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A review on application of herbals and their polymer composites in wound healing

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ABSTRACT

Biomedical applications of herbals and their derivatives for skin tissue engineering have become increasingly popular in recent years. Herbals and their derivatives can be used to create scaffolds for skin tissue engineering and wound healing, as they provide a biocompatible and biodegradable structure that can be used to promote skin tissue regeneration. In the literature search for relevant papers, sixty-eight studies have been included from January 2000 to September 2023 from PubMed and Google Scholar database sources. This review provided an overview of current knowledge on biomedical applications of herbal medicine such as *Aloe Vera*, *Calendula Officinalis, Hypericum perforatum, Lawsonia inermis*, Nicotine, Propolis, Honey, *Perovskia abrotanoides Karel,* Oak fruit inner, *Lithospermum officinale,* and their derivatives in skin tissue engineering. We showed that tissue engineering is a prominent therapeutic strategy that can be cost-effective in treatment of skin wounds by applying different natural herbal products, nanotechnology, material science, and regenerative medicine to suit the current wound care demands such as tissue repair, restoration of lost tissue integrity and scarless healing. So the design, synthesis, modification, evaluation, and characterization of herbal products are needed to target skin tissue engineering and wound healing. New strategies based on the drug delivery systems and nanocarriers such as nanofibers, nanoparticles, and vesicular structures, based on materials such as gelatin, PCL, collagen, chitosan, PLGA, PEG, PEO, PVA, natural gums, and PU can also be developed to facilitate the wound healing process. The homeostasis, re-epithelialization, regeneration, and immunocytes can be investigated by inducing fibroblasts proliferation and/or collagen production. Nevertheless, further clinical studies are needed before introducing commercial products in the market.

1. Introduction

In recent years, more and more attention has been paid to the field of interdisciplinary tissue engineering or regenerative medicine to develop modified tissues to regenerate organs. Tissue engineering uses a variety of scaffolding systems to restore, improve, and maintain organ function.

The use of new strategies, such as bioengineering techniques can revolutionize tissue engineering. Tissue engineering is an interdisciplinary research field that includes principles of engineering, life sciences, materials science, and medical research (Fig. 1) (Yang et al., 2022, Chen et al., 2023).

Human skin, as body's largest organ, is a self-regenerating tissue that protects the body against microorganisms' invasion, tissue damage, and mechanical and pressure impacts (Amiri et al., 2017). Skin is a complex

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structure consisting of the outer epidermis and the dermis, the connective tissue beneath the epidermis (Tanideh et al., 2015). The epidermis is the outermost and thinnest layer of the skin and is avascular and consists of several keratinocytes' layers. The dermis is rich in various glands, blood vessels, and nerve endings, and is mainly composed of fibroblasts that produce type I collagen for the extracellular matrix. The hypodermis is mainly composed of fat cells, which function in thermoregulation and energy storage. The hypodermis is often overlooked in skin models, but functions as a lipid barrier rich in hormones, stem cells, and growth factors. Fibroblasts and keratinocytes are the major cellular elements in the dermis and epidermis, respectively (Kaboodkhani et al., 2021, Yazarlu et al., 2021).

When wounds occur, which can be divided into acute and chronic wounds, tissue regeneration and wound healing process commence. Our brain automatically sets a series of events to repair the injured tissues. This process is often called a healing cascade, aimed at improving the injured tissue. This cascade appears to be implicated in many stages of wound healing. Wound healing is the process through which they repair themselves. It is commonly accepted that the healing of a wound can proceed through the phases of hemostasis, inflammation, proliferation, and remodeling (Tanideh et al., 2014, Maver et al., 2015, Davoodi et al., 2022). Wound healing comprises complicated processes that take place in three overlapping stages of cell migration, cell proliferation, and extracellular matrix deposition (Hashemi et al., 2019). The re-epithelialization process occurs on the edges of the wound by keratinocytes which close the wound and re-establish tissue homeostasis as soon as possible. Fibroblast migration is a key step in the wound-healing process. The dermal fibroblasts proliferate and migrate into the wound bed to form granulation tissue rich in extracellular matrix proteins and stimulate the growth of new blood vessels. This ultimately leads to the repair of the damaged tissue and restores the damaged tissue to a state similar to the condition before the injury. Alteration at any stage of the wound-healing cascade leads to the development of chronic or non-healing ulceration (Amini et al., 2010). The re-organization of the new extracellular matrix (ECM) is a key physiological process that occurs in a number of different contexts; including wound healing and cell migration. Collagen is the main structural protein of the healing conjunctive tissue and is the main component of ECM, which is organized in a thick and dynamic net, resulting from constant collagen deposition and reabsorption (Ai et al., 2012).

In order to prevent infections and scarring, particularly in some conditions such as diabetic wounds, deep injuries, burns, and wounds caused by surgeries, managing the wound healing process is necessary. The wound healing in diabetic patients occurs slowly due to the reduction of growth factors, collagen and keratinocytes' secretion as well as slow proliferation, angiogenesis and remodeling stages (Chakraborty et al., 2021). Ulcers, which are open sores, are a side effect of diabetes that can rapidly become infectious if not managed well (Monteiro-Soares et al., 2023). Different strategies in clinical care have been employed for wound treatments including skin autografts, skin allografts, xenografts, amnion, and newer approaches for tissue engineering. Due to limited sources of donor skin grafts, tissue-engineered skin substitutes present an efficient solution. Skin substitutes have been considered as an alternative to animal models for testing in the cosmetic and pharmaceutical industries (Nazempour et al., 2020).

In the past, traditional bandages served to cover wounds and wound healing (Sedighi et al., 2016). Over the last three decades, recent advances in wound care have grounded advances in polymer technology, tissue engineering, and regenerative medicine. Owning to the development of novel wound dressings, the financial and physiological burdens of the wound healing process have been alleviated. Wound dressings should have many properties, including flexibility, controlled adhesion to surrounding tissue, gas permeability, durability, and ability to prevent water loss (Mehrabani et al., 2022). Moreover, wound dressings should be capable of controlling bacterial infection and antibiotic resistances, resulting improvement of tissue regeneration (Pang et al., 2023). Wound dressing systems are commonly prepared using natural or synthetic polymers, or the combination of both, and can be designed in different forms such as films, membranes, mats, sponges, hydrogels, and so forth, using different methods such as electrospinning, casting, freeze drying, phase inversion, and the like (Naseri and Ahmadi, 2022, Mahalakshmi et al., 2023).

For instance, one of the most widely used methods of producing materials for wound healing and skin regeneration is electrospinning, which is a promising method for the fabrication of composite and nanocomposite fibers with desired diameters. The advantages of this method include easy processing for certain polymeric solutions and cost-effectivity that can provide nanoscale fibers with various physical, chemical, and biological attributes. Nanofibers produced by electrospinning can be designed to be very smooth and oriented, which can possess a well-conformable mesh structure with a desirable microenvironment for cellular infiltration and subsequent proliferation as well as tissue integration (Hashemi et al., 2024).

While recently a large number of studies have been conducted on

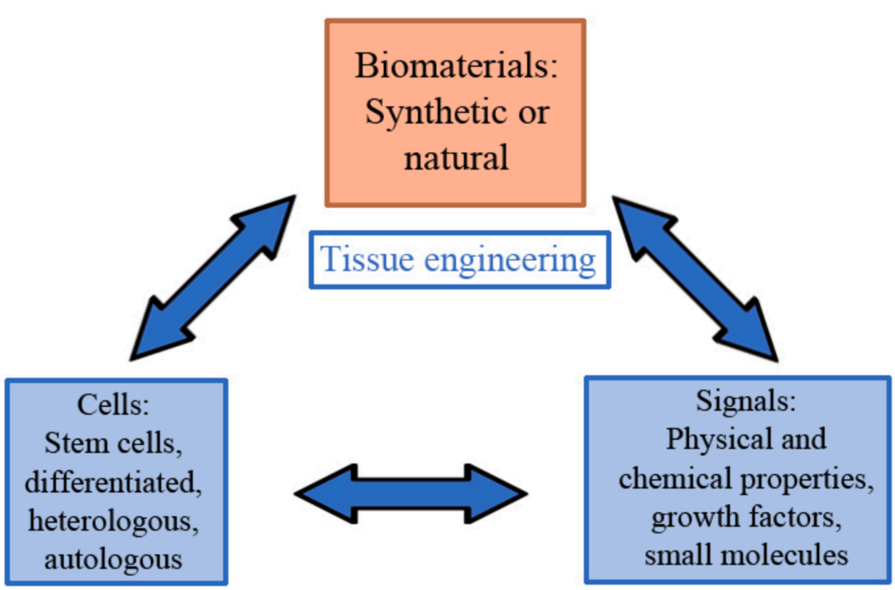

Fig. 1. The tissue engineering triad (Khodakaram-Tafti et al., 2018).

novel wound dressing systems, materials that can also promote wound healing have been used in different societies for a long time (Moses et al., 2023). Since ancient times, herbals and their derivatives have been the basis of indigenous and traditional medicine. Herbals extracts have been used as biocompatible and non-toxic drugs in burns and wound healing for thousands of years in many parts of the world owing to fewer side effects (Mehrabani et al., 2015, Bordoloi et al., 2023). Constituents present in herbal materials include agents such as alkaloids, volatile oils, flavonoids, terpenoids, tannins, saponins, phenolic compounds, and so forth, which possess anti-inflammation properties, promote collagen synthesis, induce the activation of coagulation, and protect the wound due to having antimicrobial activity during the epithelization stages of the healing process (Eğri and Erdemir, 2019). The incorporation of herbals and their derivatives as bioactive wound dressing materials in tissue engineering can significantly enhance the synergistic effects via sustained release of the pharmaceuticals to control infections and inflammation for therapeutic effects during wound healing (Huesca-Urióstegui et al., 2022). This review surveys the potential of herbals and their derivatives for wound healing and tissue engineering in regenerative medicine. Furthermore, some of the evidence supporting the use of herbals and their derivatives as effective and affordable treatments for cutaneous wounds are studied. Finally, the influence of herbals and their derivatives in combination with other biomolecules are discussed.

2. Herbals and natural products

Fabrication of new scaffolds in field of tissue engineering using natural biomaterials is very attractive because it mimics the body's natural biological and mechanical functions. Natural biomaterials can be divided into four groups of tissue/organ biomaterials (decellularized valves, heart, blood vessels, liver) (Gilbert et al., 2006), polysaccharide-based biomaterials (cellulose, chitin/chitosan, glucose) (Azuma et al., 2015), protein-based biomaterials (collagen, gelatin, silk) and glycosaminoglycan-derived biomaterials (Roberts et al., 2011). They usually display important properties such as non-toxicity, biodegradability, and biocompatibility (Shamosi et al., 2017). Naturally derived biomaterials have long been used in numerous regenerative medical applications. Natural products and their derivatives have been used for a long history of use in wound care and can be effective in facilitating the wound healing process. Today, there is a growing interest in the use of plants due to the low side effects and better compatibility of plants with the human body and also their safety compared to standard therapies (Hazrati et al., 2010). Natural products are known to be a major source of wound healing with potential pro-collagen synthesis, anti-inflammatory, antioxidant, and antibacterial properties. Various studies have shown that their medicinal properties can be due to the presence of bioactive phytochemical constituents such as flavonoids, tannins, lignins, alkaloids, phenolic compounds, and essential oils or saponins in the natural products (Sasidharan et al., 2011). Several natural products and their derivatives were shown to be effective in promoting the wound healing process discussed below.

3. The detailed data about medicinal herbs used in wound healing and skin regeneration

According to compiled data, constituents, advantages and disadvantages of studied plants are summarized and compared in Table 1.

3.1. Aloe Vera

Aloe Vera, also referred to as *Aloe barbadensis Miller*, is one of the oldest pharmaceutical herbs that has been widely used owning to its health benefits and special biological properties such as antiseptic, antibacterial, and anti-inflammatory activity, as well as its ability to promote tissue regeneration (Sholehvar et al., 2016, Hassanshahi et al., 2020) (Fig. 2). The gel obtained from Aloe Vera is widely applied to produce cosmetic products as moisturizers. Researchers have conducted extensive experiments to demonstrate the efficacy of Aloe Vera in wound healing without any side effects and tissue engineering (Hassan et al., 2023, Jithendra et al., 2023). Since the process of the regeneration of injured skin is achieved primarily through the matrix formation of connective tissue, Aloe Vera is consumed to increase the production of collagen in the skin and granulation tissue. In addition, Aloe Vera consumption can increase skin's degree of crosslinking, resulting the reduction of wrinkles (Chithra et al., 1998).

Factors such as glucomannan, a mannose-rich polysaccharide, and gibberellin, a growth hormone, interact with the growth factor receptor on the fibroblasts, thereby stimulating its activity and proliferation which, in turn, lead to a dramatic increase in collagen synthesis (Tarameshloo et al., 2012). In addition, hyaluronic acid is a major component of the ECM structure and has an important role in every stage of the healing process. Dermatan sulfate is a proteoglycan (DSPG) composition of skin wounds and its release after an injury promotes fibroblast growth factor-2 function to accelerate the healing process. In this regard, Aloe Vera plays a crucial role in wound healing and it increases levels of dermatan sulfate and hyaluronic acid in the granulation tissue of wound healing (Chithra et al., 1998). Aloe Vera can penetrate into the tissue and stimulate the biological activities involved in the regeneration of tissue such as nutrients, cells, enzymes, oxygen content, and blood flow (Choi and Chung, 2003, Tarameshloo et al., 2012). The matrix metalloproteinases (MMPs) are the major proteinases families capable of breaking down all kinds of ECM proteins (Loo et al., 2011). Moreover, Aloe Vera has been extensively used for medicinal purposes in dermatology. It can inhibit the enzyme activity of matrix metalloproteinases (MMPs) (Vijayalakshmi et al., 2012).

3.1.1. Aloe Vera/Polymer composites

Due to the extraordinary effects of Aloe Vera in wound healing, it has been extensively used in this field along with polymers to enhance the properties that make scaffolds or wound dressings suitable for skin regeneration (Chelu et al., 2023). Studies have shown that Aloe Vera/biopolymer composites have wound healing properties for various ulcers such as burns (Ranjbar and Yousefi, 2018, Retnowati et al., 2021).

Aloe Vera-based scaffolds can be manufactured using various production methods. Electrospinning is one of the techniques that has been used to produce Aloe Vera-based scaffolds. It was shown that Aloe Vera had different mechanical properties and behaviors when combined with other biomolecules such as polycaprolactone (PCL), collagen, chitosan, and polyvinyl alcohol (PVA) (Garcia-Orue et al., 2017). For instance, the morphology and structure of electrospun nanofibers made from plant extracts blended with PVA/polyvinylpyrrolidone (PVP) polymers were evaluated in a study. The results showed that the from the material and processing points of view, Aloe Vera gel concentration affected electrical conductivity and viscosity of electrospinning. Hence, Aloe Vera reduced the diameter of the produced fibers without inducing the formation of beads. These porous structures could lead to facilitated penetration of oxygen and moisture into the wound bed, which is important to the wound-healing process (AlFannakh, 2022). It has been demonstrated that the combination of Aloe Vera extract with poly (lactic-co-glycolic acid) (PLGA) and recombinant human epidermal growth factor (rhEGF) had a synergistic effect on fibroblast cell proliferation. These findings also revealed that the combination of PLGA/Aloe Vera/rhEGF compared to other compounds without Aloe Vera played a significant role in wound healing (Garcia-Orue et al., 2017).

A similar effort was made in which collagen − chitosan scaffolds supplemented with different concentrations (0.1—–0.5 %) of Aloe Vera were examined. The addition of Aloe Vera to collagen − chitosan composite increased hydrophilicity as well as the thermal stability of the scaffolds. Growth and proliferation of fibroblasts were examined on the collagen − chitosan scaffold in the presence/absence of Aloe Vera. These findings illustrated the increased growth of fibroblast cells in the presence of Aloe Vera indicating Aloe Vera utilized as a promising strategy in

Table 1
Summary of constituents, advantages and disadvantages of herbal drugs.

Herbal	Ingredients	Extraction methods	Mode of application/ methodology	Outcome		References
				Advantages	Disadvantages	
Aloe Vera	Various amino acids, carbohydrates, long-chain polysaccharides, lectin, anthraquinones, amino acids, ascorbic acid, Vitamins A and E, and salicylic acid, saponins	Washing, peeling the leaf, and filleting by hand or mechanically	Wound dressing / *in-vitro* and *in-vitro*	1.Treating skin disorders 2.Healing skin lesions and wounds 3.Alleviating pain 4.Anti-inflammatory, antimicrobial, antioxidant, and immunomodulatory properties 5.Treating hyperglycemic conditions	1.Irritates the skin and the gastrointestinal tract 2.Causes cramping and diarrhea 3.Imbalances in the blood	(Tarameshloo et al., 2012, Chandegara and Varshney, 2013, Alishbah et al., 2022, Ansari et al., 2022)
Calendula officinalis	Phenolic compounds (e.g., coumarin and flavonoids), triterpenoids, steroids, terpenoids, carotenes, phenolic acids, carbohydrates, fatty acids, tocopherols, essential oils, minerals, quinones, and tocopherols	Maceration and Soxhlet extraction or homogenizer and ultrasound assisted extraction	Sound dressing / *in-vitro* and *in-vitro*	1.Anti-inflammatory, antifungal, antiviral, antioxidant, antiviral, antibacterial activities 2. Antiseptic property 3.Free radicals' inhibitors 4.Blood coagulation activity 5.Treating gastrointestinal ulcers and dysmenorrhea	1.Causes insomnia	(Fronza et al., 2009, Dinda et al., 2015, Pedram Rad et al., 2019, Hashemi et al., 2023c) (Rad et al., 2019, Ak et al., 2020)
Hypericum perforatum	Xanthones, anthracenes, proanthocyanidins, hypericin and hyperforin, tannins, volatile oils, essential oil, hyperforins, hpericins, and flavonoids, and caffeine acid derivatives	Direct sonication, maceration, indirect sonication, Soxhlet extraction, and accelerated solvent extraction	Wound dressing / *in-vitro* and *in-vitro*	1. Antidepressant 2. Angioedema 3. Antipyretic 4. Antifungal 5. Anti-viral 6. Anti-inflammatory and antioxidant 7. Antidiabetic 8. Antispasmodic 9. Anti-genotoxic	May cause the following: 1. Feeling anxious 2. Irritation 3. Dry mouth 4. Upset stomach 5. Diarrhea 6. Headache 7. Strange dreams	(Wills et al., 2000, Nair and Laurencin, 2006, Smelcerovic et al., 2006, Dost et al., 2009, Klemow et al., 2011, Tanideh et al., 2014a, Cirak et al., 2016, Tanideh et al., 2016, Pourhojat et al., 2017, Pourhojat et al., 2018, Silva et al., 2021, Mouro et al., 2023, Nur Parin and Deveci, 2023)
Lawsonia inermis	2-Hydroxy-1, 2-hydroxy-1,4-diglucosyloxynaphthalene, 4-napthoquinone, 1,2-dihydroxy-glucoyloxynaphthalene, 1, 4dihydroxynaphthalene.1,4-naphthoquinone, napthoquinone, triterpenoids-hennadiol, isoplumbagin, aliphatics, coumarins, steroids, glucose, mannitol, gallic acid, mucilage, fat, resin,	Solvent assisted extraction, which may be coupled by ultrasonic waves	wound dressing / *in-vitro* and *in-vitro*	1.Diuretic 2.Headache 3.Hemicranias 4.Lumbago 5.Bronchitis 6.Ophthalmia syphilitic Sores 7.Amenorrhoea 8.Scabies 9.Spleen diseases 10. Nootropics activity 11.Antimicrobial and antibacterial activities 12.Wound healing activity 13.Antioxidant 14.Hepatoprotective activity 15.Antiparasitic 16. Anticancer	Inflammation of the skin (dermatitis) including redness, itching, swelling, burning, scaling, blisters	(Muhammad and Muhammad, 2005, Jeyaseelan et al., 2012, Avci et al., 2013, Tan et al., 2013, Yousefi et al., 2017, Hadisi et al., 2018, Dixit et al., 2022, Tuan et al., 2022, Zhang et al., 2022, Bayati et al., 2023, Moutawalli et al., 2023, Muheyuddeen et al., 2023a)
Nicotine	Nicotine	Maceration method, acid-base extraction, chromatography, ultrasound- and microwave-assisted extraction	wound dressing/ *in-vitro* and *in-vitro*	1.Wound healing even in low concentrations 2.Anti-inflammatory 3.Treating ulcerative colitis and obesity	Diarrhea, irritation and burning sensation in the mouth and throat, enhanced salivation, nausea, abdominal pain, vomiting, reduce revascularization and osteogenesis	(Zuo et al., 2004, Greenhalgh, 2013, Liem et al., 2013, Hu et al., 2015, Kheawfu et al., 2021)
Propolis	Terpenes, aldehydes, phenolic acids, ketones, trace minerals such as iron and zinc, vitamins, a	Maceration, Soxhlet, ultrasound- and microwave-assisted	wound dressing /	1. Anti-microbial and anti-microbial actions 2. Antifungal	skin or respiratory symptoms	(Burdock, 1998, Najafi et al., 2007, Yaghoubi et al., 2007,

(*continued on next page*)

Table 1 (*continued*)

Herbal	Ingredients	Extraction methods	Mode of application/ methodology	Outcome		References
				Advantages	Disadvantages	
	variety of hydrocarbons, enzymes, pinocembrin, acacetin, rutin, luteolin, chrysin, kaempferol, catechin, apigenin, galangin, myricetin, naringenin, quercetin, caffeic acid, phenolic acids, cinnamic acid, phenethyl ester, amino acids	method, supercritical gas extraction, and high-pressure extraction	*in-vitro* and *in-vitro*	3. Antiviral 4. Antitumor 5. Anti-oxidative 6. Immunomodulatory 7. Anti-diabetic 8. Anti-ulcer		Ahmed et al., 2011, Pessolato et al., 2011, Daleprane and Abdalla, 2013, de Almeida et al., 2013, Olczyk et al., 2013, Abu-Seida, 2015, Valenzuela-Barra et al., 2015, Alberti et al., 2020, Asri et al., 2020, Eskandarinia et al., 2020, Al-saggaf, 2021, Bankova et al., 2021, Ceylan, 2021, Sharaf et al., 2021, Hashemi et al., 2023, Mele, 2023, Phonrachom et al., 2023)
Honey	Pinobanksin 5-methyl ether, hydroxymethylfurfural, organic acids (gluconic acid, acetic acid, lactic acid, citric acid, succinic acid and formic acid), p-coumaric acid, pinocembrin, phenolic compounds, protein (proline, lysine, phenylalanine, aspartic), vitamins,	Chromatography, liquid–liquid extraction, accelerated solvent extraction, dispersive and inverse dispersive liquid–liquid microextraction, and solid-phase extraction	wound dressing / *in-vitro* and *in-vitro*	1.Antioxidant and anti-inflammatory 2. Antidepressant 3. Improve memory 4.Anti-cancer 5.Wound healing	Nausea, food poisoning, vomiting, diarrhea, heart problems, low blood pressure, and chest pain	(Molan, 2002, Al-Waili, 2003, Tonks et al., 2007, Sharma et al., 2012, Biesaga and Pyrzyńska, 2013, Arslan et al., 2014, Istasse et al., 2016, Pascual-Maté et al., 2018, Ma et al., 2019, Mukhopadhyay et al., 2020, Shamloo et al., 2021, Dumitru et al., 2022, Salama and El-Sakhawy, 2022, Sharma et al., 2022, Parvinzadeh Gashti et al., 2023)
Perovskia abrotanoides Karel	Flavonoids, anthocyanins, phenolics	Maceration, Soxhlet, and simple soaking method	wound dressing / *in-vitro* and *in-vitro*	1.Leishmanicidal 2.Anti-plasmodial 3.Cytotoxic 4.Anti-inflammatory 5.Anti-diabetic 6.Anti-lipidemic 7.Anthelmintic activity	Diarrhea, fever, and abdominal pain	(Mahboubi and Kazempour, 2009, Hashemifar and Rahimmalek, 2018, Derakhshanfar et al., 2019b, Alizadeh et al., 2021, Farzaneh et al., 2021, Bayat et al., 2022, Nazemi et al., 2023)
Quercus brantii	syringic acid, tannin, flavonoid, hexamethyl ether, isocryptomerin, β-sitosterol, amentoflavone, alkaloid, several aromatic components	Soaking and centrifugation, hydroalcoholic extraction, and maceration	Scaffolds/ *in-vitro* and *in-vitro*	1.Antibacterial and antifungal activities 2.Controls oxidative stress pathogenesis and inflammatory disease 3.Treating gastric ulcers, diarrhea, alkaloid poisoning, dysentery, hemorrhoids, hemorrhages, and tonsillitis	Bacterial resistance	(Sadeghian et al., 2012, Korbekandi et al., 2015, Aleebrahim-Dehkordy et al., 2019, Malayeri et al., 2022, Mehrabani et al., 2022)
Lithospermum officinale	Naphthoquinones, flavonoids, and phenolic acids	Solvent-assisted extraction	Scaffolds/ *in-vitro* and *in-vitro*	1.Anti-inflammatory agent 2.Treatment of burns 3.Diuretic, febrifuge and litholytic properties	Diarrhea, pyuria, haematuria, proteinuria	(Amiri et al., 2017, Al-Snafi, 2019, Al-Snai, 2019)

skin tissue engineering (Jithendra et al., 2013). In another effort, nanofiber-based PCL/chitosan/Aloe Vera composite was prepared and used as wound dressing. Aloe Vera was used as antibacterial agent in this study, showing activity of above 96 % against *Staphylococcus aureus* (*S. aureus*) and *Escherichia coli* (*E. coli*) (Yin and Xu, 2020).

In animal models, chitosan-based Aloe Vera hydrogels with the high tissue tension promoted the wound-healing process through increasing epidermal thickness (Movaffagh et al., 2022). Collagen/chitosan-glucan complex hollow fibers displayed great bactericidal activity, biocompatibility, as well as blood clotting efficiency and wound healing characteristics due to the synergistic effects of collagen and Aloe Vera (Abdel-Mohsen et al., 2020). The restorative impact of Aloe Vera gel on

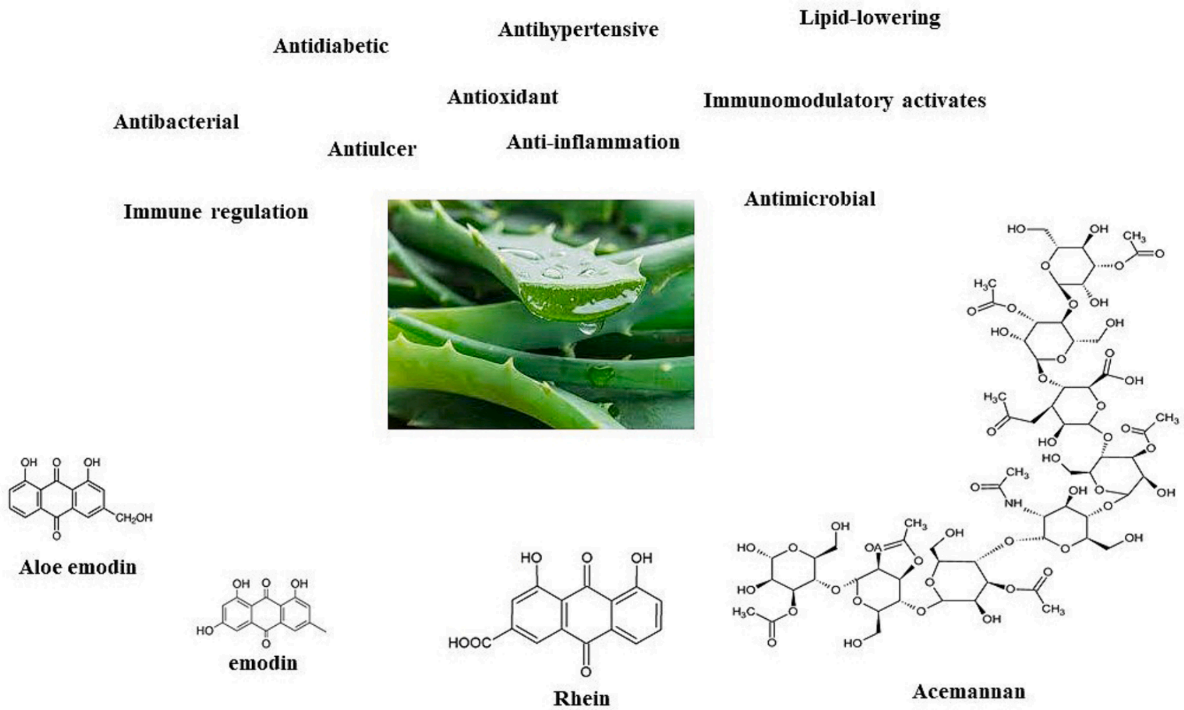

Fig. 2. Aloe Vera and its pharmacological activities. Leaf structure and important chemical constituents of Aloe Vera: Aloin, Aloe emodin, Acemannan, Rhein and Emodin (Hassanshahi et al., 2020).

acid-induced colitis was reported in rats by histopathological and molecular investigation of Bax and Bcl-2 revealing a decreased apoptosis within the colon when Aloe Vera was administered (Hassanshahi et al., 2020). Moreover, hydrogels based on chitosan/guar gum/Aloe Vera were applied on the Wistar albino model to cure burn wounds, suggesting high angiogenesis due to fibroblast cells accumulation (Ansari et al., 2022). Accordingly, these studies have shown the validity of using Aloe Vera in products used for skin regeneration.

3.2. *Calendula officinalis*

Calendula officinalis (*C. officinalis*), commonly known as marigold, is a medicinal aromatic plant with orange or yellow flowers that is most widely used to accelerate the treatment of several tissue damages through enhancement of collagen production (Mehrabani et al., 2011). *C. officinalis* extracts have been shown to have many therapeutic effects including anti-inflammatory, antioxidant, antibacterial, antiviral, antifungal, anticancer, and regenerative activities (Hashemi et al., 2023, Shahane et al., 2023) (Table 2). Many studies have shown that extracts from *C. officinalis* stimulate both fibroblast migration and proliferation, and enhance the metabolism of glycoprotein and collagen during wound healing in a PI3K-dependent manner (Dinda et al., 2015). Many studies have confirmed the effect of the extract from the flower of *C. officinalis* on granulation tissue formation by altering the expression of connective tissue growth factor (CTGF) and α-smooth actin (α-SMA) in excisional wounds of BALB/c mice (Fronza et al., 2009). It has also been demonstrated that *C. officinalis* extract can promote wound healing by nucleoprotein and glycoprotein metabolism, increasing both collagen and wound angiogenesis (Fronza et al., 2009, Hashemi et al., 2023).

3.2.1. *Calendula officinalis extract /polymer composites*

Due to the presence of evidence for the beneficial effects of *Calendula officinalis* extract for wound healing, which has been consistent with its application in traditional medicine, various studies have focused on the role of this herbal extract in wound healing along with polymers as composites. For instance, nanofibrous scaffolds based on gum Arabic and PCL were used to form hydrophilic composite via electrospinning with diameter distribution of 85–290 nm. This nanofibrous structure demonstrated good mechanical properties and porosity up 60 % to load *C. officinalis* for wound dressing. The results displayed antimicrobial activity and the proliferation of fibroblast cells (Fig. 3) (Pedram Rad et al., 2019).

Table 2
Pharmacological potentials presented in different parts of Calendula officinalis Linn (Shahane et al., 2023).

	**Volatile oils**	Sabinene, limonene, α-pinene, p-cymene, nonanal, carvacrol, geraniol, nerolidol, t-muurolol, palustron, methyllnoleate, cubenol, α-cadinol, oplopanone
	Terpinoids	Lupeol, Ψ-taraxasteol, erythrodiol, calendulaglycoside A, calendulaglycoside B, cornulacic acid acetate, calenduloside
	Flavonoids	Quercetin, isorhamnetin, isorhamnetin-3-O-D glycoside, narcissin, isoquercitrin, rutin, calendoflavoside
	Coumarins (50)	Umbelliferone, esculetin, scopoletin,
	Terpenoid	Calenduloside B
	Quinones	Phylloquinone, α-tocopherol, ubiquinone, plastoquinone (54)

In another study, the role of *C. officinalis* in tissue engineering was investigated, revealing that the incorporation of the *C. officinalis* extract in electrospun fiber scaffolds composed of PCL, Zein, and gum Arabic increased porosity and resulted in a composite with good hydrophilicity, desirable mechanical properties and suitable degradability in skin tissue engineering. It was shown that when compared to PCL/Zein/gum Arabic scaffold, PCL/Zein/gum Arabic/*C. Officinalis* nanocomposite scaffold, higher adhesion and proliferation of fibroblast cells were observed and

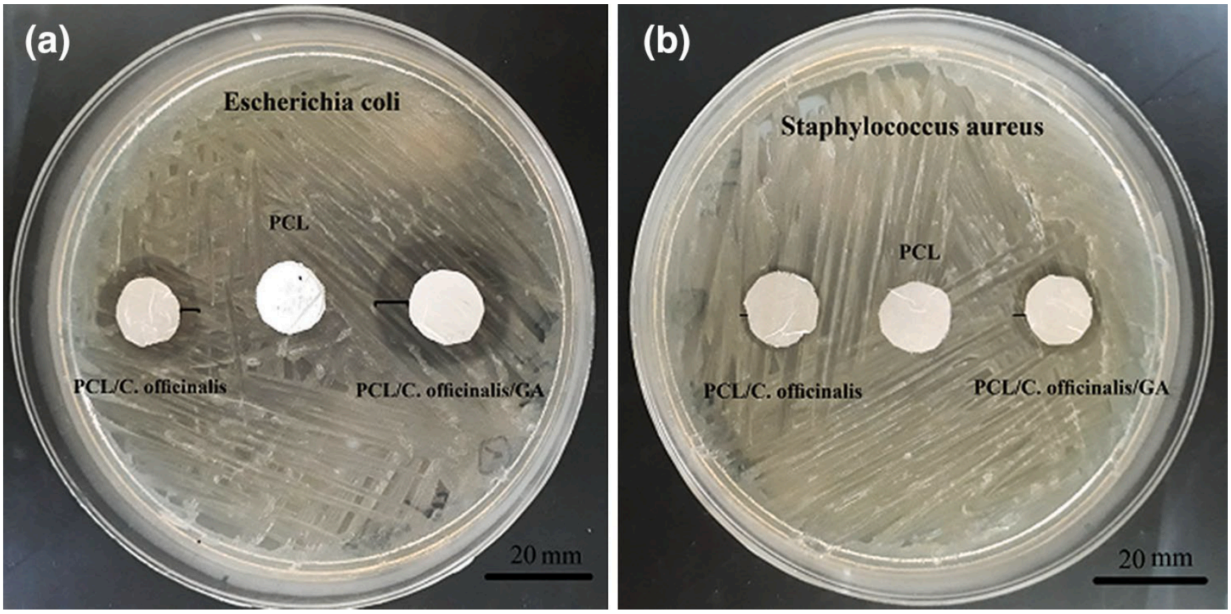

Fig. 3. Antibacterial activity of compounds containing C. officinalis against E. coli and S. aureus (Pedram Rad et al., 2019).

nanocomposite scaffolds were demonstrated to be desirable biomaterials in skin regeneration (Rad et al., 2019).

Another study showed that after loading *C. officinalis* into chitosan/polyethylene oxide (PEO) scaffolds, the mechanical and antibacterial properties were improved. In addition, *in-vitro* studies confirmed that collagen synthesis, fibroblast cells, proliferation, cell attachment and re-epithelization were induced, resulting great wound healing ability (Pedram Rad et al., 2019, Kharat et al., 2021).

3.3. Hypericum perforatum

Hypericum perforatum (*H. perforatum*), commonly known as St John's Wort, is a member of the genus Hypericum family, which is found in temperate areas of Europe, West Asia, North Africa, Madeira, and the Azores (44) (Fig. 4). *H. perforatum* extract is commonly used as a remedy for wound healing due to containing phloroglucinols, naphthodianthrones, flavonoids, bioflavonoids, and phenylpropanoids that can promote the wound repair process and can lead to anti-inflammatory, antifungal, antimycobacterial, antiviral and antiparasitic activities, providing a wide range of medicinal actions for various diseases (Wills et al., 2000, Tanideh et al., 2014, Tanideh et al., 2016). *H. perforatum* is effective in healing burn wounds and provides a rapid recovery for ulcers because of its antimicrobial activity in its crude extracts (Klemow et al., 2011). *H. perforatum* has gained a high reputation in wound healing because it plays an important role in the stimulation of fibroblasts, collagen production, and activation of fibroblast cells in a polygonal shape (Dost et al., 2009).

Fig. 4. The image of *Hypericum perforatum.*

H. perforatum has several inhibitory enzymes such as anti-hyaluronidase, anti-tyrosinase, anti-collagenase, and anti-elastase, along with anti-inflammatory and antimicrobial activities (Silva et al., 2021). The healing effect of *H. perforatum* are attributed to its phytochemicals, namely flavonoids (rutin, hyperoside, isoquercitrin, quercitrin, quercetin, amentoflavone), phloroglucinols (hyperforin), naphthodianthrones (hypericin and pseudohypericin), and phenylpropanoids (chlorogenic acid). These molecules have antibacterial, antidepressant, photodynamic, anti-aging, anti-inflammatory, antimitogenic, antiviral, antiretroviral, and antitumor bioactivities (Cirak et al., 2016).

3.3.1. Hypericum perforatum/polymer composites

Different polymers such as natural ones like chitosan and alginate can be used to load this herbal for achieving a better wound dressing due to having antioxidant properties, antimicrobial effects against E. coli and *S. aureus* as well as having a proliferative effect (Tanideh et al., 2014). In addition, PCL is a biodegradable, flexible and compatible polymer that is readily degraded by microbial agents (Nair and Laurencin, 2006). Pourhojat *et al.* investigated the advantages of wound dressings made of electrospun nanofiber scaffolds containing *H. perforatum* extract**.** They showed that human skin fibroblast cell culture on PCL nanofibrous mats including cell growth agents, increased cell accumulation and provided a compatible environment for their viability and proliferation (Pourhojat et al., 2017). In another study, electrospinning was used to produce PLGA nanofibrous scaffolds containing *H. Perforatum* alcoholic extract showing a good substrate for the growth and proliferation of fibroblast cells (Pourhojat et al., 2018). Using the electrospinning method, *H. Perforatum* was also utilized in a poly (L-lactic acid) (PLLA)/ PVA/chitosan matrix, which resulted in favorable porosity, wettability, water vapor transmission rate, and swelling behavior similar to ECM of the skin. In addition, nanofiber mats containing *H. Perforatum* were able to prohibit the growth of *S. aureus* without leading to cytotoxicity for normal human dermal fibroblasts

(Mouro et al., 2023). Parin et al. *H. Perforatum* oil in PVA/sodium carboxymethyl cellulose matrix, showing antibacterial activity against *E. coli*, *S. aureus*, and *P. aeruginosa*, along with favorable biocompatibility, which demonstrated their potential for wound dressing applications (Nur Parin and Deveci, 2023).

3.4. Lawsonia inermis

Lawsonia inermis (*L. inermis*), is a shrub or small tree widely cultivated as an ornamental and hedge plant that has been used for medicinal purposes for centuries (Fig. 5). Traditionally, the plant is called henna and is known for its medicinal properties for the treatment of jaundice, renal lithiasis, and also skin wounds to prevent inflammation. Lawsone (hennotannic acid) is the main active ingredient of *L. inermis* which can serve as a raw material to synthesize many therapeutic agents. These compounds are effective at enhancing the healing process owing to existence of various phytochemical constituents (Muheyuddeen et al., 2023). It has been shown that henna leaf extract has a significant impact on wound healing by increasing the rate of collagen organization, fibroblast proliferation, granulation tissue formation, hydroxyproline content, wound contraction, and skin-breaking strength (Muheyuddeen et al., 2023). In addition, henna leaf extract can further inhibit the growth of microorganisms for both gram-positive and gram bacteria involved in infection caused by burn wounds (Muhammad and Muhammad, 2005).

3.4.1. Lawsonia inermis/Polymer composites

Due to containing substances such as phenolic compounds, nonvolatile terpenes, oleamide, and trace elements such as Ca, Na, Mg, P, K, and Se, the potential of *Lawsonia inermis* in skin regeneration has been investigated in polymer composites (Dixit et al., 2022). It should also be mentioned that the methanolic extract of *L. inermis* (roots, leaves, and stems), has been shown to contain 12 compounds, including triterpenoids, flavonoids, two naphthoquinone derivatives, β-sitosterol, and two long-chain alcohols that can promote wound healing (Tuan et al., 2022). In a study, henna leaf extract was loaded in chitosan/PEO nanofibers produced by electrospinning process. The results revealed that the diameter of chitosan/PEO nanofibers loaded with henna extract reduced compared to nanofibers without the extract. In this study, the produced nanofibers containing henna extract increased properties such as antibacterial activity, biocompatibility, wound healing rate, and mechanical properties (Yousefi et al., 2017). The gelatin-oxidized starch nanofibers containing Lawsonia Inermis increased fibroblasts attachment, proliferation, collagen secretion, and antibacterial activity to accelerate the burn wound closure, with reducing inflammation and macrophage numbers in in-vitro studies (Hadisi et al., 2018). In addition, results of the study on nanofibers based on PEO and PVA prepared using electrospinning method and loaded by henna leaf extracts suggested that antibacterial activity of PEO/PVA nanofibers containing was higher than PEO/PVA nanofibers (Avci et al., 2013). Loading henna extract in poly (L-lactide-co-D, L-lactide) (PLDLLA) nanofibers showed that in animal models, PLDLLA/*L. inermis* considerably enhanced burn wound closure rate. Moreover, histological studies demonstrated the significant increase in the appearance of the epithelial layer. In addition to epithelialization, it was shown that the wound covered by PLDLLA/*L. inermis* composite induced the formation of condensed collagen fibers without necrosis (Bayati et al., 2023). Preclinical studies have also shown that favorable epithelial thickness, collagen deposition, and

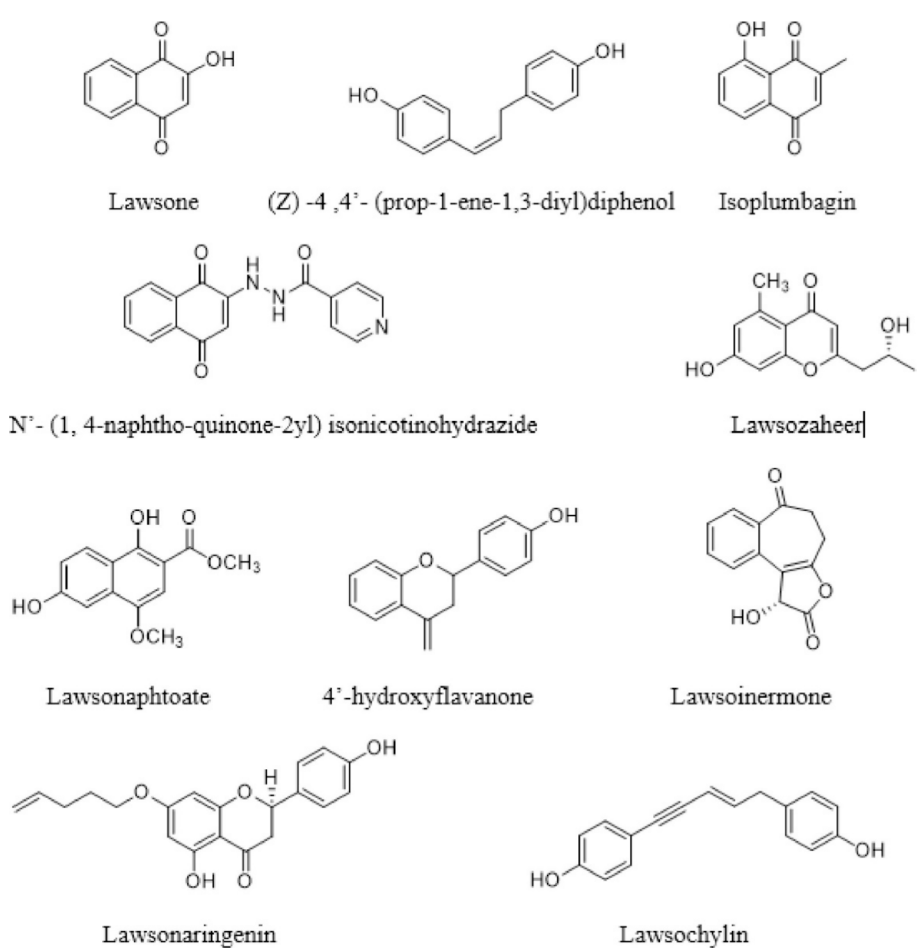

Fig. 5. Structures of some important compounds reported in Lawsonia inermis (Moutawalli et al., 2023).

angiogenesis could be obtained by using cellulose acetate scaffolds containing *L. inermis*. Additionally, gene expression studies revealed while nuclear factor-κ β (NF-κ β) and tumor necrosis factor α (TNF-α) expressions were considerably decreased by these composites, they upregulated vascular endothelial growth factor (VEGF), basic fibroblast growth factor (b-FGF), and collagen type 2 genes (Zhang et al., 2022).

3.5. Nicotine

Nicotine, an organic compound that is the main alkaloid in tobacco, has a number of effects on cell proliferation. It has recently been reported to have angiogenic effects as well (Greenhalgh, 2013). According to a report by Liem *et al.*, low nicotine concentrations can lead to increased angiogenesis, which ultimately leads to wound healing in the presence of nicotine (Liem et al., 2013). Masuoka and his colleagues assessed the wound healing process using a collagen scaffold in the presence of nicotine. They were able to treat full-thickness skin defects of the auricular cartilage in rabbits utilizing bi-layer artificial dermis with nicotine.

3.6. Propolis

Propolis and bee glue are typically produced by honey bees of the genus Apis. Honey bees produce a natural resinous substance by mixing bee wax and saliva with exudate gathered from buds and sap flows of trees, or other plant sources such as willow, poplar, elm, birch, alder, conifer, beech, and horse-chestnut trees (Kuropatnicki et al., 2013). Based on its mechanical properties and waxy nature, honey bees use propolis as a building material to build and repair their hive (Yaghoubi et al., 2007, Kuropatnicki et al., 2013). The chemical composition and nature of propolis are dependent on the geographical area, environmental conditions, season, time of collection, altitude, botanical origin of the exudates, and harvested resources; so, the chemical composition and nature of propolis can vary (Kuropatnicki et al., 2013). Propolis has been used in traditional medicine for thousands of years. In the last fifty years, scientists have proven propolis to be a useful and important substance in medicine, especially in tissue regeneration, treatment of burns, wound healing, neuro-dermatitis, psoriasis, and leg ulcers (Burdock, 1998, Najafi et al., 2007, Yaghoubi et al., 2007, Kuropatnicki et al., 2013, Hashemi et al., 2023). Several biological and pharmaceutical properties have been detected in propolis, including anti-inflammatory, antioxidant, antimicrobial, antitumor, and immunostimulant activities (Pessolato et al., 2011, Daleprane and Abdalla, 2013, Olczyk et al., 2013, Valenzuela-Barra et al., 2015).

The potential beneficial effects of propolis in treatment of burns, incision wounds, excision, and diabetes were demonstrated confirming the role of propolis in accelerating the healing process throughout the various stages of wound healing (Ahmed et al., 2011, Hashemi et al., 2023). Histologic findings have demonstrated propolis to facilitate the healing process by reducing mast and inflammatory cells. It is worth noting that wound contraction is an important part of wound healing and process of the repair. Propolis can be effective in rapid wound contraction by increasing the synthesis of collagen and stimulating the expression of collagen type I (Ahmed et al., 2011, de Almeida et al., 2013, Abu-Seida, 2015). Fig. 6 shows some of the flavonoid structures isolated from propolis.

3.6.1. Propolis/ polymer composites

Due to the extraordinary effects of propolis in wound healing and also their clinical application for wound management, in recent years, advanced dressings incorporated with propolis that can release the beneficiary substances in the wound bed based on polymer matrices have been studied (Mele, 2023). In a study by Asri *et al.*, the effects of propolis were examined in scaffolds containing composites of cellulose that could be enhanced with calcium alginate. Propolis extract was shown to have a significant effect on the growth and proliferation of fibroblasts without any toxicity. It is worth noting that the mechanical strength, water absorption, and porosity tests introduced propolis as a suitable option in tissue engineering and wound healing (Asri et al., 2020, Hashemi et al., 2023). In research conducted by Alberti *et al.*, they produced a polymeric nanofibrous wound dressing composed of PVA and propolis, and examined its effect on wound healing, showing that the association of propolis nanoparticles with PVA scaffold could lead to re-epithelialization, which could be effective in tissue regeneration, especially in healing-impaired individuals (Alberti et al., 2020). In a similar study, Eskandarian *et al.* investigated the effect of propolis on bilayer wound dressings using electrospun scaffolds composed of PCL/ gelatin in one layer consisting of polyurethane (PU) and ethanolic

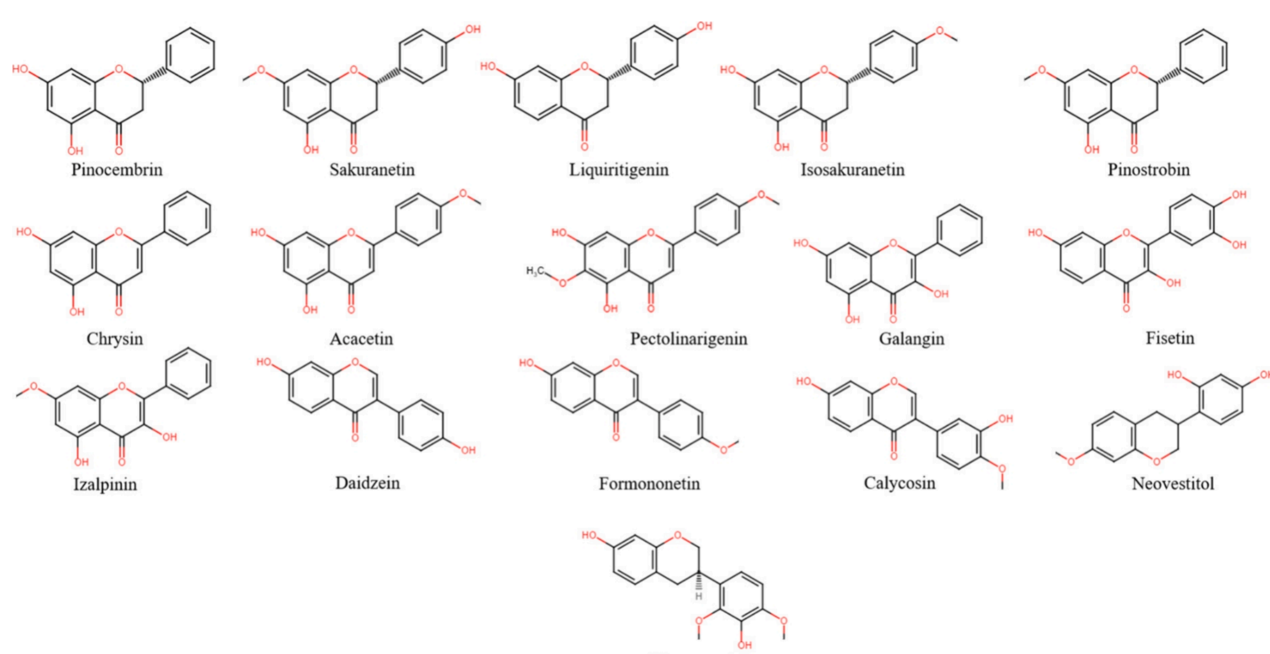

Fig. 6. The flavonoid structures isolated from propolis (Giampieri et al., 2022).

extract of propolis in the second layer. The membrane was employed as a protective layer against external factors such as dehydration and contamination. The findings revealed that the resulting wound dressing could accelerate wound healing by promoting fibroblast migration and collagen deposition in the skin wounds of Wistar rats. Also, due to its mechanical properties, antibacterial features, and wound-healing activities, this dressing was introduced as a suitable candidate for biomedical applications. This composite was shown to also have biological properties, such as antibacterial, antifungal, antiviral, anti-inflammatory, anticancer, and antitumor activity (Eskandarinia et al., 2020). In another study, silver nanoparticle-based chitosan scaffolds were prepared and loaded propolis to evaluate the antibacterial activity. The results of inhibition zones showed 26.3 and 23.4 mm against *S. aureus* and *Candida albicans*, respectively, values which were higher than commercial antibiotics. The results in *in-vitro* studies showed fast healing of wounds without signs of infection (Fig. 7) (Al-saggaf, 2021).

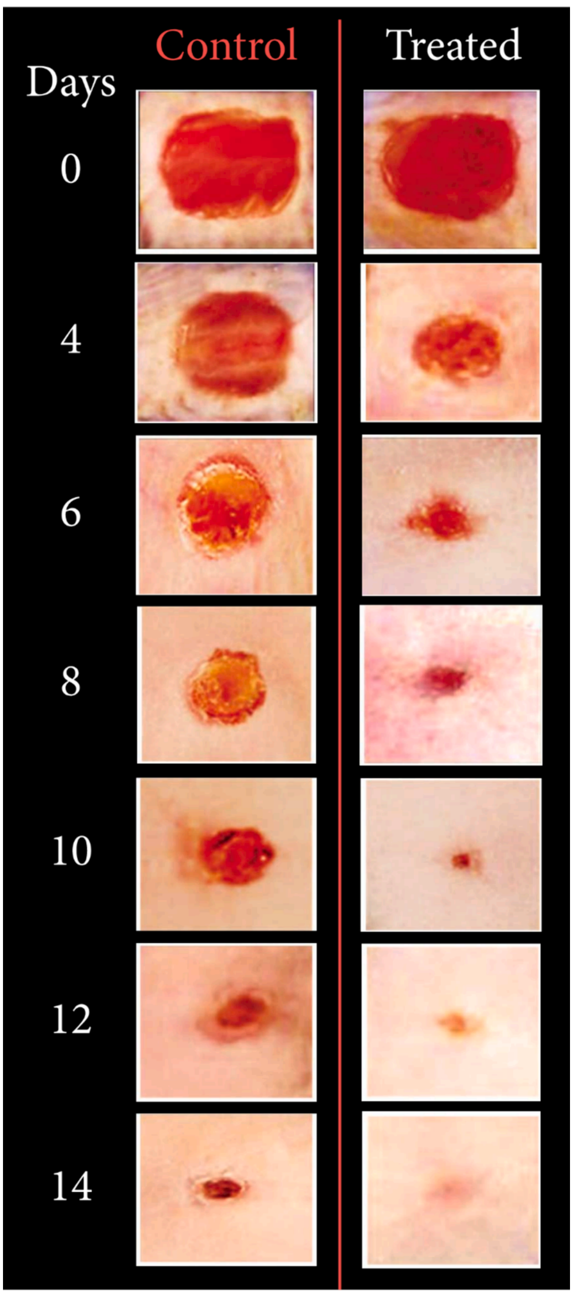

Fig. 7. Comparing the healing rate of wounds using chitosan/propolis/silver nanoparticles and control groups (untreated) during 14 days (Al-saggaf, 2021).

Due to its hydrophilic nature, propolis can also be used for decreasing water contact angle in polymer composites. For instance, in PVA/chitosan/Propolis, enhanced hydrophilicity improved cell proliferation due to the interactions between membranes and mouse embryonic fibroblasts cells, resulting wound healing ability (Ceylan, 2021). In other study, the hydrogel films-based propolis-loaded Quaternized chitosan (QCS)/pectin was fabricated and confirmed as non-toxicity candidate to mouse fibroblast cell line. QCS and pectin promoted the hydrogel stability and controlled the propolis release from the hydrogel to heal wounds. Due to bacterial growth inhibition especially against S. aureus and *Streptococcus pyogenes*, they could be considered as good candidates for wound healing applications (Phonrachom et al., 2023).

Sharaf et al. reported the preparation of nanoparticles based on chitosan and propolis, which were loaded in deacetylated cellulose acetate nanofibers, resulting in enhanced hydrophobicity. This compound was used to treat second-degree burns via propolis release to increase the healing process. In addition, 89.46 % cell viability for cellulose nanofibers/chitosan/propolis nanoparticles was obtained, the epithelial cells were repaired after 21 days, and hair follicles and sebaceous glands were formed in albino-mice models (Fig. 8) (Sharaf et al., 2021).

3.7. Honey

Honey is a natural substance with many biological activities that work in concert to accelerate the wound healing process. For thousands of years, honey has been used as a wound dressing to treat burns, ulcers, and wounds (Nejabat et al., 2009). This positive impact on the wound-healing environment and on the healing process is largely due to the intrinsic properties of honey. Honey has an acidic pH of about 3.2–4.5. The local acidification of wounds accelerates healing by increasing the release of oxygen from hemoglobin. Its acidity makes the wound environment unsuitable for protease activity (Greener et al., 2005). Honey has been shown to stimulate the growth of fibroblast and epithelial cells, collagen synthesis, preventing scar tissue and keloid formation, subsiding inflammation and pain, and development of new blood vessels, as some of the mechanisms of honey in the wound healing process (Molan, 2002, Al-Waili, 2003, Sharma et al., 2012).

Honey can play an important role in increasing the angiogenesis and proliferation of fibroblast and epithelial cells by producing certain growth factors like tumor necrosis factor (TNF-alpha) (Tonks et al., 2007). Studies on honey have shown that there are various concentrations of nitric oxide metabolites in honey (Al-Waili, 2003). Nitric oxide is a multifunctional biological gas that is involved in some biological activities such as accelerating collagen synthesis, wound healing re-epithelialization, angiogenesis regulation, immunological, and inflammatory responses (Witte and Barbul, 2002). Biological bioactive elements such as vitamin A, B1, C, B2, B6, E, K, niacin, flavonoids, fatty acids, and phenolics, hydroxybenzoic acid, octadecanoic acid, and ethyl ester exist in honey (Dumitru et al., 2022). Table 3 presents various compounds identified in the honey.

3.7.1. Honey/polymer composites

Different biomaterials along with honey have been extensively applied to increase the process of angiogenesis for wound healing. In a study, the impact of honey and chitosan on the electrospinning process of polyethylene terephthalate (PET) was compared. The results demonstrated chitosan could lead to the formation of beaded or ribbon-like/branched morphology, while it improved when honey was used. The fiber diameters decreased with an increased concentration of honey in PET solution, and resulting nanofibers did not show cytotoxic activity (Arslan et al., 2014). In another study, a scaffold of PU was prepared using honey, sesame oil, and propolis by electrospinning method. It was observed that the blending honey, sesame oil, and propolis into the PU matrix resulted in reduction of the fiber diameter and thinner fibers were able to stimulate fibroblast mobility and proliferation. So, the mixture of honey, sesame oil, propolis, and PU was suggested as an

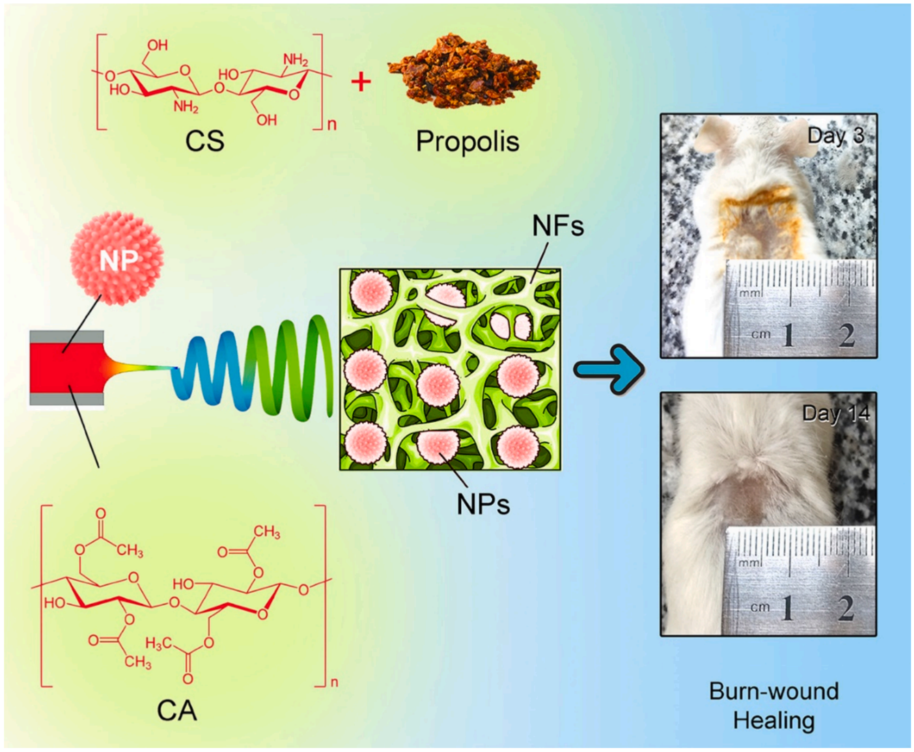

Fig. 8. The synthesis of cellulose nanofibers/chitosan/propolis nanoparticles to heal burn wound (Sharaf et al., 2021).

Table 3
The pharmacological activity of chemical propolis compounds.

	Chemical compounds	Pharmacological activity
	Acacetin	Anti-inflammatory
	Apigenin	Anti-inflammatory; Antimicrobial
	Artepilin C	Antitumor activity; Antioxidative
	Caffeic acid phenethyl ester	Antitumor activity; Anti-inflammatory
	Chrysin	Anti-inflammatory; Antibacterial
	Caffeic acid	Antifungal; Antiviral; Anti-inflammatory
	Cinnamic acid	Anti-inflammatory
	Dicaffeoylquinic acid derivatives	Hepatoprotective
	Ferulic acid, Galangin, Gallic acid	Anti-inflammatory
	Protocatechuic acid	Anti-inflammatory, Antibacterial
	Pinocembrin	Antifungal; Antimold; Local anesthesia
	Propofol	Antioxidative

appropriate combination for tissue engineering and wound healing (Salama and El-Sakhawy, 2022). The combination of honey and chitosan/ PVA to form hydrogels was shown to have wound healing effects and antimicrobial activity against *S. aureus* (Chopra et al., 2022). The cross-linked chitosan/gelatin/PVA hydrogel with the ratio of 2:1:1 (v/v) was prepared and loaded honey. Honey decreased tensile strength and of hydrogels. However, *in-vitro* studies showed accelerated wound healing in a rat model due to the formation well-structured layer of epidermis (Shamloo et al., 2021).

Dual crosslinked sodium alginate hydrogels with different concentrations of honey were fabricated by ionically and covalently interactions, and were shown to have antibacterial activities against S. aureus and E. coli. This hydrogel performed favorable regenerative healing through re-epithelialization and decreasing epithelial thickness *in-vitro* with negligible scar (Mukhopadhyay et al., 2020). Another nanofiber based on alginate/PVA was prepared by electrospinning and used for efficient wound dressing. The results of antibacterial activity (zone of inhibition) were enhanced from 7.48 ± 0.17 mm to 11.38 ± 0.42 mm for *E. coli* and from 7.51 ± 0.55 mm to 13.67 ± 1.29 mm for *S. aureus*, respectively, by increasing honey content from 0 to 20 % in the nanofibers (Tang et al., 2019).

In other study, nanofibers of poly (diallyldimethylammonium chloride) loaded with honey were prepared by electrospinning to evaluate the diabetic wound-healing using *in-vitro* experiments. In order to design the honey release and decrease the solubility of nanofibers, glutaraldehyde was used as crosslinker, showing that the release of honey could be sustained up to 125 h. Additionally, the obtained composites displayed antibacterial activities against *S. aureus* and *E. coli* bacteria. As a result, prepared nanofibers increased significantly diabetic wound-healing and decreased the acute and chronic inflammation (Fig. 9) (Parvinzadeh Gashti et al., 2023).

3.8. *Perovskia abrotanoides Karel*

Perovskia abrotanoides Karel (*P. abrotanoides*), also known as *Salvia abrotanoides* Karel, belongs to *Lamiaceae* family and is one of the most widely used pharmaceuticals in North and North East of Iran (Derakhshanfar et al., 2019). Due to its efficiency in traditional medicine, genetic structure of *P. abrotanoides* has been studied by molecular and morphological markers and topical treatment with *P. abrotanoides* has been broadly utilized for antimicrobial and healing properties (Hashemifar and Rahimmalek, 2018, Maryam et al., 2023). It has been shown that extract of *P. abrotanoides* could inhibit the release of nitric oxide and the expression of related proinflammatory enzymes (Alizadeh et al., 2021). Several researchers have successfully employed *P. abrotanoides* in treatment of burn injuries and demonstrated that *P. abrotanoides* can

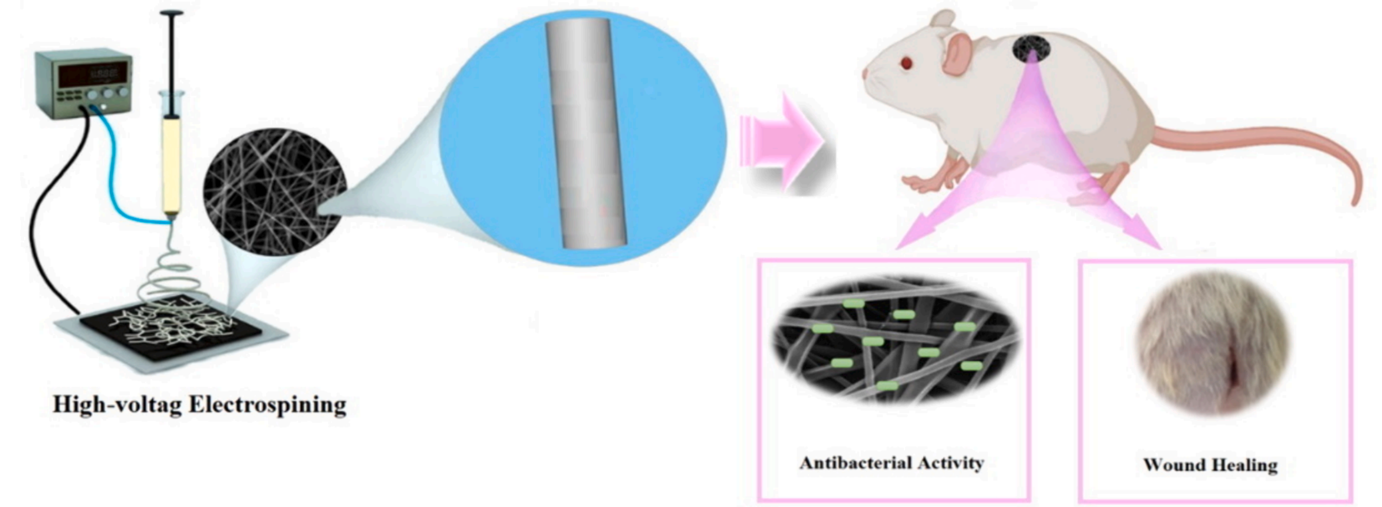

Fig. 9. The synthesis of nanofibers and the application of wound healing (Parvinzadeh Gashti et al., 2023).

successfully accelerate the proliferation of fibroblasts and increase the rate of granulation tissue formation and finally with a potential effect to accelerate burn wound healing. The antibacterial activity of *P. abrotanoides* extract was illustrated against *Escherichia coli, Staphylococcus aureus and Pseudomonas aeruginosa*, which can cause infection in burn area. *P. abrotanoides* was shown to upregulate expression of vascular endothelial growth factor (VEGF) and transforming growth factor-β (TGF-β) genes too (Derakhshanfar et al., 2019).

Leishmania is one of the most common infectious diseases of tropical countries, which mostly affects under-developed communities with lower incomes. There are cutaneous, mucosal, and visceral types. Numerous clinical considerations have been made about the importance of home-made substances against leishmaniosis due to the side effects, intake and adequacy of anti-leishmanial drugs. In Iranian traditional medicine, *P. abrotanoides* has been utilized in treatment of leishmaniosis, which has been shown to facilitate to secondary leishmaniosis contaminations, particularly against *S. aureus* (Mahboubi and Kazempour, 2009).

3.9. *Quercus brantii*

Quercus brantii, also known as the Persian Oak or Brant's oak, is a member of the *Fagaceae* family. It may be a restorative plant broadly utilized by the tribes of southwestern Iran to treat stomach ulcers. Malayeri *et al.* assessed the effect of Persian oak on burn injuries of experimental rats and found it effective in wound closure, contraction and re-epithelialization, and formation of hydroxyproline and collagen substances revealing its significant impact on tissue repair when compared to the control group (Malayeri et al., 2022). The potential application of PCL/chitosan/oak seeds (jaft) electrospun within the inward layer as a skin platform has been investigated. SEM micrographs, trypan blue test, and DAPI staining affirmed that fibroblast cells could migrate and proliferate well on PCL/chitosan/oak seeds (Hashemi et al., 2022). This bioactive platform showed promising mechanical properties and reasonable biocompatibility *in-vitro* and *in-vitro* that may be a promising candidate for skin tissue designing applications(Hashemi et al., 2022).

3.10. *Lithospermum officinale*

Lithospermum officinale, or common gromwell, is a member of *Boraginaceae* family. It consists of fatty acids, proteins, carbohydrates, alkaloids, flavonoids and other bioactive substances and has anticancer, wound healing, antioxidant and anti-inflammatory effects (Al-Snai, 2019). According to studies on burn wound healing, compared to silver sulfadiazine, Alpha burn cream, this herb can be used for topical administration as a biocompatible, cost-effective and easy to produce medicine that induces accelerated angiogenesis, granulation tissue formation, epithelialization and skin regeneration (Amiri et al., 2017). Hence, it has a great potential for application in modern wound dressings.

4. Conclusion and future propositions

As tissue engineering is a prominent therapeutic strategy for present and future medicine, developing scaffolds that mimic the architecture of tissue at the nanoscale that are cost-effective can be one of the choices in treatment of skin wounds. To improve wound healing, different natural products with the technological advances in nanotechnology, material science, regenerative medicine, and bioengineering have been investigated to suit the current wound care demands such as tissue repair, restoration of lost tissue integrity and scarless healing. So future researches and developments are needed to be directed toward the design, synthesis, modification, evaluation, and characterization of natural products targeting skin tissue engineering and wound healing. In addition, further studies about combination of plant extracts and modern drugs can be designed with the aim of improved wound healing with reduced side effects. Moreover, the new strategies based on the drug delivery systems can be developed to facilitate the wound healing process by using bioavailability and the permeation of phytoconstituents via dermal sections and localizing at wound sites both *in-vitro* and *in-vitro*. Nanocarriers such as nanofibers, nanoparticles, vesicular structures, and metal nanoparticles can assist to get these goals for better patient compliance by enhancing therapeutic efficacy due to their high surface area to volume ratio. The homeostasis, re-epithelialization, regeneration, immunocytes and non-lymphoid cells can be investigated by inducing fibroblasts proliferation and/or collagen production in animal models and also via molecular studies. Finally, clinical studies are needed before introducing commercial products in the market.

CRediT authorship contribution statement

Seyedeh-Sara Hashemi: Data curation, Methodology, Writing – original draft. **Razie Rezaeian:** Visualization, Writing – original draft. **AliReza Rafati:** Conceptualization, Writing – original draft. **Parisa Sanati:** Data curation, Writing – original draft. **Davood Mehrabani:** Supervision, Writing – review & editing. **Rahime Eshaghi Malekshah:** Writing – original draft. **Armaghan Moghaddam:** Writing – review &

editing. **Hossein Ali Khonakdar:** Project administration, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Abdel-Mohsen, A., Frankova, J., Abdel-Rahman, R.M., et al., 2020. Chitosan-glucan complex hollow fibers reinforced collagen wound dressing embedded with aloe vera. II. Multifunctional properties to promote cutaneous wound healing. Int. J. Pharm. 582, 119349.
Abu-Seida, A.M., 2015. Effect of propolis on experimental cutaneous wound healing in dogs. Veterinary Medicine International.
Ahmed, E.T., Abo-Salem, O.M., Osman, A., 2011. The influence of Egyptian propolis on induced burn wound healing in diabetic rats; antibacterial mechanism. Science Journal of Medicine and Clinical Trials.
Ai, J., Ebrahimi, S., Khoshzaban, A., et al., 2012. Tissue engineering using human mineralized bone xenograft and bone marrow mesenchymal stem cells allograft in healing of tibial fracture of experimental rabbit model. Iran. Red Crescent Med. J. 14, 96.
Ak, G., Zengin, G., Sinan, K.I., et al., 2020. A comparative bio-evaluation and chemical profiles of Calendula officinalis L. extracts prepared via different extraction techniques. Appl. Sci. 10, 5920.
Alberti, T.B., Coelho, D.S., de Prá, M., et al., 2020. Electrospun PVA nanoscaffolds associated with propolis nanoparticles with wound healing activity. J. Mater. Sci. 55, 9712–9727.
Aleebrahim-Dehkordy, E., Rafieian-Kopaei, M., Amini-Khoei, H., et al., 2019. In vitro evaluation of antioxidant activity and antibacterial effects and measurement of total phenolic and flavonoid contents of Quercus brantii L. fruit extract. Journal of Dietary Supplements. 16, 408–416.
AlFannakh, H., 2022. Impedance spectroscopy, AC conductivity, and conduction mechanism of Iron (II) chloride/polyvinyl alcohol/polyvinylpyrrolidone polymer blend. Adv. Mater. Sci. Eng. 2022.
Alishbah, S., Z. Bint e, S. Kanwal, et al., 2022. Structure and Physiology of Human Ear Involved in Hearing. Auditory System. N. Sadaf. Rijeka, IntechOpen: Ch. 1.
Alizadeh, Z., Farimani, M.M., Parisi, V., et al., 2021. Nor-abietane diterpenoids from Perovskia abrotanoides roots with anti-inflammatory potential. J. Nat. Prod. 84, 1185–1197.
Al-saggaf, M.S., 2021. Formulation of insect chitosan stabilized silver nanoparticles with propolis extract as potent antimicrobial and wound healing composites. International Journal of Polymer Science. 2021, 1–9.
Al-Snafi, A.E., 2019. Chemical constituents and pharmacological effects of Lithospermum officinale. IOSR Journal of Pharmacy. 9, 12–21.
Al-Snai, A.E., 2019. Chemical constituents and pharmacological effects of Lithospermum officinale. IOSR Journal of Pharmacy. 9, 12–21.
Al-Waili, N.S., 2003. Identification of nitric oxide metabolites in various honeys: effects of intravenous honey on plasma and urinary nitric oxide metabolites concentrations. J. Med. Food 6, 359–364.
Amini, M., Kherad, M., Mehrabani, D., et al., 2010. Effect of Plantago major on burn wound healing in rat. J. Appl. Anim. Res. 37, 53–56.
Amiri, Z.M., Tanideh, N., Seddighi, A., et al., 2017. The effect of lithospermum officinale, silver sulfadiazine and alpha ointments in healing of burn wound injuries in rat. World Journal of Plastic Surgery. 6, 313.
Ansari, M., Meftahizadeh, H., Eslami, H., 2022. Fabrication of multifunctional chitosan-guar-aloe vera gel to promote wound healing. Chem. Pap. 76, 1513–1524.
Arslan, A., Şimşek, M., Aldemir, S.D., et al., 2014. Honey-based PET or PET/chitosan fibrous wound dressings: effect of honey on electrospinning process. J. Biomater. Sci. Polym. Ed. 25, 999–1012.
Asri, M., Asefnejad, A., Naeimi, M., 2020. Construction and evaluation of composite scaffold properties of cellulose base enhanced with calcium alginate containing propolis for use in skin tissue engineering. Journal of Asian Scientific Research. 10, 229.
Avci, H., Monticello, R., Kotek, R., 2013. Preparation of antibacterial PVA and PEO nanofibers containing Lawsonia Inermis (henna) leaf extracts. J. Biomater. Sci. Polym. Ed. 24, 1815–1830.
Azuma, K., Izumi, R., Osaki, T., et al., 2015. Chitin, chitosan, and its derivatives for wound healing: old and new materials. Journal of Functional Biomaterials. 6, 104–142.
Bankova, V., Trusheva, B., Popova, M., 2021. Propolis extraction methods: A review. J. Apic. Res. 60, 734–743.
Bayat, H., Noghondar, M.A., Aminifard, M.H., 2022. Determination and comparison of total phenolic content and antioxidant activity of water, methanolic, ethanolic and hexane extracts from different parts of perovskia abrotanoides karel. Journal of Innovation Food Science & Technology. 13.
Bayati, S., Harirchi, P., Zahedi, P., et al., 2023. Lawsonia inermis-loaded poly (L-lactide-co-D, L-lactide) nanofibers for healing acceleration of burn wounds. J. Biomater. Sci. Polym. Ed. 34, 1019–1035.
Biesaga, M., Pyrzyńska, K., 2013. Stability of bioactive polyphenols from honey during different extraction methods. Food Chem. 136, 46–54.
Bordoloi, C., Kumar, S., Barbhuiya, A.M., et al., 2023. Herbal medicine used for wound healing by the tribes of the north eastern states of india: A comprehensive review. Journal of Herbal Medicine. 100697.
Burdock, G., 1998. Review of the biological properties and toxicity of bee propolis (propolis). Food Chem. Toxicol. 36, 347–363.
Ceylan, S., 2021. Propolis loaded and genipin-crosslinked PVA/chitosan membranes; characterization properties and cytocompatibility/genotoxicity response for wound dressing applications. Int. J. Biol. Macromol. 181, 1196–1206.
Chakraborty, T., Gupta, S., Nair, A., et al., 2021. Wound healing potential of insulin-loaded nanoemulsion with Aloe vera gel in diabetic rats. J. Drug Delivery Sci. Technol. 64, 102601.
Chandegara, V. and A. K. Varshney, 2013. Aloe vera L. processing and products: a review.
Chelu, M., Musuc, A.M., Popa, M., et al., 2023. Aloe vera-based hydrogels for wound healing: Properties and therapeutic effects. Gels. 9, 539.
Chen, J., Fan, Y., Dong, G., et al., 2023. Designing biomimetic scaffolds for skin tissue engineering. Biomaterials Science.
Chithra, P., Sajithlal, G., Chandrakasan, G., 1998. Influence of Aloe vera on collagen characteristics in healing dermal wounds in rats. Mol. Cell. Biochem. 181, 71–76.
Choi, S., Chung, M.-H., 2003. A review on the relationship between Aloe vera components and their biologic effects. Seminars in integrative medicine. Elsevier.
Chopra, H., Bibi, S., Kumar, S., et al., 2022. Preparation and evaluation of chitosan/PVA based hydrogel films loaded with honey for wound healing application. Gels. 8, 111.
Cirak, C., Radusiene, J., Jakstas, V., et al., 2016. Secondary metabolites of Hypericum species from the Drosanthe and Olympia sections. S. Afr. J. Bot. 104, 82–90.
Daleprane, J.B., Abdalla, D.S., 2013. Emerging roles of propolis: antioxidant, cardioprotective, and antiangiogenic actions. Evid. Based Complement. Alternat. Med.
Davoodi, F., Raisi, A., Farjanikish, G., et al., 2022. A review on wound healing with Iranian medicinal plants and microbial flora in veterinary medicine. Iranian Journal of Veterinary Surgery. 17, 146–159.
de Almeida, E.B., Cardoso, J.C., de Lima, A.K., et al., 2013. The incorporation of Brazilian propolis into collagen-based dressing films improves dermal burn healing. J. Ethnopharmacol. 147, 419–425.
Derakhshanfar, A., Hashemi, S.-S., Moayedi, J., et al., 2019a. A study on the effects of perovskia abrotanoides karel on experimental skin burn in male rat: in-vivo and in-vitro findings. Journal of Advances in Medical and Biomedical Research. 27, 17–22.
Derakhshanfar, A., Mehrabani, D., Moayedi, J., et al., 2019b. Healing effect of Perovskia abrotanoides karel and expression of VEGF and TGF-B genes in burn injury of rats. International Journal of Nutrition Sciences. 4, 175–180.
Dinda, M., Dasgupta, U., Singh, N., et al., 2015. PI3K-mediated proliferation of fibroblasts by Calendula officinalis tincture: implication in wound healing. Phytother. Res. 29, 607–616.
Dixit, K., Mohapatra, D., Senapati, P.C., et al., 2022. Formulation development and evaluation of lawsonia inermis extract loaded hydrogel for wound dressing application. Indian J. Pharm. Sci. 84.
Dost, T., Ozkayran, H., Gokalp, F., et al., 2009. The effect of Hypericum perforatum (St. John's Wort) on experimental colitis in rat. Dig. Dis. Sci. 54, 1214–1221.
Dumitru, C.D., Neacsu, I.A., Grumezescu, A.M., et al., 2022. Bee-derived products: Chemical composition and applications in skin tissue engineering. Pharmaceutics. 14, 750.
Eğri, Ö., Erdemir, N., 2019. Production of Hypericum perforatum oil-loaded membranes for wound dressing material and in vitro tests. Artif. Cells Nanomed. Biotechnol. 47, 1404–1415.
Eskandarinia, A., Kefayat, A., Agheb, M., et al., 2020. A novel bilayer wound dressing composed of a dense polyurethane/propolis membrane and a biodegradable polycaprolactone/gelatin nanofibrous scaffold. Sci. Rep. 10, 3063.
Farzaneh, M., Amirahmadi, A., Poozesh, V., et al., 2021. Study on Phytochemical diversity and antioxidant properties of extracts from different populations of Perovskia abrotanoides Kar. in Eastern Alborz. Eco-Phytochemical Journal of Medicinal Plants. 9, 16–28.
Fronza, M., Heinzmann, B., Hamburger, M., et al., 2009. Determination of the wound healing effect of Calendula extracts using the scratch assay with 3T3 fibroblasts. J. Ethnopharmacol. 126, 463–467.
Garcia-Orue, I., Gainza, G., Gutierrez, F.B., et al., 2017. Novel nanofibrous dressings containing rhEGF and Aloe vera for wound healing applications. Int. J. Pharm. 523, 556–566.
Giampieri, F., Quiles, J.L., Cianciosi, D., et al., 2022. Bee products: An emblematic example of underutilized sources of bioactive compounds. J. Agric. Food Chem. 70, 6833–6848.
Gilbert, T.W., Sellaro, T.L., Badylak, S.F., 2006. Decellularization of tissues and organs. Biomaterials 27, 3675–3683.
Greener, B., Hughes, A., Bannister, N., et al., 2005. Proteases and pH in chronic wounds. J. Wound Care 14, 59–61.
Greenhalgh, D.G., 2013. Treating a collagen scaffold with a low concentration of nicotine-promoted angiogenesis and wound healing. J. Surg. Res. 185, 543–544.
Hadisi, Z., Nourmohammadi, J., Nassiri, S.M., 2018. The antibacterial and anti-inflammatory investigation of Lawsonia Inermis-gelatin-starch nano-fibrous dressing in burn wound. Int. J. Biol. Macromol. 107, 2008–2019.
Hashemi, S.S., Mohammadi, A.A., Kabiri, H., et al., 2019. The healing effect of Wharton's jelly stem cells seeded on biological scaffold in chronic skin ulcers: A randomized clinical trial. J. Cosmet. Dermatol. 18, 1961–1967.
Hashemi, S.-S., Saadatjo, Z., Mahmoudi, R., et al., 2022. Preparation and evaluation of polycaprolactone/chitosan/Jaft biocompatible nanofibers as a burn wound dressing. Burns 48, 1690–1705.

Hashemi, S.-S., Mohammadi, A.A., Rajabi, S.-S., et al., 2023. Preparation and evaluation of a polycaprolactone/chitosan/propolis fibrous nanocomposite scaffold as a tissue engineering skin substitute. BioImpacts. 13, 275–287.
Hashemi, S.-S., Pakdin, A., Mohammadi, A., et al., 2023c. Study the effect of calendula officinalis extract loaded on zinc oxide nanoparticle cream in burn wound healing. ACS Appl. Mater. Interfaces 15, 59269–59279.
Hashemi, S.-S., Mohammadi, A.-A., Kian, M., et al., 2024. Fabrication and evaluation of the regenerative effect of a polycaprolactone/chitosan nanofibrous scaffold containing bentonite nanoparticles in a rat model of deep second-degree burn injury. Iran. J. Basic Med. Sci. 27, 223.
Hashemifar, Z., Rahimmalek, M., 2018. Genetic structure and variation in Perovskia abrotanoides Karel and P. atriplicifolia as revealed by molecular and morphological markers. Sci. Hortic. 230, 169–177.
Hassan, M.A.M., Mohammed, A.H., Hameed, E.M., 2023. Application of aloe vera gel blended polymer-collagen scaffolds for bone tissue engineering. Nano Biomedicine and Engineering.
Hassanshahi, N., Masoumi, S.J., Mehrabani, D., et al., 2020. The healing effect of aloe vera gel on acetic acid-induced ulcerative colitis in rat. Middle East Journal of Digestive Diseases. 12, 154.
Hazrati, M., Mehrabani, D., Japoni, A., et al., 2010. Effect of honey on healing of Pseudomonas aeruginosa infected burn wounds in rat. J. Appl. Anim. Res. 37, 161–165.
Hu, R.-S., Wang, J., Li, H., et al., 2015. Simultaneous extraction of nicotine and solanesol from waste tobacco materials by the column chromatographic extraction method and their separation and purification. Sep. Purif. Technol. 146, 1–7.
Huesca-Urióstegui, K., García-Valderrama, E.J., Gutierrez-Uribe, J.A., et al., 2022. Nanofiber systems as herbal bioactive compounds carriers: Current applications in healthcare. Pharmaceutics. 14, 191.
Istasse, T., Jacquet, N., Berchem, T., et al., 2016. Extraction of honey polyphenols: method development and evidence of cis isomerization ubertas academica. Anal. Chem. Insights 11.
Jeyaseelan, E.C., Jenothiny, S., Pathmanathan, M., et al., 2012. Antibacterial activity of sequentially extracted organic solvent extracts of fruits, flowers and leaves of Lawsonia inermis L. from Jaffna. Asian Pac. J. Trop. Biomed. 2, 798–802.
Jithendra, P., Rajam, A.M., Kalaivani, T., et al., 2013. Preparation and characterization of aloe vera blended collagen-chitosan composite scaffold for tissue engineering applications. ACS Appl. Mater. Interfaces 5, 7291–7298.
Jithendra, P., Mohamed, J.M.M., Annamalai, D., et al., 2023. Biopolymer collagen-chitosan scaffold containing Aloe vera for chondrogenic efficacy on cartilage tissue engineering. In: International Journal of Biological Macromolecules., p. 125948.
Kaboodkhani, R., Mehrabani, D., Karimi-Busheri, F., 2021. Achievements and challenges in transplantation of mesenchymal stem cells in otorhinolaryngology. J. Clin. Med. 10, 2940.
Kharat, Z., Goushki, M.A., Sarvian, N., et al., 2021. Chitosan/PEO nanofibers containing Calendula officinalis extract: Preparation, characterization, in vitro and in vivo evaluation for wound healing applications. Int. J. Pharm. 609, 121132.
Kheawfu, K., Kaewpinta, A., Chanmahasathien, W., et al., 2021. Extraction of nicotine from tobacco leaves and development of fast dissolving nicotine extract film. Membranes 11, 403.
Khodakaram-Tafti, A., Mehrabani, D., Shaterzadeh-Yazdi, H., et al., 2018. Tissue engineering in maxillary bone defects. World Journal of Plastic Surgery. 7, 3.
Klemow, K., A. Bartlow, J. Crawford, et al., 2011. Medical Attributes of St. John's Wort (Hypericum perforatum). Editors In: Benzie IFF, Wachtel-Galor S, editors. Source Herbal Medicine: Biomolecular and Clinical Aspects. Chapter 11, CRC Press, Boca Raton (FL).
Korbekandi, H., Chitsazi, M.R., Asghari, G., et al., 2015. Green biosynthesis of silver nanoparticles using Quercus brantii (oak) leaves hydroalcoholic extract. Pharm. Biol. 53, 807–812.
Kuropatnicki, A.K., Szliszka, E., Krol, W., 2013. Historical aspects of propolis research in modern times. Evid. Based Complement. Alternat. Med.
Liem, P.H., Morimoto, N., Ito, R., et al., 2013. Treating a collagen scaffold with a low concentration of nicotine promoted angiogenesis and wound healing. J. Surg. Res. 182, 353–361.
Loo, W.T., Wang, M., Jin, L., et al., 2011. Association of matrix metalloproteinase (MMP-1, MMP-3 and MMP-9) and cyclooxygenase-2 gene polymorphisms and their proteins with chronic periodontitis. Arch. Oral Biol. 56, 1081–1090.
Ma, S., Tang, Q., Feng, Q., et al., 2019. Mechanical behaviours and mass transport properties of bone-mimicking scaffolds consisted of gyroid structures manufactured using selective laser melting. J. Mech. Behav. Biomed. Mater. 93, 158–169.
Mahalakshmi, P., Reshma, G., Arthi, C., et al., 2023. Biodegradable polymeric scaffolds and hydrogels in the treatment of chronic and infectious wound healing. Eur. Polym. J. 112390.
Mahboubi, M., Kazempour, N., 2009. The antimicrobial activity of essential oil from Perovskia abrotanoides karel and its main components. Indian J. Pharm. Sci. 71, 343.
Malayeri, A., Golfakhrabadi, F., Basir, Z., et al., 2022. Evaluating the effectiveness of aqueous extract of persian oak (Quercus castaneifolia CA Mey.) fruit hull on dermal wound healing in the rat model. Jundishapur Journal of Natural Pharmaceutical Products. 17.
Maryam, F., Vahid, P., Amirahmadi, A., et al., 2023. Perovskia abrotanoides Kar. as a promising source of antimicrobial compounds against foodborne pathogens. Medical Laboratory Journal. 17, 45–54.
Maver, T., Maver, U., Stana Kleinschek, K., et al., 2015. A review of herbal medicines in wound healing. Int. J. Dermatol. 54, 740–751.
Mehrabani, D., Ziaei, M., Hosseini, S., et al., 2011. The effect of Calendula officinalis in therapy of acetic acid induced ulcerative colitis in dog as an animal model. Iran. Red Crescent Med. J. 13, 884.
Mehrabani, D., Farjam, M., Geramizadeh, B., et al., 2015. The healing effect of curcumin on burn wounds in rat. World Journal of Plastic Surgery. 4, 29.
Mehrabani, D., Nazempour, M., Mehdinavaz-Aghdam, R., et al., 2022. MRI tracking of human Wharton's jelly stem cells seeded onto acellular dermal matrix labeled with superparamagnetic iron oxide nanoparticles in burn wounds. Burns & Trauma. 10, tkac018.
Mele, E., 2023. Electrospinning of honey and propolis for wound care. Biotechnol. Bioeng.
Molan, P. C., 2002. Re-introducing honey in the management of wounds and ulcers-theory and practice.
Monteiro-Soares, M., Hamilton, E.J., Russell, D.A., et al., 2023. Guidelines on the classification of foot ulcers in people with diabetes (IWGDF 2023 update). Diabetes Metab. Res. Rev. e3648.
Moses, R.L., Prescott, T.A.K., Mas-Claret, E., et al., 2023. Evidence for natural products as alternative wound-healing therapies. Biomolecules 13, 444.
Mouro, C., Gomes, A.P., Gouveia, I.C., 2023. Emulsion electrospinning of PLLA/PVA/Chitosan with hypericum perforatum L. as an antibacterial nanofibrous wound dressing. Gels. 9.
Moutawalli, A., Benkhouili, F.Z., Doukkali, A., et al., 2023. The biological and Pharmacologic Actions of Lawsonia inermis L. Phytomedicine plus. 100468.
Movaffagh, J., Bazzaz, B.S.F., Taherzadeh, Z., et al., 2022. Evaluation of wound-healing efficiency of a functional Chitosan/Aloe vera hydrogel on the improvement of re-epithelialization in full thickness wound model of rat. J. Tissue Viability 31, 649–656.
Muhammad, H., Muhammad, S., 2005. The use of Lawsonia inermis Linn. (henna) in the management of burn wound infections. Afr. J. Biotechnol. 4.
Muheyuddeen, G., Divy, S.R., Gautam, S.K., et al., 2023a. Lawsonia inermis L. Phytopharmacological Characteristics and Recent Advancement. Research Journal of Pharmacognosy and Phytochemistry. 15, 11–23.
Muheyuddeen, G., Divya, S.R., Verma, S., et al., 2023b. Lawsonia inermis Linnaeus: Pharmacological Peculiarity and Modern Progression. Research Journal of Pharmacognosy and Phytochemistry. 15, 63–76.
Mukhopadhyay, A., Rajput, M., Barui, A., et al., 2020. Dual cross-linked honey coupled 3D antimicrobial alginate hydrogels for cutaneous wound healing. Mater. Sci. Eng. C 116, 111218.
Nair, L.S., Laurencin, C.T., 2006. Polymers as biomaterials for tissue engineering and controlled drug delivery. Tissue Eng. I, 47–90.
Najafi, M.F., Vahedy, F., Seyyedin, M., et al., 2007. Effect of the water extracts of propolis on stimulation and inhibition of different cells. Cytotechnology 54, 49–56.
Naseri, E., Ahmadi, A., 2022. A review on wound dressings: Antimicrobial agents, biomaterials, fabrication techniques, and stimuli-responsive drug release. Eur. Polym. J. 173, 111293.
Nazemi, Z., Sahraro, M., Janmohammadi, M., et al., 2023. A review on tragacanth gum: A promising natural polysaccharide in drug delivery and cell therapy. Int. J. Biol. Macromol. 124343.
Nazempour, M., Mehrabani, D., Mehdinavaz-Aghdam, R., et al., 2020. The effect of allogenic human Wharton's jelly stem cells seeded onto acellular dermal matrix in healing of rat burn wounds. J. Cosmet. Dermatol. 19, 995–1001.
Nejabat, M., Astaneh, A., Eghtedari, M., et al., 2009. Effect of honey in Pseudomonas aeruginosa induced stromal keratitis in rabbits. J. Appl. Anim. Res. 35, 101–104.
Nur Parin, F., Deveci, S., 2023. Production and characterization of bio-based sponges reinforced with hypericum perforatum oil (St. John′ s Wort Oil) via pickering emulsions for wound healing applications. ChemistrySelect 8, e202203692.
Olczyk, P., K. Komosinska-Vassev, K. Winsz-Szczotka, et al., 2013. Propolis induces chondroitin/dermatan sulphate and hyaluronic acid accumulation in the skin of burned wound. Evidence-Based Complementary and Alternative Medicine. 2013.
Pang, Q., Jiang, Z., Wu, K., et al., 2023. Nanomaterials-based wound dressing for advanced management of infected wound. Antibiotics 12, 351.
Parvinzadeh Gashti, M., Dehdast, S.A., Berenjian, A., et al., 2023. PDDA/Honey antibacterial nanofiber composites for diabetic wound-healing: Preparation, characterization, and in vivo studies. Gels. 9, 173.
Pascual-Maté, A., Osés, S.M., Fernández-Muiño, M.A., et al., 2018. Analysis of polyphenols in honey: extraction, separation and quantification procedures. Sep. Purif. Rev. 47, 142–158.
Pedram Rad, Z., Mokhtari, J., Abbasi, M., 2019. Preparation and characterization of Calendula officinalis-loaded PCL/gum arabic nanocomposite scaffolds for wound healing applications. Iran. Polym. J. 28, 51–63.
Pessolato, A.G.T., dos Santos Martins, D., Ambrósio, C.E., et al., 2011. Propolis and amnion reepithelialise second-degree burns in rats. Burns 37, 1192–1201.
Phonrachom, O., Charoensuk, P., Kiti, K., et al., 2023. Potential use of propolis-loaded quaternized chitosan/pectin hydrogel films as wound dressings: Preparation, characterization, antibacterial evaluation, and in vitro healing assay. Int. J. Biol. Macromol. 241, 124633.
Pourhojat, F., Sohrabi, M., Shariati, S., et al., 2017. Evaluation of poly ε-caprolactone electrospun nanofibers loaded with Hypericum perforatum extract as a wound dressing. Res. Chem. Intermed. 43, 297–320.
Pourhojat, F., Shariati, S., Sohrabi, M., et al., 2018. Preparation of antibacterial electrospun Poly lactic-co–glycolic acid nanofibers containing Hypericum Perforatum with bedsore healing property and evaluation of its drug release performance. International Journal of Nano Dimension. 9, 286–297.
Rad, Z.P., Mokhtari, J., Abbasi, M., 2019. Calendula officinalis extract/PCL/Zein/Gum arabic nanofibrous bio-composite scaffolds via suspension, two-nozzle and

multilayer electrospinning for skin tissue engineering. Int. J. Biol. Macromol. 135, 530–543.

Ranjbar, R., Yousefi, A., 2018. Effects of aloe vera and chitosan nanoparticle thin-film membranes on wound healing in full thickness infected wounds with methicillin resistant Staphylococcus aureus. Bulletin of Emergency & Trauma. 6, 8.

Retnowati, D., Sari, R., Hendradi, E., et al., 2021. The stability and irritability study of the chitosan–aloe vera spray gel as wound healing. J. Basic Clin. Physiol. Pharmacol. 32, 651–656.

Roberts, M.S., Dancik, Y., Prow, T.W., et al., 2011. Non-invasive imaging of skin physiology and percutaneous penetration using fluorescence spectral and lifetime imaging with multiphoton and confocal microscopy. Eur. J. Pharm. Biopharm. 77, 469–488.

Sadeghian, I., Hassanshahian, M., Sadeghian, S., et al., 2012. Antimicrobial effects of Quercus brantii fruits on bacterial pathogens. Jundishapur J. Microbiol. 5, 465–469.

Salama, A., El-Sakhawy, M., 2022. Polysaccharides/propolis composite as promising materials with biomedical and packaging applications: A review. Biomass Convers. Biorefin. 1–11.

Sasidharan, S., Chen, Y., Saravanan, D., et al., 2011. Extraction, isolation and characterization of bioactive compounds from plants' extracts. Afr. J. Tradit. Complement. Altern. Med. 8.

Sedighi, A., Mehrabani, D., Shirazi, R., 2016. Histopathological evaluation of the healing effects of human amniotic membrane transplantation in third-degree burn wound injuries. Comp. Clin. Pathol. 25, 381–385.

Shahane, K., Kshirsagar, M., Tambe, S., et al., 2023. An updated review on the multifaceted therapeutic potential of calendula officinalis L. Pharmaceuticals. 16, 611.

Shamloo, A., Aghababaie, Z., Afjoul, H., et al., 2021. Fabrication and evaluation of chitosan/gelatin/PVA hydrogel incorporating honey for wound healing applications: An in vitro, in vivo study. Int. J. Pharm. 592, 120068.

Shamosi, A., Mehrabani, D., Azami, M., et al., 2017. Differentiation of human endometrial stem cells into endothelial-like cells on gelatin/chitosan/bioglass nanofibrous scaffolds. Artif. Cells Nanomed. Biotechnol. 45, 163–173.

Sharaf, S.M., Al-Mofty, S.-E.-D., El-Sayed, E.-S.-M., et al., 2021. Deacetylated cellulose acetate nanofibrous dressing loaded with chitosan/propolis nanoparticles for the effective treatment of burn wounds. Int. J. Biol. Macromol. 193, 2029–2037.

Sharma, A., Chopra, H., Singh, I., et al., 2022. Physically and chemically crosslinked hydrogels for wound healing applications. Int. J. Surg. 106, 106915.

Sharma, M., Sharma, D., Khan, S., 2012. Honey as complementary medicine:-a review. International Journal of Pharma and Bio Sciences (IF:7.291 in 2017.

Sholehvar, F., Mehrabani, D., Yaghmaei, P., et al., 2016. The effect of Aloe vera gel on viability of dental pulp stem cells. Dent. Traumatol. 32, 390–396.

Silva, A.R., Taofiq, O., Ferreira, I.C., et al., 2021. Hypericum genus cosmeceutical application–A decade comprehensive review on its multifunctional biological properties. Ind. Crop. Prod. 159, 113053.

Smelcerovic, A., Spiteller, M., Zuehlke, S., 2006. Comparison of methods for the exhaustive extraction of hypericins, flavonoids, and hyperforin from Hypericum perforatum L. J. Agric. Food Chem. 54, 2750–2753.

Tan, M., Tan, C., Ho, C., 2013. Effects of extraction solvent system, time and temperature on total phenolic content of henna (Lawsonia inermis) stems. Int. Food Res. J. 20, 3117.

Tang, Y., Lan, X., Liang, C., et al., 2019. Honey loaded alginate/PVA nanofibrous membrane as potential bioactive wound dressing. Carbohydr. Polym. 219, 113–120.

Tanideh, N., Nematollahi, S.L., Hosseini, S.V., et al., 2014a. The healing effect of Hypericum perforatum extract on acetic acid-induced ulcerative colitis in rat. Ann Colorectal Res. 2, e25188.

Tanideh, N., Rokhsari, P., Mehrabani, D., et al., 2014b. The healing effect of licorice on Pseudomonas aeruginosa infected burn wounds in experimental rat model. World Journal of Plastic Surgery. 3, 99.

Tanideh, N., Haddadi, M.H., Rokni-Hosseini, M.H., et al., 2015. The healing effect of scrophularia striata on experimental burn wounds infected to pseudomonas aeruginosa in rat. World Journal of Plastic Surgery. 4, 16.

Tanideh, N., Nematollahi, L., Hosseini, V., et al., 2016. The healing effect of hydroalcoholic extract of Hypericum perforatum on acetic acid-induced ulcerative colitis in male rats. Journal of Advanced Biomedical Sciences. 6, 530–537.

Tarameshloo, M., Norouzian, M., Zarein-Dolab, S., et al., 2012. Aloe vera gel and thyroid hormone cream may improve wound healing in Wistar rats. Anatomy & Cell Biology. 45, 170–177.

Tonks, A.J., Dudley, E., Porter, N., et al., 2007. A 5.8-kDa component of manuka honey stimulates immune cells via TLR4. Journal of Leucocyte Biology. 82, 1147–1155.

Tuan, N.A., Khanh, P.N., Ha, N.X., et al., 2022. Compounds Isolated from Lawsonia inermis L. collected in vietnam and evaluation of their potential activity against the main protease of SARS-CoV-2 using in silico molecular docking and molecular dynamic simulation. Nat. Prod. Commun. 17.

Valenzuela-Barra, G., Castro, C., Figueroa, C., et al., 2015. Anti-inflammatory activity and phenolic profile of propolis from two locations in Región Metropolitana de Santiago. Chile. Journal of Ethnopharmacology. 168, 37–44.

Vijayalakshmi, D., Dhandapani, R., Jayaveni, S., et al., 2012. In vitro anti inflammatory activity of Aloe vera by down regulation of MMP-9 in peripheral blood mononuclear cells. J. Ethnopharmacol. 141, 542–546.

Wills, R.B., Bone, K., Morgan, M., 2000. Herbal products: active constituents, modes of action and quality control. Nutr. Res. Rev. 13, 47–77.

Witte, M.B., Barbul, A., 2002. Role of nitric oxide in wound repair. Am. J. Surg. 183, 406–412.

Yaghoubi, M., Gh, G., Satari, R., 2007. Antimicrobial activity of Iranian propolis and its chemical composition. DARU Journal of Pharmaceutical Sciences. 15, 45–48.

Yang, J., Yu, H., Wang, L., et al., 2022. Advances in adhesive hydrogels for tissue engineering. Eur. Polym. J. 172, 111241.

Yazarlu, O., Iranshahi, M., Kashani, H.R.K., et al., 2021. Perspective on the application of medicinal plants and natural products in wound healing: A mechanistic review. Pharmacol. Res. 174, 105841.

Yin, J., Xu, L., 2020. Batch preparation of electrospun polycaprolactone/chitosan/aloe vera blended nanofiber membranes for novel wound dressing. Int. J. Biol. Macromol. 160, 352–363.

Yousefi, I., Pakravan, M., Rahimi, H., et al., 2017. An investigation of electrospun Henna leaves extract-loaded chitosan based nanofibrous mats for skin tissue engineering. Mater. Sci. Eng. C 75, 433–444.

Zhang, A., Yang, Y., Zhang, Q., et al., 2022. Lawsonia inermis extract-loaded cellulose acetate nanofibrous wound dressings alleviate wound inflammation through PI3K/AKT/NFκB signaling pathway: A preclinical investigation. J. Biomed. Nanotechnol. 18, 1805–1815. https://doi.org/10.1166/jbn.2022.3383.

Zuo, Y., Zhang, L., Wu, J., et al., 2004. Ultrasonic extraction and capillary gas chromatography determination of nicotine in pharmaceutical formulations. Anal. Chim. Acta 526, 35–39.