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Role of Herbal Drugs in Wound Healing Mechanisms

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ABSTRACT

Wound healing is a complex and dynamic biological process and involves hemostasis, inflammation, proliferation, and remodeling of tissues that can be impaired by factors like infection, oxidative stress, and chronic inflammation. Surveying herbal drugs, which have been reported to be high in bioactive phytoconstituents such as flavonoids, terpenoids, alkaloids, tannins and phenolic drugs, have become effective in wound repair acceleration. Preclinical animal models suggest that Curcuma longa, Ocimum sanctum, Centella asiatica and Azadirachta indica extracts have significant effect on wound contraction, collagen deposition, angiogenesis, fibroblast proliferation and general tissue regeneration and decreasing oxidative damage, inflammation and microbial burden. The combination of such multifaceted microenvironmental biological activities results in a supportive microenvironment that promotes quicker and more effective wound healing, which is why they may be evaluated as cost-effective, biocompatible, and culturally acceptable alternatives or complements to traditional synthetic therapeutics. Although showing good preclinical outcomes, there are still issues of standardization of the extraction processes, doses and formulations as well as scanty clinical confirmation in humans. Such studies should be backed up by future studies in which rigorous clinical trials and molecular level mechanistic studies are performed with optimization of the delivery systems to convert these studies into safe, effective, and standard therapeutic modalities in modern wound management.

Key Words:

Wound healing, Herbal drugs, Antioxidant, Anti-inflammatory, Antimicrobial, Collagen synthesis, Angiogenesis, Tissue regeneration.

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1. INTRODUCTION

The process of wound healing is a complex biological process, which entails a sequence of interconnected events, comprising of hemostasis, inflammation, proliferation and tissue remodeling. Wound management is of great importance in order to restore the integrity of the tissues, to avoid such complications as infections, chronic ulcers or delayed recovery[1]. Synthetic drugs and new pharmaceuticals are usually employed to facilitate the healing process of wounds but have drawbacks including slowness of healing, cytotoxicity, antimicrobial resistance and side effects. These problems have motivated the development of alternative therapeutic methods, which are safe and effective.

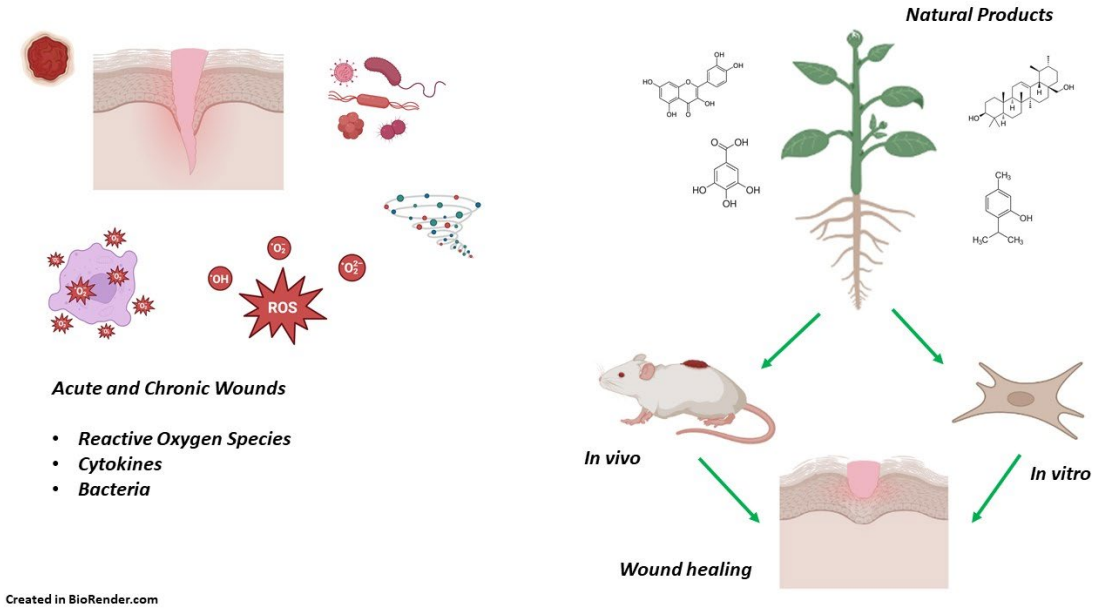

Figure 1: Wound Healing[2]

The rich source of bioactive secondary metabolites that include flavonoids, terpenoids, alkaloids and phenolic compounds has also been a promising candidate in herbal drugs. These products are multifunctional with biological functions being anti-inflammatory, antioxidant, antimicrobial, and collagen-promoting which are crucial in hastening wound healing. Herbal extracts have been shown to be effective in many studies on animals in the contraction of wounds, tensile properties, angiogenic activity, and general tissue healing. Biochemical interventions are cost-effective, biocompatible and acceptable in their culture thus the herbal interventions have a great potential in incorporating into the modern wound management strategies.

1.1 Background information and context

The process of wound healing is complex and very coordinated as it entails various cellular and molecular events in a sequential cascade: haemostasis, inflammation, proliferation, and remodelling. In haemostasis, the loss of blood is stopped by constriction of the vessels and the formation of clots, and then the inflammatory stage is observed, during which the immune cells must deposit the debris and avoid infection. The proliferative phase is characterized by the proliferation of fibroblasts, deposition of collagen and angiogenesis which eventually results in the granulation of tissues, whereas the remodelling phase is characterized by strengthening and reorganization of the extracellular matrix to reinstate tissue integrity[3]. Despite the common use of conventional synthetic drugs in the treatment of wounds, they usually have delayed healing, cytotoxicity, and the possibility of antimicrobial resistance among other adverse side effects inhibiting patient outcomes. Conversely, alternative holds promise in the form of herbal drugs that are known to contain a rich supply of bioactive secondary metabolites including flavonoids, alkaloids, terpenoids, and tannins. These compounds possess antioxidant, anti-inflammatory and antimicrobial effects which alleviate the oxidative stress and excessive inflammation, as well as prevent microbial invasion to provide a suitable environment to aid in wound repair in an effective and better manner.

1.2 Objectives of the review

The main objectives are:

- To evaluate the role of herbal drugs in accelerating wound healing through their antioxidant, anti-inflammatory, antimicrobial, and angiogenic properties.
- To analyze the effects of specific herbal extracts (e.g., Curcuma longa, Ocimum sanctum, Centella asiatica, Azadirachta indica, Aloe vera) on wound contraction, collagen synthesis, fibroblast proliferation, and tissue regeneration in preclinical animal models.
- To assess the underlying molecular and biochemical mechanisms by which herbal phytoconstituents modulate inflammation, oxidative stress, and matrix remodeling during wound repair.
- To identify the strengths, limitations, and challenges of preclinical studies, including variability in extraction methods, dosages, formulations, and lack of clinical validation.
- To highlight future research directions for translating herbal wound-healing interventions into standardized, safe, and effective clinical applications.

1.3 Importance of the topic

The investigation of herbal interventions in wound healing is rather important because it has numerous practical and therapeutic benefits. The natural agents are usually affordable, and hence they can be used by large populations especially in environments with low resource bases where traditional wound care might be prohibitive or scarce[4]. They are compatible as well as safe and the likelihood of adverse effects is lower than that of synthetic drugs which improves patient compliance and usability over a longer period. Furthermore, a range of herbal treatments are accepted in terms of culture and are widely applied, which represents a centuries-old knowledge of traditional medicine that can inform modern studies. Using this ethnopharmacological knowledge and applying it to experimental validation of its validity in a modern setting, scientists may come up with new therapeutic formulations that would not only speed up the healing process and enhance the quality of tissues, but also provide some alternative to the conventional wound-care practices that are sustainable and holistic. These translational potentials place herbal interventions in a strategic standing between the conventional medicine and evidence-based clinical practices.

2. EVIDENCE FROM ANIMAL STUDIES ON HERBAL WOUND HEALING

The therapeutic efficacy of several herbal extracts in wound healing was demonstrated in animal models to which agents such as Aloe vera, Curcuma longa (curcumin), Centella asiatica and Azadirachta indica (neem) demonstrated a promising effect on wound healing through their antimicrobial, anti-inflammatory, antioxidant and pro-regenerative properties[5]. Preclinical models that can be used in research involve excision of wound, incision or burn wound in animals such as rats and mice and the wound healing is measured in terms of wound contraction, presence of hydroxyproline, tensile strength and by histopathological examination. Even though these studies are consistent in terms of evidences of accelerated healing, certain difficulties are present, such as variations in extraction procedures, doses and formulations and a lack of molecular understanding of the mechanism of action. Besides, the majority of the results are preclinical and further clinical studies should be conducted to determine the effectiveness and therapeutic consistency of herbal wound-healing agents in humans.

Table 1: Summary of Literature on Herbal and Bioactive Interventions in Wound Healing[6]

Author(s) & Year	Study	Focus Area	Methodology	Key Finding
Feng et al. (2021)[7]	Chitosan-based functional materials for skin wound repair	Biomaterials for wound healing	Review and experimental studies on chitosan scaffolds	Chitosan scaffolds enhanced fibroblast proliferation, collagen deposition, angiogenesis, and modulated inflammatory responses; suitable for advanced wound-dressing applications
Fu et al. (2023)[8]	All-natural immunomodulatory bioadhesive hydrogel for diabetic wounds	Hydrogel-based wound healing in diabetic models	Development and evaluation of bioadhesive hydrogel in diabetic wound models	Hydrogel promoted angiogenesis, accelerated wound closure, and regulated macrophage heterogeneity, enhancing tissue repair in chronic wounds
Hariharan & Dharmaraj (2020)[9]	Role of selenium and selenoproteins in inflammation	Selenium in wound repair	Literature review on selenium and selenoproteins	Selenium regulated oxidative stress and inflammatory pathways; supplementation could reduce excessive inflammation and improve healing outcomes
Hu et al. (2018)[10]	Exosomes from human umbilical cord blood in wound healing	Exosome therapy for cutaneous wounds	Experimental studies on exosomes in wound models	Exosomes accelerated tissue repair via miR-21-3p-mediated enhancement of angiogenesis and fibroblast function; potential novel cell-free therapy
Huang, Ren, & Qu (2019)[11]	Nanozymes: classification,	Nanozyme-based	Review of nanozyme properties, catalytic	Nanozymes mimicked enzymatic activity with antioxidant and

	mechanisms, and applications	strategies for wound repair	activity, and biomedical applications	antimicrobial effects, supporting wound healing and reducing oxidative stress and infection risk
Ibrahim et al. (2018)[12]	Wound healing properties of selected natural products	Natural compounds in wound management	Experimental evaluation of plant extracts and bioactive molecules in wound models	Natural products enhanced wound contraction, collagen deposition, and epithelialization due to anti-inflammatory, antioxidant, and antimicrobial activities

2.1 Key Research Studies

It has been proven over time that herbal extracts have therapeutic potential in wound healing through animal studies done using excision, incision, and burn wound models. As an illustration, Aloe vera gel enhanced the contraction and epithelialization of wound in rats through the stimulation of moisture retention and growth factors. Curcuma longa (curcumin) having a strong antioxidant effect was discovered to alleviate oxidative stress, inhibit pro-inflammatory mediators, and stimulate collagen deposition in excision wounds, subsequently improving the strength of the healed tissue structure[13]. Centella asiatica proved to be angiogenic as it enhanced the capillary density and collagen production, which were then transferred and resulted in tensile strength and quicker wound healing in incision models. On the same note, Azadirachta indica (neem) with its antimicrobial and anti-inflammatory effects showed the ability to reduce microbial load of wounds, decrease the chance of infection and speed up the wound healing process. All these findings tend to indicate that herbal agents can behave via a synergistic action of antimicrobial, anti-inflammatory, antioxidant, and pro-regenerative action[14].

2.2 Methodologies and Findings

Most of the studies used preclinical animal models rats, mice, and rabbits since they are reproducible and easy to handle. The experimental designs tended to rely upon the establishment of experimental wounds (excision, incision, or burn) and the application of herbal preparations either as an ointment, gel, or hydro-alcoholic extracts. Various biological and biochemical markers were then used to evaluate the progress of the healing process and they included:

- Wound contraction rate to determine efficiency in closure.
- Hydroxyproline, an index of collagen deposition as a biochemical product.
- Tensile force to evaluate the mechanical stability of healed skin[15].
- H. pylori -Histopathology to evaluate fibroblast proliferation, angiogenesis, re-epithelialization, and inflammatory cell infiltration.

The agreement in the findings of all these models underscored the accelerated wound healing, lowering of inflammatory influx, increased collagen synthesis, and better growth of granulation tissue. Other more developed researches involved biochemical tests to determine the activity of

antioxidant enzymes (e.g., SOD, catalase, GSH) and molecular indicators of growth factors and cytokines to get mechanistic understanding of herbal wound-healing action[16].

2.3 Strengths and Weaknesses

The advantage of these studies is that animal wound models can be reproducible and this provides controlled experimentation and outcome measures. Quantitative evidence of healing is achieved by standardized markers like contents of hydroxyproline and tensile strength. Moreover, due to its multifunctional effect, such as antimicrobial, antioxidant, and pro-angiogenic, herbal agents prove to be promising alternatives to synthetic wound-healing agents[17].

Nevertheless, there are still a number of weaknesses and challenges. The extraction methods, dosages, and formulations have high heterogeneity and this makes it complicated to compare the findings across studies. Numerous studies end at the macroscopic and biochemical analysis, and few proceed to the molecular framework analysis which can demystify the exact processes of action, like by signaling pathway (ex. VEGF, TGF-B, NF-KB). In addition, most of the results are founded on preclinical models and the translation to human clinical efficacy has not been studied properly. These shortcomings motivated the necessity of standardized procedures and clinical validation to determine the therapeutic reliability of herbal wound-healing agents[18].

3. THEMATIC MECHANISMS OF HERBAL DRUGS IN WOUND HEALING

Curcuma longa (curcumin), *Ocimum sanctum* (holy basil), and *Centella asiatica, Azadirachta indica (neem),* and Aloe vera, are herbal compounds that are essential in wound healing due to their antioxidant, anti-inflammatory, antimicrobial, and angiogenic effects[19]. They lower the oxidative stress levels, regulate inflammatory reactions, encourage the production of collagen, prevent and combat infections, and increase the formation of blood vessels, thus improving tissue regeneration, decreasing scarring, and shortening wound healing.

Figure 2: Herbal Plants Used in Wound Healing[20]

3.1 Antioxidant and Anti-inflammatory Properties

Among the key obstacles to effective wound healing is the oxidative stress that is brought about by an imbalance between the reactive oxygen species (ROS) and the antioxidant defense of the body in response to the presence of reactive oxygen species. High levels of ROS cause cell membrane damage, protein degradation and damage to DNA which results in delayed epithelialization and cellular tissue repair. Herbal extracts like Curcuma longa (curcumin) and Ocimum sanctum (holy basil) have also been found to possess strong antioxidant property in free radical scavenging and also improving the activity of native antioxidant enzymes like catalase and superoxide dismutase (SOD). These herbs reduce oxidative stress and contribute to the integrity of the cell and early repair phases[21].

These herbs have strong anti-inflammatory effects in addition to the anti-oxidant effect. A typical feature of chronic wounds is prolonged inflammation, which is usually accompanied by increased concentrations of pro-inflammatory cytokines, including TNF- -, IL-1 - and IL-6. Research indicates that curcumin and Ocimum sanctum are able to regulate such cytokines, suppress the NF- kB signaling pathways and neutrophil infiltration in the wound area. This dual action, reduction of oxidative damage in addition to balancing inflammatory reactions, reduces the inflammatory stage of wound healing and generates a beneficial microenvironment in which fibroblast expansion, angiogenesis and tissue regeneration are promoted[22].

3.2 Collagen Synthesis and Matrix Remodeling

The process of wound repair involves collagen deposition to serve as a structural basis of tissue regeneration. Such herbs as Centella asiatica and Lawsonia inermis (henna) dramatically increase the level of hydroxyproline an immediate biochemical indicator of collagen synthesis. The experimental models prove that extracts of these plants enhance the activity of fibroblasts, and the result will be more collagen fibers deposited. Not only does this accelerate wound contraction, but it also enhances structure of reproduced tissue[23].

The next step after initial collagen deposition is matrix remodeling which makes sure that the collagen fibers are properly oriented and cross-linked to maximize tensile strength. Research has indicated that centella asiatica specifically improves cross-linking of the collagen fibrils and the resultant tissue is stronger and less susceptible to re-injury. Lawsonia inermis plays its role in regulating miRNA, extra-cellular matrix, proteins, enhancing the formation of granulation tissue and speeding up dermal matrix maturation. Combined, these effects give greater and more orderly healed wounds with enhanced functionality and cosmetic results[24].

3.3 Antimicrobial Effects

Infection is one of the greatest impediments in wound healing because the growth of bacteria may slow the process of epithelialization, elevate inflammation, and result in necrosis. The extract of Azadirachta indica (neem) and Calendula officinalis (marigold) has been shown to possess an antimicrobial activity that is broad spectrum against Gram-positive and Gram-negative bacteria. Neem has such bioactive compounds as azadirachtin and nimbidin which interfere with the cell wall of the bacteria whereas calendula has flavonoid and terpenoid compounds that prevent the growth of microorganisms. The properties are useful in keeping the location of the wound sterile and lower the chances of secondary infections[25].

These herbs help in the enhancement of healing effects on top of direct antimicrobial effect, via anti-biofilm and immune-modulating effects. As an example, neem extracts have been reported to inhibit biofilm formation by pathogenic bacteria, a critical determinant in the case of non-healing wounds. Calendula promotes immunity in the area and decreases bacterial load hence stimulating the healing process. Both plants reduce the time of wound closing as well as enhance the

histological recovery by reducing the complications of infections, which would guarantee more effective regeneration with less scarring[26].

3.4 Angiogenesis and Granulation Tissue Formation

Angiogenesis or development of new blood vessels is necessary to provide the supply of oxygen and nutrition to the regenerating tissue. An Aloe vera and Ficus benghalensis (banyan tree) herbal extracts have been demonstrated to have great angiogenic ability in promoting fibroblast proliferation and increased vascular endothelial growth factor (VEGF). Aloe vera gel is most useful in endothelial cell migration and neovascularization that guarantees the improvement of perfusion of the wound area. Increased blood circulation does not only increase the speed of the healing of tissues, but also boosts the immune system against infection[27].

Another important wound healing step is granulation tissue formation because it forms the basis of cell migration of epithelial cells and collagen deposition. The extracts of both Aloe vera and Ficus benghalensis stimulate a vigorous granulation tissue through elevated fibroblast densities, collagen mesh-work arrangement, and vascular structure formation. According to studies conducted on animal wound models, it has been demonstrated that wounds that are treated with these herbal extracts have earlier and mature granulation tissue in comparison to controls. This will lead to quicker wound healing, lessening of the scar and better functionality recovery of the skin[28].

4. MECHANISMS OF ACTION OF HERBAL DRUGS IN WOUND HEALING

The wide variety of phytoconstituents present in herbal drugs, such as flavonoids, tannins, alkaloid, glycosides, terpenoid, etc., are largely attributed to the wound-healing potential. The bioactive molecules have synergistic effects and have the ability to regulate various steps of the healing cascade, including the control of inflammation and tissue remodelling. Indicatively, flavonoids and polyphenols are strong antioxidants that destroy reactive oxygen species (ROS), hence safeguarding fibroblasts, keratinocytes, and endothelial cells against oxidative damage[29]. This type of antioxidant protection plays a significant role in inhibiting chronic inflammation and facilitating a switch to the proliferative stage. Rodent model research has shown lower lipid peroxidation levels, increased activity of antioxidant enzymes such as catalase and superoxide dismutases and reduced levels of oxidative stress indices, which promote rapid wound healing and production of a healthy granulation tissue[30].

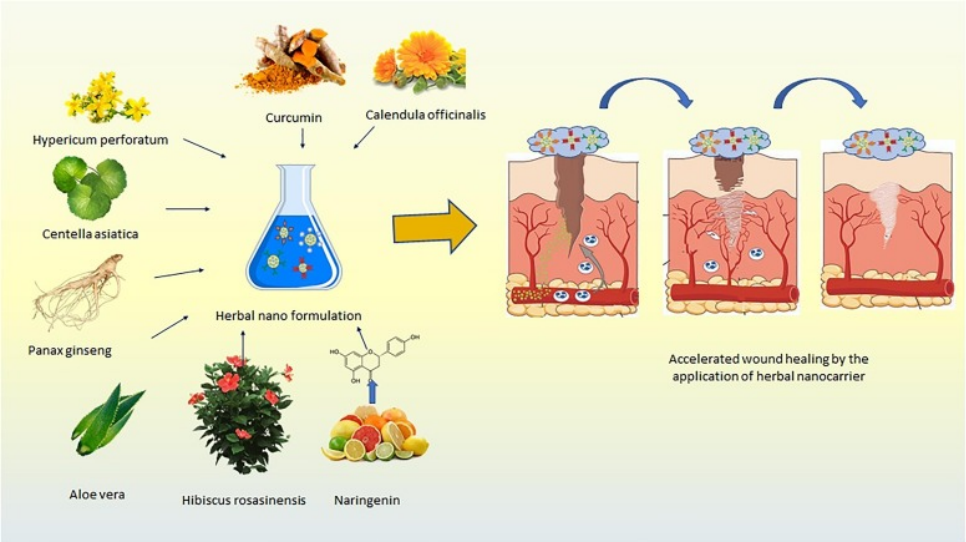

Figure 3: Herbal Nano-formulations and Their Role in Accelerated Wound Healing[31]

Other than in fighting oxidative damage, herbal agents would have a major part in regulating inflammatory reactions, which is usually of paramount importance in both acute and chronic wounds. Excessive release of pro-inflammatory cytokines like TNF- 2, IL-6 and IL-1 2 can slow healing by inhibiting fibroblast activity and increasing tissue damage. Herbal extracts like Ocimum sanctum (holy basil), and Lawsonia inermis (henna) have been demonstrated to inhibit NF- -signaling and release of these cytokines, thus reducing neutrophil infiltration and edema of wound sites. These herbs reduce the inflammatory phase and thereby provide a more balanced immune environment upon which fibroblasts and endothelial cells can proliferate well. At the same time, their phytochemicals improve the secretion of anti-inflammatory mediators such as IL-10 that helps in tissue recovery and reducing the risk of excessive scarring[32].

The herbal compounds play a significant role in the regenerative stage of wound healing by activating the growth of fibroblasts, collagen synthesis, antimicrobial response and angiogenesis. As an example, Centella asiatica can stimulate fibroblast growth and cross-linking of collagen that would result in greater extracellular matrix deposition and increased tensile strength of healed skin, whereas Aloe vera boosts the migration of epithelial cells and the formation of granulation tissue. Other antimicrobial herbs like Azadirachta indica (neem) also play a role by preventing colonization and biofilm formation by microbes hence keeping the environment sterile to allow healing. Moreover, angiogenic actions of Ficus benghalensis extracts are supported by increased vascular endothelial growth factor (VEGF) which has the effect of ensuring any given wound bed receives enough blood and nutrients. This combination of antioxidation, inflammatory, collagen remodeling, antimicrobial and angiogenic effects offers a multifactorial therapeutic approach that makes herbal drugs particularly effective in hastening wound recovery without harm to the tissue quality and functionality[33].

5. DISCUSSION

The animal research indicates that herbal compounds facilitate wound healing by antioxidant, anti-inflammatory/antimicrobial and angiogenic effect. Curcuma longa, Ocimum sanctum and Centella asiatica are herbs that synergistically control oxidative stress, inflammation, collagen synthesis and tissue regeneration[34]. Though these results have shown the potential of herbal treatment, more clinical trials, standardization of preparations, and molecular studies are required to confirm their effectiveness and optimal application in a human being.

5.1 Interpretation and Analysis of Findings

The evidence gathered in animal research shows that the herbal drugs have numerous mechanisms that play an important role in healing wounds. Phytogenic compounds (flavonoids, terpenoids, tannins, and glycosides) have synergies, which control the oxidative stress, inflammation, deposition of collagen, and angiogenesis. The antioxidant and anti-inflammatory effects of such herbs as Curcuma longa and Ocimum sanctum decrease the reactive oxygen species (ROS) and regulate the pro-inflammatory cytokines, which shortens the inflammatory response and provides a good condition to repair damaged tissues[35]. At the same time, Centella asiatica and Lawsonia inermis increase collagen synthesis and matrix remodeling, which strengthen the tensile strength and wound integrity.

Antimicrobial plants, such as Azadirachta indica and Calendula officinalis, cause a decrease in the microbial burden and inhibition of infection, whereas angiogenic plants, such as Aloe vera and Ficus benghalensis, enhance the growth of fibroblasts and neovascularization leading to the formation of granulation tissue and accelerated epithelialization[36]. Together, these results imply that herbal therapy is a synergistic and holistic wound management intervention, combining several biological pathways, which are crucial in the regeneration of tissues.

5.2 Implications and Significance

The results of these studies have important implications to preclinical and translational studies. Plant-based drugs provide affordable, biocompatible substitutes to synthetic medicines, and the promise to deal with the issue of slow recovery, drug resistance, and unwanted side-effects[37]. This makes them very promising to develop the standardized formulations in modern wound care by virtue of their being multifunctional, oxidative stress, inflammatory, microbial infection, and tissue remodeling simultaneously. These results support the importance of traditional medicinal knowledge and the combination with the experimental research based on the evidence, and give the path to new effective, safe, and efficient therapeutic approaches[38].

5.3 Gaps and Future Research Directions

Even though the results are positive, there are a number of gaps. A majority of the evidence has been based on preclinical animal research, and there is little validation in humans. Extraction methods, dosages and formulations are very heterogenous and it is hard to find standard procedures[39]. Moreover, only a small number of studies give more detailed information on the molecular aspects of signaling (NF- -KB, TGF- -B, VEGF) in herbal-mediated wound healing. Future studies on herbs ought to be done through rigorous clinical trials to validate safety and efficacy in human subjects, standardization of herbal preparations and the study at the molecular level to provide clarification on the exact mechanisms of action. Moreover, the discussion of synergistic regimes of herbal compounds, as well as their combination with state-of-the-art drug delivery systems, can maximize the quality of treatment and improve the transfer of preclinical results into the clinical practice[40].

6. CONCLUSION

The potential of herbal drugs in wound healing is quite high owing to their multifactorial and synergistical biological functions such as antioxidant, anti-inflammatory, antimicrobial, collagen enhancing and angiogenic. The preclinical animal studies have given strong evidence in support of the effect of extracts of plants like Curcuma longa, Ocimum sanctum, Centella asiatica, Azadirachta indica and Aloe vera in expediting wound healing process, increase tensile strength, granulation tissue quality, proliferate fibroblasts and overall tissue regeneration. All of these multifaceted effects provide a favorable microenvironment in which herbal interventions can be effectively applied to reduce the risk of infection and oxidative damage, and facilitate the efficient repair, making herbal interventions cost-effective, biocompatible, and culturally acceptable options or supplements to conventional synthetic drugs. Regardless of these encouraging results, there are still issues of standardization of extraction procedures, dosages and formulations and little clinical validation has been done in humans. These well-planned clinical trials, molecular level research studies, and designing better delivery systems will be essential in the future to transfer the preclinical results into safe, effective and standardized therapeutic uses in the contemporary wound management.

CONFLICT OF INTEREST

The authors have no conflicts of interest regarding this investigation**.**

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