



Received on 18 September 2020; received in revised form, 24 January 2021; accepted, 29 January 2021; published 31 January 2021

## THERAPEUTIC POTENTIAL OF NOVEL PHYTO-MEDICINE FROM NATURAL ORIGIN FOR ACCELERATED WOUND HEALING

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### Keywords:

Wound healing, *Centella asiatica*,  
*Anana scomosus*, *Aloe vera*, Comfrey,  
Ocimum

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**ABSTRACT:** Nature has always provided a remedy for most ailments that man has ever faced; wounds are no such exception. The wound healing process is complex and consists of overlapping phases, mainly haemostasis, inflammation, proliferation, and remodeling. There is the interplay of various sub-stages, mediators, biomarkers, enzymes, growth factors to form a complex system. Several other conditions like oxygen/blood supply, nutrition, diabetes, infections, aging, obesity, and other diseases make this more perplexing. On this background, faster and better healing of the wound is of paramount importance. Humans have employed different phytomedicines for accelerating the healing of wounds. These phytomedicines are traditionally used natural actives employed in the treatment of wounds as a modality to accelerate wound healing. This article delineates the basics of the wound healing process along with the therapeutic potential of some phytomedicines.

**INTRODUCTION:** The healing of wounds is a complex and dynamic process that is still being studied and not yet completely understood<sup>1</sup>. The wounds and ulcerations are known to deeply affect the quality of life of the patients suffering from them and, in most common cases, amount up to an annual cost of \$25 treatment<sup>2</sup>. Plants having therapeutic properties of medicinal plants have been used across the globe for ages as a traditional treatment method for numerous diseases. For instance, there were about 65 herbs included in traditional Persian medicine, which is a holistic system of medicine, which provided valuable insights on the natural remedies<sup>3</sup>.

Nearly 80% of the population residing in developed countries, including economic leaders like India and China, still employ traditional medicine as the treatment for a wide spectrum of diseases<sup>4</sup>. The natural products derived from these medicinal plants have been proven to be an abundant source of bioactive compounds, of which many have been employed to start the development of new chemicals for the pharmaceutical company<sup>5</sup>.

**The Continuum of the Skin:** The human skin is composed of three distinct layers, namely, the epidermis, dermis, and hypodermis, with a varying level of adeptness within each layer. The epidermis and dermis are well characterized, but not much attention and research have been dedicated to the hypodermis and retinacula of the dermal tissues<sup>6</sup>. The basement membrane is a complex assembly, primarily comprising of Type-IV collagen, laminin, nidogen/entactin, and heparin Sulphate proteoglycans.



Additionally, other proteins, particularly the Anchoring fibril collagen type-VII, help attach the reticular lamina to the basal lamina in the basement membrane, which further promotes epidermis to dermal adhesion<sup>7</sup>. The comprehensive proteomic analysis of the micro-dissected skin has discovered that there exist nearly 155 different proteins in the leg dermal samples in contrast to the 174 different proteins found in the breast tissue, and these proteins in collaboration with the collagen (I, II, III, VI, XII, and XIV), and extracellular matrix proteins (major ones include elastin, mimecan, prolargin, decorin, lumican, and periostin), cellular proteins (actin, myosin, vimentin, laminin, tubulin, desmoplakin, annexins, histones, and 14-3-3 protein) and keratins [Includes both (Type-I cytoskeletal 9, 10, 13, 14, 15 and 16) and (Type-II cytoskeletal 1, 2, 5 and 75)]<sup>8</sup>.

In the forthcoming years, these targets can provide valuable leads and boost research in the area of wound healing.

**The Epidermis:** Although the skin as a whole actively participates in the host defense mechanisms, the epidermis is always regarded as more important in preventing and minimizing the loss of water and other components of the body into the external environment (inside-outside barrier) with a combined effect of protecting the body from a variety of environmental stresses (outside-inside barrier)<sup>9</sup>.

The *raison d'être* of the epidermal layer spans from limiting passive water loss from the body, reducing the absorption of chemicals and radiations from the immediate environment to the prevention of microbial infections. These defensive functions reside primarily in the top stratum of the epidermis, referred to as the stratum corneum (SC), at which they are integrated with the formation of the stratum corneum and its homeostasis. Thus the proper growth, development, and maintenance of homeostasis are linked to the ability of the body or the individual to defend against both chemical and microbiologic attacks as well as dehydration<sup>10</sup>. The epidermis is further composed of numerous layers or strata, initiating from the basal layer (basement membrane or stratum basales) just positioned above the dermis proceeding upward layer by layer passing through the prickly layer (stratum

spinosum) and the granular layer (stratum granulosum) and clear layer (stratum lucidum) to the uppermost layer the horny layer (stratum corneum)<sup>11</sup>. The physical barrier is mainly formed and defined by the integrity of the stratum corneum, although the cellular junctions and cellular proteins and formed cytoskeleton in the subsequent layers may provide further protection and serve the purpose<sup>12</sup>. The biochemical basis of the latter consists of a complex integration of numerous lipids, acids, peptides (antimicrobial and structural), and hydrolytic enzymes. The immunologic barrier is formed by an immense repertoire composed of both the humoral and cellular constituents (tissue-resident sentinel cells) of the immune system<sup>13</sup>.

**Dermis:** The dermis is a heterogeneous layer that is composed of collagen and elastic fiber and is innervated by a rich vascular network and sensory nerve endings for sensing a tactile response. It also houses numerous sweat glands and hair follicles characterized by specialized epithelial invaginations. The primary functions of the dermis comprise of sweating (eccrine sweat glands innervated by the cholinergic fibers of the sympathetic nervous system), thermal sweating (response to increases in body temperature), emotional sweating (response to pain or emotional stress), and initiation and conduction of a tactile response<sup>14</sup>. The mammalian dermis is akin to an archetypal mesenchymal tissue, comprising majorly of type-I and type-III collagen, but also contains several other subtypes of collagen, proteoglycans, and elastin which functions as a structural scaffold, and a basement membrane rich in type-IV collagen<sup>15</sup>.

The dermis is histologically bifurcated into a superficial layer, termed as the papillary dermis, which lies immediately at the end of the epidermis, and is known to be comprised of dense but poorly oriented bundles of collagen, which attributes to its structural support delivered to the overlying basement membrane. This layer lies over the reticular dermis, which has some intervening spaces between the directionally oriented and relatively thicker bundles of collagen fibers. The components of the Extracellular Cellular Matrix (ECM) on the ultrastructural level that differentiates between the papillary and reticular dermis. This has further led to many different studies regarding the composition

of the Extracellular Matrix (ECM) reflects the differences in the fibroblast identity in the tissue compartments<sup>16</sup>.

**The Hypodermis:** The innermost part of the human skin, the hypodermis is regarded as a subcutaneous fat compartment and thus functions as a natural mechanical shock absorber, and helps in thermoregulation by protecting the body against external heat and cold, and is active in general energy metabolism and storage. It mainly consists of loose connective tissue, which regarding the site, differentiates into gliding layers or large adipose pockets, despite performing the same function. The tissue is particularly abundant in the content of proteoglycans and glycosaminoglycans, which helps in attracting fluid in the tissue, giving the tissue its characteristic mucous-like property<sup>17</sup>. The majority of the cells that are conspicuous in the hypodermis include fibroblasts, adipocytes, and macrophages, which have a niche role in adipocyte homeostasis, fat tissue remodeling, and in certain cases, even stimulate thermogenesis of fat in response to cold exposure or exercise<sup>18</sup>. This study and the thorough study of these layers of the skin are of paramount importance to unravel the mechanisms involved in increasing the drug transport across the skin and the effect of vesicles on the drug permeation rate, the permeation pathway, and the ultrastructure of the skin perturbations are to be thoroughly analyzed<sup>19</sup>.

**Physiology of Wound Healing:** On the occurrence of a skin-deep or superficial injury, an innumerable cascade of systems are activated to primarily exterminate the foreign materials, essentially as the primary protective function of the skin membrane has been compromised, and to reinstate the normal functioning of the cutaneous membrane. It is also evident only to a finite degree, as the wound will never reach the maximum tensile impregnability as that of the unwounded one, and at best, would only make up to near 70% of the latter<sup>20</sup>.

**Inflammation Phase of Wound Healing:** The process of repair and regeneration begins instantly after the injury and is facilitated by the release of a multitude of Growth Factors, Cytokines, and certain other Low-Molecular-Weight compounds from the serum of the affected blood vessels and degranulating platelets. The consecutive derange-

ment of blood vessels also paves the way for the formation of blood thrombus explicably comprising cross-linked fibrin protein and proteins of the extracellular matrix such as Fibronectin, Vitronectin, Hyaluronan, and Thrombospondin<sup>21</sup>.

However, in cases excluding the hemorrhage, the platelets are impotent to wound healing, so innumerable vasoactive mediators and chemotactic factors are procreated by the coagulation and by the injured parenchymal cells, which facilitate the inflammatory leucocytes to the site of injury<sup>22</sup>.

Also, during this phase of hemostasis, the neutrophils and the macrophages traverse to the injured tissue and generate chemical inflammatory mediators, such as Interleukin-4 and Transforming Growth Factor  $\beta$  (TGF- $\beta$ ). Moreover, the ecstatic levels of the Reactive Oxygen Species within the blood components, specifically within the neutrophils and the macrophages, set to initiate the extrinsic coagulation pathway by invoking the platelets to release coagulation factors which fundamentally construct the hemostatic fibrin clots, which serve as supporting framework or scaffold for the migration of cells into the wounds, thus acting as a temporary reservoir of the cells during wound healing. The inflammatory sequence is marked by termination induced by chemotactic signals including lipoxins and TGF- $\beta$ <sup>23</sup>.

**Proliferation Phase of Wound Healing:** The proliferative phase is marked by the primordial stages of cutaneous wound repair, where the new stroma is alternatively addressed as the granulation tissue, concerning the granular appearance of the budding tissue when examined microscopically, begins to develop approximately 4-5 days after the injury. This tissue is endowed by the infiltration of the numerous new capillaries alongside its granular appearance. The macrophages still provide a perpetual source of cytokines, which are considered pivotal for the stimulation of fibroplasia and angiogenesis<sup>24</sup>.

This and certain other cellular processes of the blood stimulate the traversing of endothelial cells into the injury *via* the production of Vascular Endothelial Growth Factor (VEGF) and certain other factors, resulting in profound angiogenesis, which facilitates the hypervascular character of the

newly formed granulation tissue. The profound re-epithelialization is also marked during this stage, which primarily involves the migration, proliferation, and differentiation of keratinocytes which are acquired from both the injured site and the stem cell populations found in the hair follicular region <sup>25</sup>.

**Remodeling Phase of Wound Healing:** This is the final and the most prolonged stage of wound healing that is characterized by the decrease in the fibroblast content with a simultaneous deposition of collagen, and may usually span anywhere between 3 weeks to 2 years, depending upon a plethora of factors which are known to have a pronounced effect on the healing process. The intact skin comprises both type-I and type-III collagen, in contrast to the granulation tissue, which shows a more type-III collagen content, which is more unorganized and haphazard in its arrangement <sup>26</sup>.

This phase shows a steady transition in the conversion of the skin from type-III to a more of

type-I collagen content, with the subsequent disposition of the cells from the primitive stages.

This collagen remodeling entails Matrix Metallo-Proteinases (MMPs) and altered collagen synthesis to yield a scar. The tensile strength of the injured tissue increases, thereby regaining about 40% of its original strength by 1 month and approximates to 70% of the latter by the conclusion of 1 year <sup>27</sup>.

Notable chronic wounds are a matter of grave concern, primarily for patients ailing with co-morbidities like diabetes mellitus, as most of the wound infections affect the foot wound and especially in neuropathic ulceration. The associated risk factor predominantly stated as for a duration of 1 month and a history of recurrent foot ulcerations, causing it to be the most renowned cause of lower extremity amputation, hence comprising a conspicuous load on both the physicians and the patients <sup>28</sup>.

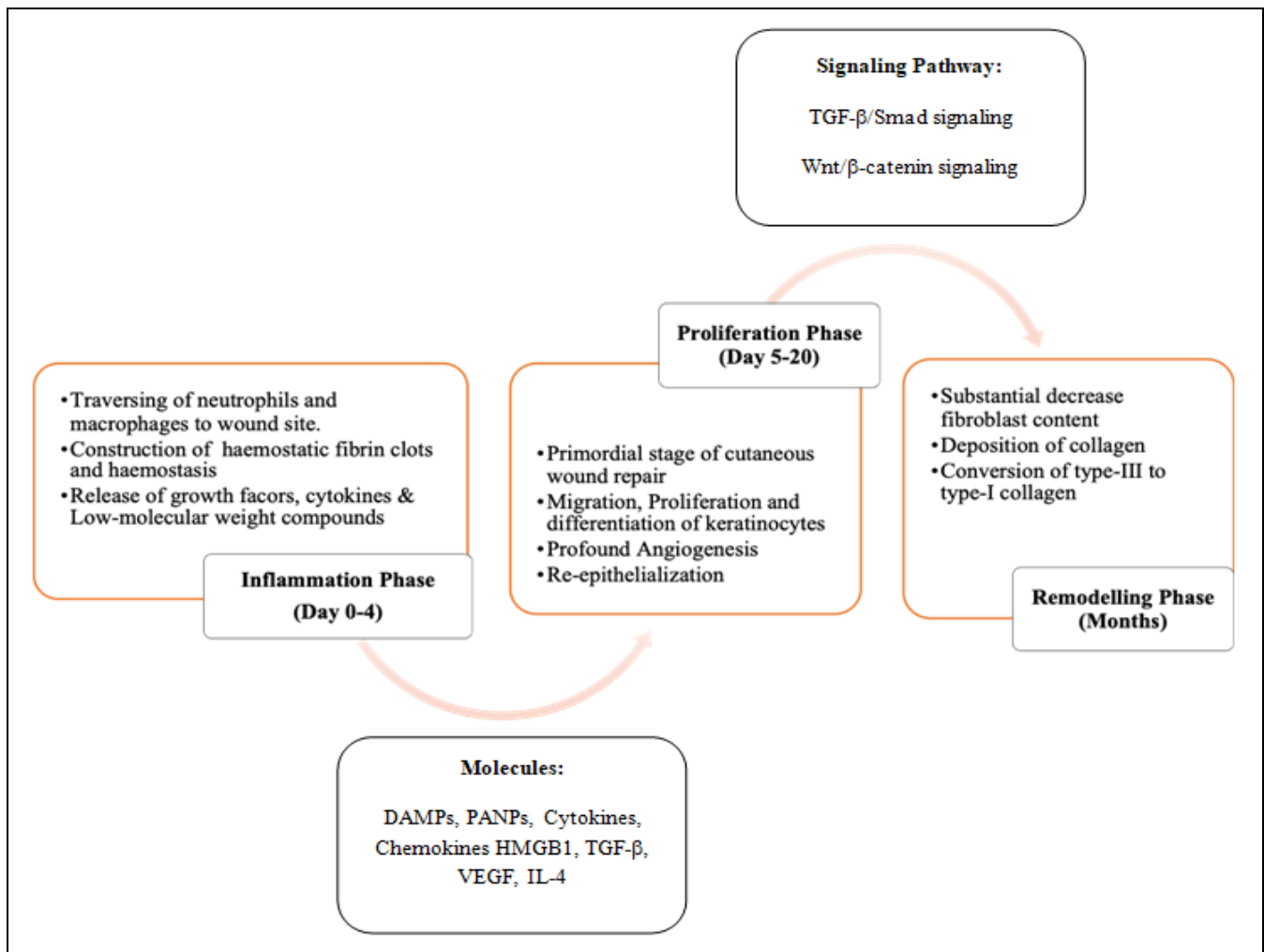


FIG. 1: PHYSIOLOGY OF WOUND HEALING ALONG WITH EMERGING TARGETS

**Natural Actives in Wound Healing:** Nature has been a consistent source for a multitude of medicinal treatment regimens, and plant-based systems continue to play a key role in primary health care around the globe, with many natural and nature-derived constituents being used in skin and wound care primarily due to their proven anti-inflammatory, anti-microbial and cell-proliferative properties<sup>29</sup>. During the last two decades, there has been a phenomenal increase in the number of the plants that have been assessed for phytoconstituents and plant extracts that promote or modulate healing effects; the majority of them were assessed for anti-microbial, anti-oxidant, and angiogenic properties<sup>30</sup>. Some of the most widely accepted and studied plants for their active-constituents and active Phytoextracts are enlisted below:

***Centella asiatica*:** The *Centella asiatica*, popularly known as the Indian Pennywort or Asiatic Pennywort, has been used for ages as a traditional herbal medicine in a multitude of the Asiatic countries in the Asian sub-continent, as a use in the wound healing process, and it has recently gained a lot of popularity in the western countries<sup>31</sup>. The plant species are known to find their presence in most tropical and subtropical countries, pertaining to their conducive growth conditions, including the swampy areas. These parts include most regions, including most areas in India, Pakistan, Madagascar, Sri-Lanka and South Africa, and South Pacific and Eastern parts of Europe, to name a few<sup>32</sup>. *Centella asiatica* belongs to the family apiaceae, but the different parts of the plant, where the whole plant extract is used in the assessment methods with animal wound models are applicable in the excision models in the normal as well as the Sprague-Dawley rats, in contrast to where the excision, incision and dead space in Wistar Albino rats are used as the experimental animals in the assessment of the aerial parts of the latter<sup>30</sup>. The efficacy of the *Centella asiatica* in their promotion of the wound healing process was extensively researched both *in-vitro* and *in-vivo* and was found to promote incision type wounds and open wounds as represented by a greater collagen content and thickness of the epithelium<sup>33</sup>.

A comparison of figures measured after both oral and subcutaneous modalities of administration of the madecassoside, asiaticoside, asiatica acid, and

madecassic acid in the experimental studies on rats revealed a varying bioavailability varies between 30% and 50%<sup>34</sup>.

The pharmacodynamic effects of the *Centella asiatica* species have been investigated and, in particular, a wound-healing, ulcer-protective, psychoneurotic-pharmacological, antimicrobial, and as an antiviral effect of the *Centella* or asiaticoside extract<sup>35</sup>.

In a multitude of experiments, including the *in vivo* studies on the human fibroblasts, the clinical and mechanical studies have been merged with their chemical and biochemical aspects, where the topical preparations of the *Centella* extracts are known to be associated with accelerated wound healing, especially in the abnormal conditions of the skin associated with a reduction of granuloma weight, and an increase in the force needed to produce rupture (Rupture-strength) of the wound tissue<sup>36</sup>. Furthermore, advanced research has proven that a dose-dependent increase in the synthesis of collagen, intracellular fibronectin content, and combined with the increase in mitotic activity of the germ layer and the enlargement of the kerato-hyaline granules within the scarred tissue<sup>37</sup>.

The active constituent named asiaticoside is known to enhance the induction of antioxidant enzymes at an early wound healing phase<sup>38</sup>, with an independent increment in hydroxyproline, tensile strength, and total content of the collagen, which leads to better epithelialization<sup>39</sup>. The treatment modality formed from the extract was marked by the profound increment of the cellular proliferation and subsequent synthesis of collagen at the wound area and was proved experimentally by the increase in the total content of DNA, proteins, and collagen content of the granulation tissues, which resulted from an increase in the faster epithelialization with a faster wound contraction rate<sup>40</sup>. But, the oil-water partition coefficient of the asiaticoside and the marked low solubility of the latter is known to limit its applicability and reduced effect and bioavailability<sup>41</sup>, as the asiaticoside is defined as a sparingly ionized pentacyclitriterpene with a notable molecular weight of 959.12 g/mol, which attributes to its lower aqueous solubility<sup>42</sup>. A recent induction of the porous microsphere was

established as a novel carrier for the sustained released delivery of the poorly soluble asiaticoside, with enhanced absorption and therapeutic efficacy, and is believed to be a promising topical preparation with excellent regenerative effects on the wounds, helping to shape the future of the wound therapy management<sup>43</sup>.

**Anana scomusus:** Pineapple has been a part of traditional folk medicine for ages and continues to be present in many herbal preparations<sup>44</sup>. Bromelain has been known as a chemical since 1875, and since then has been applied as a phytotherapeutic medical agent<sup>45</sup>. The term bromelain was initially used as a substitution to describe a mixture of proteolytic enzymes and other non-enzymatic substances found in the Bromeliaceae species, particularly in pineapple (*Anana scomusus* L.) and its various other parts like the stem, fruits, and leaves<sup>46</sup>.

Bromelain is a crude extract obtained from the pineapples which contain many natural active components, of which the most conspicuous are a group of numerous closely related proteinases, which both *in-vitro* and *in-vivo* portray profound anti-edematous, anti-inflammatory, anti-thrombotic and fibrinolytic effects. Bromelain has gained a lot of acceptance and compliance as a phytotherapeutic drug due to its safety and absence of the undesired side effects or adverse reactions even after oral administration, without any loss of efficacy<sup>47</sup>. Recent studies and clinical trials have demonstrated the numerous positive outcomes of Bromelain for the prevention of post-operative and post-procedure ecchymosis and edema<sup>48</sup>. Although it has been used as the therapy for many problems and has a multitude of pharmacological effects, the mechanism of its action remains unclear and uncomprehensive. However, many clinical trials have shown its efficacy in the therapy as a treatment regimen in the treatment of some disorders like chronic inflammation and autoimmune disorders, including osteoarthritis and rheumatoid arthritis<sup>49</sup>. *In-vitro*, it has portrayed its ability to help in the modulation of the immune response in allergic conditions and modulating macrophages, Natural-Killer (NK) Cells, and T-cells. Furthermore, it has also been known to increase the secretions of IL-1 $\beta$ , IL-6, and TNF- $\alpha$ <sup>50</sup>.

Mainly because of the aforementioned reasons, this is one of the few natural actives that has been approved in Europe for both its topical application and oral administration, particularly for surgical wounds, inflammation due to trauma, surgery, and even the debridement of deep burns<sup>51</sup>. There are new researches produced in the last decade which demonstrate the acceleration of healing of the burn wounds, primarily due to the influence of Bromelain<sup>52</sup> primarily due to its antimicrobial and antioxidant properties<sup>53</sup>.

**Aloe vera:** *Aloe vera* is a tropical herb that is cultivated in hot and dry climates and is distributed in the arid and semi-arid regions of Asia, Africa, and other few tropical zones<sup>54</sup>. *Aloe vera* is a plant that belongs to the Liliaceae family that characteristically grows in hot and arid conditions. The mucilaginous tissue that exists at the center of the leaves in this plant, which is usually deemed as the aloe-gel, is used for numerous cosmetic and medicinal applications<sup>55</sup>.

*Aloe vera* or yellow aloe as it is known, is a herbaceous and perennial plant with thick, succulent, and long leaves. The thistle is also formed, which is a little curl in the margin of its leaves. *Aloe vera* is endemic to the African regions, and it is also called Desert Lily (*Hesperocallis*)<sup>56</sup>. The oldest usage of the *Aloe vera* plant as a treatment regimen for wound burnings and infections dates back to the Egyptians. It spread far and wide and was later adopted by the Greeks, Spanish and African populations, to name a few, to treat many more such diseases<sup>57</sup>. It has been duly classified as a characteristic hot and dry humor in the classical medicine system of Iran, and its extract is used for medicinal purposes<sup>58</sup>. *Aloe vera* is highly therapeutic, accounting for the presence of 75 potentially active constituents, including vitamins, enzymes, minerals, sugars, lignin, amino acids, saponin, and salicylic acid and their derivatives<sup>59</sup>. It also exerts exemplary pain and inflammation relief properties due to its inherent prostaglandin and bradykinin-hydrolyzing enzymes, carboxypeptidase, and bradykinesia<sup>60</sup>. It is also abundant in the polysaccharide, named Mannose-6-phosphate, which supports the re-epithelialization process and plays a key role in tissue reorganization, induces the proliferation of fibroblasts, and activates the collagen deposition,

and accelerates the overall process of wound healing<sup>61</sup>. Another potent polysaccharide, Acemannan, is known for its white-blood-cell activation property, which is of great importance in the wound healing process<sup>62</sup>. The multitude of anthraquinones and certain other closely related compounds have profound antibacterial activity<sup>63</sup>. Only minimally adverse reactions, like mild pain or a sense of discomfort without any statistical significance, were attributed to the use of Aloe vera both orally and topically<sup>64</sup>. Additionally, nearly all of them associated with them were reversible in nature, and *Aloe vera* is generally very well tolerated<sup>65</sup>.

**Comfrey:** The roots of the Comfrey (*Symphytum officinale* L.) plant have been native to the European traditional medicine regimen but have also extrapolated to some parts of Asia and South America. In the traditional medicine system, comfrey roots are used topically, particularly for wound treatment, joint disorders, and injuries pertaining to the musculoskeletal system, especially caused due to pyrrolizidine alkaloids that have been linked to liver toxicity (hepatotoxicity) and cancer-formation (carcinogenicity)<sup>66</sup>. Several cellular mechanisms have been put forth to explain their mechanism of action, particularly the ones that target different intracellular signaling pathways triggered by NF- $\kappa$ B, AP-1, PPAR, Nrf2, and MAPKs<sup>67</sup>. The active constituents have portrayed the key role in comfrey root, which primarily include allantoin, mucilaginous polysaccharides, phenolic compounds such as rosmarinic acid, chlorogenic acid, caffeic acid, and their derivatives and salts, glycopeptides, and triterpenesaponins<sup>68</sup>. Comfrey also encompasses pyrrolizidine alkaloids namely, 7-acetylintermedine, 7-acetyllycopsamine, intermidine, lycopsamine, and symphytine which are usually attributed to their inherent hepatotoxic nature, and therefore newer medicinal products use pyrrolizidine alkaloid-depleted or absent extracts as active agents<sup>69</sup>.

The recent results were published to shed light on a comparative study between three topical formulations, namely, carbomer gel, glycerol-alcoholic solution, and an O/W emulsion (soft lotion), which led to significant experimental differences, particularly due to its intensity and rate. The results showed that the emulsion induced

the largest amount of re-epithelialization and had the furthest repair of damaged tissue. This could be evidenced by the collagen deposition increment from 40% to a humongous 240% from day 4 to 28, with a reduction in the cellular inflammatory infiltrate from 3% to 46%. Furthermore, an 8% emulsion of the prepared has presented the best efficacy<sup>70</sup>.

**Ocimum:** *Ocimum* is a well-known plant in Indian medicine and has been one of the first plants to be introduced into the treatment regimen in the traditional medicine system. It exhibits different therapeutic effects such as repair properties and cytokine induction<sup>71</sup>. The wound healing activity was assessed by the induction of the cold aqueous extract of *Ocimum sanctum* leaves along with its effect on the Tumour Necrosis Factor- $\alpha$  (TNF- $\alpha$ ) using the excision model of wound repair in Wistar Albino rats. After application of the 10% extract of *Ocimum sanctum* in the petroleum jelly proved to be successful with an increased rate of epithelialization and an increased wound contraction<sup>72</sup>. The extracts of *Ocimum sanctum* may also be efficacious in the treatment of the management of abnormal wound healing such as keloids and hypertrophic scars, owing to its high antioxidant activity<sup>73</sup>. Currently, topical formulations, prepared by the incorporation of optimized Silver-Nanoparticles (AgNPs) into the Carbopol gel base, followed by *in-vivo* evaluation using the rat model of skin wound healing, showed a 96.20% wound healing activity and the inhibitory efficiency of prepared nano gel was akin to the commercial product against the *Staphylococcus aureus*, *E. coli* and *Pseudomonas aeruginosa*<sup>74</sup>.

Furthermore, in several other studies, the extract-treated wounds were known to re-epithelialize faster, and the rate of wound contraction had significantly increased, followed by a notable increment in wet and dry granulation tissue weight, granulation tissue breaking strength, and hydroxyproline content in dead space wound model was seen. The extract is known to have greatly decreased the anti-healing activities of dexamethasone in all wound models<sup>75</sup>. The extract helps in the management of abnormal healing and hypertrophic scars as both the doses of alcoholic and aqueous extracts are known to significantly increase wound breaking strength, hydroxyproline,

hexuronic acid, hexosamines, superoxide dismutase, catalase, reduced glutathione with the significantly decreased percentage of wound contraction and lipid peroxidation<sup>76</sup>.

**TABLE 1: NATURAL ACTIVES EMPLOYED IN WOUND HEALING**

S. no.	Botanical Name	Common Name	Family	Mechanism
1	<i>Centella asiatica</i> L. <sup>71, 77, 78</sup>	Indian Pennywort or Asiatic pennywort	Apiaceae	Procollagen type-III synthesis
2	<i>Anana scomosus</i> L. <sup>79-81</sup>	Pineapple	Bromeliaceae	Inhibition of pro-inflammatory prostaglandin synthesis
3	<i>Aloe vera</i> L. <sup>59, 82-85</sup>	Indian Aloe, Chinese Aloe, Burn Aloe	Asphodelaceae	Indirect Collagen synthesis stimulation by stimulation of growth factor receptors on fibroblast
4	<i>Symphytum officinale</i> L. <sup>68, 70, 71, 86-88</sup>	Comfrey	Boraginaceae	NF-κB Pathway
5	<i>Ocimum sanctum</i> L. <sup>71-76, 89, 90</sup>	Holy Basil	Lamiaceae	Upregulation of TNF-α

**Advents and Clinical Trials of Natural Actives in Wound Healing:** The list of all the recent clinical trials on the novel therapies of wound healing is appended as follows with reference to

and was compiled as “Wound healing” and “extracts” on the official website “clinical trials.gov” and “Pub Med”.

**TABLE 2: RECENT ADVANCEMENTS IN NATURAL ACTIVES EMPLOYED IN WOUND HEALING**

S. no.	Name	Condition	Intervention	Status	Reference
1	Effectiveness and tolerability of Fitostimoline Plus Cream and Gauze vs. Connettivina Bio Plus Cream and Gauze	<ul style="list-style-type: none"> <li>Wound Heal</li> <li>Wound Infection</li> <li>Wounds and Injuries</li> </ul>	<ul style="list-style-type: none"> <li>Device: Fitostimoline Plus</li> </ul>	Recruiting	NCT04596124
2	Patch with Onion Extract and Allantoin for C-section Scar	<ul style="list-style-type: none"> <li>Cesarean Section;</li> <li>Dehiscence</li> <li>Scar Keloid</li> <li>Wound Heal</li> </ul>	<ul style="list-style-type: none"> <li>Device: Patch</li> </ul>	Completed	NCT04046783
3	Influencing Wound Healing Through the Application of Hyaluronic Acid with <i>Perfluoro decalin</i> and <i>Physalis angulata</i> extract after split skin removal from the thigh – A study in “Split Wound design”	<ul style="list-style-type: none"> <li>Wound Heal</li> </ul>	<ul style="list-style-type: none"> <li>Drug: Ready Medical post-treatment</li> <li>Device: Conventional Treatment</li> </ul>	Withdrawn	NCT03668665
4	Efficacy and Safety of <i>Gynostemma pentaphyllum</i> (Dungkulcha) Extract on Alleviation of Chronic Stress-Induced Strain	<ul style="list-style-type: none"> <li>Chronic Stress</li> <li>Induced Strain</li> </ul>	<ul style="list-style-type: none"> <li>Dietary Supplement: <i>Gynostemma pentaphyllum</i> (Dungkulcha) Extract (400mg/day)</li> <li>Dietary Supplement: Placebo</li> </ul>	Completed	NCT03277833
5	Effect of <i>Vitisvinifera</i> extract on oxidative stress, Inflammatory biomarkers, and Hormones in high Trained Subjects	<ul style="list-style-type: none"> <li>Athletic Injuries</li> </ul>	<ul style="list-style-type: none"> <li>Dietary Supplements: Grape fruits (<i>Vitis vinifera</i>) extract in a capsule with 205 mg</li> </ul>	Unknown (Study has passed its completion date and status has not been verified in more than two years)	NCT01875497
6	Efficacy of RPh201 applied topically for the treatment of hard to heal chronic ulcerated wounds	<ul style="list-style-type: none"> <li>Chronic Wounds</li> </ul>	<ul style="list-style-type: none"> <li>Drug: RPh201, Botanical drug product</li> </ul>	Terminated	NCT01429519
7	Effect of Cranberry Extract on Infections in Burn Patients	<ul style="list-style-type: none"> <li>Burn</li> </ul>	<ul style="list-style-type: none"> <li>Dietary Supplement: Cranberry Extract</li> <li>Drug: Inert Placebo Capsule</li> </ul>	Withdrawn	NCT01225107

The last two decades have witnessed a sea of changes in the field of natural product research<sup>91</sup>.

As the research in the field of wound healing is under continuous update, there are new targets and



new treatment regimes as well. Many phyto-medicines are proving beneficial in wound healing<sup>92, 93</sup>. On this background, there is no wonder natural actives are preferred. Because of the immense therapeutic potential of natural actives, they are employed as a part of various treatment modalities through ages.

**CONCLUSION:** The process of wound healing, being complex in nature, necessitates the use of novel therapeutics approaches for faster and better healing. With mounting evidence, these phyto-medicines are being extensively studied for extracting actives and use them as prologues for the development of numerous chemical moieties of medicinal and therapeutic value. There are many such phytomedicines that have been extensively studied but only a few were selected and elucidated above as these are currently studied for future utilization in medicaments and formulations.

A tremendous effort has been put in to demonstrate the potential application and utility of the natural extracts and their isolated actives for developing formulations, which aims at their application in wound therapy and healing. In coming years, one can find the use of these phytomedicines in novel therapeutic forms for better wound healing.

**ACKNOWLEDGEMENT:** Authors are thankful to Bharati Vidyapeeth Deemed Universty, Poona College of Pharmacy, Pune.

**CONFLICTS OF INTEREST:** There are no Conflicts of Interest.

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**How to cite this article:**

Varghese R and Shinde V: Therapeutic potential of novel phyto-medicine from natural origin for accelerated wound healing. Int J Pharmacognosy 2021; 8(1): 14-24. doi link: [http://dx.doi.org/10.13040/IJPSR.0975-8232.IJP.8\(1\).14-24](http://dx.doi.org/10.13040/IJPSR.0975-8232.IJP.8(1).14-24).

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