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Aloe vera and the Proliferative Phase of Cutaneous Wound Healing: Status Quo Report on Active Principles, Mechanisms, and Applications

Authors
Zhuang Min Lee[1,2], Bey Hing Goh[2,3,4], Kooi Yeong Khaw[5]

Affiliations
1 School of Biomedical Sciences, University of Western Australia, Perth, Western Australia, Australia
2 Sunway Biofunctional Molecules Discovery Centre (SBMDC), School of Medical and Life Sciences, Subang Jaya, Malaysia
3 Biofunctional Molecule Exploratory (BMEX) Research Group, School of Pharmacy, Monash University Malaysia, Subang Jaya, Malaysia
4 Faculty of Health, Australian Research Centre in Complementary and Integrative Medicine, University of Technology Sydney, Ultimo, NSW, Australia
5 Biopharmaceutical Research Group, School of Pharmacy, Monash University Malaysia, Subang Jaya, Malaysia

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70469 Stuttgart, Germany

Correspondence
Bey Hing Goh, PhD
Sunway Bifunctional Molecules Discovery Centre (SBMDC), School of Medical and Life Sciences, Sunway University
No. 5, Jalan Universiti, Bandar Sunway, 47500 Subang Jaya, Selangor, Malaysia
Phone: + 6 03 74 91 86 22
beyhingg@sunway.edu.my

Correspondence
Kooi Yeong Khaw, PhD
School of Pharmacy, Monash University Malaysia
Jalan Lagoon Selatan, Bandar Sunway, 47500 Subang Jaya, Selangor, Malaysia
Phone: + 6 03 55 14 61 35
khaw.kooiyeong@monash.edu

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ABSTRACT

Aloe vera is commonly used as traditional medicine for cutaneous wound healing. Nonetheless, the wound healing mechanisms of *Aloe vera* remain unclear. This review aims to provide insight into the molecular mechanisms of *Aloe vera* in promoting cutaneous wound healing, with particular emphasis on the mechanisms that stimulate cell proliferation and migration. *Aloe vera* has been shown to upregulate growth factors such as keratinocyte growth factor-1 (KGF-1), transforming growth factor-β (TGF-β), cyclin D1, insulin-like growth factor 1 (IGF-1), vascular endothelial growth factor (VEGF), basic fibroblastic growth factor (bFGF), and microfibril-associated glycoprotein 4 (MFAP4), as well as collagen, fibrillin, elastin, α-smooth muscle actin (α-SMA), integrins, and platelet endothelial cell adhesion molecule 1 (PECAM-1, also known as CD31), while downregulating the expression of matrix metalloproteinases (MMPs). In addition, *Aloe vera* was also found to upregulate PI3K/Akt and MAPK pathways, as well as the TGF-β signalling pathway via Smad proteins. Furthermore, molecular docking studies revealed that certain chemical constituents of *Aloe vera* bind to some of the forementioned growth factors or signalling molecules. With regards to current applications, although human clinical trials have reported positive results from using *Aloe vera* in healing open wounds and burns and alleviating some inflammatory skin diseases, the current commercial uses of *Aloe vera* remain largely focused on cosmetic products. Thus, greater advances are required to promote the use of *Aloe vera* products in clinical settings.

Introduction

Aloe vera (L.) is a drought-resistant xerophyte (botanical name: *Aloe barbadensis* Miller, family: *Liliaceae*) that is found perennially in dry regions of Africa, Asia, Europe, and America [1–3]. The plant has been used as traditional medicine for long periods of time. For example, in ancient Egypt, *Aloe vera* was documented as a laxative in papyrus and the plant was also used for cosmetic purposes by the royalty. *Aloe vera* was also documented in Sumerian clay tablets [2], and in ancient Greece, the plant was used to

heal wounds of injured soldiers. In the early 1800 s, *Aloe vera* was used as a laxative in the United States and was later commercially sold as a wound healing agent during the 1950 s and 1960 s [2, 3]. Recent scientific studies have associated *Aloe vera* with various therapeutic effects including promoting wound healing, preventing peptic ulcers, and promoting laxation, as well as having antioxidant, antimicrobial, and antitumour properties [1, 4]. *Aloe vera* has low cellular toxicity and is relatively cheap and easy to extract; these advantages confer high practicality in its applications [1, 5, 6].

Wound healing is a complex multistep process that involves haemostasis, inflammation, cell proliferation, and remodelling [7]. In particular, during the cell proliferative phase, fibroblasts proliferate and differentiate into myofibroblasts that secrete the extracellular matrix (ECM). Keratinocytes also proliferate and migrate towards the centre of the wound by adhering to the ECM, resulting in re-epithelialisation. The combination of these two mechanisms promotes wound closure. At the same time, revascularisation occurs via endothelial cell proliferation and migration. Blood flow is essential for the transport of growth factors and leukocytes to the site of injury, as well as to facilitate removal of infective agents and necrotic debris.

Aloe vera has been well established as a promoter of wound healing [8]. Nevertheless, the majority of the literature reviews on *Aloe vera* have discussed the various therapeutic effects of *Aloe vera* [1, 2, 4], with few focussing solely on wound healing [8] and even fewer on the mechanisms [9]. Moreover, due to the vast composition of the plant, the particular chemical constituents of *Aloe vera* that mediate wound healing remain unclear. To acquire a deeper understanding of the wound healing mechanisms of *Aloe vera* at the molecular level, a cardinal step is to identify the growth factors that are upregulated by *Aloe vera*. Findings acquired from such studies may even be of use in identifying potential drug candidates or drug targets.

The aim of this article is to review the molecular mechanisms of *Aloe vera* in promoting cutaneous wound healing, with particular emphasis on the cell proliferative phase. First, the article briefly discusses the chemical constituents of *Aloe vera* that contribute to wound healing. Afterwards, the article highlights the growth factors, signalling molecules, and promigratory factors that are upregulated in response to *Aloe vera* treatment, followed by a discussion on the findings obtained from molecular docking studies. Then, this article evaluates the clinical effectiveness of *Aloe vera* in promoting wound healing and alleviating skin diseases, as well as the current commercial uses of *Aloe vera* products from 2013 to 2023. Lastly, suggestions and directions for future research are provided.

Search Strategies

To locate relevant articles, a Boolean search was initially conducted in PubMed, Scopus, and SciFinder using key words such as “aloe vera”, “aloe”, “grow”, “factor”, “skin”, “wound”, “heal”, “proliferate”, “migration”, etc. No restrictions were implemented on the year and location of publication. However, only articles that were written in English and available in full texts were accepted. Next, to further investigate the relationship between different *Aloe vera* chemical constituents and associated growth factors or signalling molecules, additional key words were used such as “acemannan AND tgf”, “aloe AND mapk”, “aloe AND akt”, “emodin AND akt”, etc.

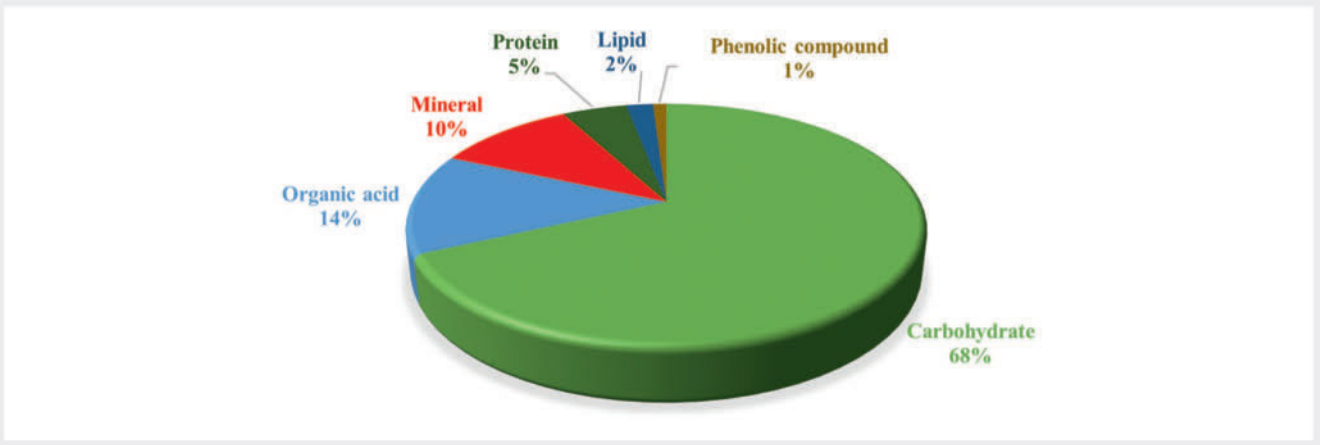
Chemical Constituents of Aloe Vera that Contribute to Wound Healing

The *Aloe vera* plant comprises the leaf and the flower, both of which have been shown to contribute to wound healing. The components of the leaf include the following, from the inner to outermost layer: the gel, latex, and rind [4]. While *Aloe vera* is mostly composed of water (99–99.5%), other constituents have been isolated from the plant including carbohydrates, amino acids, hormones, enzymes, vitamins, and anthraquinones [4]. The plant has been reported to contain over 200 active compounds [2]; therefore, obtaining an accurate representation of the chemical composition of *Aloe vera* remains a challenge. The dry matter of *Aloe vera* has been reported to contain mostly carbohydrates (68%) and organic acids (14%), followed by minerals (10%), proteins (5%), lipids (2%), and phenolic compounds (1%) [4, 10–13]. ▶ **Fig. 1** provides a reference to the chemical composition of *Aloe vera* dry matter.

The wound healing properties of *Aloe vera* have been attributed to the high carbohydrate content in its gel [6]. Acemannan (IUPAC: Man3Ac4Me(a1-4)Man3Ac(a1-4)ManA3Ac(a1-4)Man3Ac(a1-4)ManNAc(a1-4)Man3Ac(a1-4)Man3Ac(a1-4)a-Man1Me3Ac), a major carbohydrate found in the gel [1], has been reported to accelerate wound closure and promote granulation tissue formation [14, 15]. In addition, *β*-sitosterol (IUPAC: (3S,8S,9S,10R,13R,14S,17R)-17-[(2R,5R)-5-ethyl-6-methylheptan-2-yl]-10,13-dimethyl-2,3,4,7,8,9,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-3-ol), a sterol that is also found in the gel [4], was reported to induce similar effects and promote angiogenesis [16, 17]. Other constituents associated with wound healing acceleration include anthraquinones such as aloesin (IUPAC: 7-hydroxy-5-methyl-2-(2-oxopropyl)-8-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]chromen-4-one) and emodin (IUPAC: 1,3,8-trihydroxy-6-methylanthracene-9,10-dione) [4, 18, 19], as well as phenolic compounds such as quercetin, apigenin, myricetin, rutin, and kaempferol [20]. ▶ **Fig. 2** shows the chemical structures of some *Aloe vera* chemical constituents highlighted in this article. Nevertheless, most studies that investigate the wound healing effects of *Aloe vera* use whole plant extracts, rather than isolated chemical constituents, in their studies. Thus, further work is required to fully understand the contribution of each compound in wound healing promotion.

Growth Factors and Cytokines Upregulated by Aloe Vera

Growth factors play a vital role in mediating cell proliferation, cell migration, and angiogenesis [21]. This section discusses the growth factors that have been reported to be upregulated by *Aloe vera* and the chemical constituents responsible. ▶ **Table 1** pro-



▶ **Fig. 1** Chemical constituents of *Aloe vera* dry matter.

vides a list of the growth factors and their biological effects, as well as their sources of expression. A summary of the following discussion is outlined in ▶ **Fig. 3** and **Table 1S** (Supporting Information).

Keratinocyte growth factor-1 (KGF-1)

KGF-1 is secreted from fibroblasts and promotes proliferation of fibroblasts and keratinocytes [22]. The effect of *Aloe vera* on KGF-1 expression has not been studied on cutaneous skin. However, an *in vitro* study on human gingival fibroblasts reported that acemannan extracted from *Aloe vera* increased KGF-1 expression and promoted cell proliferation within 24 and 48 hours. Additionally, an *in vivo* study on Sprague–Dawley rats showed that acemannan accelerated oral wound closure, decreased the number of inflammatory cells, and increased the formation of rete ridges and dermal papillae within a week [14]. Thus, in future, similar studies can be done to investigate KGF-1 expression in dermal fibroblasts after treatment with acemannan.

Transforming growth factor-β (TGF-β)

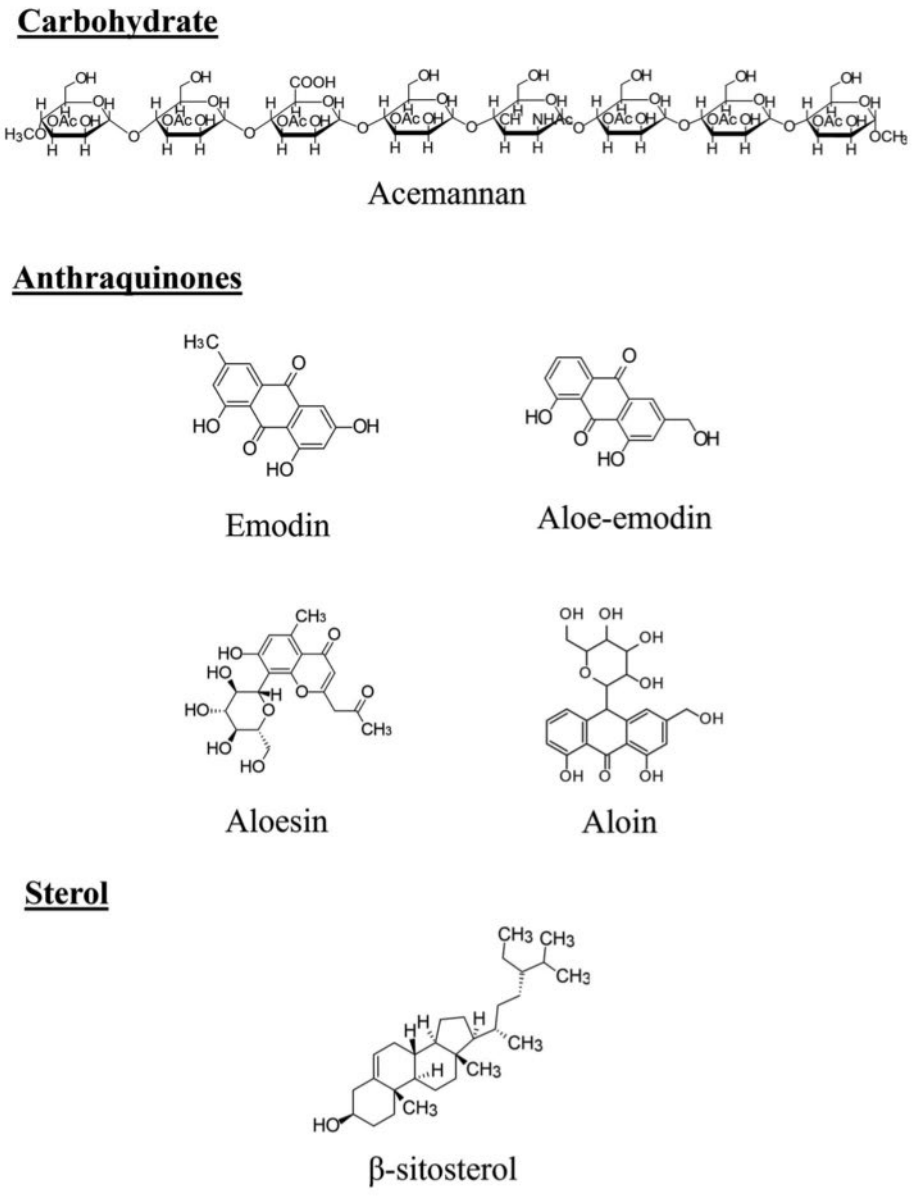
TGF-β is a family of cytokines secreted by multiple cells including fibroblasts, epithelial cells, endothelial cells, and inflammatory cells, and the cytokines have been reported to promote cell proliferation, angiogenesis, and collagen deposition [21, 23]. With regards to *in vitro* studies, elevated TGF-β-1 expression was observed in healthy normal human dermal fibroblasts (NHDF) [24], c147 (normal mouse fibroblast cell line) [20], and mouse embryonic fibroblasts [25] after *Aloe vera* treatment for 48, 24–48, and 12 hours, respectively. The level of TGF-β-1 expression was also observed to be dose-dependent [25]. Additionally, 72 hours of *Aloe vera* treatment elevated expression of TGF-β-1 and type I procollagen in NHDF obtained from a young human male who underwent ultraviolet B (UVB) radiation [26].

Findings from *in vivo* studies support those reported *in vitro*. Increased expression of TGF-β protein and mRNA were observed in burn or excisional rat wound models after *Aloe vera* treatment [27–30]. Response was observable approximately within a week, and topical application was found to be more effective than oral administration, with topical application conferring higher TGF-β expression, faster re-epithelialisation, greater formation of collagen, and blood vessels with better organisation [27]. Additionally, twice daily topical application of *Aloe vera* conferred faster wound healing compared to once daily application [30]. Although the contributing compound of *Aloe vera* that upregulates TGF-β has not been investigated, emodin derived from the *Rheum officinale* Baill plant has been shown to increase TGF-β gene and protein expression in Sprague–Dawley rats. Response was observed within a week in a dose-dependent manner, and histological sections obtained from the excisional wounds showed greater wound contraction, on-going re-epithelialisation, a higher number of fibroblasts, greater blood vessel formation, and collagen organisation [19]. Hence, future studies may investigate whether emodin extracted from *Aloe vera* will produce a similar effect on TGF-β expression.

Nonetheless, TGF-β expression was found to decrease during later stages of the wound healing process. In an *in vitro* study using mouse embryonic fibroblasts, higher TGF-β gene and protein expression were observed in the group given 12-hour treatment of *Aloe vera* compared to the group given 24-hour treatment. On the other hand, when TGF-β proteins were blocked using monoclonal antibodies, the inhibition on TGF-β expression was removed in the 24-hour treatment group [25]. Dampened expression of TGF-β was also reported in burn and excisional Sprague–Dawley rat wound models examined 28 days after application of *Aloe vera* hydrogel loaded with adipose-derived stem cells [28]. Since TGF-β increases collagen deposition and prevents collagen degradation, this feedback inhibition may be crucial during later stages of the wound healing process in preventing fibrosis [25].

Cyclin D1

Cyclin D1 is a key regulator of the cell cycle. Cyclin D1 forms a complex with cyclin-dependent kinase 4 (CDK4), and the cyclin D1-CDK4 complex phosphorylates Retinoblastoma (Rb) protein, thus removing inhibition of Rb protein on transcription factors involved in promoting G1 to S phase progression [31, 32]. In an *in vitro* study using primary skin fibroblasts isolated from BALB/c

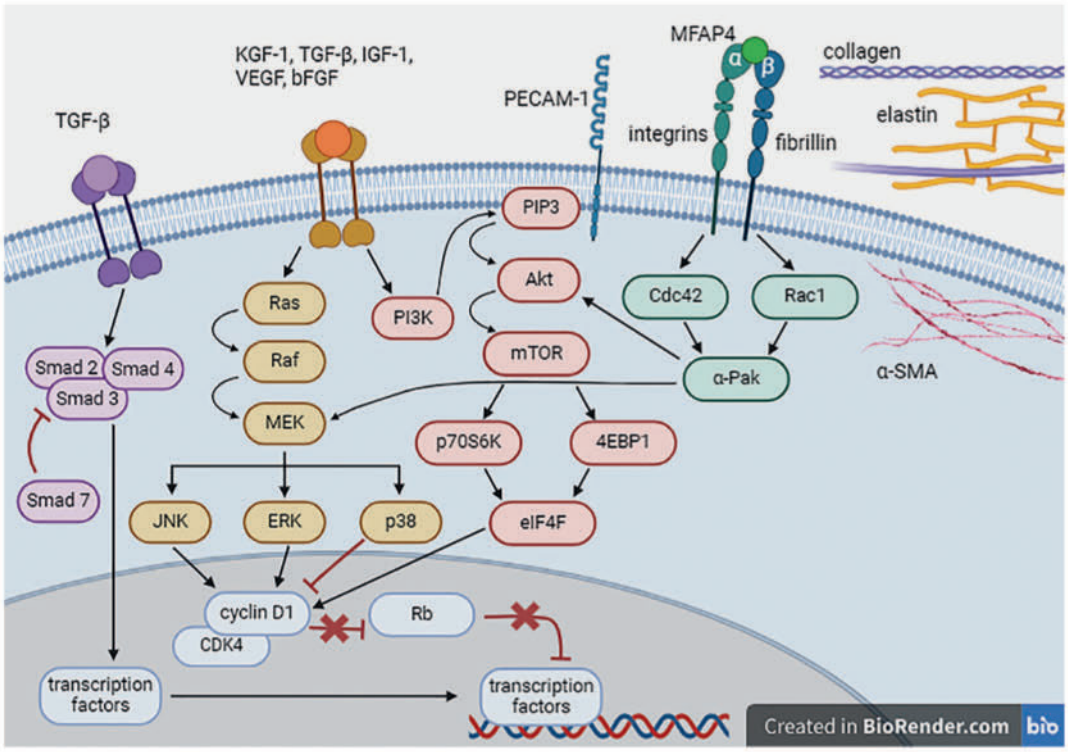


▶ **Fig. 2** Chemical constituents of *Aloe vera* that have been shown to upregulate growth factors, promigratory factors, or signalling molecules involved in cutaneous wound healing.

mice, fibroblasts treated with 150 µg/mL acemannan showed increased protein expression of cyclin D1 and greater G1 to S phase progression within 48 hours. CDK4 expression did not change significantly; nonetheless, accumulation of cyclin D1-CDK4 complexes was still observed in the cells, inferred from the increased expression of phosphorylated Rb protein. Expression of cyclin D1 mRNA, however, was not affected by acemannan; moreover, acemannan-induced proliferation of mouse primary skin fibroblasts was inhibited by cyclin D1 siRNA. These findings suggest that acemannan regulates cyclin D1 expression via translational modifications [33].

Insulin-like growth factor 1 (IGF-1)

IGF-1 plays a major role in promoting cell growth and proliferation by working synergistically with growth hormone (GH) and promoting glucose uptake [34, 35]. Increased expression of IGF-1 mRNA and protein were observed *in vivo* in excisional wounds of diabetic BALB/c mice treated with topical *Aloe vera* gel for seven days. Other findings that indicated improved wound healing were observed concurrently, including upregulated protein and mRNA expression of glucose transporter 1 (GLUT-1), increased fibroblast proliferation and collagen synthesis, faster re-epithelialisation, and decreased inflammatory cell count. Wound closure was complete by day 14, and IGF-1 expression subsequently declined [36].



▶ **Fig. 3** Molecular signalling pathway putatively affected by *Aloe vera*. Created with BioRender.com. [rerif]

▶ **Table 1** Biological effects and sources of expression of different cellular growth factors upregulated by *Aloe vera*. Asterisks (*) indicate that the growth factor contributes to the respective biological effect.

Growth factor	Biological effect			Sources of expression	Reference
	Angiogenesis	Cell proliferation	Cell migration		
KGF-1		*		Fibroblast, epithelial cell	[22]
TGF-β	*	*	*	Endothelial cell, fibroblast, inflammatory cell	[21, 23]
Cyclin D1	*	*		Endothelial cell, fibroblast, epithelial cell	[31, 32]
IGF-1	*	*		Fibroblast, epithelial cell, liver	[21, 34, 35]
VEGF	*	*		Endothelial cell, fibroblast, inflammatory cell	[23]
bFGF	*	*	*	Endothelial cell, fibroblast, inflammatory cell	[23]
MFAP4	*	*	*	Epithelial cell, vascular smooth muscle cell	[42–45]

Patients with Type II diabetes often present with chronic wounds caused by delayed wound healing as a result of increased inflammatory activity and downregulation of growth factors such as IGF-1 [36–38]. The results from this study indicate that *Aloe vera* may be able to promote healing of chronic diabetic wounds by upregulating expression of IGF-1 and GLUT-1 [36].

Vascular endothelial growth factor (VEGF)

VEGF is a common angiogenic factor that is secreted from endothelial cells, inflammatory cells, and fibroblasts [23]. With regards to *in vitro* studies, *Aloe vera* treatment increased VEGF protein expression in normal human dermal fibroblasts (NHDF) [24], while increased mRNA expression was observed in a normal mouse fibroblast cell line (c147) [20] and in fibroblasts isolated from diabetic albino Wistar rats [39]. In all three studies, upregulated expression of VEGF was observed within 48 hours.

Findings from *in vivo* studies support those reported *in vitro*. Topical and oral application of *Aloe vera* increased VEGF mRNA expression in Sprague–Dawley rat burn models and diabetic BALB/c mice excisional wound models [27, 36, 40], with greater effect observed in groups given topical treatment [27]. Elevated VEGF levels were concurrently observed with increased capillary formation and blood perfusion at the wound sites [40]. In line with normal negative feedback, VEGF levels peaked around 1–2 weeks and declined thereafter when wound healing was close to completion [36, 40, 41]. The upregulated expression of VEGF could be attributed to acemannan, as shown by the increased levels of VEGF mRNA in Bergamasca sheep after topical treatment of commercial acemannan gel for 15 days [15]. Overall, these findings suggest that acemannan derived from *Aloe vera* promotes wound healing by promoting VEGF expression in fibroblasts, and the upregulated response occurs in a timely manner without disrupting normal negative feedback.

Basic fibroblast growth factor (bFGF)

Another common angiogenic factor is bFGF, which is secreted by fibroblasts, inflammatory cells, and endothelial cells and is involved in promoting VEGF production and collagen synthesis [21, 23]. Similar to TGF-*β*, *in vitro* mouse embryonic fibroblasts increased bFGF expression within 12 hours of *Aloe vera* treatment, and the bFGF levels subsequently declined after 24 hours. Response was also observed in a dose-dependent manner [25]. With regards to *in vivo* studies, both topical and oral *Aloe vera* treatment upregulated bFGF protein and/or mRNA expression in burn models [27], excisional wound models with predisposing diabetes [36], and excisional wound models that received prior treatment of burns or radiation [28, 29]. Accelerated wound closure, increased blood vessel formation, and collagen deposition were concurrently observed in these studies. Onset of action occurred around one week, and continuous improvement was observed with prolonged administration (up to 30 days) [27]. These results suggest that, similar to VEGF, *Aloe vera* upregulates bFGF expression in fibroblasts, therefore promoting angiogenesis and granulation tissue formation, ultimately accelerating wound closure.

Microfibril-associated glycoprotein 4 (MFAP4)

Microfibril-associated glycoproteins (MFGP) are a class of multifunctional proteins secreted by keratinocytes and vascular smooth muscle cells and are involved in promoting cell proliferation, cell migration, and ECM synthesis [42–45]. Elevated expression of MFAP4 mRNA and protein was observed in NHDF *in vitro* after combined treatment of *Aloe vera* gel and *Aloe vera* flower for 48 hours. Additionally, treated cells were induced to progress to S phase. The combined treatment was also shown to counteract the depressed migratory rate of MFAP4 knockdown NHDF [24].

Signalling Molecules

TGF-*β*-1, IGF-1, VEGF, bFGF, and MFAP4 confer similar effects on cell proliferation and wound healing, which may be explained by the shared downstream signalling pathways such as the PI3K/Akt and MAPK signalling pathways [43, 46–50]. Moreover, these signalling pathways also regulate the expression of cyclin D1 [51]. Consequently, in addition to the effects of *Aloe vera* on the expression of growth factors, the expression of signalling molecules should also be discussed. A summary of the following discussion is outlined in ▶ **Fig. 3** and **Table 1S** (Supporting Information).

Phosphoinositide-3-kinase/protein kinase B (PI3K/Akt) signalling pathway

Aloe vera has been shown to upregulate signalling molecules in the PI3K/Akt pathway, one of which is Akt (or PKB for protein kinase B). NHDF treated with *Aloe vera* for 48 hours showed increased Akt protein expression and cell proliferation [24]. The upregulation of Akt could be attributed to acemannan [33]. In addition, acemannan was also shown to upregulate signalling molecules in the mTOR pathway, a downstream pathway of PI3K/Akt. In an *in vitro* study, BALB/c mice-derived primary skin fibroblasts incubated with 150 ug/mL acemannan for 48 hours showed increased cell viability and proliferation. When the fibroblasts were treated with acemannan for 60 minutes at 15 intervals, increased expression of mTOR, p70S6K, and 4EBP1 in their active phosphorylated forms were observed over time. On the other hand, when acemannan was administered together with VIII (inhibitor of Akt) or rapamycin (inhibitor of mTOR), the expression of these signalling molecules was downregulated. Moreover, cyclin D1 expression was in accordance with the expression of signalling molecules in the mTOR pathway. These findings were supported by *in vivo* studies using BALB/c mice excisional wound models, whereby acemannan accelerated wound closure by two days, and the expression of phosphorylated mTOR (p-mTOR) and cyclin D1 were inhibited following co-administration of 0.1 µM rapamycin. In addition, acemannan was also found to upregulate expression of the eIF4F complex, although whether VIII or rapamycin could inhibit the expression of the eIF4F complex was not investigated in this study [33].

Mitogen-activated protein kinase (MAPK) signalling pathway

The MAPK pathway can be further segregated into three pathways: c-Jun N-terminal kinase (JNK) pathway, extracellular signal-regulated kinase (ERK) pathway and p38 pathway [52]. NHDF treated with *Aloe vera* for 48 hours showed increased expression of phosphorylated ERK (p-ERK) and increased cell proliferation [24]. Similarly, fibroblasts isolated from diabetic albino Wistar rats were treated with *Aloe vera* for 48 hours and showed increased expression of JNK-1 mRNA and increased cell proliferation [39]. The induced expression of MAPK signalling molecules could be attributed to the anthraquinones of *Aloe vera*, namely emodin, aloe-emodin (IUPAC: 1,8-dihydroxy-3-(hydroxymethyl)anthracene-9,10-dione), and aloesin. In an *in vitro* study using CCD-1078Sk (human skin fibroblast cell line), fibroblasts were incubated for 24 hours with either 6.25 µM emodin or 2.5 µM aloe-emodin. The authors found that emodin significantly increased expression of p38 mRNA, while aloe-emodin upregulated expression of JNK mRNA. In both cases, treated fibroblasts showed higher migratory rates. However, p38 and JNK expressions were downregulated at high concentrations of emodin and aloe-emodin, respectively, conferring to the inhibitory feedback nature of the pathway. ERK

expression was found to be unaffected by emodin and aloe-emodin [52]. In an *in vivo* study conducted on SKH-1 hairless mice, excisional wounds were treated for seven days with 0.1% and 0.5% aloesin. The authors found that aloesin increased expression of phosphorylated JNK (p-JNK) and p-ERK, but not p38. Aloesin-treated wounds also showed faster re-epithelialisation, wound closure, and greater collagen deposition [18]. Thus, these findings suggest that emodin upregulates JNK; aloe-emodin upregulates p38, while aloesin upregulates both JNK and ERK. Nevertheless, further investigations are still required to fully understand the effect of different anthraquinones on the expression of MAPK signalling molecules.

Smad proteins

Smad proteins are involved in an intracellular TGF-β signalling pathway not shared by other growth factors mentioned above. Smad 2, Smad 3, and Smad 4 contribute to the conduction of TGF-β signalling, while Smad 7 has an inhibitory effect [53]. Some Smad proteins have been reported to be upregulated by aloesin. In an *in vivo* study on SKH-1 hairless mice, excisional wounds were topically applied with 0.5% aloesin for a week. The authors found that aloesin increased expression of phosphorylated Smad 2 and Smad 3, while expression of Smad 7 protein was unaffected [18].

Promigratory Factors

In addition to cell proliferation, cell migration is also a vital process in the cell proliferative phase of wound healing. Migration of fibroblasts and keratinocytes mediates wound closure, while migration of endothelial cells further facilitates angiogenesis. Some growth factors previously discussed, such as TGF-β, bFGF, and MFAP4, promote cell migration and ECM synthesis, as well as cell proliferation. The following discusses some other promigratory factors or biomarkers that have been shown to be upregulated by *Aloe vera*. A summary of the discussion in this section is outlined in ▶ **Fig. 3** and **Table 1S** (Supporting Information).

Upregulation of promigratory factors

The ECM is largely composed of collagen fibres, which are bundles of fibrous protein secreted by myofibroblasts [54]. Collagen is mechanically strong and contributes to the tensile strength of the tissue. Elastin is another type of fibrous protein that is elastic and allows tissue stretching. Fibrillin is a glycoprotein that interacts with elastin to form elastic fibres [55]. Cells express adhesion receptors on their surfaces, which bind to the ECM, thereby allowing cells to sense and respond to changes in the microenvironment. One such adhesion receptor is integrin, a heterodimer composed of one α subunit and one β subunit. Integrins recognise specific motifs on the extracellular proteins and promote interaction between actin and myosin by initiating the integrin signalling pathway. The actomyosin complex mediates cell movement and migration [56]. Similarly, platelet endothelial cell adhesion molecule 1 (PECAM-1, also known as CD31) is another adhesion molecule found on the surface of fibroblasts and endothelial cells and mediates cell migration and angiogenesis [57]. In addition, crosstalk exists between integrin signalling, the PI3K/Akt pathway, and the MAPK pathway [58]. Several factors favouring migration have been observed to be upregulated by *Aloe vera*. In an *in vivo* study on Wistar rats with grade II burns, *Aloe vera* promoted mRNA expression of collagen I and III within one week, and the levels peaked after two weeks. Treated rats also showed accelerated wound closure [41]. In an *in vitro* study on NHDF, fibroblasts given combined treatment of *Aloe vera* gel and *Aloe vera* flower for 48 hours showed upregulated expression of collagen I, α-smooth muscle actin (α-SMA), fibrillin and elastin [24]. Increased cell migration was also observed from scratch-test assays. In another *in vitro* study, IBRC C10003 (human fibroblast cell line) and IBRC C10638 (endothelial cell line) were incubated with *Aloe vera* for 24 hours. The authors found that *Aloe vera* increased mRNA expression of integrin-α-1, integrin-β-1, and PECAM-1 (CD31) in both cell lines, with fibroblasts showing a greater response and increased migratory rate. Protein expression of PECAM-1 was found to be unaffected by 48-hour *Aloe vera* treatment; however, the authors observed an eightfold higher expression of PECAM-1 protein in fibroblasts compared to endothelial cells [57].

Aloesin may be the contributing chemical constituent for the upregulation of some promigratory factors. In an *in vivo* study, SKH-1 hairless mice with excisional wounds were treated with 0.1% or 0.5% aloesin for a week. The authors observed that aloesin treatment induced expression of phosphorylated Rac1 (p-Rac1), phosphorylated Cdc-42 (p-Cdc42), and α-Pak, all of which are signalling molecules involved in the integrin signalling pathway. Further investigations revealed that aloesin treatment accelerated re-epithelialisation, increased collagen deposition and improved organisation of skin layers and granulation tissue. In an *in vitro* study, HaCaT cells (keratinocyte cell line) treated with aloesin for four or eight hours showed increased cell migratory rate in a dose-dependent manner, while human umbilical vein endothelial cells (HUVECs) treated with aloesin for 16 hours showed increased capillary formation (measured as the number of branches per field of microscopy) [18]. These results suggest that aloesin may be responsible for inducing cell migration in keratinocytes and endothelial cells by upregulating expression of promigratory factors. As is apparent, there are many promigratory factors that mediate cell movement and migration; therefore, much further study is required to fully understand the effect of *Aloe vera* on their levels of expression.

Downregulation of matrix metalloproteinases (MMPs)

The ECM forms a dynamic microenvironment, and there is a constant process of breaking, reforming, and remodelling of the matrix. Matrix metalloproteinases (MMPs) are a family of enzymes that degrade the ECM [59]. TGF-β plays a role in inhibiting MMPs to prevent collagen degradation [25]. *Aloe vera* has also been reported to downregulate MMPs; 72-hour *Aloe vera* treatment resulted in decreased expression of MMP-1 and MMP-3 proteins in NHDF obtained from a young human male who underwent UVB radiation. Increased expression of type I procollagen (precursor of collagen I) was also observed [26]. Oral administration of *Aloe vera* to diabetic BALB/c mice resulted in decreased expression of MMP-2 and MMP-9 proteins after the first and second week of treatment [40]. MMP expression has been reported to be regulated by anthraquinones such as aloin A (IUPAC: (10S)-1,8-dihydroxy-3-(hydroxymethyl)-10-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-

6-(hydroxymethyl)oxan-2-yl]-10H-anthracen-9-one) and aloin B (stereoisomer; IUPAC: (10R)-1,8-dihydroxy-3-(hydroxymethyl)-10-[(2S,3R,4R,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)oxan-2-yl]-10H-anthracen-9-one). Both aloin A and aloin B have been shown to inhibit granulocyte MMP (PMN-MMP) from collagenase assays [60]. On the other hand, 24-hour aloesin treatment had no effect on MMP-1 expression in UVB- irradiated NHDF but was found to increase mRNA expression of type 1 procollagen [26]. Taken together, the proposed chemical constituents responsible for promoting cell migration are aloesin and aloin, in which aloesin upregulates expression of promigratory factors, while aloins downregulate expression of MMPs.

Molecular Docking Studies

So far, the previous sections have discussed the growth factors, signalling molecules, and promigratory factors that are upregulated by *Aloe vera*. Subsequently, further studies were conducted to investigate how *Aloe vera* upregulates the expression of these factors. In structure-based drug design, the drug discovery process follows a series of steps: 1) identification of target protein that mediates cellular response; 2) characterisation of target protein binding site; 3) identification of ligand (or "hit"); 4) conduct functional assays to study the effect of ligand on target protein activity; 5) characterisation of ligand-target interaction; 6) structural modification of the ligand. In the context of this review, the potential target proteins are the growth factors and their associated receptors, signalling molecules, and promigratory factors; the potential ligands are the *Aloe vera* chemical constituents. *In vitro* and *in vivo* studies have shown that certain *Aloe vera* chemical constituents are associated with the upregulation of some growth factors, signalling molecules, or promigratory factors, thereby promoting cell proliferation or migration. To investigate whether this association occurs via a direct or indirect interaction between the ligand and the target, *in silico* molecular docking studies can be conducted to determine the binding affinity and types of interaction involved between the ligand and the target protein. **Table 2S** (Supporting Information) summarises the findings from molecular docking studies that investigated the binding affinity between an *Aloe vera* chemical constituent and a growth factor receptor or signalling molecule.

Emodin was found to bind to JNK and MMP-13 by forming hydrogen bonds [52, 61] and to the TGF-β-1 receptor by forming hydrogen and ionic bonds [38]. Similarly, aloe-emodin was also found to bind to the forementioned proteins [38, 52, 61]. Additionally, molecular dynamic simulation studies revealed that aloe-emodin and the TGF-β-1 receptor form a stable ligand-protein complex; moreover, aloe-emodin showed good intestinal absorption and distribution, as well as a Class 5 toxicity level [38]. In addition, aloe-emodin and β-sitosterol were found to bind to other MAPK signalling molecules such as Myc and Jun, as well as Akt-1 from the PI3K/Akt pathway [62, 63]. Molecular docking studies provide insight into whether the change in expression of growth factors and promigratory factors are induced by direct interaction with *Aloe vera* chemical constituents, thereby providing a deeper understanding of the molecular mechanisms of *Aloe vera* in promoting cutaneous wound healing. Nonetheless, molecular docking studies are limited to providing information on binding affinities and the types of interactions involved; no information is provided on the effect of ligand on target protein activity (activation or inhibition). In addition, acemannan is a relatively large compound (molecular weight: 1691.5 g/mol) and is hence not a suitable ligand for molecular docking studies. As such, findings from molecular docking studies are informative but not definitive, and results obtained from this predictive tool ought to be confirmed in wet bench studies.

Clinical Trials

Aloe vera treatment has generally shown positive results in healing wounds in mice [40], rats [30], sheep [15], dogs, and cats [64]. Subsequently, further research was done to investigate the effectiveness of *Aloe vera* in healing wounds among human subjects. In February 2024, a search was conducted on SciFinder using the key words "*Aloe vera*" and filtered for clinical trials. No restrictions were implemented on the year and location of publication. 155 results were generated from this search, and relevant trials were manually located by reading the full abstracts. Clinical trials related to cutaneous wound healing or skin diseases were included, whereas articles were excluded if the clinical trial recruited non-human subjects, was not written in English, provided insufficient data, was published as a forum article, or was unavailable in full text; 21 clinical trials met the inclusion and exclusion criteria, of which 11 were related to wound healing and the other 10 to skin diseases. **Table 3S** (Supporting Information) summarises the findings from the clinical trials discussed in this section.

Wound healing

On the whole, results reported from human clinical trials were in line with those reported from animal studies. Topical application of *Aloe vera* has been shown to accelerate wound healing in burns, pressure ulcers, and various surgical wounds.

Burns

Aloe vera dressings have been shown to be more effective than routine care dressings in healing burn wounds. An example of routine care dressing commonly used for burns is 1% silver sulfadiazine, an antibiotic. In two independent clinical trials, patients with second-degree burns were given twice-daily applications of either *Aloe vera* dressing or 1% silver sulfadiazine for around 21 to 26 days. In both cases, patients treated with *Aloe vera* dressing showed faster epithelialisation [65, 66]. Moreover, *Aloe vera*-treated patients experienced less pain, and the *Aloe vera* dressing was also reported to be cheaper than 1% silver sulfadiazine [66]. Another common routine care dressing for burns is 0.5% chlorohexidine acetate, an antiseptic. Similarly, burn patients given *Aloe vera* dressing showed faster wound healing and reduced pain and had shorter duration of hospital stays compared to those given 0.5% chlorohexidine acetate. Hence, *Aloe vera* is suggested to be a cheaper and more effective alternative to routine care dressings in healing burn wounds [67].

Pressure ulcers and chronic anal fissures

Aloe vera has been shown to be effective in alleviating pressure injuries and chronic anal fissures. Hospital-acquired pressure injuries are often a result of long hospital stays. In one study, patients who were hospitalised for at least 10 days were given twice-daily application of fresh *Aloe vera* gel directly on the hip, sacral area, and heel for 10 days. This treatment was shown to be effective in reducing the likelihood of developing grade I pressure ulcers in the forementioned areas [68]. Daily application of *Aloe vera* gel for 15 days reduced pain in patients with grade II pressure ulcers [69]. In another study conducted on 240 intensive care unit (ICU) patients, application of *Aloe vera* and olive oil in a 3 : 2 ratio three times a day (TID) for 30 days conferred reduced and delayed development of pressure ulcers at the sacral, buttock, and iliac areas [70]. Additionally, in patients with chronic anal fissures, TID application of *Aloe vera* cream for six weeks improved wound healing, reduced pain, and reduced occurrence of haemorrhage on defecation [71]. Hence, these results suggest that *Aloe vera* could be used to prevent and delay formation of pressure injuries, improve healing of anal fissures, and alleviate symptoms associated with these injuries.

Surgical wounds

Furthermore, *Aloe vera* has been shown to accelerate healing of surgical wounds. In mothers with caesarean wounds, immediate application of fresh *Aloe vera* gel after operation decreased the Scale of Redness, Edema, Ecchymosis, Discharge, Approximation of the Two Edges of the Wounds (REEDA) scale within 24 hours. However, the lack of continuous treatment after 24 hours resulted in higher REEDA scales on day eight of follow-up, suggesting that frequent application of *Aloe vera* is required for better wound improvement [72]. This observation is in line with that reported in Wistar rat incisional wound models [30]. *Aloe vera* has also been shown to accelerate healing of post-haemorrhoidectomy wounds. Patients were given *Aloe vera* cream immediately after surgery, and TID applications continued post-surgery for two weeks. Reduced pain on defecation and reduced overall pain were also reported [73].

In addition, *Aloe vera* may aid the healing of wounds at split-thickness skin graft donor sites. Daily application of *Aloe vera* dressing conferred faster epithelialisation compared to glycerine (11.5 vs. 13.67 days) [74]. However, in a clinical trial using ointment containing *Aloe vera*, honey, and peppermint, while reduced erythema was observed, wound size reduction was not statistically significant compared to the group treated with petroleum jelly [75]. Discrepancies in findings may be due to the different frequencies of administration (daily application in the former study vs. application on days 0, 4, 7, and 14 in the latter study). Both studies found no significant differences in pain reduction compared to the control groups; nonetheless, the former study reported that the pain experienced was not clinically significant [74].

Limitations of clinical studies on wound healing

The majority of the forementioned clinical trials used relatively small sample sizes (< 100); thus, larger sample sizes are needed to confirm these findings. Nevertheless, *Aloe vera* proved to be a cheaper and more effective alternative to routine care dressings in alleviating burns, pressure ulcers, surgical wounds, and traumatic wounds. Moreover, frequent application is important in achieving clinical effectiveness. Notably, various types of media have been used to prepare the dressings: fresh gel, cream, ointment, gauze, etc. The type of media used will also affect the speed and quality of wound recovery and requires further optimisation [76].

Another limitation is the wide range of *Aloe vera* concentrations used in the commercial gels and self-made creams. Furthermore, the composition of *Aloe vera* varies in response to temperature, humidity, nutrient availability, and the age of the plant [26, 77]. Such parameters may also change during the process of extraction [6]. Additionally, the direct application of fresh *Aloe vera* gel, while shown to be effective, is difficult to standardise. Results from these studies are therefore difficult to replicate. Future studies may consider using wound dressings incorporated with specific concentrations of *Aloe vera* chemical constituents, as opposed to using whole *Aloe vera* extracts, in order to improve the standardisation of methods. In addition, future clinical trials may consider investigating the effectiveness of *Aloe vera* in wound healing in patients with comorbidities such as diabetes.

Skin diseases

Wounds are often found on inflamed or infected skin as a result of scratching, cracks, scaling, or burst papules or pustules. *Aloe vera* has been shown to be effective in alleviating some, but not all, skin diseases related to inflammation and infection. Skin diseases that responded to *Aloe vera* treatment were pruritus, psoriasis, scabies, diaper dermatitis, and intertrigo, while radiation-induced skin reactions were unaffected by *Aloe vera* treatment.

Inflammatory skin diseases and skin infections

Aloe vera was found to be comparable to corticosteroids in alleviating skin inflammation. Twice-daily application of *Aloe vera* for six weeks was comparable to 0.1% betamethasone treatment in decreasing pruritus frequency and alleviating burning sensations, scaling, and skin dryness [78]. Similarly, twice-daily application of *Aloe vera* cream for eight weeks was superior over 0.1% triamcinolone acetonide treatment in decreasing the Psoriasis Area and Severity Index (PASI) score, and the patients reported an improvement on their quality of life [79]. In addition, compared to 1% hydrocortisone cream, twice-daily application of *Aloe vera* for two weeks conferred better outcome in patients with intertrigo by reducing erythema, decreasing the number of papules and pustules, and alleviating scaling and skin dryness [80]. Hence, *Aloe vera* can be a superior alternative to corticosteroids in alleviating skin inflammation and does not confer long-term local and systemic side effects.

TID application of *Aloe vera* for four weeks was superior to the negative control in decreasing the PASI score and reducing desquamation, erythema, and infiltration. *Aloe vera* treatment also promoted complete resolution of psoriatic lesions and psoriatic plaques, with no relapse observed during follow-up eight months later [81]. However, twice-daily application of *Aloe vera* for 12 weeks was inferior to water in decreasing the PASI score and reducing desquamation and infiltration [82]. However, the study

▶ **Table 2** A summary of *Aloe vera* chemical constituents and the growth factors, promigratory factors, and signalling pathways upregulated (except for MMPs which are downregulated).

Chemical constituent	Factors/pathways in favour of proliferation and migration	Reference
Acemannan	KGF-1, cyclin D1, VEGF, PI3K pathway	[14, 15, 24, 33]
Aloesin	MAPK pathway, Smad proteins, Cdc42, Rac1, α-SMA, type 1 procollagen	[18, 26]
Emodin	TGF-β-1 (from study using emodin isolated from *Rheum officinale* Baill), MAPK pathway	[19, 52]
Aloe-emodin	MAPK pathway	[52]
Barbaloin (aloin A and aloin B)	↓ MMPs	[60]
β-sitosterol	MAPK and PI3K pathway (from molecular docking studies)	[62, 63]

design of this particular clinical trial allowed participants to apply Vaseline and other emollients on psoriatic areas. It is possible that water, in combination with other emollients and Vaseline (which contains petroleum jelly), was more effective than *Aloe vera* in the alleviation of psoriasis.

Furthermore, TID application of cream comprising *Aloe vera* and olive oil at a 3 : 2 ratio decreased the severity of diaper dermatitis in female infants under three years after 10 days of treatment, conforming to the anti-inflammatory properties of olive oil and *Aloe vera* [83]. Daily application of fresh *Aloe vera* gel for three days (repeated one week later) was superior to benzyl benzoate treatment in alleviating symptoms and the underlying cause of scabies by reducing the itching intensity and drying the vesiculopapular lesions and by eliminating *Sarcoptes scabiei* mites, conforming to the antimicrobial properties of *Aloe vera* [84].

Radiation-induced skin reactions

Nevertheless, *Aloe vera* was not found to be effective in alleviating radiation-induced skin reactions. One study recruited female breast cancer patients who received 50 Gy radiotherapy at 2 Gy/day. *Aloe vera* lotion failed to improve radiation-induced erythema despite immediate application of lotion after radiotherapy and at four hours post-radiotherapy [85]. A similar study that administered *Aloe vera* cream more frequently (TID during and after radiotherapy for four weeks) reported that *Aloe vera* treatment did not clinically improve the Catterall Skin Scoring Profile (CSSP) [86].

Another study recruited both male and female participants with squamous cell carcinoma of the head and neck, and each participant received a total dose of ≥ 50 Gy of radiation. Similarly, twice-daily applications of *Aloe vera* gel for two weeks had no significant effect on alleviating itching, burning sensations, pain, and the limit on daily activities. Nevertheless, slight improvements on erythema and moist desquamation were observed [87]. Radiation induces DNA damage within the cell and causes cell apoptosis or necrosis, resulting in an inflammatory reaction. These findings suggest that the regenerative and anti-inflammatory effects of *Aloe vera* are not fast or strong enough to mitigate the rapid, large-scale cellular deaths and subsequent inflammation induced by radiotherapy.

Limitations of clinical studies on skin diseases

Overall, *Aloe vera* has been shown to be effective in alleviating common skin inflammatory diseases owing to its anti-inflammatory and antimicrobial properties. However, further investigations are required to confirm the ineffectiveness of *Aloe vera* in preventing radiation-induced skin reactions as successful results have been reported before [88, 89]. If possible, investigators should avoid allowing participants to apply other emollients or moisturising creams on tested areas as these products may interfere with the results. The same limitations apply with regards to the type of media used in the dressing and the concentration of *Aloe vera* or chemical constituent used in the dressing. Of note, this review did not include clinical trials studying the effects of *Aloe vera* on alleviating fibrosis, sunburns, photoaging, and acne. Alleviation of signs and symptoms of skin diseases such as itching, cracks, and formation of papules and pustules can prevent the formation of wounds. Thus, more clinical studies are needed to study the effectiveness of *Aloe vera* on alleviating the symptoms of other skin diseases.

Adverse effects of Aloe vera

Majority of clinical trials did not observe any adverse effects with the application of *Aloe vera*. However, one clinical study reported skin dryness accompanied by fissures, a stinging sensation, and soreness. Nevertheless, these signs and symptoms may be attributed to the combined hypersensitivity to *Aloe vera* and the media used because skin tightness and tingling sensation were also reported in the placebo group [82]. Hypersensitivity to *Aloe vera* is possible, and in clinical studies that excluded participants with a positive hypersensitivity test to *Aloe vera*, no other adverse effects were reported during the actual study [68, 71].

Commercial Uses

To investigate the current commercial uses of *Aloe vera*, in February 2024, a search was conducted on SciFinder using the key words "*Aloe vera*" and filtered for patents registered during 2013 to 2023. No restrictions were implemented on the country of registration; 21,697 results were generated from this search, of which 3562 constituted the "top 100 formulation purposes" generated by SciFinder. As the overlapping of categories was apparent, further categorisation and subsequent calculations were

done manually. Additionally, upon further inspection, it was observed that the categorisations generated by SciFinder were not always accurate; therefore, the results reported herein can only be used as a guiding reference.

Among the top 100 formulations, half of the formulation purposes were skin-related pharmaceuticals, followed by other pharmaceutical products (25%), soaps and disinfectants (12%), agricultural products (9%), products related to oral hygiene, teeth, and bone care (3%), food industry (1%), and coating materials and adhesives (< 1%).

Pertaining to skin-related pharmaceuticals, 40% of the formulations were facial cosmetics including moisturisers [90], skin lightening agents [91], sunscreens [92], and anti-aging agents [93]. By contrast, only 4% of formulations were agents used for wound healing and skin diseases such as pruritus and psoriasis [94–97], in line with the positive results reported from clinical trial studies. Other skin diseases included were athlete's foot and miliaria [98, 99].

With regards to other pharmaceutical formulations, these formulations included anti-diabetic products or products aimed at improving metabolic parameters [100, 101], laxatives [102], gastrointestinal protective agents [103], analgesics [104], antipyretics [105], antitussives [106], anti-inflammatory agents [107], antimicrobial agents [108], antitumour agents [109], ophthalmic agents [110], and neuroprotective agents [111].

While the various kinds of formulations highlight the many uses of the *Aloe vera*, pharmaceuticals developed for cutaneous wound healing and skin diseases are relatively few compared to cosmetic products. Going forward, more pharmaceuticals of clinical standards are required to improve the clinical relevance of *Aloe vera*.

Future Directions

The effect of *Aloe vera* on the expression of growth factors, signalling molecules, and promigratory factors have been studied via *in vitro* and *in vivo* experimentations, and the changes in expression have been observed to occur in a dose-dependent manner. Phenotypic events observed following *Aloe vera* administration were consistent, and when *Aloe vera* was administered at similar doses, these events occurred within a relatively consistent time frame. The proposed molecular mechanisms herein do not contradict the consensus understanding of the biology of wound healing. In addition, some plants other than *Aloe vera* have also been shown to promote wound healing. Taking these into consideration, *Aloe vera* has a possible causative effect on promoting wound healing. Nevertheless, further investigation is required to verify the causative relationship between *Aloe vera* and wound healing.

One key aspect is to standardise the extraction method of *Aloe vera* to obtain consistent concentrations. This is a particularly challenging area as the composition of *Aloe vera* varies with the age of the plant, the season, and nutrient availability [26, 77]. Thus, the ability to isolate *Aloe vera* chemical constituents or synthesise these compounds would not only help to improve the reproducibility of results but also improve our knowledge on the wound healing mechanisms of *Aloe vera*. Characterisation studies on chemical constituents and the molecules they bind to can further improve our understanding of the mechanisms and also help to identify potential drug candidates or drug targets. The effects of isolated *Aloe vera* chemical constituents on wound healing have not been studied in clinical trials.

Nevertheless, *Aloe vera* should not be forgotten as a plant containing multiple active ingredients and is multi-functional by acting through multiple pathways that may regulate each other [112]. Hence, the effect observed from a single compound may not be comparable to that observed from using the whole extract. Ultimately, multiple chemical constituents formulated at different concentrations may be needed to produce a clinically significant effect. Alternatively, single isolated chemical constituents may be incorporated into existing treatments for enhanced effect. In one recent study, aloesin was incorporated into a chitosan-cellulose-based scaffold and the composite material showed good biocompatibility, as well as sustained release of aloesin. Furthermore, incorporation of 0.025% aloesin into the scaffold was found to accelerate wound closure and promote re-epithelialisation and collagen deposition [113].

Furthermore, although *Aloe vera* has been shown to be a comparable or better alternative over corticosteroids, antibiotics, and antiseptics, various studies have found other substances that have similar or greater efficacy in promoting wound healing or alleviating skin diseases. For example, *Rheum officinale* Baill [19], *Vitis vinifera* [20], *Teucrium polium* [36], *Centella asiaticosa* [67], and chitosan [41] have also been shown to promote wound healing. Moreover, clinical trial studies revealed that olive oil and non-metallic baby powder/cornstarch were more effective in alleviating pruritus and radiation-induced skin reactions, respectively [70, 86]. *Calendula officinalis* was more effective than *Aloe vera* in treating diaper dermatitis [83]. In addition, *Aloe vera* was less effective than recombinant human granulocyte-macrophage colony-stimulating factor (rhGM-CSF) in healing third-degree frostbites [114]. Nonetheless, synergistic effects have been observed when *Aloe vera* was co-administered with other therapeutic agents [36, 70].

On the other hand, the use of mesenchymal stem cells (MSCs) in wound healing still requires optimisation and, as of the present, is less effective than *Aloe vera* in promoting wound healing [28, 41]. Nevertheless, co-administration of *Aloe vera* with MSCs or HUVECs have produced better results of wound healing than when each component was administered alone [28, 40, 41, 115]. Furthermore, polycaprolactone scaffolds incorporated with *Aloe vera* have shown effectiveness in promoting cell proliferation and wound healing [115, 116]. As is evident, composite formulations have potential in combination therapy or even as promoting agents *in vitro* to encourage cellular growth and migration [117].

With regards to the use of *Aloe vera* in clinical settings, hypersensitivity tests should first be performed before administration to avoid potential side effects. Topical application is recommended over oral administration for better wound healing effects [27]. Moreover, patients should also be advised to apply *Aloe vera* frequently [30, 72]. *Aloe vera* is relatively cheap compared to most synthetic drugs and should not result in great financial burden to the patient.

Conclusion

In summary, this review discussed the mechanisms of *Aloe vera* in promoting cell proliferation and migration during cutaneous wound healing. *Aloe vera* upregulates growth factors such as KGF-1, TGF-β-1, cyclin D1, IGF-1, VEGF, bFGF, and MFAP4, increases the expression of signalling molecules in the PI3K/Akt and MAPK pathways, and also upregulates TGF-β signalling via Smad proteins. In addition, promigratory factors such as collagen, fibrillin, elastin, α-SMA, integrins, and PECAM-1 are also upregulated by *Aloe vera*. Of note, some chemical constituents of *Aloe vera* have been suggested to be responsible for the upregulation of some of those factors (▶ **Table 2**). Results from molecular docking studies support these findings and pave the way to a deeper understanding of the mechanisms of action. Wound healing effects of *Aloe vera* are translatable in clinical trials. Moreover, while *Aloe vera* is effective in alleviating common skin inflammatory diseases, the effectiveness of *Aloe vera* in alleviating radiation-induced skin dermatitis remains questionable. Nonetheless, despite the majority of positive results from clinical trials, pharmaceutical products for wound healing and skin diseases comprise merely 4% of the current commercial uses of *Aloe vera*. Thus, greater efforts are required from researchers and pharmaceutical companies to advance *Aloe vera* into clinical use.

Contributors' Statement

Z. M. L.: Conceptualisation, Writing – original draft, Writing – review & editing. B. H. G.: Conceptualisation, Writing – review & editing. K. Y. K.: Writing – review & editing.

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Conflict of Interest

The authors declare that they have no conflict of interest.

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