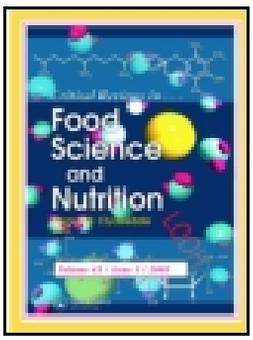

Critical Reviews in Food Science and Nutrition

ISSN: 1040-8398 (Print) 1549-7852 (Online) Journal homepage: http://www.tandfonline.com/loi/bfsn20

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To cite this article: Yan Gao, Kit Ieng Kuok, Ying Jin & Ruibing Wang (2018): Biomedical Applications of *Aloe vera*, Critical Reviews in Food Science and Nutrition

To link to this article: https://doi.org/10.1080/10408398.2018.1496320

Accepted author version posted online: 12 Jul 2018.

Biomedical Applications of *Aloe vera*

Yan Gao, Kit Ieng Kuok, Ying Jin and Ruibing Wang*

State Key Laboratory of Quality Research in Chinese Medicine, and Institute of Chinese Medical Sciences, University of Macau, Taipa, Macau SAR, China.

* Correspondence should be addressed to Prof. R. Wang at +853-8822-4689 or rwang@umac.mo.

Highlights

• It is the first systematicreview of the full spectrum of bioactivities of *Aloe vera*

• Comprehensive overview of the clinical applications of *Aloe vera* is also provided, as well as the underlying mechanism

• Quality control, preparations and current products of *Aloe vera* are discussed

• The application of *Aloe vera* in food chemistry is discussed

Abstract

Over the last centuries, *Aloe vera*, a plant species belonging to the genus Aloe, have been extensively studied for various therapeutic activities, including anti-bacterial, anti-viral, anti-cancer activity, as well as immunoregulative and hepatoprotective properties, although some of these claimed efficacies are controversial as demonstrated by some of the recent studies. In spite of the intensive historic and recent use of this herb and its extracts in various areas, a well-balanced, systematic review seems crucial in order to gain in-depth comprehensive knowledge about this plant and to reflect and revive the use of *Aloe vera* in biomedical sciences. This review will focus on summarization of the pharmacological activities and clinical studies of *Aloe* and various extracts, as well as its extensive application in food chemistry, and will also discuss the future prospects of biomedical applications of this herb.

Keywords: *Aloe vera*, Natural products, Bioactivities, Clinical Applications, Toxicology, Food

1. Introduction

Aloe vera is a species of plant belonging to the genus Aloe, where "*aloe"* is the ancient Arabic name for the plant while vera means true or genuine (Reynolds 2004).

It is a traditional herbal medicine recorded in different ancient cultures such as Chinese, Egyptian and Indian. In addition, various cultures including the Greeks, Romans and Babylonians reported the medicinal use of *Aloe vera* leaves particularly as an ointment for the skin (Bayati Zadeh and Moradi Kor 2014). According to the Chinese Pharmacopoeia, *Aloe vera* has a cold and bitter nature (Committee 2010), and it has been recorded as one of the ten most frequently used herbs for constipation (Zhong, Zheng et al. 2016). In fact, modern societies have accepted the use of *Aloe vera* as an ingredient of functional foods and cosmetics, as well as pharmaceutical products (Chen, Hsieh et al. 2004). Numerous pharmacological and clinical studies have identified various therapeutic efficacies of *Aloe vera* extracts, including anti-bacterial, anti-viral, anti-cancer (Chen, Zhang et al. 2014) activity, as well as immunoregulative and hepatoprotective properties. However, some of these advantages of *Aloe vera* are controversial. For instance, a study has indicated that *Aloe vera* gel delayed the wound healing process (Schmidt and Greenspoon 1991) and another investigation suggested that the oral consumption of *Aloe vera* products caused hepatitis in some patients (Lee, Lee et al. 2014). Consequently, it is crucial to gain in-depth knowledge about this plant, in order to fully utilize the beneficial components while eliminating any unwanted side-effects caused by the use of toxic components extracted from *Aloe vera*. With increasing acceptance of *Aloe vera* in

various biomedical applications, it is worthwhile to identify the components present in this plant and understand their related biological effects in order to gain insight and fully develop the potential of this natural product for more evidence-based biomedical purposes. While several systematic reviews regarding *Aloe vera* have been published elsewhere (Reynolds and Dweck 1999, Hamman 2008, Steenkamp and Stewart 2008, Sanchez-Machado, Lopez-Cervantes et al. 2017), this review will focus on the pharmacological activities and clinical studies of *Aloe* and components extracted from its leaves.

Essentially, the *Aloe vera* leaf can be divided into three parts shown in Fig. 1. *Aloe vera* latex which contains mainly anthraquinones, *Aloe vera* leaf gel which contains aloe polysaccharide, and green rind or cuticle of the plant. Various chemical compounds can be found in different parts of the plant, and they comprise a library of chemicals ranging from simple minerals to more complex anthraquinones and polysaccharides (Reynolds 1985, Reynolds and Dweck 1999).

Fig. 1. Bottom: *Aloe vera* plant; Top: cross section of an *Aloe vera* leaf, i) *Aloe vera* latex and ii) *Aloe vera* inner gel.

2. Functional compounds

Aloe vera has been known as a medicinal plant for millennia. There are many studies about isolation, characterization and pharmacological activities of components from the *Aloe* genus**.** According to the previous reports, the *Aloe vera* (and species) have many interesting and valuable components and compounds (Dagne, Bisrat et al. 2000), mainly including anthraquinones and naphthalenones, polysaccharides, proteins and enzymes, organic acids, etc. Among these chemical components, anthraquinones are the main active components found in the bitter yellow latex of *Aloe vera*, and they include aloin A (Barbaloin, Fig. 2a), aloin B (Isobarbaloin, Fig. 2b), aloe-emodin (Fig. 2c), chrysophanol (Fig. 2d), aloenin (Fig. 2e) and aloesaponol I, II, III, IV (Reynolds 1985). With regard to aloe polysaccharide (AP), in addition to water, AP is main ingredient of *Aloe* gel and the most common AP is glucose-mannose polysaccharide (Paulsen, Fagerheim et al. 1978). Further on, an NMR and rheological study of *Aloe vera* showed that the polysaccharidic fraction of *Aloe vera* is mainly constituted by a partially acetylated 4-linked-β-D-glucomannan (Campestrini, Silveira et al. 2013). Moreover, other active components that were isolated from fresh *Aloe vera* (and species) contain aloe lectin, cellulase, catalase, as well as superoxide dismutase (Suzuki, Saito et al. 1979, Sabeh, Wright et al. 1996).

Fig. 2. Chemical structures of aloin A (a), aloin B (b), aloe-emodin (c), chrysophanol (d) and aloenin (e).

3. Quality control

The traditional method of identification of *Aloe vera* as stated in the Chinese Pharmacopoeia (CHP) is thin layer chromatography (TLC). According to the provision established by the CHP, when calculated on the anhydrous substance of original medicinal, the content of aloin A should not be less than 28.0% in *Aloe vera*, and in the *Aloe ferox*, the content of aloin A should not be less than 18.0%. Aloin A and aloe-emodin are key compounds in the *Aloe*, at the same time; they are also the markers of *Aloe* L. in the phytochemistry taxology. By means of high-speed counter-current chromatography (HSCCC) and gel column chromatography, separation and purification of active components in Aloe can be achieved. In addition, high performance liquid chromatography (HPLC) can be used for the quantitative analysis of aloin A and aloe-emodin (Dagne, Bisrat et al. 2000, Chen 2004, Wang 2011). Furthermore, the phenol - sulphuric acid method can be applied for quantitative analysis of AP (Zhang 2007). Besides, NMR spectrometry method was

also developed and validated for quantification of organic compounds in *Aloe vera*, such as acetylated polysaccharides, glucose, malic acid, et.al., and was used as quality control method for *Aloe vera* product afterwards (Jiao, Jia et al. 2010). Mass spectrometry can be used in conjunction with other methods providing valuable information for overall quality assessment of *Aloe vera*, such as high-performance liquid chromatography-diode array detector–electrospray ionization-tandem mass spectrometry (HPLC-DAD–ESI-MS/MS), liquid chromatography–mass spectrometry-ion trap-time-of-flight (LCMS-IT-TOF) and high performance liquid chromatography-diode array detector (HPLC-DAD) (Wu, Ding et al. 2013).

4. Pharmacology

Traditionally, *Aloe vera* was used to relieve symptoms of constipation and topically used to treat skin and heal wounds in various cultures. More recently, modern pharmacology studies have established that *Aloe vera* exhibits a range of therapeutic activities such as anti-microbial, anti-viral, anti-cancer, anti-oxidant, anti-inflammation, skin protection, wound healing properties as well as the regulation of blood glucose and cholesterol. The section below will summarize studies regarding the various therapeutic properties of *Aloe vera*.

4.1 Anti-microbial activity

It has been revealed that various microbes are sensitive to different *Aloe vera* extracts while different components demonstrate different mechanisms of action for their anti-microbial effects (Cock 2008). Nonetheless, studies have established that the juice from cold pressed leaves of *Aloe vera* exhibits anti-microbial activities (Alemdar and Agaoglu 2009). A comparison of *Aloe vera* leaf extract in water, methanol and acetone has demonstrated that an acetone extract has the greatest growth inhibitory effect on *Staphylococcus aureus and Escherich*ia *coli* (Nejatzadeh-Barandozi 2013). Meanwhile, another investigation tested the inner gel of leaves of a 5-year-old plant of *Aloe vera* against 14 clinical strains from patients and one reference strain of *Helicobacter pylori*. The results showed that the MIC values of *Aloe vera* inner gel against these 14 strains were ranging from 6.25 mg mL^{-1} to 800 mg mL^{-1}, comparable to other bactericidal species. (Cellini, Di Bartolomeo et al. 2014). Therefore, researchers have suggested that *Aloe vera* gel can be used in conjunction with anti-microbial agents in the treatment of *Helicobacter pylori* infection by modulating the drug resistant behavior of *Helicobacter pylori* towards anti-microbial agents (Nejatzadeh-Barandozi 2013). Moreover, the

anthraquinones found in *Aloe vera* can inhibit the ability of microbes to synthesize proteins, thus impeding their growth. Furthermore, polysaccharides found in *Aloe vera* leaf can inhibit bacterial growth via the activation of phagocytic cells (Pugh, Ross et al. 2001). These antimicrobial studies used different components extracted from *Aloe vera* leaves demonstrated that multiple components found in *Aloe vera* leaves exhibit anti-microbial activities.

4.2 Anti-viral activities

A variety of ingredients in *Aloe vera* have been shown to have good anti-viral activities. Lectin isolated from *Aloe vera* leaf gel could possibly interfere with protein synthesis and inhibit the proliferation of Cytomegalovirus (Sahu, Giri et al. 2013). Meanwhile, *Aloe vera* emodin can effectively reduce the Influenza virus via galectin-3 up-regulation (Li, Yang et al. 2014). It is also effective against infections of type I and type II Herpes simplex virus and it is capable of deactivating other viruses, including *Varicella Zoster* virus, *Influenza* virus, and *Pseudo Rabies* virus by partially disrupting the envelopes of those viruses, as has been observed via electron micrographs (Zandi, Zadeh et al. 2007). Moreover, preliminary investigations have suggested that *Aloe vera* consumption improves the immune system by increasing

the CD4 count which may be beneficial to HIV-infected patients (Olatunya, Olatunya et al. 2012). These anti-viral constituents from *Aloe vera* leaves could be further developed to treat diseases caused by viral infections such as HIV and other viruses.

4.3 Anti-cancer activity

Numerous studies have shown that different components in *Aloe vera* leaves provide anti-cancer efficacies by modulating the growth of various cancers (Unlu, Nayir et al. 2016). An evaluation showed that *Aloe vera* treatment containing aloin and aloe-emodin can significantly reduce the proliferation of Ehrlich ascites carcinoma cells (Kuo, Lin et al. 2002). Aloe-emodin has been widely studied in various cancer cell lines, with regard to its cellular growth inhibition efficacy on a number of tumor cells, such as lung carcinoma (Lee, Hsu et al. 2001), hepatoma (Kuo, Lin et al. 2002), and leukemia cell lines (Chen, Hsieh et al. 2004). Aloe-emodin can inhibit the formation and growth of tumor blood vessels by blocking signal transducers and transcription activators, and exhibit anticancer activities, as promising candidates for cancer treatment (Kuo, Lin et al. 2002). In a cellular apoptosis study using hepatocellular carcinoma cells, aloe-emodin was found to promote p53 and p21 expression causing cell apoptosis (Kuo, Lin et al. 2002). On the other hand,

aloe-emodin could suppress the transcription of estrogen receptor (ER) α protein and down regulate ERα levels, thus inhibiting breast cancer cell proliferation (Huang, Huang et al. 2013). Another study also demonstrated that aloe-emodin caused cell apoptosis in human colon cancer cells by the activation of caspase-6 within cancer cells (Suboj, Babykutty et al. 2012). However, aloe-emodin is not the only compound from *Aloe vera* that has been identified as a potential anti-cancer candidate. Studies have also suggested that glycoproteins present in *Aloe vera* demonstrated anti-tumor efficacies (Yagi, Egusa et al. 1997), while a polysaccharide fraction isolated from *Aloe vera* could prevent the formation of potentially cancer-initiating benzopyrene-DNA adducts in primary rat hepatocytes (Kim and Lee 1997). However, further research will be required to support the clinical use of *Aloe vera* for cancer treatment (Kim and Lee 1997). Nonetheless, previous studies on the anti-cancer properties of various *Aloe vera* extracts have suggested that these components could modulate different pharmacological pathways related to cancer growth.

4.4 Immunomodulatory activity

The immunomodulatory activity of Aloe vera comes from its macromolecular polysaccharides and glycoproteins. It is generally believed that the immunoregulatory

activity of acemannan is related to the activation of macrophages, to produce cytokines IL-6 and TNF-α, and to act together with interferon IFN-γ to promote the release of NO and expression of surface antigens, and to induce morphological changes of the cells (Zhang and Tizard 1996). An immunomodulatory study on rats showed that *Aloe vera* gel extract taken orally at a dose of 200 and 400 mg/kg exhibitedsignificant phagocytic activity as compared with aspirin (a positive control group) (R. R. Bhalsinge 2018). The orally administered *Aloe vera* supplemented probiotic lassi was found to prevent shigella infiltration from epithelial barrier into systemic blood flow and thus showed immunoprotective effects in a mouse model and acted against shigella dysenteriae induced infection (Hussain, Patil et al. 2017). *Aloe vera* extract from leaf gel was also reported to modulate immune response by augmenting secondary humoral immunity and decreasing cell-mediated immunity when treated orally in rats (Halder, Mehta et al. 2012). As mentioned in the previous section, *Aloe vera* consumption improves the immune system by increasing the CD4 count, which may be beneficial to HIV-infected patients (Olatunya, Olatunya et al. 2012). In addition, the effect of *Aloe vera* on immune regulation of the skin has also been studied. The extract of *Aloe vera* gel can prevent immune suppression caused by UV exposure and reduce the risk of skin cancer, possibly by modulating DNA-damage-activated signal transduction pathways (Strickland 2001). All these

findings provide scientific basis for the immunomodulatory effects of *Aloe vera*, as either a food supplement or a medical ingredient.

4.5 Anti-oxidant activity

Aloe vera contains many antioxidants, including α-tocopherol (vitamin E), carotenoids, ascorbic acid (vitamin C), flavonoids and tannins (Choi and Chung 2003) . Earlier studies have revealed that reactive oxygen species (ROS) was found to play a role in the development of diseases such as cancer (Borek 1997). These antioxidants contribute to the regulation or neutralization of ROS in the body, thus providing treatment for various diseases such as diabetes (Ceriello, Mercuri et al. 2001). *Aloe vera* gels extracted with methanol and acetone exhibited radical-scavenging activities towards 1,1-diphenyl-2-picrylhydrazyl (DPPH) free radical and superoxide (Mansourian, Saheb-Jamee et al. 2011). Meanwhile, polysaccharides isolated from *Aloe vera* gel were shown to provide protective effects against 2,2′-azobis(2-amidinopropane) dihydrochloride (AAPH)-induced oxidative stress in an *in vitro* kidney epithelial cell model as well as *in vivo* zebrafish model (Kang, Kim et al. 2014). Fig. 3 showed that addition of *Aloe vera* polysaccharide (APS) reduced the level of ROS and decreased cell deaths in an oxidative stress

induction assay in a zebrafish model. Meanwhile, an *in vivo* study revealed that hepatic glutathione (GSH) and uric acid levels were restored to normal levels after oral administration of *Aloe vera* gel extract in an azoxymethane -induced oxidative stress rat model (Anilakumar, Sudarshanakrishna et al. 2010). In summary, components found in *Aloe vera* exhibited anti-oxidation activities *in vitro* and *in vivo*, suggesting that *Aloe vera* could be beneficial in combating diseases related to oxidation stress in the body such as cancer, diabetes, as well as cardiovascular (Yang, Yang et al. 2017) and neurodegenerative diseases (Uttara, Singh et al. 2009).

Fig. 3. Influence of APS against AAPH-induced oxidative stress. A) ROS level and B) cell deaths in the zebrafish model. Experiments were performed in triplicate and the data are expressed as mean ± SE. $*P < 0.05$ and $**P < 0.01$. Addition of APS decreased both the ROS level and cell death. Reprinted from (Kang, Kim et al. 2014), Copyright (2017) with permission from Elsevier.

4.6 Anti-inflammation activity

Inflammation is a natural response in the body against infections or pathogens, however, chronic inflammation is related to various diseases such as cancer,

atherosclerosis (Libby, Ridker et al. 2002) and obesity (Xu, Barnes, Yang, Tan, Yang, Chou, et al., 2003). *Aloe vera* extracts exhibit anti-inflammatory effects by inhibiting prostaglandin E2 production from arachidonic acid both *in vitro* and *in vivo* (Vazquez, Avila et al. 1996). An *in vitro* study based on human colorectal mucosa and carrageenan-induced rat paw edema models, showed that aqueous extract of *Aloe vera* inhibited prostaglandin E2 production from arachidonic acid (Langmead, Makins et al. 2004). In a rat adjuvant-induced arthritic inflammatory model, *Aloe vera* extract can reduce the inflammatory response by 48% (Hanley, Solomon et al. 1982). Studies on the anti-inflammatory substances present in *Aloe vera* extracts showed that lupeol was the most active anti-inflammatory steroid in aloe extract (Davis, Donato et al. 1994). These sterols were able to reduce inflammation by up to 37% in a croton oil-induced oedema in an investigation on mice. With Lupeol being the most active anti-inflammatory sterol (Davis, Donato et al. 1994), as well as these reported anti-inflammatory effects of *Aloe vera* extract, *Aloe vera* extracts hold great potential for the treatment of inflammatory diseases and further investigations are warranted.

4.7 Skin protection

Aloe vera also exhibits skin protective properties, and it has been used as in this role throughout history since the ancient times (Pereira and Bartolo 2016). However, modern pharmacological studies have also provided evidence of these protective effects. *Aloe vera* keeps the skin moist and thus it is widely used as a moisturizer for the treatment of dry skin. For instance, *Aloe vera* gel gloves can improve skin integrity and reduce the appearance of fine lines and erythema (West and Zhu 2003); *Aloe vera* gel can be used as a curative for the treatment of pimples. Among different *Aloe vera* extracts, aloe mucopolysaccharides help to combine water with the skin (Sahu, Giri et al. 2013), thus providing moisturizing effects. The leaf gel materials of *Aloe vera* was approved in a clinical trial to improve skin entropy, homogeneity and energy at 30 and 90 min after application and thus have a larger hydrating effect that is superior to deionized water (Fox, du Plessis et al. 2014). *Aloe vera* also protects the skin from aging and it is thus used in the cosmetics fields (Sahu, Giri et al. 2013). In a clinical trial of radiation-induced dermatitis, *Aloe vera* extract can reduce the impact of ultraviolet light on the skin, as some of the antioxidants and vitamins found in *Aloe vera* leaf can neutralize the impact of ultraviolet (UV) radiation (Haddad, Amouzgar-Hashemi et al. 2013). *Aloe vera* gel can modulate the release of skin keratinocytes derived from immunosuppressive cytokines such as interleukin-10 (IL-10), thereby preventing UV-induced delayed hypersensitivity reactions (Byeon,

Pelley et al. 1998). Studies have shown that *Aloe vera* gel contains small molecule immunomodulators, such as G1C2F1, which prevents epidermal Langerhans cells from UV-induced skin immune responses (Lee, Han et al. 1999). These studies provided scientific evidence supporting the historical use of *Aloe vera* as a skin protective agent.

4.8 Wound healing properties

Aloe vera gel has historically been considered to be a skin healing plant in traditional medicine (Grace, Simmonds et al. 2008). While wound healing processes can usually be divided into three phases, including inflammation, hyperemia (removal of dead tissue) and the third phase of leukocyte infiltration that includes epithelial regeneration and the formation of fibrous tissue (Pereira and Bartolo 2016). Acemannan, one of the abundant active ingredients in *Aloe vera* gel, helps accelerate wound healing and activate macrophages to stimulate the release of fibrotic cytokines (Zhang and Tizard 1996). *Aloe vera* gel also showed beneficial effects on the epidermal keratinocytes during the wound healing process (Moriyama, Moriyama et al. 2016), as scratch wound healing assay demonstrated that both *Aloe vera* gel (AVG) and Cape aloe extract (CAE) promoted the migration of keratinocytes hence promoted

wound closure (Fig. 4). *Aloe vera*, together with other 2 aloe species, have shown the ability to speed up the healing of wounds in keratinocytes with negligible toxicity on normal human keratinocyte cells (Fox, Mazumder et al. 2017). Acemannan directly binds to the growth factors and promotes the prolonged stimulation of granulation tissues (Zhang and Tizard 1996). Moreover, evidence indicates that mannose-6-phosphate in *Aloe vera* gel plays a key role in the treatment of first and second degree burns (Liu, Chen et al. 2010). Due to the effectiveness of mannose-6-phosphate, a topical formulation prepared from the natural gel of leaves of *Aloe vera* have cured human second-degree burn wounds at a healing rate about one-half faster than that of silver sulfadiazine (Abdolhossein, Abdolazim et al. 2007). These aloe polysaccharides promote fibroblast proliferation and produce hyaluronic acid and hydroxyproline in fibroblasts, both of which play a role in extracellular matrix remodeling during the wound healing process (Chantarawaratit, Sangvanich et al. 2014). *Aloe vera* gel has been used to treat radioactive burns and radioactive ulcers (Sato, Ohta et al. 1990). A clinical study has shown that the healing rate of burns in patients treated with *Aloe vera* is faster than that of patients treated with 1% silver sulfadiazine cream (Shahzad and Ahmed 2013). These studies not only provided supporting evidence of the healing efficacy of *Aloe vera*, they also identified the components in *Aloe vera* that are responsible for the wound healing process, such as

acemannan and mannose-6-phosphate found in *Aloe vera* leaf gel.

Fig. 4. Effects of AVG and CAE on the wound healing in human epidermal keratinocytes. A) HPEKs were treated with AVG or CAE, and subjected to the scratch wound healing assay over 8 h. White dotted lines indicate wound margins. The graph indicates the mean ± SEM values for wound closure rate. B) Addition of AVG or CAE onto a superficial incisional wound (the epidermis had been removed) from human full-thickness skin equivalents and cultured at the air-liquid interface for 3 days. Representative images of hematoxylin and eosin staining of each group are shown. Arrowheads indicate wound margins (Moriyama, Moriyama et al. 2016).

4.9 Blood glucose and cholesterol modulation

Diabetics are associated with high blood glucose levels, and *Aloe vera* also plays a role in the treatment of diabetes and its associated symptoms (Hui, Tang et al. 2009). Clinical studies have shown that *Aloe vera* gel has anti-hyperglycemic and anti-hypercholesterolemia effects in patients with type 2 diabetes (Pothuraju, Sharma et al. 2016). In addition, *Aloe vera* gel also helps to improve carbohydrate metabolism. For example, a study has shown that *Aloe vera* gel can reduce the body weight, body

fat, fasting blood glucose and fasting serum insulin in obese patients, helping to improve the metabolic status of obese patients with diabetes and early untreated diabetes (Choi, Kim et al. 2013). Jain et al. established a study demonstrating that *Aloe vera* gel not only had anti-diabetic effects but also had cardioprotective activity since it can significantly reduce oxidative stress and alleviate the antioxidant status in STZ-induced diabetic rats (Jain, Vijayaraghavan et al. 2010).

In addition, *Aloe vera* also helps to relieve hyperlipidemia. In a randomized, double-blind, placebo-controlled clinical trial, *Aloe vera* gel was found to significantly reduce total cholesterol (by 8.35%, compared with the baseline level) and low-density lipoprotein levels (by 4.48%, compared with the baseline level) in patients with hyperlipidemia type 2 diabetes (Huseini, Kianbakht et al. 2012). While hyperlipidemia is one of the causes of polycystic ovary syndrome (PCOS), reports have indicated that the treatment of PCOS rats using *Aloe vera* gel could reduce the plasma triglyceride and low-density lipoprotein cholesterol levels (Desai, Maharjan et al. 2012).

4.10 Hepatoprotective activity

Several studies have shown that *Aloe vera* extracts exhibited hepatoprotective

activities. An investigation on *Aloe vera* demonstrated the hepatoprotective activity against carbon tetrachloride (Chandan, Saxena et al. 2007). On the other hand, *Aloe vera* gel could suppress the mRNA expression of lipogenic genes in the ethanol-induced fatty liver investigation by modulating various pharmacological pathways. (Kumar, Rakesh et al. 2013). The administration of fresh *Aloe vera* leaf extracts at concentration of 1.0 mL/kg body weight reduced the serum level of hepatic enzyme markers such as glutamate pyruvate transaminase (GPT) (41.8%), and gamma-glutamyl transferase (GGT) (14.3%) in a lindane-induced hepatoxicity rat model (Etim, Farombi et al. 2006). In a paracetamol-induced hepatotoxicity investigation, single day as well as seven day treatments using a concentration of 250 and 500 mg/kg aqueous extract of *Aloe vera* significantly reduced the levels of aspartate transaminase (AST), alanine transaminase (ALT) and alkaline phosphatase (ALP) while restoring the depleted liver thiol levels that had been otherwise depleted by exposure to paracetamol (Nayak, Gincy T.B et al. 2011). All of these studies demonstrated the hepatoprotective effects of *Aloe vera* leaves with various pharmacological roles.

5. Clinical applications

Aloe is a common plant with great medicinal value in traditional medicine and has attracted much attention in the modern medical field due to its various pharmacological activities. Here, we systematically summarized the studies of *Aloe* and its active components in preclinical experiments, and the progress of toward the application of these medicines in clinical treatments. According to the modern pharmacological studies, *Aloe* and its active components have various pharmacological activities such as anti-inflammatory, antibacterial, antiviral, anti-cancer, anti-ulcer and antioxidant properties. The range of clinical applications involves multiple aspects (Singab, El-Hefnawy et al. 2015)

5.1 Treatment of skin diseases

Many related studies have demonstrated that *Aloe* and its active components have powerful therapeutic effects on several chronic skin diseases such as psoriasis and acne (Miroddi, Navarra et al. 2015), as well as many types of skin inflammations. Syed et al. conducted a double-blind, placebo-controlled study to assess the clinical efficacy of topical *Aloe vera* extract (0.5 w/w%) in a hydrophilic cream on patients with psoriasis. Sixty patients (36M/24F, mean 25.6 years old) with slight to moderate chronic psoriasis were randomly divided into two groups and given cream

containing 0.5 w/w% *Aloe vera* extract or an equal percentage of a placebo, respectively. Each patient administered the trial medication topically 3 times daily for 5 consecutive days per week (with a maximum of 4 weeks of active treatment) and were checked by physicians weekly after administration. The results suggested that after treatment for 4 weeks, 45% of the patients in the 0.5 w/w% *Aloe vera* extract treatment group showed significantly improved symptoms, including a progressive reduction of lesions, desquamation followed by decreased erythema, infiltration and lowered PASI score without exhibiting obvious side-effects (Syed, Ahmad et al. 1996). In addition, it has been reported that *Aloe vera* lotion has a prophylactic use for reducing the intensity of radiation-induced dermatitis (Haddad, Amouzgar-Hashemi et al. 2013). Many previous studies have indicated that *Aloe vera* and its active components have promising potential for the effective treatment of skin diseases with minimal side-effects.

5.2 Wound healing

A number of clinical studies have demonstrated that *Aloe* has potential applications for the treatment and healing of wounds. Results of a prospective double blind clinical trial to assess the efficiency of a topical cream containing 0.5 wt% *Aloe vera* inner

leaf juice powder on the chronic anal fissures showed that, after 1 week of treatment, the pain of patients in aloe cream group was dramatically relieved and wound healing time was significantly decreased in comparison to the non-aloe cream group (Rahmani, Khademloo et al. 2014). Xu and co-workers investigated the clinical efficiency of *Aloe vera* on second degree burns. The results suggested that a combination of scald ointment and powder of *Aloe vera* internal layer showed higher therapeutic efficacy and provided faster recovery than was achieved via treatment with the scald ointment alone (Xu 2004).

5.3 Treatment of oral diseases

Several pharmacological studies have demonstrated that *Aloe* can be used for alleviating various kinds of oral inflammations such as periodontitis. In the treatment of oral diseases, it also can help to fight dental diseases and oral mucosal diseases, and protect the oral environments (Nair, Naidu et al. 2016). For instance, Mansourian et al. compared the therapeutic effects of *Aloe vera* mouthwash with triamcinolone acetonide (TA) 0.1 wt% mouthwash on oral lichen planus (OLP) by a randomized double-blinded clinical trial (Mansourian, Saheb-Jamee et al. 2011). Results showed that the *Aloe vera* and TA mouthwash had comparable therapeutic effects, which

indicated that *Aloe vera* mouthwash could provide a substitute for TA mouthwash in the treatment of OLP. Moreover, a randomized triple-blinded clinical trial revealed that mouthwash containing *Aloe vera* was as beneficial as benzydamine mouthwash in the treatment of radiation-induced mucositis in patients suffering from head and neck cancers (Sahebjamee, Mansourian et al. 2015). According to the investigation by Alam and co-workers, in the treatment progress of oral submucous fibrosis (OSMF), the group treated with *Aloe vera* gel exhibited a significant alleviation of most OSMF symptoms, in comparison to the non-*Aloe vera* gel group, suggesting that *Aloe vera* gel was an effective agent in treatment of OSMF (Alam, Ali et al. 2013). In addition, findings of a randomized clinical trial on dental care products indicated that toothpaste containing an *Aloe vera* has an impressive effect on oral care like improving plaque index scores (Pradeep, Agarwal et al. 2012).

5.4 Treatment of diabetes

On the basis of a randomized double-blinded placebo-controlled clinical trial investigating the anti-hyperglycemic effects of *Aloe vera* leaf gel, the combination of *Aloe vera* leaf gel and conventional therapeutic drugs (glyburide and metformin) obviously decreased the fasting blood glucose, total cholesterol (TC) and low density

lipoprotein (LDL) levels of hyperlipidemic type 2 diabetic patients who had a tolerance to glyburide and metformin without adverse effects, indicating that *Aloe vera* leaf gel has anti-hyperglycemic activity (Huseini, Kianbakht et al. 2012). Another randomized controlled clinical trial on prediabetes and early non-treated diabetic patients showed that *Aloe vera* supplementation significantly reduced the concentrations of fasting blood glucose, triglyceride, TC, and LDL-cholesterol (Zhang, Liu et al. 2016). All of these findings demonstrated that *Aloe vera* and its active components have positive effect on the treatment of diabetes.

5.5 Liver protection

Several clinical trials have demonstrated *Aloe* genus has protective effects on the liver. For example, Zhang et al. investigated the protective effect of aloe polysaccharide (AP) on acute and chronic liver injuries induced in mice. They found that AP can significantly decrease ALT and AST activities in serum, increase SOD activity in the hepatic tissue and reduce necrosis of the hepatic lobules, which indicated that AP exhibits a protective effect on the livers of mice (Zhang and Yang 2007). In addition, preliminary clinical trials have reported that *Aloe* genus and its active components, especially aloe-emodin, have therapeutic efficacy against hepatitis

(Wan, Xu et al. 2012).

5.6 Adjuvant therapy of HIV

Olatunya and coworkers studied the role *Aloe vera* gruel plays in the adjuvant therapy of HIV infection. According to the results of this preliminary trial that was over a 1-year period, patients given a combination of antiretroviral drugs and *Aloe vera* gruel daily had enhanced body immunity and increased CD4 count (CD4 cell is the target of attack of human immunodeficiency virus) with no significant side-effects, in comparison to patients who were given only antiretroviral drugs, suggesting that the consumption of *Aloe vera* may be beneficial to HIV-infected individuals (Olatunya, Olatunya et al. 2012). The reasons of the benefit of *Aloe vera* on HIV therapy are varied. Firstly, the acemannan in *Aloe vera* was reported to inhibit HIV *in vitro* (Kahlon, Kemp et al. 1991). In addition, the *Aloe vera* components have immune-modulatory effects, and the highly nutritive ingredients such as vitamins, trace mineral elements, amino acids also contributed to the well-being of patients with HIV infection (Olatunya, Olatunya et al. 2012). Lastly，due to the excellent absorption of Aloe vera gel across various membranes, such as skin (Cole and Heard 2007) and intestinal epithelia (Lebitsa, Viljoen et al. 2012), *Aloe vera* gel has been

reported to improve the absorption of vitamins C and E (Vinson, Al Kharrat et al. 2005). For the antiretroviral drug didanosine in the treatment of HIV infection and AIDS，*Aloe vera* has also exhibited great permeation enhancing property across buccal mucosa, thus improving anti-HIV and AIDS therapy (Ojewole, Mackraj et al. 2012). In summary, the clinical applications of *Aloe vera* and its active components have attracted increasing attention in recent years due to the confirmation of various pharmacological activities of these compounds. Bearing this in mind, the prospects for the further development of clinical applications based on Aloe and their active component appears very bright.

6. Food applications

The use of *Aloe vera* gel has attracted increasing interest in the food industry, where the *Aloe vera* can be used as a source of functional foods in heath drinks, beverages, milk, ice cream confectionary and so on (Sanchez-Machado, Lopez-Cervantes et al. 2017, Hassan, Chatha et al. 2018). These products often claim many health benefits，such as mitigative effect on rheumatoid arthritis, cancer, diabetes, digestive and intestinal disorders, or ulcers (Lopez, Nunez-Jinez et al. 2017). At the same time, *Aloe vera* is also used as a medicinal and edible plant, to relieve diarrhea, detoxify, and

improve human immunity, and provide supplements of amino acids, vitamins, trace elements and minerals. For instance, Vitamin B_{12}, usually available from an animal source, has been found in trace amount in Aloe gel (Rodriguez Rodriguez, Darias Martin et al. 2010). There are some bottled *Aloe vera* gel or juice that has claimed to have therapeutic effects against gout, constipation, arthritis and many other illnesses in the USA (Eshun and He 2004). More and more scientific research proves promising health benefits by drinking *Aloe vera* juice, such as strengthening cardiac contraction, lowering cholesterol and triglyceride level, reducing risks for cardiovascular disease, decreasing blood glucose, and promoting cell regeneration after being ingested (M.A. Elbandy 2014). A 12-week, randomized, double-blinded, placebo-controlled study found that oral Aloe sterols derived from *Aloe vera* can reach the peripheral tissues through bloodstream when ingested, and may also stimulate the increase of the collagen content in the dermis, maintaining healthy skin (Tanaka, Yamamoto et al. 2016).

Aloe is currently approved by the US FDA as a food flavoring agent in accordance with good manufacturing practices (Ulbricht, Armstrong et al. 2009). In addition, because of its antimicrobial properties, *Aloe vera* can also be used as edible coating material to prevent food from microbial growth, reduce the loss of nutrients and the

evaporation loss of water of fruits and vegetables, thereby prolonging the shelf life and improving the food quality (Hassan, Chatha et al. 2018). One successful example of edible coating with *Aloe vera* is with table grape and sweet cherry to maintain the quality of the fruits (Martinez-Romero, Alburquerque et al. 2006, Castillo, Navarro et al. 2010). What's more, *Aloe vera* has also attracted emerging attention in poultry farming industry for its application in broiler diets, utilizing its impacts on intestinal microflora, growth performance, and anticoccidial effects, making *Aloe vera* a natural feed additive instead of antibiotic agents and thus contributing to healthy chickens, and ultimately healthy human (Babak and Nahashon 2014). The Annex I of Regulation (EC) No 1831/2003 has listed *Aloe vera* as sensory additive functional group "flavoring compounds", which can be used by the feed industries to increase smell or palatability of feeding stuffs (Ch. Franz 2005).

The extensive application of *Aloe vera* in the food industry has further promoted the flourishing of *Aloe vera* industry worldwide, making *Aloe vera* a "wonder plant" and gift to the humanity by nature. It is rather common to find *Aloe vera* as valuable functional ingredient incorporated in the food industry (Guo and Mei 2016), especially in today's society, people tend to search for more natural and organic food in the pursuit of a healthy lifestyle .

7. Preparations & Products

At present, the pharmaceutical activities of the *Aloe* species have been investigated extensively, but many studies conducted in China have mainly been based on the conventional applications of *Aloe* and were mainly fundamental studies rather than application-based research. Thus, aloe studies conducted have not focused on the practical applications of these compounds, and thus the commercial and medicinal developments of Aloe products have been limited. On the other hand, when we look through the situation of research and development of aloe products worldwide, we can see their research on *Aloe* have focused on the treatment of serious diseases such as diabetes and HIV infection. What is noteworthy is that the object of many foreign studies has been generally a single-component or a sample with clearly-defined components.

Even though *Aloe* is a promising plant with various pharmaceutical activities, more clinical research will need to be undertaken to validate the therapeutic efficacy of human serious diseases of aloe-based pharmaceuticals. At present, most aloe products which have been approved for the marketplace are health care products and cosmetics, which are not used for treatment of diseases. Examples of such products include Colon Cleanse® capsules developed from By-Health® Company and 92% *ALOE*

VERA soothing gel from Nature Republic® Company**.**

8. Toxicology

Overall, research has demonstrated that *Aloe vera* contains a variety of ingredients, some of which are toxic and are responsible for some of the toxic events reported (Boudreau and Beland 2006, Lee, Lee et al. 2014, Guo and Mei 2016) . Furthermore, *Aloe vera* extract can be derived from three different parts of the plant, including the whole *Aloe vera* leaves, *Aloe vera* inner gel and *Aloe vera* latex (Sahu, Giri et al. 2013). In 2016, researchers summarized the cytotoxicity, genotoxicity, carcinogenicity and adverse clinical response caused by different components of the *Aloe vera* leaf (Guo and Mei 2016). The toxicity of *Aloe vera* mainly originates from anthraquinones and phenolic compounds found in *Aloe vera* latex (Boudreau, Beland et al. 2013). Therefore, the International Aloe Committee of Science Standards has determined that the maximum allowable *Aloe vera* juice content for oral medical use should be less than 10 ppm and should not exceed 50 ppm for non-medicinal use (Dentali 2013).

9. Summary and Future prospects

In summary, *Aloe vera* has a long history of medicinal uses in various cultures and its pharmacological applications have been demonstrated by many studies that have complied with the modern Western medical standards. In addition, the use of *Aloe vera* has been growing with increasing applications as health and cosmetic products. It is important to clarify the efficacy and mechanism of *Aloe vera* products in these areas and meanwhile it is equally important to expand its use in new areas. For instance, the application of *Aloe vera* as bio-engineering materials has emerged recently. *Aloe vera* gel extracts were used as a scaffold for tissue engineering, which increased cell growth (Jithendra, Rajam et al. 2013), as well as cornea endothelial cell regeneration (Kim, Sim et al. 2016). *Aloe vera* was also used for bone regeneration with anti-infection properties demonstrated (Selvakumar, Pawar et al. 2016). However, as the safety studies have shown conflicting results, more studies regarding the toxicology profile of *Aloe vera* would also be useful to avoid any potential adverse effects arising from the use of *Aloe vera* in order to foster the development of this natural product for the benefits of the global populations.

Acknowledgement

This paper was supported by the Research Committee, University of Macau (Grant

No.: MYRG2017-00010-ICMS) and Macau Science and Technology Development Fund (Grant No.: FDCT 030/2017/A1). We are also grateful to Dr. Ian Wyman for assisting proofreading of the manuscript.

Conflict of interest

The authors have declared that there is no conflict of interest.

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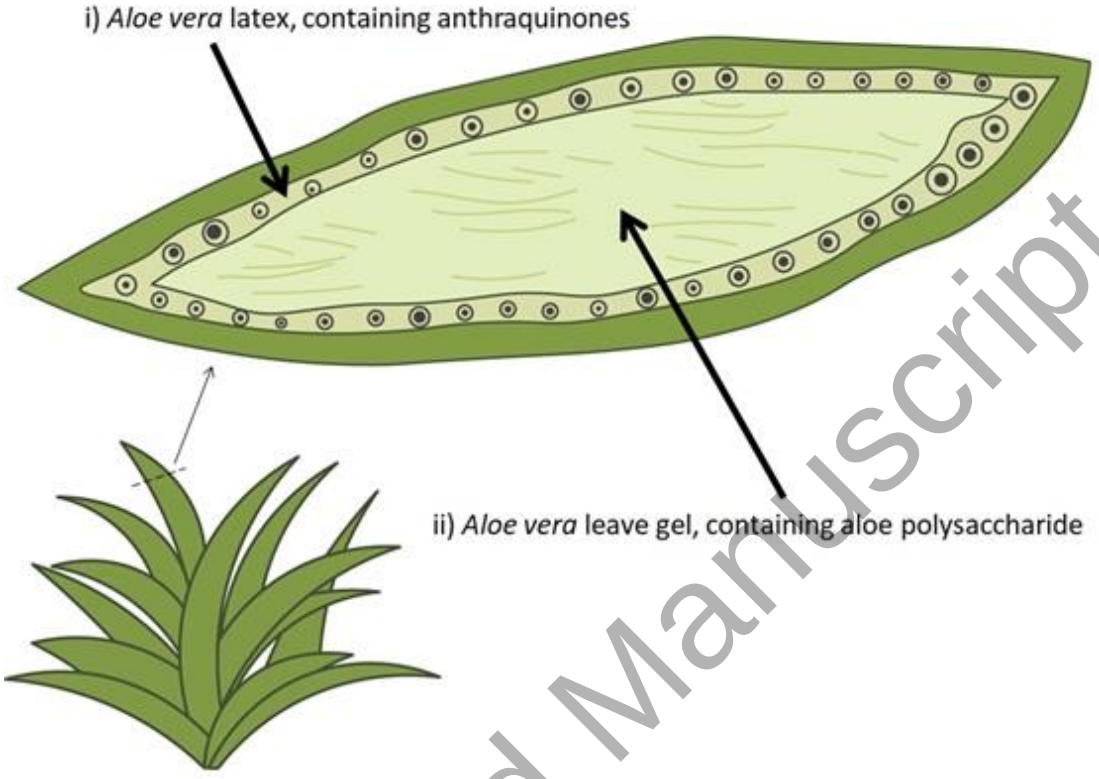
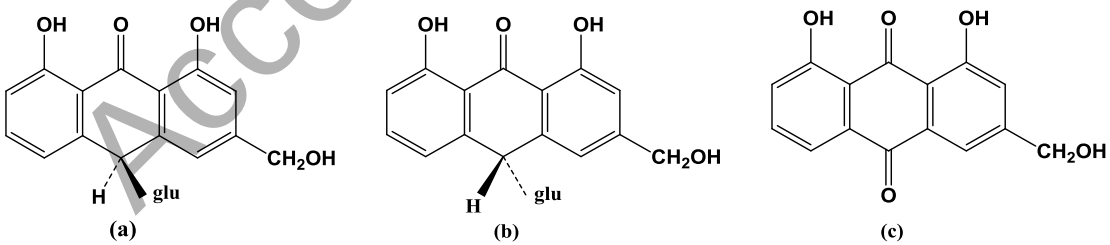


Fig. 1. Bottom: *Aloe vera* plant; Top: cross section of an *Aloe vera* leaf, i) *Aloe vera* latex and ii) *Aloe vera* inner gel.



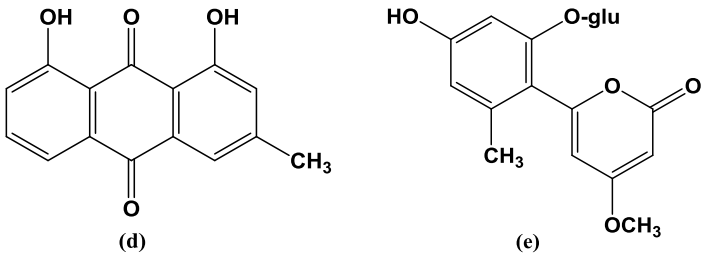


Fig. 2. Chemical structures of aloin A (a), aloin B (b), aloe-emodin (c), chrysophanol (d) and aloenin (e).

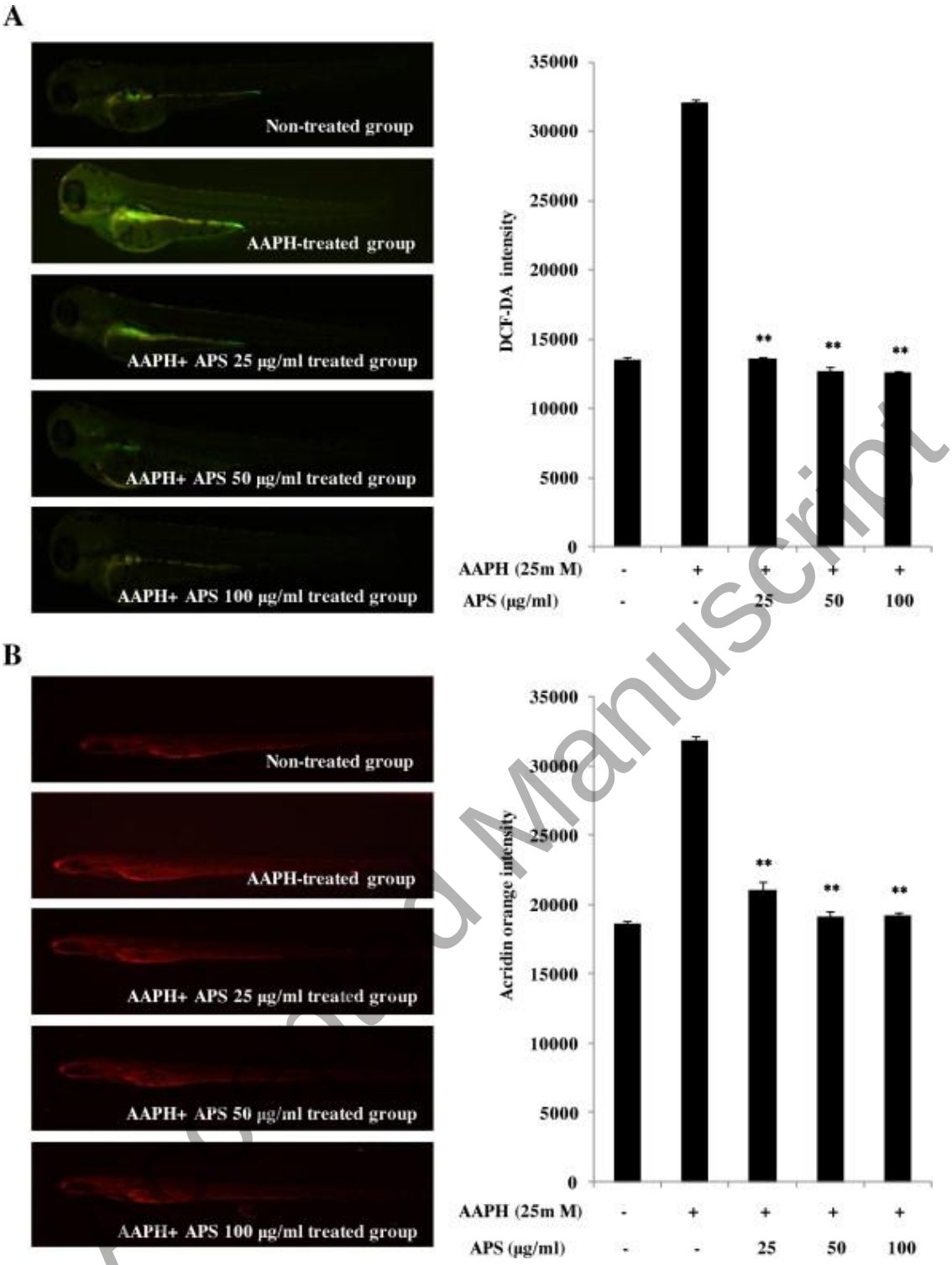


Fig. 3. Influence of APS against AAPH-induced oxidative stress. A) ROS level and B) cell deaths in the zebrafish model. Experiments were performed in triplicate and the data are expressed as mean ± SE. $*P < 0.05$ and $**P < 0.01$. Addition of APS decreased both the ROS level and cell death. Reprinted from (Kang, Kim et al. 2014), Copyright (2017) with permission from Elsevier.

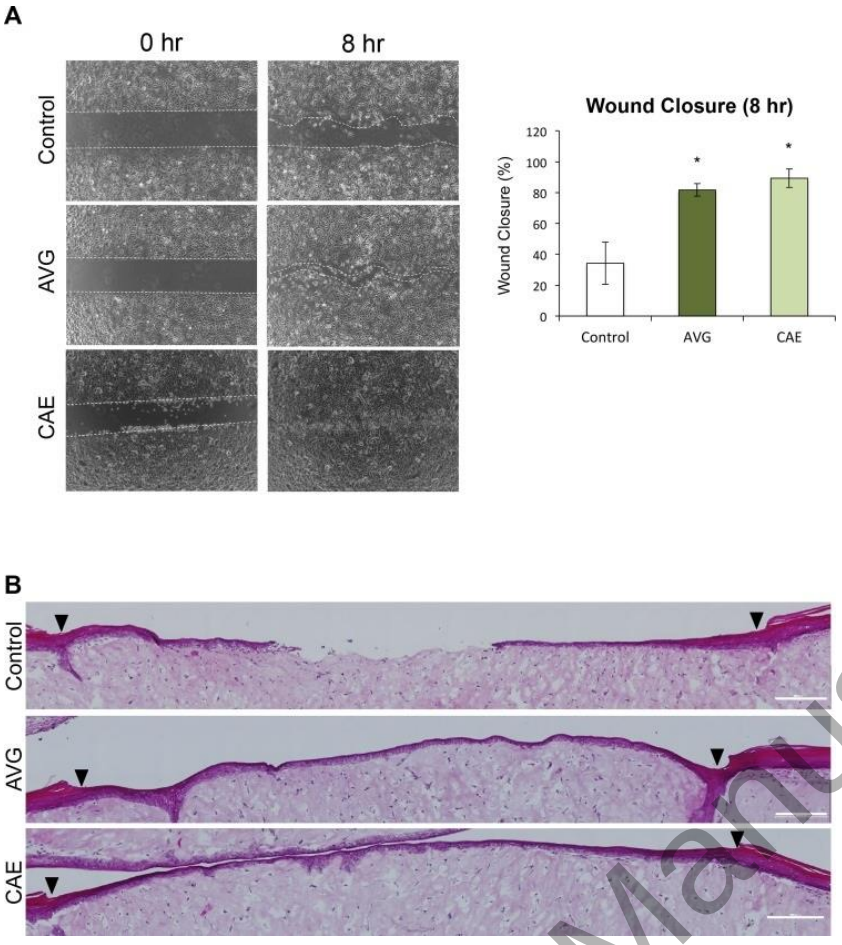


Fig. 4. Effects of AVG and CAE on the wound healing in human epidermal keratinocytes. A) HPEKs were treated with AVG or CAE, and subjected to the scratch wound healing assay over 8 h. White dotted lines indicate wound margins. The graph indicates the mean ± SEM values for wound closure rate. B) Addition of AVG or CAE onto a superficial incisional wound (the epidermis had been removed) from human full-thickness skin equivalents and cultured at the air-liquid interface for 3 days. Representative images of hematoxylin and eosin staining of each group are shown. Arrowheads indicate wound margins (Moriyama, Moriyama et al. 2016).