Novel nanofibrous honey as a wound dressing material– A Review

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Abstract

Honey is a sweet and naturally obtaining substance from the floral parts of the plants which has been used for the treatments of wounds since 2200BC by the Egyptians. The presence of hyaluronic acid in honey is made it use in the eschar free wound healing. The wide ranges of administration of honey in wounds are clay tablets, plasters, topical ointments, and dressing such as gauze, hydrogel, hydrocolloid and alginate dressing. Every method has been made different kind of disadvantages like biofilm formation, biofouling, Microbial infection and also removal of grown neogenic tissue at frequent dressing are delay the wound healing time and also leads to chronic condition and necrosis. The draw backs might be overcome by modified form of natural honey only by the fabrication technique Electrospinning to produce the honey in the form of nanofibrous scaffold. The Electrospun scaffold will mimic the ECM and will prevent the infection free wounds, high absorption, high oxygen permeability, high porosity, eschar free wound healing, providing moist environment, anti-fouling and also safe wound sterilization. Hence, the organic band aid would be the promising novel wound healer for deep wound with patient friendly administration method.

Keywords: *Honey, Dressing, Eschar, Electrospinning, Anti-fouling*

1. Introduction

Recent advances in tissue engineering have approached to provide signals to the cells to enhance the proliferation and differentiation and tissue formation enables the self- assembly of cells into its functional units [1]. Wound has been occurred as the result of lack of integrity of tissue in the region getting injured [2]. 1 to 2% of the populations in the developed countries were evaluated to be suffered from chronic wounds in their life time [3]. Chronic wounds has been characterized by perpetuated inflammation, incessant infections, bio-film formation, impotency of cuticular cells in responding to the external stimuli, high level of protease, raised quantity of cytokines like IL-1α,IL-1β, IL-6, TNF-α, TGF-β, IFN-γ, G-CSF, GM-CSF and excessive level of MMPs like MMP-1 & MMP-8 (collagenase), MMP-2 & MMP-9 (gelatinases) with decreased quantity of TIMP [4,5,6].Several strategies have been evaluated to improve the healing efficiency of chronic wounds while decreasing the sufferings of patients.

Traditionally, Honey has been engaged for treating wounds since 3rd and 4th centuries BC by Hippocrates and the ancient Egyptians, Assyrians, Chinese, Greeks and Romans because of its anti-bacterial and anti-inflammatory property [7, 8]. Different composition of honey such as topical application and dressings like honey based hydrogel dressing, honey based gauze dressing, honey- alginate dressing and honey based polyurethane film dressing has been prosperously experimented in many previous preclinical studies [9, 10, 11, 12]. However, in

ISSN: 2233-7857 IJFGCN

this occasion, Nanofibers assists as an acceptable technique to treat the chronic wounds with its efficient mimicking property and its large surface area allows the magnified cellular adhesion [13]. In this aspect, we tend to review honey loaded nanofibrous scaffold is a band-aid for the treatment of chronic wounds and represents as a economical wound care.

2. Wound Healing Behavior Of Honey:

The Phytochemical property of honey was mainly responsible for wound healing and it varied consistent with the floral supply of the plant. The suppression of cyclooxygenase – 2, inducible nitric oxide synthetase, TNF-alpha and interleukin-6 exhibit the anti-inflammatory property of the honey [14]. The wound healing mechanism of honey was shown in the Fig.1

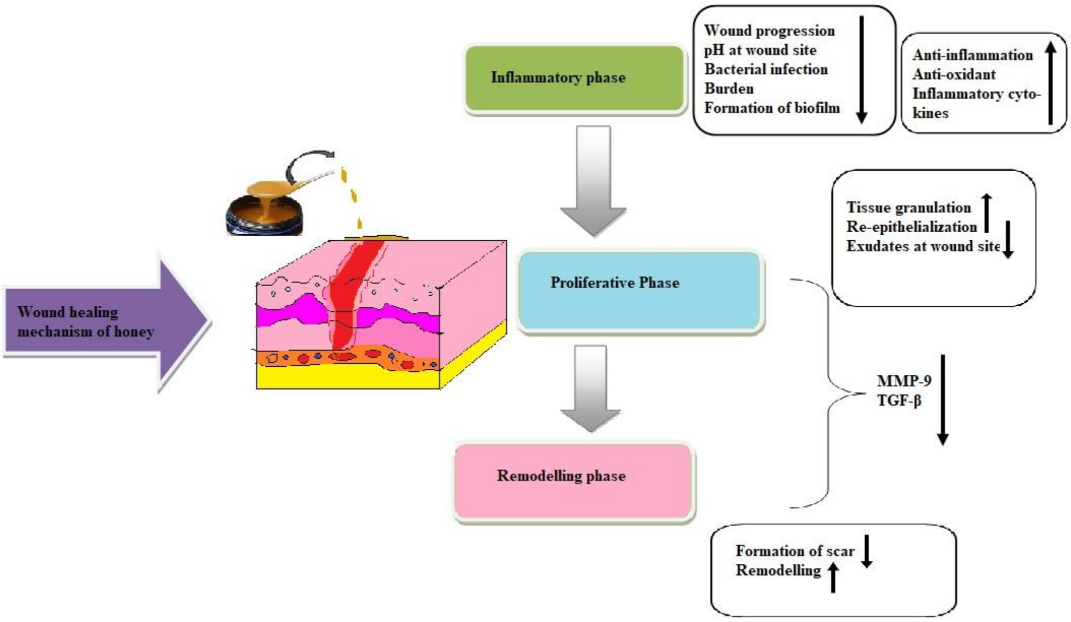

Fig.1 wound healing mechanism

Polyphenols are the naturally existing chemical compounds found largely in honey and it can be classified into flavonoids and non-flavonoids (phenolic acid). Initially, it occur in the conjugated form of sugar molecules linked with the hydroxyl groups and aromatic carbon linked with sugar also exists [15]. The presence of phenolic compounds in honey is depends upon its floral source and it is main reason for the anti-oxidant property of the honey that is mainly concerned in the free radical scavenging by stabilise the free radicals while release the hydrogen from their hydroxyl group present in it [16]. The phenolic composition of honey is shown in the Fig.2. Flavanoids are natural substances with different phenolic structures having remarkable anti- inflammatory, anti- carcinogenic and anti-oxidant property found more in the composition of honey [17].Apigenin, pinocembrin, fisetin, galagin, acacentin, kaemepferol, cizysin are the most common flavonoids found in the honey [18].

ISSN: 2233-7857 IJFGCN

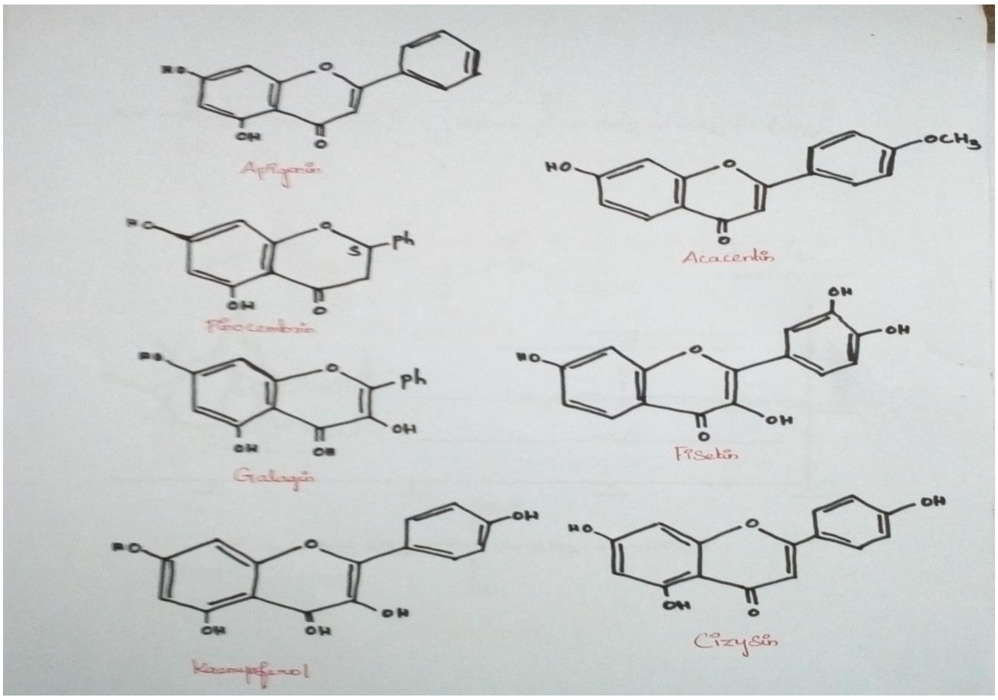

Fig.2 Phenolic compounds present in honey

Gauze Shen K H et al., (2010) have been reported that the acacentin, flavonoid has a significant properties like anti-inflammatory and anti-peroxide activity and also inhibits the excessive amount of MMPs [19] . Governa B et al.,(2019) described in their research that pinocembrin has anti-bacterial activity and reduce the pro inflammatory cytokines such as TNF-α, IL-6, IL-β and IL-10 by decreasing the activity of NF-κB and MAPK [20]. Table 1 shows the activity of different flavonoids present in honey

Table 1. Activity of different flavonoids present in honey

FLAVONOIDS	PROPERTY	REFERRENCE
Acaacentin	Anti-peroxide and anti-inflammatory activity	Gauze Shen K H et al., (2010)
Pinocembrin	Anti- bacterial and anti – inflammatory activity	Governa B et al.,(2019)
Apigenin	Anti- inflammatory, anti- oxidant and anti- carcinogenic property	V Elayne Arterbery et al., (2018) [21]
Fisetin	Anti- oxidant, pro apoptotic and neuro protective activity	Junjain et al., (2018) [22]
Kaempferol	Anti- oxidant, anti- inflammatory and anti- tumor activity	Youyou et al., (2016) [23]

ISSN: 2233-7857 IJFGCN

Phenolic acids (Pheno-carbolic acid) that contains phenols with carboxylic acid and it is classified according to is structure [24]. P. Olczyk et al., (2008) have been reported in his work that gluconic acid was a source of hyaluron which plays an important role in the phases of wound healing by stimulating cell differentiation, proliferation and migration [25]. Agarwal K S et al., (2017) have prepared an acetic acid dressing in his research and described that acetic acid inhibits the bacterial growth at the wound region by eliminates the infection and contamination of the microorganisms [26]. Table 2 shows the wound healing role of different acids present in honey.

Table 2. Wound healing role of different acids present in honey

ACIDS	ROLE IN WOUND HEALING	REFERRENCE
Gluconic acid	A source of hyaluron supports for cellular migration and proliferation.	P. Olczyk et al., (2008)
Acetic acid	Anti-bacterial activity	Agarwal K S et al., (2017)
Citric acid	Anti-bacterial and anti-septic property and enhances the epithelization process of wound Healing	Basavraj et al., (2011) [27]
Butyric acid	Apoptosis and cellular proliferation	Michael et al., (2015) [28]
Pyro glutamic acid	Anti- oxidant activity - reduces the ROS levels	Michael et al., (2014) [29]

The inference for the advanced epithelization and scar less wound healing was due to the organization of hyaluronic acid (HA) with the collagen and fibrin [30]. Hyaluronic acid (combination of gluconic acid and glucosamine) was one of the main component of ECM which was also present in the honey that the glucose present within the applied honey was converted into hyaluronic acid in the region of the wound [30,31] The receptor for the hyaluronan was CD44 which was present in all the membranes of the cell within the human body can further interacting with the other ligands such as fibronectin and collagen after receiving the signal from the HA and promotes the collagen synthesis by the urging the surrounded fibroblast to the wounding area [31].

3. Nanofibrous Scaffolds for Wound Dressings:

Nano fibrous scaffolds, 3D scaffolds plays a vital role in the field of regeneration of tissues and wound dressing by mimicking the Extracellular Matrix (ECM) having high surface to volume ratio, adequate mechanical stability and high porous structure [32,33]. Phase separation, freeze drying, self-assembly, drawing, template synthesis, electrospinning, fibre mesh and fibre bonding are the wide varieties of fabricating nanofibrous scaffold [32,34]. Among them electrospinning technique is an easy, low expensive, simple and efficient technique for nanofibrous scaffolds. Electrospun scaffolds were fabricated by applying high voltage to the

ISSN: 2233-7857 IJFGCN

polymeric solution to overcome the surface tension of the solution and extruded as fibre jet where the solvent was evaporated and the jet was collected by a collector [32, 35].

The factors that affecting the interconnected porous structure, shape, surface to volume ratio, mechanical stability and behaviour of the electrospun scaffolds are solution parameters (Viscosity, molecular weight of the polymer, conductivity of the solution, surface tension), process parameters (flow rate of the dispensing polymeric solution. Strength of the applied electric field, distance between the collector and tip) and other parameters such as humidity and temperature [35]. Natural polymers such as collagen, hyaluronic acid, gelatine, chitosan and synthetic polymers such as polyurethane (PU), Polyethylene glycol (PEG), and Polyethylene oxide (PEO) and Polyvinyl alcohol (PVA) has been incorporated into the scaffolds for the purpose of healing the wounds [36,34].

Advanced, bioactive, passive and interactive wound dressings are the general classifications of wound dressing where advanced wound dressings are loaded with drugs, bioactive is utilised frequently in biological dressing and drug delivery systems, passive dressing is suited for providing the required moist environment to the wound site and prevent it from mechanical stresses and interactive wound dressings at the wound area would reducing the bacterial infection[37]. Electrospun nanofibrous scaffolds were comes under the category of bioactive wound dressing, multifunctional dressing inducing the produced immunogenic response [34].

The characteristics of a perfect wound dressings are providing adequate pore size for better cellular migration, preventing bacterial infection, rate of degradation of dressings would be compensate with the recovery rate of wounds, having the capacity to remove the existing pus and fluids at the wound area, suitable moist environment with better transmission rate for water and gas to the wound site, giving comfortable surface area which facilitates for the attachment, differentiation, migration and proliferation of the cells, cost effective and easy to remove, reducing pain while removing [38, 39]. Electrospun scaffolds meet the requirements of the above mentioned characteristics of the perfect dressings and producing homogeneity and decreasing the morbidity rate among the patients [39].

4. Behavior of Honey Loaded Scaffolds:

Honey loaded scaffolds enhances the permeability of the scaffold in the wound site which paves the way for the improved cell adhesion, migration, proliferation and differentiation [40]. A scaffold incorporated with honey induces the fibroblast proliferation and infiltration of cells which will lead to the synthesis of ECM matrix and protects the tissues from the pathogen infections [40, 4, 41]. It also triggers the leukocytes (Monocytes and lymphocytes) and releases the cytokines for the phagocytosis function and immune response against further infection [42, 4].

The nanofiber with honey has large surface to volume ratio that further increases the behaviour of honey in the wound site mainly the concentration of honey plays an important role in the function of scaffolds by affecting the fibre diameter, permeability and degradation behaviour [43]. According to Z. Li and C. Wang, as the concentration increases the diameter of the fibre and viscosity has been increases which will be related with one another [44].

ISSN: 2233-7857 IJFGCN

Muhammad suggested that the concentration of honey was the reason for the increase in the diameter of the fibre [45].

The structure of the scaffold plays a vital role in tissue regeneration and it should possess the proper mechanical property, bioactivity, and compatibility and degradation rate. It encourages the growth and differentiation of stem cells whereas honey incorporated scaffolds probably increases the uptake of fibroblast into it and enhances the production of collagen, healing rate of the wound and increases the efficiency of the dressing [46, 47]. The honey present in the scaffold material improves the water intake because of this high water intake, the degradation rate of the fibre increases [48].

5. Conclusion:

Honey, the natural component which has been used for the treatment for wounds since ancient times. This review article suggested that the honey loaded electrospun scaffolds could be the suitable mode of wound treatments which will reduces the sufferings of patients from the prolonged unhealed wounds. The innovation in the field of dressings used for wound was brought through the Nanotechnology which would meet the requirements such as earlier recovery, reducing the morbidity and mortality. Therefore the electospun nanoscaffolds would be the suitable and ideal dressing for the treatment of chronic wounds.

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