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Wound healing potential of Indian traditional tree– Ficus Religiosa

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Abstract

In recent years, peoples were affected by the chronic wounds (non-healed wounds) because of the hierarchical problems occurred in healing mechanism. The external or internal breakage of tissues caused by physical, chemical and microbial actions are often called as wounds. Several modern medicines had been invented to treat it, but it exhibits some limitations over that process. The existence of herbal and ayurvedic medicines over 4000 years had great impact towards the wound treatment. Moving in the natural path, Ficus Religiosa (Arasamaram), an herbal tree which has many medicinal applications such as for gynecological problems, dysentery, wound healing, inflammatory, analgesic and anti-lipid- peroxidation activity. This review has been focused on phytochemical studies and ethnomedical applications mainly on wound healing mechanisms. Breaking strength, epithelization, wound contraction and preferable wound dressing methods of Ficus Religiosa were elaborately discussed.

Keywords: *Ficus Religiosa, Wound Healing, Breaking strength, Chronic wounds, Epithelization, Ethno medical application.*

1. Introduction

In the developing countries, 1-2% of population has been affected by chronic wounds. Chronic wound and excessive wound are the types of wound that takes prolonged period to heal. Normal structure of the skin tissues which has been disturbed by the wound through the way of injuries. The requirement of high recovery time and high cost for treating the wounds, affects the patient's quality of life[1].Therapeutic treatment has been the most common process followed but possessing the challenges like lack of cell type and interaction between the mediators.[1,2].The reconstruction process of the skin in wound healing has four stages like hemostasis, inflammation, proliferation and remodeling[3,4, and 5].

Hemostatic has been the first stage of the healing mechanism in which platelets secretes vasoconstriction to seal the damaged vessels by means of clot. At this part, ADP (adenosine diphosphate) reveals the type I collagen to secrete the adhesive glycoproteins, where it would also help in blood clotting. On other hand, Platelets itself have the thrombin which could aid in the formation of fibrin from fibrinogen to stimulate the intrinsic blood clotting cascade [6, 7, 10].

The second stage of wound healing mechanism is Inflammation, which proceeds with swelling warmth and clean up the debris of the tissues. Two types of defense occur in this stage. Firstline of defense provides Neutrophils phagocytes against debris of the tissues and microorganisms, which could deliver the intracellular enzymes into the surrounding matrix against infection. Fibroblast and cells of fibrin have also breakdown for cleanup process which supports to the process of neutrophils phagocytes respectively. Wound repairing requires

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Cytokines and growth factors which have liberated by one cell that bind to a receptor of a target cells through cell to cell communication. Extra cellular matrix has been used to produce different collagens depends on the suitable cells it needs for repairing [6,8,9]. Macrophages which have been the second line of defense after Neutrophils phagocytes that could secrete a kind of proteases MMP (Matrix Metalloproteinase) for further process. Cytokinesis and growth hormones are secreted by these macrophages for cell repairing process. Other than MMPs proteases (breaks down protein molecules) Tissue Inhibit of Metalloproteinase (TIMPs) has been another one which has been balanced by the MMP secreted. If MMPs were uncontrolled it would degraded the newly formed tissues and destroyed the four types of growth factors present in this stage, which are Fibroblast Growth Factor (FGF), Epidermal Growth Factor (EGF), Transforming and Interleukin-I Growth Factor (TGF-β) [6].

Proliferation is the third stage of healing mechanism by providing contraction and possible epithelial barrier to stimulate keratinocytes [8,9,7]. This stage includes1. Angiogenesis, 2. Fibro plasma and 3. Reepithelialization.1. Angiogenesis improve endothelial cellular proliferation and rearrangement of basal membrane, whereas the collagens are secreted by fibroblast called framer cells and the outer layer of capillaries and endothelial cells are regenerated by pericytes [11,12and 13].2. Fibroblastic proliferation process needs granulation tissue which would require four days for formation [8]. After the granulation tissue formed, three-dimensional extra cellular matrix, collagenous and elastic biosynthesis has also created by fibroblastic proliferation along with type III collagen [14, 15]. In addition to that, MMPs balanced TIMPs proteases proceeds the remodeling process of the damaged tissues with type III collagen.3. Epithelialization is the formation of new epithelial cells to prevent fluid loss and microbial invasion which could be increased the rate of wound healing in a nominal way [14].

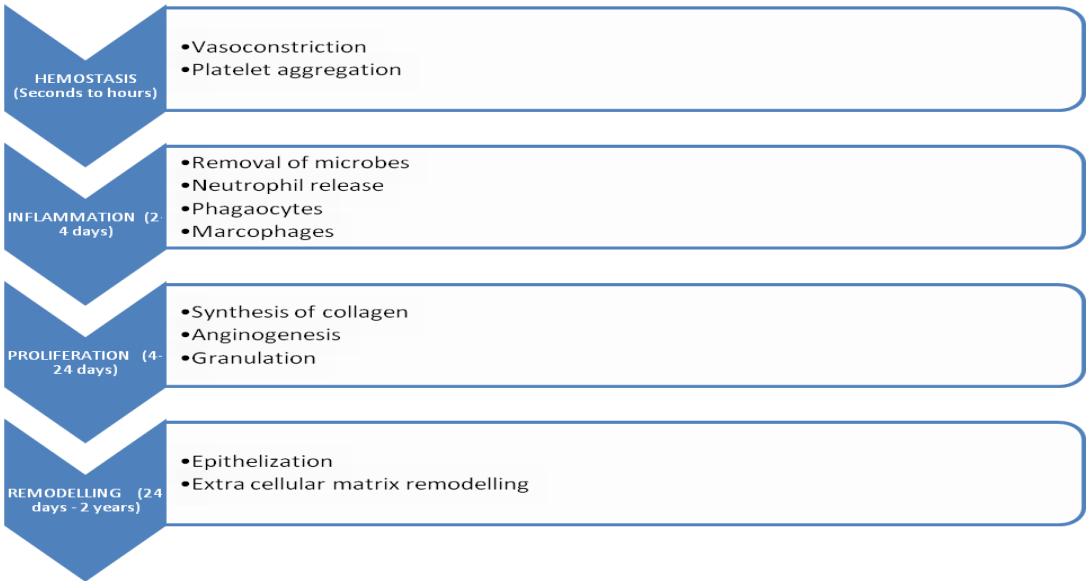

Fig.1 Mechanisms of wound healing process

The fourth final stage of wound healing is remodeling of damaged tissues. Here collagens have been produced continuously from fibroblast in proliferation stage (i.e., third stage in wound healing) which randomly laid a bundle like structure. The debulking of the collagen in the surface has been reorganized into parallel arrangement in which the wound contraction has

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increased [6, 14]. In case of any default occurs in the four-process mentioned above, chronic wound would occur. If the MMPs should not get degraded in the stage of proliferation, it leads to degradation of extracellular matrix that would affect the other stages of wound healing mentioned above [6].

Comparing with the modern medicines, herbal medicines had given a new input for pharmaceutical industries [16]. From the report of World Health Organization, it could be clear that, nearly 80% of plant extracts have been used for therapeutic medicines. Certain extracts which have been derived from the plants shows improvement in the life of human health, particularly in the areas of infection, cosmetics and dyes. Many works and researches which have been analyzed in previous and present reports have focusing on the ethno medicinal plants in our country [17]. *Ficus Religiosa,* a type which comes under the traditional plant, had been utilized for medicinal applications from ancient days since. The Phytochemical studies of this plant have shown that they have natural texture which can improve to treat the health issues faced by the patients [16]. In this review article, we have been demonstrated the medicinal impacts and structural behavior of *Ficus Religiosa* in wound healing mechanisms.

2. History

Ficus Religiosa is a religious, mythological, medicinal plant and sacred plant noticed since ancient days by Buddhist and Hindus. Between 3000BC-1700BC this tree has been marked by Alok Tripathi *as Ficus Religiosa [18]*. *Ficus Religiosa (*Moraceae) genus (*Ficus*) is a rapid growing tree with 30m long generally known as "Peepal tree" by the people with large branched tree and leathery long tripped leaves.[18]. In South East Asia, particularly in India this tree was generally seeded and grown as spontaneous way. Itis popularly known as ethnomedicinal tree in Ayurveda used as antioxidants relive pain in the body. Other than this, *it holds* different names such as scared fig in Bengali, Arayal in Malayalam, Ravi in Telugu, Arasu in Tamil, Peepal in Hindi and Pipal in English [18,19].

2.1 *Ethnomedicinal uses of Ficus Religiosa*

Ficus Religiosa shows many biological activities and every part of the tree have been used to treat various diseases [20,21]. Here some of the medicinal qualities of the trees have been explained in the below table.

Table 1: Medicinal uses possessed by different parts of the plants

S.NO	PLANT PARTS	USES
1.	Root	Inflammation, treatment for gout, skin disease, lower back pain, inflammatory disease of the mouth and ulcer and purgative.
2.	Seed	Bladder condition, refrigerant and laxative.
3.	Leaf juice	Asthma, Cough, Sexual disorder, Diarrhea, Hematuria, toothache, eye trouble and gastric problem.
4.	Fruit	Asthma, laxative, digestive, dehydration, fever, and paralysis.
5.	Dried fruit	Tuberculosis, fever.

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6.	Bark	Anti-inflammation, gastrohelcosis, astringent and aphrodisiac.
7.	Leaves	Wounds, scabies, diarrhea, skindiseases, asthma and cough.

2.2 Phytochemical studies of *Ficus Religiosa*

Phytochemical study is usually done to identify the chemical compounds present in the plants such as tannins, steroids, cardiac by using a method followed by called Trease and Evans in 1983.This compounds mentioned above could be used as a natural drug in pharmaceutical industries [19].From the study done, it has been clear that the leaves of this plant owned campestral, stigmasterol, lupeol, tannic acid, valine, serine, aspartic acid, glycine, threonine, alanine, proline, tryptophan, isofucosterol, tyrosine, methionine, isoleucine and hexa-cosanol in which most of the compounds comes under the category of national drug pharmaceutical industries [21,22,23]

3. Role of *Ficus Religiosa* in wound healing

Chronic non healing wounds result from the abnormal inflammatory response due to their lack of neutrophils which could affect wound repairing process [24]. In the phase of inflammation and proliferation stage the repairing process delays the functionality of MMPs. That delay is due to the enormous tissue destruction, which causes the inflammatory cytokines and collagens (such as MMPs) to reduce the growth factor level in the wounds [25]. Fig 2 shows the healing mechanism of wounds in a hierarchical manner

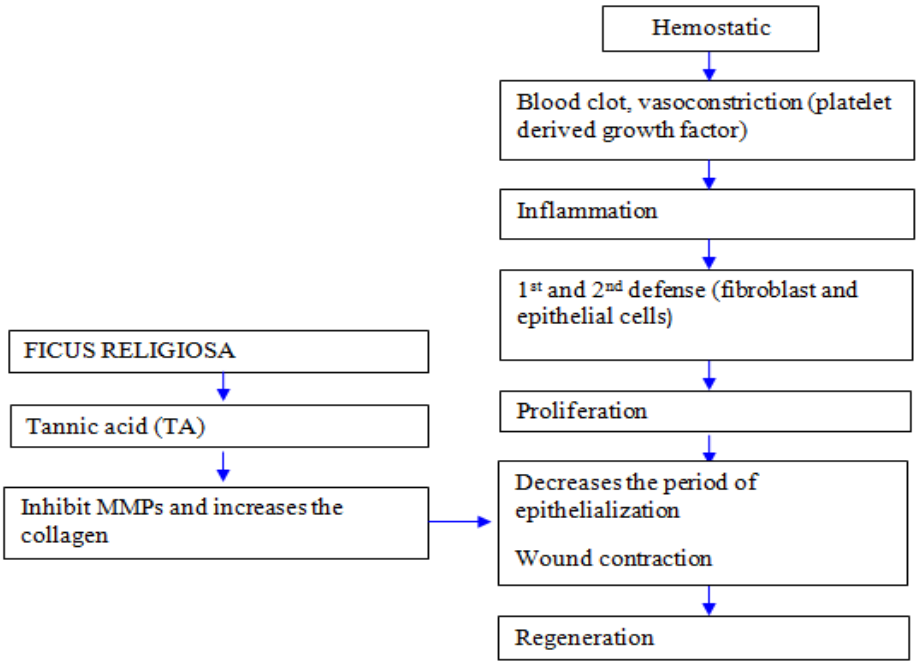

Fig 2: Hierarchical view of wound healing mechanism

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Tannic acid a polyphenol group which extracted from the Ficus Religiosa leaves which could act as a defensive layer for injured epithelial tissue and it have high antimicrobial activity. Here Tannic acid can increase the capillary vessels formation and proliferation of fibroblast, inhibits MMPs and increases the collagen by reducing MMPs synthesis wound contraction is increased and period of epithelialization is decreased which medicate Extracellular destruction [25].

4. Effectiveness in breaking strength

Comparatively, the normal breaking strength of the standard provide iodine content of 571±8.84**and the standard nitrofurazone is of 463.33±11.94**. But the extract of Ficus Religiosa with different method of preparation method shows different breaking strength of the animal respectively.

First clinical trial for an animal with (n=5) have been conducted with Wistar albino rats (either male or female) through the effectiveness of hydro alcoholic ointment by applied daily manner which is extracted from the *Ficus Religiosa*. The breaking strength of the species is measured using standardized tool with 10^{th} post wounding day reported that concentration of 5% shows 562.2±7.25 and Concentration of 10% shows 5712±8.83.(Kalyon Roy,2009)

Secondary clinical trial (n=5) has conducted over the species of albino rats (Sprague dwaly) by daily applying the extract of hydro alcoholic emulsifying with Ficus Religiosa. The breaking strength of the species is measured on 10^{th} day has reported as 518.33±11.37 and 641.66±11.94 with the concentration of 5% and 10% has been demonstrated through the work N Nayeem, 2009.

Rita M. Charde, 2010reported in his work about the Male Wistar rats had been the third clinical trial (n=5) through the extract of ethanolic assessed from Ficus Religiosa which had been exposed daily. 379.00±6.32 has been the breaking strength of the species, measured with the concentration of 5%. The different concentration of different extract from *Ficus Religiosa* shows multiple breaking strength has been explained by the table 2 shown below.

Table 2. shows the breaking strength of animals with varying concentration

S. No	Preparation method	Concentration	Breaking strength	Author	Year
1	Hydro alcoholic extract FR	5%	18±0.54**	Kalyon Roy	2009
2	Hydro alcoholic extract FR	10%	571±8.84**	Kalyon Roy	2009
3	Hydro alcoholic extract FR emulsifying	5%	518±11.37**	N Nayeem	2009
4	Hydro alcoholic extract FR emulsifying	10%	641.66±11.94**	N Nayeem	2009
5	Ethanolic extract FR	5%	379.00±6.32**	Rita M. charde	2010

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5. Effectiveness in Epithelization and Wound Contraction

To analyze the effectiveness of epithelialization of the regular method of healing effect such as standard nitrofurazone are 18.83±0.25 and 33.51±2.64 and the wound contraction of the normal method of standard nitrofurazone is 96.61±3.73.

First line of clinical test with the extract of hydro alcoholic in ointment of same species with epithelialization concentration rate of 5% of is 20.2±0.58 and exhibits wound contraction rate of77.76±4.80 by 16th day and epithelialization concentration rate of 10% is 18.0±0.60 withs wound contraction rate is 93.22±3.72.

Second line of clinical test with the extract of hydro alcoholic extract in emulsifying provides the result of 17.33±0.21 in the epithelialization concentration rate of 5% and7.83±0.30 in the wound contraction for about 50% days. At 10% of epithelialization concentration rate the result would be 14.83±0.40 and wound contraction rate of 6.50±0.42.

Third test line with the ethanolic extract for the wound contraction of 5% concentration is 73.09±1.37 (18th day) has shown in the table 3.

Table 3 shows the wound contraction and epithelization with varying concentration

S. No	Preparation method	Conc.,	Wound contraction	Epithelization	Year
1	Hydro alcoholic extract FR	5%	77.76±4.80 16th day	Kalyon Roy	2009
2	Hydro alcoholic extract FR	10%	93.22±3.72 16th day	Kalyon Roy	2009
3	Hydro alcoholic extract FR emulsifying	5%	7.83±0.30 50% days	N Nayeem	2009
4	Hydro alcoholic extract FR emulsifying	10%	6.50±0.42 50% days	N Nayeem	2009
5	Ethanolic extract FR	5%	73.09±1.37 18th day	Rita M. charde	2010

6. Wound Dressing

Dressing is done to make contact with the wound which can improve chemotactic, proteinases, and growth factors where the Modern dressing starts at 20th century [29]. Dressing material is one of the major thing for the promotion of wound repairing which could help to maintain moist environment, removing odor, removing bacterial infection, improving blood flow, promoting angiogenesis, connective tissue synthesis, improve skin regeneration and also it would allow gas exchange between wound tissue and environment. There are different styles of wound dressing present depends on the materials used like gauze dressing, semi-permeable dressing film

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dressing, hydrogel, hydrocolloid dressing and bioactive wound dressing material etc. According to surveys, among these types, Gauze wound dressing is the most common and efficient wound dressing found [30].

Gauze wound dressing is made up of woven and non-woven materialto absorb the fluid from the wound which could prevent from painful deeper wound formation. Traditional wound dressing material had been used to clean the dry wound with mild exudate leaves and but it has the limitation of protecting the wound from moist environment [30,31].

Bioactive wound dressing materials having biodegradability, biocompatibility and non-toxic from natural tissues or artificial sources. Biomaterial such as collagen, hyaluronic acid alginate and elastin plays a vital role in enhancing the healing property of wound through promoted growth factor and antimicrobials. These bioactive materials could be incorporated with electrospun scaffolds that can improve healing capacity [30].

7. Electrspun scaffold for wound dressing

Scaffold with 3D structure and high surface volume ratio plays an important role in the tissue regeneration and wound dressing material which can resembles the Extracellular Matrix [32]. An ideal scaffold requires biocompatibility, biodegradability, mechanical property, scaffold architecture, and manufacturing technology [33]. There are different fabrication techniques involved in the synthesis of scaffold such as freeze drying, self-assembly, template synthesis, phase separation, electrospinning.

Comparing with the various techniques used, Electrospinning technique is simple and cost effective which could use electrical charge to draw a unique structure with uniform surface ratio and high porosity.

The Electrospinning setup needs three major components:

- A capillary tube with needle
- A high voltage
- A metal collecting screen.

With varying parameters, could get varying diameters of scaffolds which could possess different properties. Such parameters which involves in these techniques are solution parameter, process parameter, and ambient parameter [34]. Solution parameters consist of viscosity, conductivity, molecular weight, surface tension, polymer structure, solution parameter. Process parameter involves applied electric field, tip to collector distance, flow rate, plate movement. Ambient parameter have humidity and temperature of the surroundings, solution temperature, and air flow rate. The production of nanofibrous scaffold is controlled by adjusting the parameters.

8. Conclusion

In this work, a traditional herbal tree *Ficus Religiosa*and its impact in medicinal applications were analyzed. The presence of Tannic acid and MMPs in this plant promotes the wound healing mechanism to the next stage. Four stages of wound healing mechanismincludehemostasis,

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inflammation, proliferation and remodeling have been explained through the involvement of multiple collagens, cytokines, growth factor, hormones, and proteases. The various parts of plants have been used to cure most common diseases like asthma, inflammation, and skin diseases. According to survey, Animal studies were conducted over the Male Wistar rats and albino rats where the highest breaking strength and wound contraction observed were 641.66±11.94 and 77.76±4.80 through the Hydro alcoholic emulsified FR extract by the 16^{th} day. Electrospun scaffolds have high porosity that could mimic the extracellular matrix so that it could increase the rate of wound recovery process. Thus, the ethno medical based traditional *Ficus Religiosa*, couldbe a promising bio active material for future bio mimetic applications, invasive surgeries and targeted drug delivery purposes.
For Example:

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