Bulletin of Environment, Pharmacology and Life Sciences
Bull. Env. Pharmacol. Life Sci., Vol 12 [2] January, 2023: 118-129

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

REVIEW ARTICLE **OPEN ACCESS**

Wound Health: Advances in Natural Product Delivery

Kshitija Phatak, Shivali Tank, Pradnya Korlekar, Supriya Shidhaye*
Vivekananda Education Society's College of Pharmacy, Hashu Adwani Memorial complex, Collector colony, Chembur, Mumbai, Maharashtra, India.
***Correspondence E-mail**- s.shidhaye@ves.ac.in

ABSTRACT
Wound healing is a complex process involving various cellular mechanisms. Despite of recent medical advances in drug therapeutics, treating chronic wounds still remain a challenge. There are several naturally occurring materials which have been explored and studied widely for their wound healing potential as well as for relieving the wound associated complications. These phytoconstituents have potential anti-inflammatory, antioxidant activity along with skin regeneration and tissue repair properties which aids in wound healing. Incorporating these natural products into smart delivery systems would help to enhance their efficacy and help the wounds heal faster. We describe the potential natural products along with their specific wound healing properties and advancements in the delivery systems which would enhance the effect of these products.Of the discussed natural products, few species covered in details include Aloe, Honey, Papaya and Pomegranate. Also, the article mentions the patented herbal formulations for wound healing.
Keywords: *Wound healing, herbal agents, delivery systems, nanostructures, wound dressings*

Received 25.08.2022 Revised 15.11.2022 Accepted 19.12.2022

INTRODUCTION:

Skin forms a major obstacle between the internal body system and the external environment. It plays a vital role in sensing the environmental changes, maintaining bodies homeostasis, storing and providing essential micronutrients, managing passive and active defence system and combating injuries and wounds.(1) Wound is a severe condition involving disruption or breakage of various cellular systems, tissues, tendons, muscles and bones.(2) Wounds are broadly classified as acute and chronic wound. Acute wounds are characterized by disruption of external intact skin and are recovered within four weeks through the natural wound healing process. Chronic wounds include foot, leg ulcers and pressure sores, wounds in patients with metabolic diseases like diabetes mellitus and immunocompromised conditions such as AIDS or patients undergoing chemotherapy and radiation therapy. It could be aggravated by obesity, smoking and age. The main problem associated with chronic wound is bacterial contamination which worsens the condition. Wound contamination, wound colonization and wound infection delays the normal recovery due to which healing takes more than four weeks.(3)

Wound healing is a cycle of events which involves multiple phases. Figure 1 explains the phases and associated factors of wound healing.(2) Interaction and imbalance between the phases with overlapping cellular factors and mechanisms makes wound healing a difficult process. This is dependent on local wound factors, systemic factors and various disease conditions.(4)

Available topical formulations for wound healing include solutions, suspensions, emulsions, creams and ointments of conventional anti-microbial agents such as silver sulphadiazine, silver nitrate, povidoneiodine, polyhexamethylene biguanide. Saline solutions are used as cleansing agents. Natural products areexplored extensively to treat wounds due to their multiple benefits. Natural products contain several active constituents which help to heal the wounds and also relieve the other associated symptoms. Also, the associated adverse effects of natural products are less compared to the synthetically derived products. Whole-plant extracts or extracts of specific part of plant contain various phytoconstituents which acts as antioxidants, antimicrobials, anti-inflammatory agents, and re-epithelialization enhancers. This can offer synergistic effect for wound healing and help the wounds to heal faster.(5) Table No. I summarize examples of Natural Products and their actives exhibiting collective effect at the wound site.

Figure 1: Phases of wound healing and associated factors

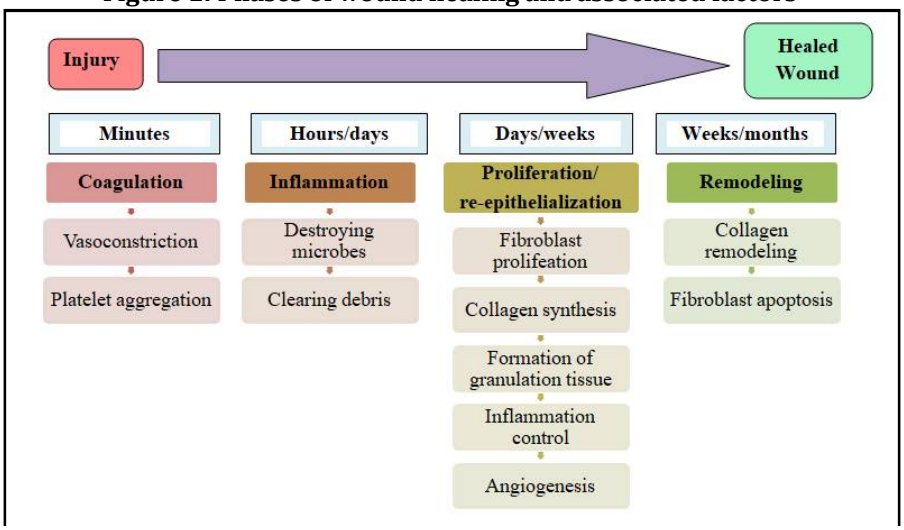

Table no. I: List of Natural Products and their actives

Source	Active constituents	Assessment method used for wound healing potential	Activities
Aloe barbadensis miller	Monosaccharides and Polysaccharides, 20 Out Of 22 Essential Amino Acids, Lectin Arachidonic Acid, G-Linolenic Acid, Campesterol, Cholesterol, B-Sitosterol, Triglycerides, And Lignins Salicylic Acid	Thermal wound model, incision wound model, Carrageenan-induced paw edema.(6)	Antibacterial Anticancer Antifungal Anti-inflammatory Antioxidant
Honey	High Sugar Content	Incisional wound model in rabbits(7)	Anti-inflammatory Antimicrobial Antioxidant Immunomodulating(8)
Carica papaya	Papain And Chymopapain	Excision wound model	Anti-inflammatory Antimicrobial(9)
Punica granatum	Polyphenols, Alkaloids, Flavanoids, Tannins	Excision wound model	anti-inflammatory Antioxidant, Antiartherogenic Antimicrobial
Hibiscus rosasinensis	Anthocyanins Flavonoids Polyphenolic acids Protocatechuic acid	Excision, incision and dead space wound models in rats	Antibacterial antitumor, antihypertensive, antioxidant(10)(11)
Cinnamomum cassia	Cinnamaldehyde	In vitro and in vivo angiogenic activity assay Excision wound model in rats(12)	Antidiabetic Anti-inflammatory Antimicrobial Antioxidant
Curcuma longa	Curcuminoids	Antioxidant analysis	Antidiabetic Anti-inflammatory Antimicrobial Antioxidant(13)
Panax ginseng	Ginsenosides	Laser burn and excision wounds models in mice Cell migration and wound healing assays	Anti-inflammatory Antimicrobial Antioxidant Immunomodulating(14)
Calendula officinalis	Esculetin Quercetin-3-Oglucoside	Scratch assay Excision wound model in BALB/c mice Punch wound model in rats, Burn wounds, full thickness wounds(7)	Antibacterial Anticancer Antifungal Anti-inflammatory Antioxidant(7)(15)

ADVANCEMENTS IN DRUG DELIVERY SYSTEMS:

Chronic non-healing wounds remain a significant public health issue especially in case of people affected with diabetes and other chronic disorders and require advanced therapeutics. The treatment involves development of new drug therapeutics or incorporating the existing therapeutic entities in novel delivery systems which would enhance its efficacy. Several entities have been proved to show wound healing activity by showing promising results in pre-clinical trials. Physical barriers and biological degradation at the wound site limit the efficacy of drug delivery systems in wound healing. Despite of the recent advancements, efficient delivery of these therapeutics at the wound site and its retention in harsh wound environment still remains a challenge.(16) Scientists have worked on developing the new drug delivery systems including cell or sealant-sprays, nanoparticles, hydrogel and nanofiber scaffolds, and transdermal formulations which improve the effectiveness of several natural, biological and RNA based therapies.(17)

Phytochemicals and several naturally derived products have immense ability and application in wound healing due to their multiple active ingredients and minimum side effects.(5) Integration of naturally available products with novel delivery formulation will help to improve the overall effect of the natural therapeutics and aid in wound healing. Delivery of natural products by incorporating them into advanced nano delivery systems has been explored for the management of chronic wounds. Nanoformulationsof phytochemicals are found to improve their bioavailability, provide sustained delivery of the active ingredient to the wound site, and improve the permeability of these actives to the deeper layers of skin which is vital in the process of wound healing.(18)

1. Nanoemulsion:

Nanoemulsion provides a platform for nanosizing different essential oils thereby enhancing their effect. Upon application of these nanoemulsions on the injury site, they leave a film after evaporation of liquid content in it. Since essential oils have gained importance due to their versatile active ingredients, they can be easily formulated in the form of nanoemulsion for improved effectiveness. Table no. II describes natural products formulated as nanoemulsions.

2. Hydrogels:

Hydrogels and nanohydrogels have been widely explored for topical treatment of chronic wounds. These systems have advantages like great flexibility and mechanical strength, hydrophilic, and the capacity to adsorb wound exudates. These systems can be used to sustain the release of the incorporated entity at the wound site thereby giving better results.(19) Table no. II describes natural products formulated as hydrogels/nanohydrogels.

3. Liposomes/Nanoliposomes:

Nanoliposomes are the potential nanoformulation which can helpto enhance the solubility and effectiveness of poorly soluble herbal-agents. These nanoliposomal systems have advantages of encapsulating both hydrophilic and hydrophobic moieties in their aqueous core or lipid layer thus, altering the physicochemical properties to the active agent and help in better permeation and sustained effect of the drug. Liposomes can be modified further with polymers to sustain the drug delivery. Table II includes natural products formulated as liposomes/nanoliposomes

4. Nanoparticles:

Researchers have reported the encapsulation of nanoparticles specifically zinc oxide, titanium oxide and silver particles which are proven antibacterial agents in the hydrogel like formulation. Also, formulating several natural products/extracts as nanoparticles in combination with silver or zinc nanoparticles is found to exhibit multiple benefits. Such combinations have proven to show anti-inflammatory and anti-bacterial effect along with the wound healing activity. Table no. II includes few examples of natural products delivered in the form of nanoparticles.

5. Nanofibers:

Nanofiber membranes and electrospun nanofiber scaffolds are explored extensively for their application in wound dressing. The porous structure of these nanofibers allows oxygen permeation through the dressing making it an ideal dressing for the management of non-healing wounds. Several studies have been reported where in these herbal phytoconstituents are fused with nanofibrous membranes which combine the benefits of these fibrous scaffolds and herbal agents in restructuring chronic wounds.(18) Table no. II shows few natural products formulated as Nanofibers.

Table no. II: Natural products formulated as nanoemulsions

NANOEMULSIONS				
Sr. No.	**Natural Product**	**Study Summary**	**Inference**	**Reference**
1	Eucalyptus oil	Ultrasonic emulsification was carried out to get nanoemulsion having droplet size 3.8 nm. Using *Staphylococcus aureus* the antibacterial studies were carried out \ to study the bacterial kill time and wound healing potential.	Eucalyptus oil nanoemulsion was non-irritant and by the virtue of its antibacterial and anti-inflammatory activity exhibited greater wound contraction rate when compared with the control and neomycin treated Wistar rats	(20)
2	Clove oil	Clove oil was encapsulated into nanoemulsion with an optimum droplet size of 29.01nm and its wound healing activity in rats was examined	Treated rats showed no signs of inflammation. Wound healing capacity was significantly enhanced in contrast with pure oil and control	(21)
3	Curcumin	Nanoemulsion of curcumin was formulated for transdermal delivery to check its potential wound healing properties and anti-inflammatory activity.	The optimized nanoemulsion formulation showed good anti-inflammatory activity and the outcome of wound healing process were statistically significant in rat paw edema model.	(22)
HYDROGELS				
1	Curcumin	Injectable in situ nano-composite hydrogel was prepared and evaluated for dermal wound dressing properties. The hydrogel included curcumin, N,O-carboxymethyl chitosan and oxidized alginate . It was testedby injecting hydrogels on rat dorsal wounds.	DNA, protein and hydroxyproline was tested in animals after 7days. Nano-curcumin and CCS-OA hydrogel dramatical increase in the rate of wound healing process.	(23)
2	Alginate-Gum Arabic	Alginate-Gum Arabic Hydrogel with Micro/Nano-scale Structures was formulated for Controlled Drug Release in Chronic Wound Healing.	Invitro studies confirmed higher rate of re-epithelization in treating dermal wounds in mouse model. In vivo studies facilitated wound healing in mouse model.	(24)
LIPOSOME/ NANOLIPOSOME				
1	Curcumin	Curcumin loaded liposomes were prepared, optimized and investigated for their potential to cure wounds.	Good permeation, small size, and greater entrapment proved liposomes to be a promising drug delivery system. It showed acceptable results by enhancing wound healing effect.	(25)
2	Silymarin	Silymarin Nanoliposomes were formulated and tested for its anti-bacterial potential against Methicillin-resistant Staphylococcus aureus which is responsible to cause infections at the wound site.	Silymarin-loaded nanoliposomes showed higher killing rate when compared with free silymarin.The MICs of Silymarin nanoliposome was 500mg/ml while that for free Silymarin was around 125mg/ml when tested against isolated strainely and can be thus considered further for preventing bacterial infections at wound site.	(26)
3	Curcumin	Propylene glycol based nanoliposomes of average size 145 nm containing curcumin were prepared and evaluated using burn	Curcumin nanoliposomal formulation in low doses effectively enhanced the recovery from injuries and	(27)

		wound model in rat. The cytotoxicity was tested on human dermal fibroblast (HDF) cells.	infections associated with burn wounds by exhibiting activity similar to standard 1% silver sulfadiazine cream, hence can be considered to have a good potential in burn therapy.	
NANOPARTICLE				
1	Pluchea indica	The effect of ethanolic *Pluchea indica* leaf extract and its nanoparticle formulation usedas an oral spray for the treatment of oral cavity wounds was investigated	The formulation helped in enhancing the colloidal stability of the herbal extract. Also the wound healing process was ameliorated due to increased rate of the cell migration at low concentration	(28)
2	Droserabinata	The investigation focused on evaluating the antibiotic properties of silver nanoparticles containing Droserabinata extract using resistant *Staphylococcus aureus*.	It was found to exhibit excellent anti-bacterial effect and had no cytotoxicity on human keratinocytes even at smaller concentrations of both the agents.	(29)
3	Bambusabambos	The wound healing properties of silver nanoparticles and bamboo cellulose nanocrystals delivered as in situ nanobiocomposites was evaluated.	It was found to be highly effective, biocompatible and showed anti-inflammatory and antibacterial action.	(30)
NANOFIBRES				
1	Fenugreek	An antioxidant silk fibroin nanofiber scaffold was prepared by incorporating fenugreek. Wound healing activity was tested using full thickness excisional wounds in rat model.	This scaffold demonstrated increased epithelialization, enhanced collagen formation and faster wound healing.	(31)
2	Curcumin	Nanofiber mats were designed and developed by electrospinning for prevention and accelerating the rate of wound healing and minimizing the severity of infection at wound site. Curcumin was loaded in polycaprolactone and poly ethylene glycol base to increase the rate of wound healing.	The rate of wound closure using Curcumin loaded nanofiber was found to increase significantly (99%) after 10 days in comparison with plain polycaprolactone fiber mat (59%). Thus, incorporation of curcumin showed enhanced wound healing.	(32)
3	Spirulina	Spirulina extract loaded Polycaprolactone nanofibers were synthesized and evaluated for cutaneous wound healing.	Spirulina loaded PCL nano fibers showed promising results by skin regeneration and enhancing antioxidant effect by scavenging excessive ROS.	(33)

NATURAL POLYMERS AS WOUND DRESSINGS:

Natural products are widely utilized as wound dressings since they are claimed to be biocompatible and biodegradable. These natural polymers induce wound healing and also help in regenerating the damaged tissues. The polymers have a three-dimensional structure and are of utmost importance in wound dressing, drug delivery and tissue engineering. Commonly used natural polymers as wound dressings are Homoglycans, α and β Glucans, Dextran, Cellulose, chitosan, Alginates, Heteroglycans, Carrageenan, Glycosaminoglycans, Gelatin, Fibrin, Silk fibroin, Keratin, etc.(34) These polymers are subjected to electrospinning in order to form a biomimetic dressing with improved bioactivity for promoting tissue regeneration.(35) Table no. VII explains the properties of these dressings designed with naturally available polymers.

Table no. III: Natural polymers as wound dressings

Natural Polymers	Properties of Dressings	References
Collagen and Gelatine	• Wound re-epithelialization • Enhanced proliferation of fibroblasts and keratinocytes.	(36)
Fibrinogen	• Haemostatic and anti-inflammatory activity • Tissue remodelling	(37)
Chitosan	• Haemostatic and antibacterial activity • Wound re-epithelialization	(38)
Silk fibroin	• Haemostatic and anti-inflammatory activity • Reduced scar formation	(39)
Alginate	• Anti-inflammatory activity • Absorption of exudates.	(40)

NATURAL PRODUCTS AND THEIR DELIVERY STRATEGIES:

Several natural products have been investigated for their wound healing activity as presented in Table no.I. Studies have reported the potential advantages of these natural actives and their effect at the wound site. This review focuses on Aloe, Honey, Papaya and Pomegranate as potential natural products with respect to their wound healing activity, efficacy studies, formulations, novel drug delivery strategies and advanced delivery systems associated.

1. Aloe:

Scientists have been exploring Aloe and its biological activity through various studies. Aloe vera is known to be the most biologically active form amongst the 420 known species of Aloe. The potentially active constituents in aloe vera are known to possess different properties such as anti-inflammatory, antiseptic, wound and burn healing, antifungal, antioxidant, etc.(41)

Aloe vera is reported to exhibit wound healing property by the activation of Fibroblasts and macrophages. Fibroblast activation increases collagen synthesis after topical application of aloe vera. It also changes the type and structure of collagen and its crosslinking which further helps in faster wound healing. Also, aloe vera consists of cinnamonic acid, lupeol, salicylic acid, phenols and sulphur which help to inhibit fungal and bacterial infection at the wound site giving additional benefit.(42) An increased synthesis of dermatan sulfate and hyaluronic acid upon topical and oral treatment of aloe vera has been reported by Warren J. Goux et. al. which contributes in wound healing.(43)

A study was carried out by Ahmad Oryan *et. al*. to explore the effect of topical application of Aloe vera on cutaneous wound healing in rats. Aloe vera gel was applied topically on 2 x 2 cm wound and wound surface contraction and epithelization were observed. Decrease in inflammation and scar tissue, dose dependent increase in collagen and regenerated tissue thereby proving the wound healing activity of aloe was observed.(44) Similar study has been carried out by Dr. Subramanian et. al. wherein the ethanolic leaf extract was applied as a 10% ointment on the rabbit wounds. The results obtained supported the efficiency of aloe vera in healing and sealing the wounds.(45) Aloe vera is also explored for its efficiency in treating harsh burn wounds. Afshar Bargahi *et. al.* via their study emphasized on its burn healing activity.(46)Seyed Jalal Hosseinimehr *et. al.* performed a comparative study between Aloe Cream and Silver Sulfadiazine to study their effect on burn wound healing in rats. A thermal burn wound was induced in rats and further they were treated by topical application for 25 days. The results depicted that aloe vera cream had a significant potential in healing the burn wound as compared to the silver sulfadiazine.(47)

Since the effectiveness of Aloe Vera gel is proven in conventional systems, it can be further coupled with the novel drug delivery system to get an effective delivery of Aloe vera. Paulo Bártolo *et. al*. investigated the effect of alginate-aloe vera hydrogel films on wound healing and potential of hydrogel system in drug delivery. They inferred that the hydrogel film can be effectively used as a wound dressing for dry and exuding wounds.(48) Ahmad Oryan *et al* also evaluated *in vivo* efficacy of Aloe vera loaded hydrogel on rat burn wound model. This hydrogel was intradermally injected into wound area and was observed to be effective in burn wound healing in rat models.(49) Hydrogel made by combining aloe vera with PVA and PVP mixture were reported to cure the wounds in rats in 15 days even in the absence of pre-dressing as studied by Young Chang Nho et. al thereby proving the efficiency of hydrogel formulation.(50) Narayan Bhattarai *et. al.* prepared electro spun nanofibers containing aloe vera blended with polycaprolactone (PCL). The results of *in vitro* testing of these nanofibers depicted that they demonstrated higher cell affinity, increased adhesion and caused fibroblast proliferation near the wound and enhanced skin regeneration.(51) Silver nanoparticles containing aloe vera extract can be used as an antibacterial at the wound site due to its synergistic antibacterial activity as studied by Patcharaporn Tippayawat *et. al*.(52) Md Abul Barkat *et. al.* developed and studied the effect of silver sulfadiazine nanosuspension loaded in

aloe vera gel. Nanogel application for 14 days showed increased wound healing rate in rats compared to the marketed formulation.(53) Nanocomposites Zinc oxide containing aloe vera were found to show a good antibacterial effect and can be used at the wound site as studied by A. Ayeshamariam *et. al*.(54)]

2. Honey:

The osmotic effect causing dehydration of bacterial cell produced by high sugar content of honey along with its low pH value of 4.4 makes honey exhibit a strong anti-microbial effect.(55)(56)(57)(58) It also has effect on bacterial cell size and shape. Lu et al in their study observed that when a sub lethal dose of manuka honey was incubated with *Staphylococcus aureus* and Bacillus subtilis significant reduction in size was seen with DNA condensation when compared with non-honey treated bacteria.(59) The anti-microbial activity is still noticeable even after dilution with water because of continuous production of hydrogen peroxide. An increase in reactive oxygen peroxide activity was observed along with antimicrobial activity of honey reported by Cooke et al.(56)(57)(60)In a study it was proved that Manuka honey had significantly caused partial detachment of Proteus biofilms at 50% concentration of honey.(61)

Honey comprises of numerous compounds which exhibit varied mechanisms and are thereby responsible for significant immunomodulatory activity. Majtan postulates that honey has the ability to produce inflammatory cytokines, TNF-a and interleukin-bwhen the infection rate is low and can alsostop the production of the same cytokines during the infection. Honey is popularly known for its antioxidant properties where in inhibiting neutrophilic respiratory burst(61)(59) and decreasing the production of human neutrophilic superoxide.(62)

The process of wound healing involves various steps like coagulation, inflammation, proliferation and wound remodelling.(63) Honey can contribute in some of the steps there by improving the physiology of wound healing. It can reduce edema and oozing of exudates from wounds.(64) Topical application of honey can change the inflammatory action by increasing the nitric oxide end product formation and decreasing prostaglandin levels.(65) Studies have reported that honey can help in rapid autolytic debridement of wounds, restore epithelialization and keep the microenvironment around the wound moist to slow down scar formation.(64),(55) One of the specific honey type, Fir honeydew can change the effect of a protease, matrix metalloproteinase-9 (MMP-9), involved in matrix degradation and cell growth promoting agents which are found in the fluid of chronic wounds of human keratinocytes.(66)

A wound gel based dressing of Medihoney®contains active Leptospermum Manuka honey, along with the excipients like myristyl myristate, Plantacare is further gamma irradiated at a 25–45 kGy dosage. This is widely given as OTC for Minor abrasions, lacerations, minor cuts, minor scalds, and burns. The same is prescribed in controlling diabetic foot ulcers, leg ulcers including arterial, venous stasis ulcers, for non-draining to moderately exuding wounds, 1st and 2nd degree partial thickness burns, traumatic and surgical wounds.

Maghsoudi *et al.* compared the days required for epithelialization of fresh partial burns using unprocessed pure honey dressings and mafenide acetate in 50 patients. Patients treated using honey dressings showed 84% and 100% recovery while those treated with mafenide acetate showed 72% and 84% recovery in 7 days and 21 days respectively. Novel honey-based hydrogel has been investigated for the treatment of burn wounds and compared with marketed formulation. The hydrogel was found to exhibit a higher *in vitro* and *in vivo* performance in comparison with the marketed formulation.(67) Honey/Chitosan Nanofiber Wound Dressing was designed and developed by Hassan Azazzy *et. al*. These nanofiber mats helped in improved wound healing and wound closure. It was also found to show a good antimicrobial effect thereby reducing the microbial load at the wound site.(68)

3. Papaya:

The botanical name of Papaya is *Carica papaya* and is investigated for several biological applications.(69) The important constituent in papaya is papain which is responsible for its ulcer protective effect. Papaya is used for treating several skin conditions including wound healing. It also contains antibacterial and anti-inflammatory characteristics which help to heal the wounds faster.

Researchers have explored its wound healing activity by testing the extracts on animal models. Dr. BS Nayak *et. al*. tested the wound healing efficacy of ethanolic extract of Carica papaya seeds. The seed extract was tested on Sprague-Dawley rats and rate of wound contraction was observed. The results suggested that C. papaya promoted significant healing of wounds in test rats.(70) Further, in order to test the potential of root extract, Prashant Tiwari *et. al*. performed activity testing on Albino rats. They tested aqueous extract of C. papaya roots on wounds of Albino rats and found a higher rate of epithelization compared to the control rats.(71) Rachmi Fanani Hakim *et. al*. tested the effect of Carica papaya extract on oral wound incision in mice for 10 days by topical application. The result was clinically noted by measuring the length of wound closure. It was inferred that the extract showed significant effect on the wound healing process and has the potential to cure the wounds in oral cavity by formation of perfect epithelial layer, fibrillation and wound contraction.(9)

Carica papaya is also explored for its burn wound healing property. Papaya latex formulated in Carbopol hydrogel (1% and 2.5%) were used to treat burn wounds in Swiss albino mice. The efficacy of treatment was evaluated based on the hydroxyproline content, wound contraction and epithelialization time and compared with silver sulphadiazine and chlorhexidine gluconate cream. Significant wound contraction and increased hydroxyproline content was observed in case of hydrogel containing papaya latex.(72)Bapurapu Rajaram et. al. demonstrated the use of papaya dressing in the treatment of Diabetic foot ulcers. The study included 94 patients with diabetic foot ulcers and their wounds were treated with grated papaya dressing. The dressing was changed every 24 hours. It was concluded that topical grated papaya dressings lead to successful enzymatic wound debridement and also reduced the healing time thereby reducing the incidences of amputation.(73) The use of papaya for treating patients with postoperative wound gape was studied by Mangala B. Murthy et. al. They compared the activity of papaya dressing with hydrogen peroxide solution on patients with post-caesarean section. The patients with papaya dressing were treated in less duration of time, decreased hospitalization of patients and development of healthy granulation tissue in comparison with the hydrogen peroxide solution.(74)

Further, considering the wound healing potential of Carica papaya, incorporating it into novel systems would make its delivery more efficient. J. Balavijayalakshmi *et. al*. designed and synthesized Carica papaya peel mediated silver nanoparticles which would provide anti-bacterial activity along with wound healing. These nanoparticles showed good anti-bacterial activity against several pathogens and can be used to prevent bacterial infection at the wound site.(75) Bioactive polymers are being utilized for preparation of nanofiber scaffolds which can be used as wound dressings for chronic non-healing wounds. Scientists have tried the incorporation of Carica papaya into polyvinyl alcohol-gelatin based nanofiber scaffold by electrospinning method. These scaffolds were tested for its antibacterial activity as well. It was found that it has a good antibacterial activity against *Staphylococcus aureus* and Escherichia coli which would minimize the possibility of bacterial infection. The formulated nanofibers allow re-epithelization and wound healing process at a faster rate and show a great potential in wound healing process.(76)

4. Pomegranate:

Punica granatum of Punicaceae family have been used in treating opthalmic disorders ulcers, cardiovascular ailment, snakebites, dysentery, acquired immune deficiency syndrome (AIDS), oral hygiene. It has important constituents like polyphenols, alkaloids, flavanoids,tannins which exhibit antibacterial, anticonvulsant, anti-inflammatory,antifungal, immunomodulatory.(77)(78)(79)

E.A. Hayouni *et al*, formulated ointment containing 5%w/w methanolic extract and evaluated on guinea pigs. The formulation was applied uniformly on the paravertebral part for ten days daily on twelve pigs. The extract exhibited a potential wound healing property with increase in wound contraction, enhanced epithelialization process and promising histopathological features. Strong anti-bacterial and anti-fungal activity against various bacterial and fungal strains including *Pseudomonas aeruginosa, Escherichia coli, Salmonella anatum, Candida albicans* and *Aspergillus niger* helped in better infection control over the wound.(80)

The semisolid formulations used for wounds healing have now been replaced with membranes containing some additive agents which form in situ delivery system. These membranes are usually gelatin based as they provide sustained release of drug along with prevention of fluid loss because of exudation. Gelatin acts as a film forming agent which is biodegradable as it enhances the physiological absorption thus easing the removal of dressing. Recently these gelatin membranes contain biointeractive materials which acts as anti-microbial, antioxidant and anti-inflammatory agents which decrease the severity of wound and reduce the time of healing. Marismar F. do et al., developed a biointeractive membrane containing extract of punica granatum. The gelatin containing membranes was compared with the membrane containing *P. granatum* extract on the basis of tensile strength, swelling index and water permeability. Based upon the statistical analysis the extract containing membrane showed good tensile strength, optimum swelling properties and lower water permeability with p values 0.021,0.003 and 0.033 respectively. The formation of granular tissues, collagen deposition with early epithelialization was seen in case of extract containing membrane showing an improved dynamics of wound healing.(81)

Aline Fleck *et al*., in their report mentioned a case of a 76-year-old patient with no prior history of any vascular disease suffering from non-healing left leg ulcer with intense pain and swelling. Various conventional treatments including topical steroids like betamethasone, gentamicin, clostebol, advanced dressings were used but there was no positive outcome. When 2% (w/w) *Punica granatum* peel ethanolic extract (PGMF) based on a hydrophilic cream and zinc oxide was applied on the ulcer once a day the ulcer size was reduced by one quarter and was entirely cured in six weeks after ninety applications with no side effects.(82)

Table no. IV Patented herbal formulations for wound healing

Sr. No.	Patent Number	Patent Title	Summary	Reference
1.	US 7,714,183 B2	Use of honey in dressings	Designed for acute and chronic wounds. Honey is saturated in alginate fibre sheet which when applied on wound, the exudates is formed which is gel like in appearance. It includes 11 claims with various combinations of medicinal extracts.	(83)
2.	US 2013/0323337 A1	Herbal composition for the treatment of wound healing, a regenerative medicine	Mentions about the preparation of novel herbal extract combinations of Curcuma longa, Glycyrrhiza glabara, Hamiltonia suaveolens, Tipha angustifolia, and Azadirachta indica, at their effective concentration with Pig fatin Sesamum indicum (Til) oil as a base for wound healing	(84)
3.	E P 2 896 396 A1	Herbal formulation for topical wound treatment	This invention discusses about the solution and gel based formulation containing Comfrey Symphytum officinale L. extract and/or Commiphora molmol tincture having potential anti-bacterial, analgesic and anti-inflammatory activity. Along with herbal extract they propose the use of anti-microbial agent, polyhexamethylene biguanide, and poloxamer amer. It will be useful in treating oromucosal wounds.	(85)
4.	GB254091A	A Topical Wound Healing formulation	This invention concerns about developing formulation which will be used in treating wound, prevent scar formation and helps in re growth of hair in the affected area. Herbal agents having both anti-inflammatory and anti-microbial properties like Gotu kola (Centella asiatica), Figwot (scrophularia nodosa), yarrow (Achillea millefolium), Plantago major, and Echinacea purpurea will be incorporated.	(86)

CONCLUSION

Natural products have constituents like phenols, polyphenols, tannins, glycosides which possesses anti-oxidant, anti-inflammatory and anti-microbial activity there by reliving symptoms associated with acute and chronic wounds. We have presented here some detailed information on the potential herbal agents and their probable mechanisms to improve the rate of wound healing. With advancements in pharmaceutical sciences there are numerous drug delivery platforms developed to alter the physicochemical properties of the active thereby enhancing the delivery of active molecules in and around wounds thus improving bioavailability and therapeutic effects of the molecules. With the use of such advances, better and more reliable drug delivery systems should be designed and tested to improve the bioavailability of these naturally occurring therapeutics at the site of injury.Few novel technologies can be developed to upgrade the characterization of the developed delivery systems which will ultimately indicate the site improvement in would healing process.

REFERENCES

1. Shedoeva, A., Leavesley, D., Upton, Z., & Fan, C. (2019). Wound healing and the use of medicinal plants. *Evidence-Based Complementary and Alternative Medicine*, *2019*.
2. Tsala, D. E., Amadou, D., & Habtemariam, S. (2013). Natural wound healing and bioactive natural products. *Phytopharmacology*, *4*(3), 532-60.
3. Okur, M. E., Karantas, I. D., Şenyiğit, Z., Okur, N. Ü., & Siafaka, P. I. (2020). Recent trends on wound management: New therapeutic choices based on polymeric carriers. *Asian Journal of Pharmaceutical Sciences*, *15*(6), 661-684.
4. Salcido R. (2017) Editorial Healing by Intention. Journal of Advances in Skin & Wound Care.30(6):246.
5. Sivamani, R. K., Ma, B. R., Wehrli, L. N., & Maverakis, E. (2012). Phytochemicals and naturally derived substances for wound healing. *Advances in wound care*, *1*(5), 213-217.
6. Balaji, A., Vellayappan, M. V., John, A. A., Subramanian, A. P., Jaganathan, S. K., SelvaKumar, M., ... & Yusof, M. (2015). Biomaterials based nano-applications of Aloe vera and its perspective: a review. *RSC advances*, *5*(105), 86199-86213.
7. Givol, O., Kornhaber, R., Visentin, D., Cleary, M., Haik, J., & Harats, M. (2019). A systematic review of Calendula officinalis extract for wound healing. *Wound Repair and Regeneration*, *27*(5), 548-561.

8. Saikaly, S. K., & Khachemoune, A. (2017). Honey and wound healing: an update. *American Journal of Clinical Dermatology*, *18*, 237-251.
9. Hakim, R. F. (2019). Effect of Carica papaya extract toward incised wound healing process in mice (Mus musculus) clinically and histologically. *Evidence-Based Complementary and Alternative Medicine*, *2019*.
10. Bhaskar, A., & Nithya, V. (2012). Evaluation of the wound-healing activity of Hibiscus rosa sinensis L (Malvaceae) in Wistar albino rats. *Indian journal of pharmacology*, *44*(6), 694.
11. P. V, V. J, A. M.(2020) Hibiscus Rosa Sinensis Loaded Solid Lipid Nanoparticles and in Vivo Wound Healing Activity in Wistar Albino Rats. International Journal of Current Pharmaceutical Research. 12(3):78–83.
12. Farahpour, M. R., & Habibi, M. (2012). Evaluation of the wound healing activity of an ethanolic extract of Ceylon cinnamon in mice. *Vet Med*, *57*(1), 53-57.
13. El-Refaie, W. M., Elnaggar, Y. S., El-Massik, M. A., & Abdallah, O. Y. (2015). Novel curcumin-loaded gel-core hyaluosomes with promising burn-wound healing potential: development, in-vitro appraisal and in-vivo studies. *International journal of pharmaceutics*, *486*(1-2), 88-98.
14. Kim, Y. S., Cho, I. H., Jeong, M. J., Jeong, S. J., Nah, S. Y., Cho, Y. S., ... & Bae, C. S. (2011). Therapeutic effect of total ginseng saponin on skin wound healing. *Journal of ginseng research*, *35*(3), 360.
15. Jiménez-Pérez, Z. E., Singh, P., Kim, Y. J., Mathiyalagan, R., Kim, D. H., Lee, M. H., & Yang, D. C. (2018). Applications of Panax ginseng leaves-mediated gold nanoparticles in cosmetics relation to antioxidant, moisture retention, and whitening effect on B16BL6 cells. *Journal of ginseng research*, *42*(3), 327-333.
16. Whittam, A. J., Maan, Z. N., Duscher, D., Wong, V. W., Barrera, J. A., Januszyk, M., & Gurtner, G. C. (2016). Challenges and opportunities in drug delivery for wound healing. *Advances in wound care*, *5*(2), 79-88.
17. Saghazadeh, S., Rinoldi, C., Schot, M., Kashaf, S. S., Sharifi, F., Jalilian, E., ... & Khademhosseini, A. (2018). Drug delivery systems and materials for wound healing applications. *Advanced drug delivery reviews*, *127*, 138-166.
18. Hajialyani, M., Tewari, D., Sobarzo-Sánchez, E., Nabavi, S. M., Farzaei, M. H., & Abdollahi, M. (2018). Natural product-based nanomedicines for wound healing purposes: therapeutic targets and drug delivery systems. *International journal of nanomedicine*, *13*, 5023.
19. Tavakoli, S., & Klar, A. S. (2020). Advanced hydrogels as wound dressings. *Biomolecules*, *10*(8), 1169.
20. Sugumar, S., Ghosh, V., Nirmala, M. J., Mukherjee, A., & Chandrasekaran, N. (2014). Ultrasonic emulsification of eucalyptus oil nanoemulsion: antibacterial activity against Staphylococcus aureus and wound healing activity in Wistar rats. *Ultrasonics sonochemistry*, *21*(3), 1044-1049.
21. Alam, P., Ansari, M. J., Anwer, M. K., Raish, M., Kamal, Y. K., & Shakeel, F. (2017). Wound healing effects of nanoemulsion containing clove essential oil. *Artificial cells, nanomedicine, and biotechnology*, *45*(3), 591-597.
22. Ahmad, N., Ahmad, R., Al-Qudaihi, A., Alaseel, S. E., Fita, I. Z., Khalid, M. S., & Pottoo, F. H. (2019). Preparation of a novel curcumin nanoemulsion by ultrasonication and its comparative effects in wound healing and the treatment of inflammation. *RSC advances*, *9*(35), 20192-20206.
23. Li, X., Chen, S., Zhang, B., Li, M., Diao, K., Zhang, Z., ... & Chen, H. (2012). In situ injectable nano-composite hydrogel composed of curcumin, N, O-carboxymethyl chitosan and oxidized alginate for wound healing application. *International journal of pharmaceutics*, *437*(1-2), 110-119.
24. Li, M., Li, H., Li, X., Zhu, H., Xu, Z., Liu, L., ... & Zhang, M. (2017). A bioinspired alginate-gum arabic hydrogel with micro-/nanoscale structures for controlled drug release in chronic wound healing. *ACS applied materials & interfaces*, *9*(27), 22160-22175.
25. Choudhary, V., Shivakumar, H., & Ojha, H. (2019). Curcumin-loaded liposomes for wound healing: Preparation, optimization, in-vivo skin permeation and bioevaluation. *Journal of Drug Delivery Science and Technology*, *49*, 683-691.
26. Faezizadeh, Z., Gharib, A., & Godarzee, M. (2015). In-vitro and in-vivo evaluation of silymarin nanoliposomes against isolated methicillin-resistant Staphylococcus aureus. *Iranian Journal of Pharmaceutical Research: IJPR*, *14*(2), 627.
27. Kianvash, N., Bahador, A., Pourhajibagher, M., Ghafari, H., Nikoui, V., Rezayat, S. M., ... & Partoazar, A. (2017). Evaluation of propylene glycol nanoliposomes containing curcumin on burn wound model in rat: biocompatibility, wound healing, and anti-bacterial effects. *Drug delivery and translational research*, *7*, 654-663.
28. Buranasukhon, W., Athikomkulchai, S., Tadtong, S., & Chittasupho, C. (2017). Wound healing activity of Pluchea indica leaf extract in oral mucosal cell line and oral spray formulation containing nanoparticles of the extract. *Pharmaceutical biology*, *55*(1), 1767-1774.
29. Krychowiak, M., Grinholc, M., Banasiuk, R., Krauze-Baranowska, M., Głód, D., Kawiak, A., & Królicka, A. (2014). Combination of silver nanoparticles and Drosera binata extract as a possible alternative for antibiotic treatment of burn wound infections caused by resistant Staphylococcus aureus. *PLoS One*, *9*(12), e115727.
30. Singla, R., Soni, S., Kulurkar, P. M., Kumari, A., Mahesh, S., Patial, V., ... & Yadav, S. K. (2017). In situ functionalized nanobiocomposites dressings of bamboo cellulose nanocrystals and silver nanoparticles for accelerated wound healing. *Carbohydrate polymers*, *155*, 152-162.
31. Selvaraj, S., & Fathima, N. N. (2017). Fenugreek Incorporated Silk Fibroin Nanofibers A Potential Antioxidant Scaffold for Enhanced Wound Healing. *ACS applied materials & interfaces*, *9*(7), 5916-5926.
32. Bui, H. T., Chung, O. H., Dela Cruz, J., & Park, J. S. (2014). Fabrication and characterization of electrospun curcumin-loaded polycaprolactone-polyethylene glycol nanofibers for enhanced wound healing. *Macromolecular Research*, *22*, 1288-1296.
33. Jung, S. M., Min, S. K., Lee, H. C., Kwon, Y. S., Jung, M. H., & Shin, H. S. (2016). Spirulina-PCL nanofiber wound dressing to improve cutaneous wound healing by enhancing antioxidative mechanism. *Journal of nanomaterials*, *2016*.

34. Mogoşanu, G. D., & Grumezescu, A. M. (2014). Natural and synthetic polymers for wounds and burns dressing. *International journal of pharmaceutics*, *463*(2), 127-136.
35. Mele, E. (2016). Electrospinning of natural polymers for advanced wound care: towards responsive and adaptive dressings. *Journal of Materials Chemistry B*, *4*(28), 4801-4812.
36. Yao, C. H., Lee, C. Y., Huang, C. H., Chen, Y. S., & Chen, K. Y. (2017). Novel bilayer wound dressing based on electrospun gelatin/keratin nanofibrous mats for skin wound repair. *Materials Science and Engineering: C*, *79*, 533-540.
37. Wnek, G. E., Carr, M. E., Simpson, D. G., & Bowlin, G. L. (2003). Electrospinning of nanofiber fibrinogen structures. *Nano letters*, *3*(2), 213-216.
38. Vega-Cázarez, C. A., Sánchez-Machado, D. I., & López-Cervantes, J. (2018). Overview of electrospinned chitosan nanofiber composites for wound dressings. *Chitin-Chitosan-Myriad Functionalities Science and Technology*, 157-81.
39. Ju, H. W., Lee, O. J., Lee, J. M., Moon, B. M., Park, H. J., Park, Y. R., ... & Park, C. H. (2016). Wound healing effect of electrospun silk fibroin nanomatrix in burn-model. *International journal of biological macromolecules*, *85*, 29-39.
40. Mokhena, T. C., Mochane, M. J., Mtibe, A., John, M. J., Sadiku, E. R., & Sefadi, J. S. (2020). Electrospun alginate nanofibers toward various applications: A review. *Materials*, *13*(4), 934.
41. Balaji, A., Vellayappan, M. V., John, A. A., Subramanian, A. P., Jaganathan, S. K., SelvaKumar, M., ... & Yusof, M. (2015). Biomaterials based nano-applications of Aloe vera and its perspective: a review. *RSC advances*, *5*(105), 86199-86213.
42. Sharma, K., Mittal, A., & Chauhan, N. (2015). Aloe vera as penetration enhancer. *Int J Drug Dev Res*, *7*(1), 31-43.
43. Chow, J. T. N., Williamson, D. A., Yates, K. M., & Goux, W. J. (2005). Chemical characterization of the immunomodulating polysaccharide of Aloe vera L. *Carbohydrate research*, *340*(6), 1131-1142.
44. Oryan, A., Mohammadalipour, A., Moshiri, A., & Tabandeh, M. R. (2016). Topical application of Aloe vera accelerated wound healing, modeling, and remodeling: an experimental study. *Annals of plastic surgery*, *77*(1), 37-46.
45. Subramanian, S., Kumar, D. S., & Arulselvan, P. (2006). Wound healing potential of Aloe vera leaf gel studied in experimental rats. *Asian J Biochem*, *1*(2),
46. Farzadinia, P., Jofreh, N., Khatamsaz, S., Movahed, A., Akbarzadeh, S., Mohammadi, M., & Bargahi, A. (2016). Anti-inflammatory and wound healing activities of Aloe vera, honey and milk ointment on second-degree burns in rats. *The international journal of lower extremity wounds*, *15*(3), 241-247.
47. Hosseinimehr, S. J., Khorasani, G., Azadbakht, M., Zamani, P., Ghasemi, M., & Ahmadi, A. (2010). Effect of aloe cream versus silver sulfadiazine for healing burn wounds in rats. *Acta Dermatovenerologica Croatica*, *18*(1), 0-0.
48. Pereira, R., Mendes, A., & Bártolo, P. (2013). Alginate/Aloe vera hydrogel films for biomedical applications. *Procedia CIRP*, *5*, 210-215.
49. Oryan, A., Alemzadeh, E., Mohammadi, A. A., & Moshiri, A. (2019). Healing potential of injectable Aloe vera hydrogel loaded by adipose-derived stem cell in skin tissue-engineering in a rat burn wound model. *Cell and tissue research*, *377*, 215-227.
50. Park, K. R., & Nho, Y. C. (2001). Preparation and characterization of hydrogels of PVA and PVP containing chitosan by radiation. *POLYMER-KOREA*, *25*(5), 728-735.
51. Carter, P., Rahman, S. M., & Bhattarai, N. (2016). Facile fabrication of aloe vera containing PCL nanofibers for barrier membrane application. *Journal of Biomaterials science, Polymer edition*, *27*(7), 692-708.
52. Tippayawat, P., Phromviyo, N., Boueroy, P., & Chompoosor, A. (2016). Green synthesis of silver nanoparticles in aloe vera plant extract prepared by a hydrothermal method and their synergistic antibacterial activity. *PeerJ*, *4*, e2589.
53. Barkat, M. A., Ahmad, I., Ali, R., Singh, S. P., Pottoo, F. H., Beg, S., & Ahmad, F. J. (2017). Nanosuspension-based aloe vera gel of silver sulfadiazine with improved wound healing activity. *AAPS PharmSciTech*, *18*, 3274-3285.
54. Ayeshamariam, A., Kashif, M., Vidhya, V. S., Sankaracharyulu, M., Swaminathan, V., Bououdina, M., & Jayachandran, M. (2014). Biosynthesis of (ZnO–Aloe Vera) nanocomposites and antibacterial/antifungal studies. *J. Opto. Bio. Mat*, *6*(3), 85-99.
55. Carter, D. A., Blair, S. E., Cokcetin, N. N., Bouzo, D., Brooks, P., Schothauer, R., & Harry, E. J. (2016). Therapeutic manuka honey: no longer so alternative. *Frontiers in microbiology*, *7*, 569.
56. Saikaly, S. K., & Khachemoune, A. (2017). Honey and wound healing: an update. *American Journal of Clinical Dermatology*, *18*, 237-251.
57. Yaghoobi, R., & Kazerouni, A. (2013). Evidence for clinical use of honey in wound healing as an anti-bacterial, anti-inflammatory anti-oxidant and anti-viral agent: A review. *Jundishapur journal of natural pharmaceutical products*, *8*(3), 100-104.
58. Israili, Z. H. (2014). Antimicrobial properties of honey. *American journal of therapeutics*, *21*(4), 304-323.
59. Lu, J., Carter, D. A., Turnbull, L., Rosendale, D., Hedderley, D., Stephens, J., ... & Harry, E. J. (2013). The effect of New Zealand kanuka, manuka and clover honeys on bacterial growth dynamics and cellular morphology varies according to the species. *PloS one*, *8*(2), e55898.
60. Cooke, J., Dryden, M., Patton, T., Brennan, J., & Barrett, J. (2015). The antimicrobial activity of prototype modified honeys that generate reactive oxygen species (ROS) hydrogen peroxide. *BMC research notes*, *8*, 1-5.
61. Majtan, J. (2014). Honey: an immunomodulator in wound healing. *Wound Repair and Regeneration*, *22*(2), 187-192.
62. Leong, A. G., Herst, P. M., & Harper, J. L. (2012). Indigenous New Zealand honeys exhibit multiple anti-inflammatory activities. *Innate immunity*, *18*(3), 459-466.

63. Velnar, T., Bailey, T., & Smrkolj, V. (2009). The wound healing process: an overview of the cellular and molecular mechanisms. *Journal of international medical research*, *37*(5), 1528-1542.
64. Bsc PM. Molan PC. (2011).Wound Practice and Research.;19(4):204–20.
65. Al-Waili, N., Salom, K., & Al-Ghamdi, A. A. (2011). Honey for wound healing, ulcers, and burns; data supporting its use in clinical practice. *TheScientificWorldJournal*, *11*, 766-787.
66. Majtan, J., Bohova, J., Garcia-Villalba, R., Tomas-Barberan, F. A., Madakova, Z., Majtan, T., ... & Klaudiny, J. (2013). Fir honeydew honey flavonoids inhibit TNF-α-induced MMP-9 expression in human keratinocytes: a new action of honey in wound healing. *Archives of dermatological research*, *305*, 619-627.
67. El-Kased, R. F., Amer, R. I., Attia, D., & Elmazar, M. M. (2017). Honey-based hydrogel: In vitro and comparative In vivo evaluation for burn wound healing. *Scientific reports*, *7*(1), 9692.
68. Sarhan, W. A., Azzazy, H. M., & El-Sherbiny, I. M. (2016). Honey/chitosan nanofiber wound dressing enriched with Allium sativum and Cleome droserifolia: enhanced antimicrobial and wound healing activity. *ACS applied materials & interfaces*, *8*(10), 6379-6390.
69. Silva, J. D., Rashid, Z., Nhut, D. T., Sivakumar, D., Gera, A., Souza, M. T., & Tennant, P. (2007). Papaya (Carica papaya L.) biology and biotechnology. *Tree and Forestry Science and Biotechnology*, *1*(1), 47-73.
70. Nayak, B. S., Ramdeen, R., Adogwa, A., Ramsubhag, A., & Marshall, J. R. (2012). Wound-healing potential of an ethanol extract of Carica papaya (Caricaceae) seeds. *International Wound Journal*, *9*(6), 650-655.
71. Kapupara, P. P., Dholakia, S. P., Patel, V. P., & Suhagia, B. N. (2011). Journal of Chemical and Pharmaceutical Research preparations. *Journal of Chemical and Pharmaceutical Research*, *3*(4), 287-294.
72. Gurung, S., & Škalko-Basnet, N. (2009). Wound healing properties of Carica papaya latex: in vivo evaluation in mice burn model. *Journal of Ethnopharmacology*, *121*(2), 338-341.
73. Rajaram, B., Venkanna, M., Kumaraswamy, B., Kumar, D. R., Patlolla, S. R., Maripeddi, K., & Puligilla, S. (2015). The role of papaya dressings in the management of diabetic foot ulcers: A prospective study. *J Evid Based Med Healthc*, *2*, 7365-71.
74. Murthy, M. B., Murthy, B. K., & Bhave, S. (2012). Comparison of safety and efficacy of papaya dressing with hydrogen peroxide solution on wound bed preparation in patients with wound gape. *Indian journal of pharmacology*, *44*(6), 784.
75. Balavijayalakshmi, J., & Ramalakshmi, V. (2017). Carica papaya peel mediated synthesis of silver nanoparticles and its antibacterial activity against human pathogens. *Journal of applied research and technology*, *15*(5), 413-422.
76. Ahlawat, J., Kumar, V., & Gopinath, P. (2019). Carica papaya loaded poly (vinyl alcohol)-gelatin nanofibrous scaffold for potential application in wound dressing. *Materials Science and Engineering: C*, *103*, 109834.
77. Hayouni, E. A., Miled, K., Boubaker, S., Bellasfar, Z., Abedrabba, M., Iwaski, H., ... & Hamdi, M. (2011). Hydroalcoholic extract based-ointment from Punica granatum L. peels with enhanced in vivo healing potential on dermal wounds. *Phytomedicine*, *18*(11), 976-984.
78. Kaur, G., Jabbar, Z., Athar, M., & Alam, M. S. (2006). Punica granatum (pomegranate) flower extract possesses potent antioxidant activity and abrogates Fe-NTA induced hepatotoxicity in mice. *Food and chemical toxicology*, *44*(7), 984-993.
79. Jang, M. H., Piao, X. L., Kim, J. M., Kwon, S. W., & Park, J. H. (2008). Inhibition of cholinesterase and amyloid-β aggregation by resveratrol oligomers from Vitis amurensis. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives*, *22*(4), 544-549.
80. Hayouni, E. A., Miled, K., Boubaker, S., Bellasfar, Z., Abedrabba, M., Iwaski, H., ... & Hamdi, M. (2011). Hydroalcoholic extract based-ointment from Punica granatum L. peels with enhanced in vivo healing potential on dermal wounds. *Phytomedicine*, *18*(11), 976-984.
81. do Nascimento, M. F., Cardoso, J. C., Santos, T. S., Tavares, L. A., Pashirova, T. N., Severino, P., ... & Albuquerque-Junior, R. L. D. (2020). Development and characterization of biointeractive gelatin wound dressing based on extract of punica granatum linn. *Pharmaceutics*, *12*(12), 1204.
82. Fleck, A., Cabral, P. F., Vieira, F. F., Pinheiro, D. A., Pereira, C. R., Santos, W. C., & Machado, T. B. (2016). Punica granatum L. hydrogel for wound care treatment: From case study to phytomedicine standardization. *Molecules*, *21*(8), 1059.
83. Application F, Data P, Examiner P, Lewis KM. (2010)United States Patent.;2(12).
84. Patankar, S. B. (2014). *U.S. Patent No. 8,709,509*. Washington, DC: U.S. Patent and Trademark Office.
85. Abem Kimya Tibbi Malzemeler Yönetim Danismanligi Temizlik Servis Hizmetleri Sanayi Ve Dis Ticaret Limited Sirketi Istanbul (TR). EUROPEAN PATENT APPLICATION (43) Date of publication: (71).
86. Weller, K. A. C., Weller, K. F., & McLoughlin, N. J. (2020). *U.S. Patent Application No. 15/767,047*

CITATION OF THIS ARTICLE

Kshitija Phatak, Shivali Tank, Pradnya Korlekar, Supriya Shidhaye. Wound Health: Advances in Natural Product Delivery. Bull. Env. Pharmacol. Life Sci., Vol 12[2] Jan 2023: 118-129.