

Aloe vera and wound healing: a brief review

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Aloe vera possesses a great therapeutic importance in traditional medicine. It has attracted the attention of modern medical fields due to its wide pharmacological applications. The bioactive substances in *Aloe vera* proved to have antioxidant, anti-inflammatory, antibacterial, and antiviral properties. Taken into our consideration the long history of clinical applications of *Aloe vera* in traditional medicine, especially for promoting the healing of cutaneous wounds with rare adverse effects, it provides a cheap alternative to many expensive synthetic drugs. Recent techniques in tissue engineering created novel scaffolds based on Aloe gel extracts for wound healing applications. Nonetheless, further guided research is required to foster the development of *Aloe vera* based scaffolds for the benefit of worldwide populations. Here, I systemically summarize the main events following wounding and the mechanism of action of *Aloe vera* in promoting the healing process. I hope to provide a solid piece of information that might be helpful for designing new research studies into this topic.

Keywords: Wound phases. *Aloe vera*. Wound healing. Mechanism of action. Bioactive substances.

INTRODUCTION

Mammalian skin serves as a protective physical barrier against mechanical and chemical injuries, as well as microbial invasion (Plotczyk, Higgins, 2019). The loss of skin integrity requires rapid and efficient amendments of the ruptured tissue to maintain body homeostasis, in a process known as wound healing (Rittié, 2016; Sorg *et al.*, 2017). The healing of a skin wound is a complicated and dynamic process necessitating integrative reactions of multiple structures, mediators, and cell lines (Rodrigues *et al.*, 2019). Wounds may result from several conditions including skin injuries, burns, accidents, surgery, arterial disease and trauma. They can be broadly categorized into acute and chronic wounds (Hughes *et al.*, 2017).

All wounds could be considered acute at the advent of injury, regardless of cause (Whitney, 2005). Wound

closure taking place in a predictable and acceptable amount of time characterizes acute wounds, and it restores the structural and functional integrity of the skin at a definite time. In contrary, chronic wounds occur when the healing trajectory is disrupted and doesn't follow an expected time course, hence the entire process is delayed (Galea, 2018). The main objective of wound treatment is to accelerate the closure rate of a wound as much as possible with minimal pain, anxiety and scarring. Thus, continuously exploring new innovative interventions will pave the way for a better quality of life for patients who suffer wounds. Moreover, it will lower the total cost of wound-related health maintenance (Teplicki *et al.*, 2018).

PHASES OF WOUND HEALING

The mechanism underlying the healing process involves cellular, subcellular, physiological, and biochemical events which act together to repair injuries (Velnar, Bailey, Smrkolj, 2009; Goldberg, Diegelmann 2017; Teplicki *et al.*, 2018). It involves three main

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intersecting phases: inflammatory, proliferative, and tissue remodeling (Gonzalez *et al.*, 2016; Han, Ceilley, 2017), (Figure 1). In normal conditions, these phases

aren't discrete. However, in cases of initiation due to physical injury, they must continue to the end in order for complete healing to be achieved (Richardson, 2004).

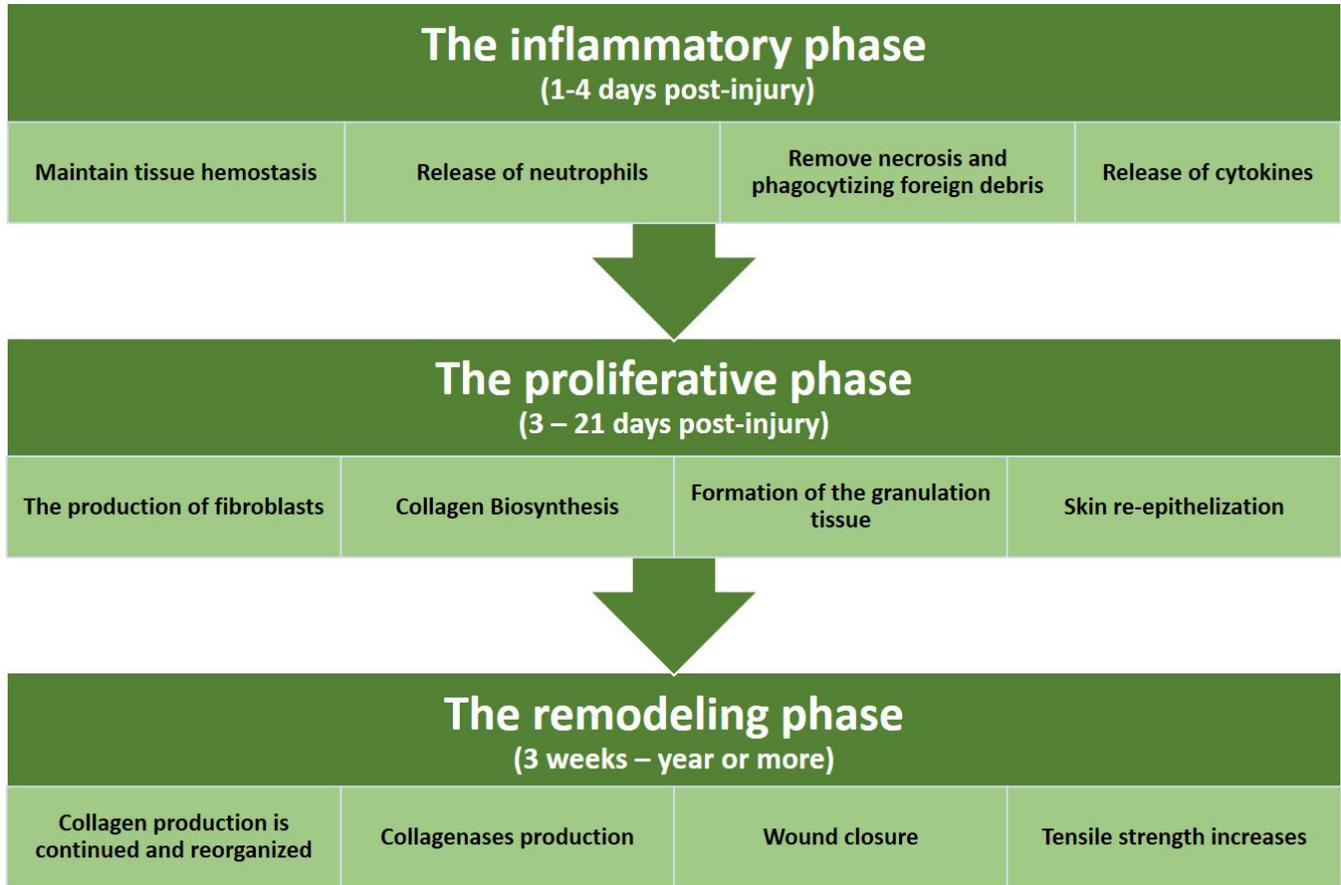


FIGURE 1 - Normal wound Phases and main events included.

The inflammatory phase

The inflammatory phase immediately follows the wounding incidence, and it takes approximately four days (Coger *et al.*, 2019). It mainly fulfills two main goals. The first is to maintain tissue hemostasis, which this could be achieved by contraction of the smooth muscle cells, closure of the ruptured large blood vessels, and accumulation of platelets to thrombose the smaller damaged vessels (Nurden, 2018). The second goal is to rid the wound of contaminants, bacteria and other unfavorable debris (Landén, Li, Ståhle, 2016). Instantly after wound incidence polymorphonuclear leukocytes (neutrophils) migrate from the adjoining microvasculature and act to accomplish this mission. Neutrophils seem to be short-lived cells and undergo apoptosis after a

few hours at the site of injuries. Nevertheless, some scientist assumed that neutrophil behavior is more sophisticated and that they may migrate back into the nearby vasculature (de Oliveira, Rosowski, Huttenlocher, 2016). Another type of cell called (macrophages), appears at the wounding site approximately two days post-injury (Hesketh *et al.*, 2017). These type of cells acts to remove necrotic tissue and phagocytizing bacteria and foreign debris (Goldberg, Diegelmann, 2017). Moreover, macrophages initiates two crucial events in the healing process; namely angiogenesis and fibroplasia (Gonzalez *et al.*, 2016). These events are mediated by cytokines released by the activated macrophages (Minutti *et al.*, 2017). Angiogenesis begins three days post-injury and is a prerequisite to provide the metabolic requirements of the

healing process, while collagen synthesis and fibroplasia occur by the third to the fifth-day post-wounding (Hanna, Giacomelli, 1997).

The proliferative phase

The proliferative phase may last as long as three weeks post-injury. The activated macrophages mediate the release of fibroblast stimulating factors and angiogenesis factors (AGF) (Delavary *et al.*, 2011; Landén, Li, Stähle, 2016). Fibroblast stimulating factors promote the proliferation of fibroblasts, which plays an essential role in the proliferative phase. In turn, the fibroblasts produce collagen and proteoglycans (Tracy, Minasian, Caterson, 2016). AGF promote the growth of the new blood vessels and capillary buds (Oike *et al.*, 2004). The neovasculature together with the collagen and proteoglycans constitute the granulation tissue which, fills the wounded defects (Teller, White, 2011). The synthesis of collagen increases wound tensile strength (Panchatcharam *et al.*, 2006; Darby *et al.*, 2014). The borders of the wound come closer to each other due to the contraction of the wound, decreasing the wounded area. This process is mediated by a distinct type of fibroblast that have a contractile nature known as myofibroblasts (Li, Wang, 2011). The proliferative phase also includes the re-epithelization process, in which the surrounding epithelial cells actively divide and migrate over the granulation tissue to link both edges of the wound (Rousselle, Braye, Dayan, 2019). The re-epithelization process is critical in wound closure as the newly generated epithelial tissue acts as a physical barrier blocking contaminant and microbial invasions from the external environment and precluding body fluid leaks. The wound closure rate is directly affected by wound size as larger defects require more time to close because migrating epithelial cells have to travel longer distances to link both edges (Taniguchi, Matsumoto-Oda, 2018). Moreover, the moist wound surface facilitates epithelial cell migration, while, dry surface inhibits epithelial cell migration (Hamman, 2008). Hence, the primary goal of new wound dressing compounds is to provide a humid microenvironment for the wound to facilitate re-epithelization (Chiaula *et al.*, 2019; Weller, Team, 2019).

The remodeling phase

The remodeling or maturation phase is the final step in the healing process. It begins approximately three weeks post-wounding and may last for more than one year (Gonzalez *et al.*, 2016). In this phase, the production of collagen by fibroblasts is continued. Collagenases are a group of enzymes secreted during this phase, which act to re-organize collagen bundles in a parallel arrangement, and lysis the collagen bundles produced during the proliferative phase (Qing, 2017). The closure of the wounded area and a gradual increase in tensile strength still progress in this phase. The ultimate strength of a healed wound depends on the quantity of collagen biosynthesis and the extent of crosslinking between neighboring collagen bundles. At the end of the maturation phase, the wound reaches maximal tensile strength, which is typically 80% of the strength of the original uninjured cutaneous tissue (Bowden *et al.*, 2016).

Generally, wounds heal in a timeframe of four to six weeks. However, chronic wounds fail to heal within this period. Several factors can impair the healing process including; diabetes, hypoxia, ischemia, bacterial infection, collagen synthesis defects, malnutrition, smoking, and dehydration (Wallace, Basehore, Zito, 2020).

***Aloe vera* history and its clinical relevance**

Aloe vera is a perennial succulent plant that belongs to the family Liliaceae. More than 400 species have been identified in this family (Sánchez-Machado *et al.*, 2017). This xerophytic herbaceous plant developed an ability to store water in the tissue of leaves, hence it is indigenous to arid subtropical and tropical regions. It has characteristic short stem, and fleshy leaves with lance shaped apex, tapered end, and serrate margin (Steenkamp, Stewart, 2007). Two main products are produced from these plants; the aloe gel and yellow latex (aloe juice). Aloe gel, is extracted from the core leaf pulp present in the innermost part and is composed of parenchymal cells which act to store water and other nutrients. The Aloe juice is a yellow and better latex, produced from the marginal cells of the leaves (Gupta,

Malhotra, 2012). Historically, several cultural traditions have considered *Aloe vera* a potent medicinal plant with therapeutic and cosmetic applications. The clinical applications of *Aloe vera* are wide and include: anti-inflammation, immunomodulatory, cardiovascular, and antibacterial (Maan *et al.*, 2018; Gao *et al.*, 2019; Kumar *et al.*, 2019). Furthermore, the healing properties of *Aloe vera* have been proposed for curing wounds since ancient times. The Pharaohs first used *Aloe vera* for wound remedy (Yohannes, 2018; Akbar, 2020). Other cultures worldwide followed them, such as Chinese, Greek, Spanish, Indian, and Iranian. *Aloe vera* is well-known for its magnificent healing properties, being called the silent healer or the healing plant (Singh *et al.*, 2018; Ibrahim *et al.*, 2019).
Clinical Uses and Toxicity of Aloe vera: An Evidence-Based Comprehensive Retrospective Review (2007-2017. Many studies demonstrated that the benefits of *Aloe vera* are always associated with high polysaccharide content (Minjares-Fuentes, Femenia, 2017; Chen *et al.*, 2019; Soares *et al.*, 2019). Recent studies showed that *Aloe vera* extract triggers the proliferation of several cell lines and accelerates the wound closure in both standard and diabetic rats (Atiba, Ueno, Uzuka, 2011; Galehdari *et al.*, 2016; Mohi-Eldin, Allaam, 2017; Gao *et al.* 2019; Abdel-Mohsen *et al.*, 2020).

Chemical composition of *Aloe vera*

Aloe vera is a succulent plant that can store a huge amount of water in its inner tissue, hence water contributes approximately 99 to 99.5% of its chemical constituents (Kumar *et al.*, 2019). The remaining part consists of a wide range of fat and water-soluble components including minerals, amino acids, enzymes, vitamins, polysaccharides, phenols, sterols and additional organic compounds (Boudreau, Beland, 2006; Hashemi, Madani, Abediankenari, 2015). Aloe gel is comprised of about 55% polysaccharides, 17% sugars, 16% minerals, 7% amino acids, 4% fatty acids, and 1% phenolic compounds. The major components of the yellow bitter latex are anthraquinones and glycosides (Rahman, Carter, Bhattarai, 2017). The chemical constituents of the *Aloe vera* plant vary according to the species, climatic conditions, and the growth environment (Klein, Penneys, 1988). It has been postulated that the heterogeneous composition of *Aloe vera* gel perhaps contributes to its therapeutic and pharmacological properties (Talmadge *et al.*, 2004; Hamman, 2008). More than 240 bioactive substances with medicinal and nutritional properties were identified in the *Aloe vera* leaves (Singh *et al.* 2019). The main chemical constituents and their recognized biological activities are listed in (Figure 2).

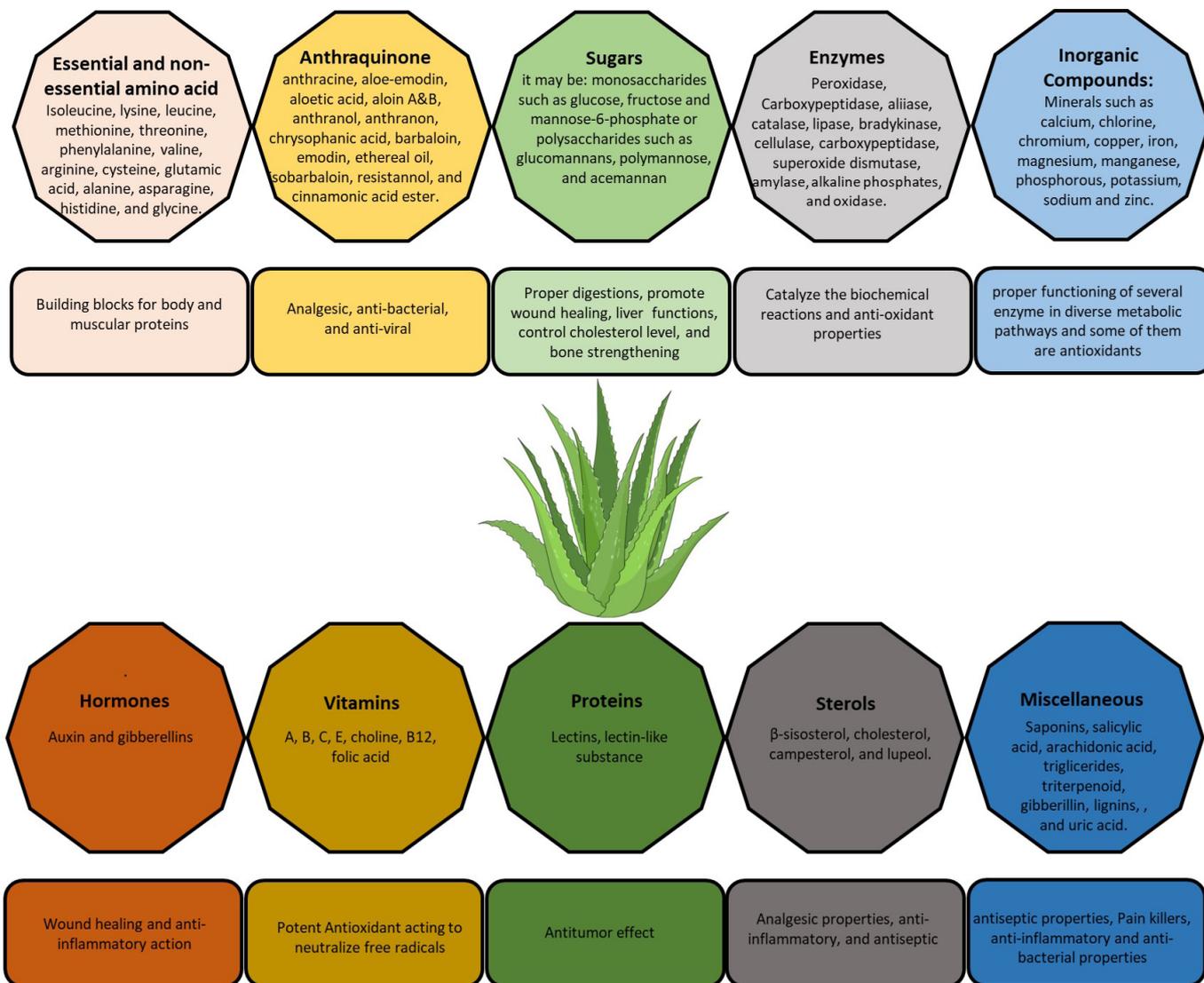


FIGURE 2 - Aloe vera bioactive ingredients and its biological activities.

Aloe vera and wound healing

In traditional medicine, *Aloe vera* had been considered a healing plant acting to accelerate the closure rate of a wound. The usage of *Aloe vera* as skin curative acts also to reduces the severity of mucocutaneous problems including gingivitis (Al-Maweri *et al.*, 2020) type:”article-journal”, volume:”18”, uris:”[“http://www.mendeley.com/documents/?uuid=2bb55554-8178-46c3-8824-5d81bd6d7402”]”, mendeley:”{“formattedCitation”:”(Al-Maweri et al. 2020, oral submucosa fibrosis (Al-Maweri *et al.*, 2019), vaginal atrophy in

menopausal women (Palacios, Mejía, Neyro, 2015), and mucosa damage induced by chemotherapy and radiotherapy (Sahebnaasagh *et al.*, 2017; Alkhouli, Laflouf, Alhaddad, 2021). The mechanism of action of *Aloe vera* on promote the wound healing has been extensively studied on experimental animals (Bunyapraphatsara *et al.*, 1996; Choi *et al.*, 2001; Choi, Chung, 2003; Mendonça *et al.*, 2009; Oryan *et al.*, 2016). Several hypotheses have been postulated for this crucial role in reducing pain, fighting inflammation, moisturizing the wound, quantitative and qualitative improvement in the collagen composition, and increasing the migration of the wound’s neighbouring epithelial cells (Gupta,

Malhotra, 2012), (Figure3). The key regulator of the action of *Aloe vera* in prompting healing is the existence of a mannose-rich polysaccharide; called glucomannan which acts together with gibberellin and growth hormone stimulating fibroblasts to actively proliferate. Upon triggering fibroblast activation and proliferation, the collagen biogenesis significantly increases both quantitatively and qualitatively (Surjushe, Vasani, Saple, 2008). The amount of collagen in the wounded area not only increases, but the transversal connections between bands also increase and other subtypes of collagen are created. Consequently, the wounded area decreases and the healing process accelerates significantly (Surjushe, Vasani, Saple, 2008; Hashemi, Madani, Abediankenari, 2015). Interestingly, (Teplicki *et al.*, 2018) reported that *Aloe vera* accelerates wound healing not only through promoting the active proliferation of fibroblasts and keratinocytes but also because it showed protective action for keratinocytes against preservative-induced death. Moreover, the biogenesis of hyaluronic acid and dermatan sulfate significantly increased in the granulation tissue after oral and topical therapy with *Aloe vera* (Mahor, Ali, 2016). The topical application of *Aloe vera* gel may also stimulate angiogenesis and increases the blood supply to the wound, thus better fulfilling its metabolic requirements (Sargowo, Handaya, Tjokroprawiro, 2012; Hamid, Soliman, 2015). The humectant action of mucopolysaccharides contained in *Aloe vera* gel contributes to the moisturizing of the skin (Dal'Belo, Gaspar, Maia Campos, 2006).

The anti-inflammatory and anesthetic action of *Aloe vera* may be attained by the inhibition of the cyclooxygenase pathway by decreasing prostaglandin E2. C-glycosyl chromone, a novel anti-inflammatory agent was isolated from the gel extract (Hutter *et al.*, 1996).

Moreover, hydrolyzing enzymes such as carboxypeptidase and bradykinase were isolated from Alo; both enzymes act as potent anti-inflammatory substances, by breaking down bradykinin which induces pain (Takzare *et al.*, 2009; Anuradha, Patil, Asha, 2017; Maan *et al.*, 2018). Recent studies in mice, showed that the anti-inflammatory properties of *Aloe vera* are related to its strong ability to inhibit cytokines, ROS production and blocking the signaling of JAK1-STAT1/3 (Sánchez *et al.* 2020). Additionally, rhein (0.3 μM), rhein sulfates/glucuronides (1.0 μM), and aloe-emodin sulfates/glucuronides (0.5 μM) suppressed nitric oxide production, iNOS expression, pro-inflammatory cytokines, and phosphorylation of MAPKs (Li *et al.*, 2017). Acemannan is an additional polysaccharide extracted from *Aloe vera* that act as a potent anti-inflammatory agent on the upregulation of white blood cell activity during the healing process (Tamura *et al.*, 2009; Liu *et al.*, 2019). (Thunyakitpibal *et al.*, 2017) demonstrated that acemannan improved IL-6 and IL-8 expression and NF- κ B/DNA binding in human gingival fibroblast through a toll-like receptor signaling pathway. Aloin also modulates oral inflammatory diseases through the inhibition of salivary IL-1 β -prompted IL-8 production by reducing p38 and extracellular signal-regulated kinase pathways (Na *et al.*, 2016). AVH200[®], is a standardized *Aloe vera* extract which contains mainly aloin and acemannan, and acts to reduce cytokine production and activation of T cells in healthy human individuals aged 18 – 60 years (Ahluwalia *et al.*, 2016).

Additionally, anthraquinone is another organic compound with natural pigments which is responsible for the characteristic color of *Aloe vera* leaves, and has been postulated to play an important role in minimizing bacterial infection and viral invasion (Kuzuya *et al.*, 2001; Tamura *et al.*, 2009).



FIGURE 3 - Action mechanism of *Aloe vera* in promoting wound healing.

Side effects

Due to its wonderful healing properties *Aloe vera* is widely considered as an efficient herbal medicine with therapeutic uses for both diabetic and normal wounds. *Aloe vera* is considered much more reliable and cost-effective in terms of the consistency and speed of wound healing when compared to the alternative therapies currently available.

No serious adverse reactions were demonstrated following topical application of *Aloe vera*. Nonetheless, recent studies reported that *Aloe vera* extracts may contain

toxic components and may cause some adverse impacts. The topical application of *Aloe vera* on cutaneous wounds may cause minimal transient pain, a stinging sensation, burning, redness and rare cases of dermatitis in sensitive persons. The allergic reactions mainly originate from anthraquinones. Hence, it would be advisable to smear it on a small area first to test the potential allergic reaction (Surjushe, Vasani, Saple, 2008; Mahor, Ali, 2016). On the other hand, oral ingestion of *Aloe* preparations may be associated with some problems such as hypokalemia, diarrhea, pseudomelanosis coli, nephrotoxicity, and hepatotoxicity, in addition to phototoxicity and

hypersensitive reactions (Guo, Mei, 2016). Moreover, whole leaf extract of *Aloe vera* induce carcinogenicity in rats, hence it was classified as a possible carcinogen for human by the international agency for research on cancer (Grosse *et al.*, 2013; Cancer, 2015).

CONCLUSION AND FUTURE PROSPECTIVES

In conclusion, *Aloe vera* derivatives have a long history of pharmaceutical applications. Moreover, the usage of *Aloe vera* as a skin curative is still growing. Recent techniques in tissue engineering created novel scaffolds based on *Aloe vera* gel extracts for wound healing applications (Gil-Cifuentes, Jiménez, Fontanilla, 2019; Rubio-Elizalde *et al.*, 2019). Incorporation of *Aloe vera* within natural and synthetic polymers built to mimic the original architecture of the human body may reduce their adverse effects (Tran, Hamid, Cheong, 2018; Ezhilarasu *et al.*, 2019; Ghorbani, Nezhad-Mokhtari, Ramazani, 2020). Hence, further guided studies are required to foster the development of *Aloe vera* based products for the benefits of worldwide populations.

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