement, hypnotic and liver protection effects. In a study, the antioxidant and antibacterial effects of the plant were investigated and found that it has potent antioxidant effects with phenolic and flavonoid compounds. However, it did not have antibacterial effects on Escherichia coli, Staphylococcus aureus, Proteus mirabilis and Enterococcus faecalis [89]. The methanolic extract of the leaves of *Berula angustifolia (L.) Mertens* on wounds in a diabetic animal model has accelerated wound healing.[90] In another study effects of Lycium depressum on wound healing in streptozotocin-induced diabetic rats was assessed and significantly improved wound healing.[91]

Probiotics

One of the most important probiotic bacteria is lactic acid bacteria, which have specific species and strains. Researchers need to discern the exact strain of the bacteria in their studies because the beneficial effects may be related to only one strain.[92] The probiotic effects of lactic acid bacteria and fermented dairy products are also due to metabolites such as peptides and extracellular polysaccharides produced during fermentation.[93] The production of exopolysaccharides in any probiotic strain is substantial because these exopolysaccharides attach microorganisms to the intestinal wall and stimulate the immune system, gastric anti-ulcer activity, and reduce cholesterol.[94] Probiotic bacteria are also known as activators of the main constituents of pro-inflammatory cytokines and chemokines.[95] The results of a study conducted by Sokouti *et al*. on effects of Lactobacillus casei on the healing of gastric ulcers induced by acetic acid revealed that the rate of wound healing increased significantly in the early days. In an investigation, Mashayekh *et al*. evaluated the effects of dead Lactobacillus casei bacteria on wound healing in rats, the results showed that the wound healing rate on days 3 and 7 increased significantly in the experimental group compared to other groups. Additionally, there was a significant decrease in the level of inflammation, average number of macrophages and neutrophils.[96] In another study, Zahedi *et al*. examined the effect of Lactobacillus brevis on skin wound healing in rats and the results indicated a significant increase in wound healing on days 7 and 21 in the treatment group. The wound was completely healed on day 21 and the wound area showed a significant difference with the control groups on days 7 and 21.[97] In a study on the healing effects of Lactobacillus pentosus, native to Iran, on gastric ulcer triggered by acetic acid in male Wistar rats, a significant increase in gastric ulcer healing percentage was observed in the treatment group compared to other groups.[98] The research by Heydari Nasrabadi *et al*. on the effects of Lactobacillus plantarum on skin wound healing in rats, as well as other studies, revealed a significant reduction in wound area.[99] Effects of honey bee-specific lactic acid bacteria was assessed in horses for wound healing and results indicated that after the initial application of the ointment all wound healed less than 20 days.[100] Another study examined the effect of probiotics on the

Table 1: Iranian medicinal plants with healing effects on wounds, family, Persian name and their most important properties.

Scientific plant name	Family	Persian Nam	Properties
Olea europaea	Oleaceae	Zeytun	Strong antioxidant, improves blood flow, antibacterial and anti-dry skin
Lawsonia inermis	Lythraceae	Hanna, Khine	Antibacterial, antifungal and anti-inflammatory
Myrtus communis	Myrtle	Murd	Anti-inflammatory, antiseptic, emollient
Lavandulla officinalis	Lamiaceae	Ostukhodus, Kharama	Soothing, anti-epileptic, antibacterial, anti-inflammatory
Camellia sinensis	Theaceae	Chaye sabz	Anticoagulant, anti-thrombosis, antioxidant, anti-inflammatory
Artemisia aucheri Boiss	Asteraceae	Dermane kuh	Disinfectant, analgesic, antioxidant, vasodilator
Teucrium Polium	Lamiaceae	Kalpure	Analgesic, anti-inflammatory, antimicrobial
Silybum marianum	Asteraceae	Khar maryam	Antioxidant, anti-inflammatory, anti-cancer, vasodilator
Salvia miltiorrhiza	Lamiaceae	Maryam goli	Strong antioxidant, anti-inflammatory and antibacterial
Matricaria chamomilla	Asteraceae	Babuneh	Anti-inflammatory, antioxidant, pain reliever
Falcaria vulgaris	Apiaceae	Ghazyaghi	Strong anti-inflammatory, vasodilator
Verbascum thapsus	Scrophulariaceae	Gole mahur	Disinfectant, anti-inflammatory, antioxidant
Daphne mucronata	Thymelaeaceae	Mazeryon	Anti-inflammatory, antimicrobial
Calotropis procera	Asclepiadaceae	Estabragh	Anti-inflammatory, anti-tumor, anti-microbial
Elaeagnus angustifolia	Elaeagnaceae	Senjed	Anti-inflammatory, anti-seizure, analgesic
Melissa officinalis	Lamiaceae	Badrajbuye	Antioxidant, anti-tumor, analgesic, anti-inflammatory, antimicrobial
Trachyspermum ammi	Apiaceae	Zenyan	Antimicrobial, antihistamine, antispasmodic, anti-inflammatory
Achillea millefolium	Asteraceae	Bumadaran	Anti-inflammatory, anti-fever, anti-spasm, antibacterial
Ferula assa-foetida	Apiaceae	Anghoze	Analgesic, anti-inflammatory, antioxidant, anticonvulsant
Berula angustifolia (L.) Mertens	Apiaceae	Khashak	Diuretic, hypnotic, antipyretic, antibacterial, antioxidant

healing of equine distal limb wounds and the group treated with probiotic indicated 50% decrement in wound area in half of the time of the control group.[101]

Conclusion

Wounds are a growing medical and global concern that requires intensive care services. Wounds have a wide range of pathophysiology and are divided into acute, chronic and burn wounds.[6] Herbal products, including plant extracts, have long been used to treat wounds and have significant effects on wound healing. In recent years, the use of natural products, especially herbal products, has increased. The World Health Organization has estimated that more than 80% of the world's population trusts traditional treatments for various skin diseases. It is estimated that 1-3% of modern drugs are produced to the cure wounds compared to one third of all traditional drugs that are effective in wound healing.[102] Several previous studies on produced chemical drugs for wound healing demonstrated numerous side effects after using these drugs. For instance, nitrofurazone is a broad-spectrum antibiotic, but reduced epithelization, delayed wound contraction and carcinogenic effects were reported following application of the drug.[103] Hence, using plant-based drugs and ointments are developing all over the world in animals. Most of the plants native to Iran were examined in wound healing in dogs, cats, and horses. However, several plants have not been studied yet in the veterinary medicine. It is recommended that researchers consider native plants of Iran in their studies concerning wound healing in veterinary medicine. According to the plants that have been studied in wound healing so far, it can be concluded that the majority of them are rich in antioxidant and anti-inflammatory properties and the beneficial effects observed in wound healing are due to these properties. Moreover, according to Table 1, most of the effective plants on wound healing belong to the families of Lamiaceae or Mint, Asteraceae and Apiaceae or Umbelliferae. Considering many opportunities given in various therapeutic fields to discover and develop new medicinal plants effective in wound healing, we can anticipate to see many more scientific articles in the future. In addition, with regard to the speed with which research is being done on the potential use of herbs

against wounds, it would be beneficial to review this field at shorter intervals. Consequently, the prospect of using herbs in the treatment of various wounds seems more necessary than ever.

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Conflict of Interest

Authors declare no conflict of interest.

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