Sys Rev Pharm. 2019;10(1):118-125.
A multifaceted Review journal in the field of Pharmacy

Review article

Molecular Mechanism of *Aloe barbadensis* Miller as a Potential Herbal Medicine

Nur Atik[1]*, Alfya Nandika[2], Putu Indra Cyntia Dewi[1], Erda Avriyanti[3]
[1]Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, Bandung, INDONESIA.
[2]Undergraduate Program, Faculty of Medicine, Universitas Padjadjaran, Bandung, INDONESIA.
[3]Department of Dermatology and Venereology, Faculty of Medicine, Universitas Padjadjaran, Bandung, INDONESIA.

ABSTRACT

Currently, the trends of alternative and complementary medicine are highly developed. In the last few decades, the National Health Statistics Report (NHSR) in America has shown a substantial increase in the use of alternative and complementary drugs. The use of herbs as medications or supplementations should result from a right decision between patient and physician regarding potential risks, benefits, and other alternatives. Although many herbs exhibit promising effects, most herbs have not been yet scientifically approved, including their molecular mechanism process. In this review, *Aloe barbadensis* Miller or popularly known as *Aloe vera* will be discussed as a potential local medicinal plant from cellular and molecular mechanisms aspect. Thorough studies over the last few decades have demonstrated that *Aloe vera* possesses various bioactive compounds that are responsible for its medicinal properties. G1G1M1DI2 glycoprotein fraction, for example, as one of the bioactive compound found in this plant, has shown to accelerate the wound healing process. The present review reports the findings of the underlying cellular and molecular mechanisms of *Aloe vera* pharmacological activity from the extensive literature search and our previous reports. This review may help to promote local medicinal plant such as *Aloe vera* in order to improve its value and utilization in the community setting.

Key words: *Aloe vera*, molecular, cellular, mechanism.
Correspondence:
Nur Atik
Department of Biomedical Sciences, Faculty of Medicine, Universitas Padjadjaran, Bandung, INDONESIA.
E-mail: n.atik@unpad.ac.id
DOI : 10.5530/srp.2019.1.20

INTRODUCTION

Health is an indicator of the success of human capacity building that has a significant influence on the economy, social, and education. Health problems can be classified into infectious diseases, non-communicable diseases, and injuries, which may result in decreased productivity and quality of life and even death. Based on WHO data, 70% of 56.4 million global health problems in 2015 are associated with cardiovascular disease, cancer, diabetes, and chronic lung disease. Barriers to cure those diseases are still considered an issue in low- and middle-income countries, including Indonesia.[1,2]

Currently, the trends of alternative and complementary medicine are highly developed. In the last few decades, the National Health Statistics Report (NHSR) in America has shown a substantial increase in the use of alternative and complementary drugs. An interview conducted in America revealed that 40% of American adults used alternative and complementary medicine. This high demand is influenced by several factors, such as accessible factors, relative affordability, and the common perception that alternatives and complementary medicine are safer, as well as more effective even if the scientific evidence has not been obtained.

It is estimated that there are 420,000 plant species in the world, yet very limited are known to be useful and scientifically proven as an alternative or complementary medicine. Herbs can be any kind of plant or product derived from plants including leaves, flowers, roots, seeds or fruit. The plant may be used in raw form or processed, where the plant will be macerated with water, alcohol, or other solvents that are generally used for chemical extraction. The resulting product contains many chemicals, for example, fatty acids, sterols, alkaloids, flavonoids, glycosides, saponins and others. Since herbs contain various components, some companies manufacture standardized herbal products by identifying the active ingredients candidates and maintaining the number of active ingredients in the product consistent.[3,4,5]

The use of herbs as medications or supplementations should result from a right decision between patient and physician regarding potential risks, benefits, and other alternatives. Although many herbs exhibit promising effects, most of the herbs have not yet been scientifically tested and their use has not been monitored properly, on top of that, the interaction of their use when combined with existing drugs, could have serious side effects.[4,5,6]

Indonesia is a tropical country that has abundant biological wealth. Various methods of healing known as herbal medicine are mostly done by using various plants in the community setting. However, the mechanisms of such treatment are still poorly understood. In this article, we will discuss one of the potential local medicinal plants mechanisms as herbal medicine as a result of our research.

MOLECULAR MECHANISM OF ALOE BARBADENSIS MILLER AS POTENTIAL HERBAL MEDICINE

The effects of *Aloe barbadensis* Miller gel on wound healing

A study to see the benefits of *Aloe barbadensis* Miller has been conducted in our faculty to determine the difference in the effect between Aloe as a topical gel and povidone-iodine solution on the wound healing process in mice. After treatments on experimental animals, skin tissue was then prepared for histology assessment. The preparations were assessed by observing the thickness of the epithelium, the number of fibroblasts, blood vessels, and the expression of vascular endothelial growth factor-A (VEGF-A). The results of each parameter were subsequently analyzed statistically. The results of this study indicate that the effect of *Aloe barbadensis* Miller on wound healing in all parameters have the higher outcome (statistically significant) compared with povidone iodine or wound healing without intervention.[7]

The effect of *Aloe barbadensis* Miller on this healing process is because of its ability to stimulate re-epithelialization due to the presence of G1G1M1DI2 glycoprotein fraction, which could stimulate keratinocyte proliferation. The G1G1M1DI2 glycoprotein fraction will increase the multiplication of keratinocytes, migration of the involved factors, and formation of the epidermis, continued by progress to wound healing. G1G1M1DI2 fraction also increases DNA synthesis and expression of epithelial growth factor (EGF) receptor. The ligand will bind to the EGF receptor, then it will transmit the proliferation signal from G1G1M1DI2. Alternatively, G1G1M1DI2 may activate general metabolism and increase metabolic activity which would then increase the expression of EGF receptors (Figure 1). This effect can speed up re-epithelialization

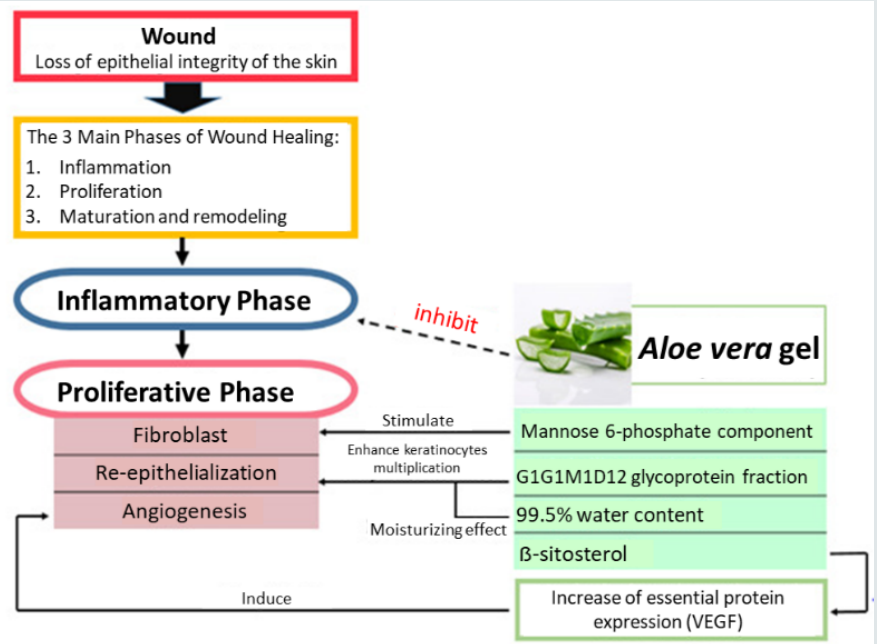

Figure 1: The molecular mechanism of *Aloe vera* (*Aloe barbadensis* Miller) in the wound healing process.

by increasing the multiplication and migration of keratinocytes and increase the period of epidermal closure of the wounded skin.[7,8]

In our study, the average number of fibroblasts in the *Aloe barbadensis* Miller group was higher than the control or povidone iodine group. The increased amount of fibroblasts may be due to the activity of the manosa-6-phosphate component which can bind to the receptor of IGF-2 / manosa- 6-phosphate that present on the cell surface of fibroblasts. It causes the stimulation of fibroblasts to proliferate, differentiate into myofibroblasts, or produce collagen and other matrix proteins in huge quantities. Another possibility is the effect of G1G1M1DI2 glycoprotein fraction on *Aloe barbadensis* Miller that can stimulate cell proliferation by increasing the expression of EGF receptors. As our previous data, cell proliferation, including fibroblasts, is strongly influenced by EGF. TGF-ß produced by platelets, macrophages, and neutrophils will initiate this cascade by activating target cells (fibroblasts) to produce CTGF and become responsive to CTGF. If there is a co-mitogen in the environment (PDGF or EGF), along with CTGF, both factors will stimulate fibroblasts to proliferate. In other words, increased expression of EGF receptors by G1G1M1DI2 glycoprotein fraction may increase the proliferation of fibroblasts (Figure 1).[7,8,9]

The number of blood vessels and expression of VEGF-A were also higher in the group treated with *Aloe barbadensis* Miller compared with the control group or group treated with povidone-iodine. This is in accordance with studies that prove the angiogenic effects of β-sitosterol from *Aloe barbadensis* Miller can increase the formation of new blood vessels. Essential proteins in angiogenesis will increase as a consequence of stimulation of β-sitosterol, including VEGF, VEGF Flk-1 receptor, von Willebrand factor, and laminin. The increase of their expression could enhance the proliferation and migration of endothelial cells, which later increase the formation of new blood vessels. Another mechanism of ß-sitosterol in angiogenesis is mentioned in other studies that shows β-sitosterol compound may induce the formation of new blood vessels in chorio-allantoic membrane (CAM) in chicken embryos. ß-sitosterol stimulates the human umbilical vein endothelial cell (HUVEC) motility in vitro, which in turn increases the migration of these cells. The angiogenic effects on the wound healing process may be caused by β-sitosterol that found in *Aloe barbadensis* Miller.[9,10,11]

The effect of *Aloe barbadensis* on wound healing may also be due to the acemannan content as a potent agent that activates macrophages. In the inflammatory phase, macrophages have a crucial role in regulating tissue repair. Macrophages release cytokines and growth factors (such as PDGF, TGF-α, TGF-β, EGF VEGF), which further recruit keratinocytes, fibroblasts, and endothelial cells to repair the tissue. Afterward, these substances bind to growth factors as well as maintain the stability of the activity. [10,11]

The protective effects of Aloe barbadensis Miller *gel on lungs of cigarette smoker*

As already well known, the number of chronic obstructive pulmonary disease (COPD) patients could increase because of cigarette smoke exposure. The cigarette smoke that inhaled into the lungs increased alveolar macrophage cells as the body's initial defense response. This evidenced by an increase in the number of alveolar macrophages isolated from the broncho-alveolar lymphoid tissue (BALT) in lung smokers. Additionally, the toxin content in cigarette smoke decreases the expression of Toll-like receptor 2 (TLR2), followed by the decreased activity of macrophage phagocytosis. Exposure to cigarette smoke may also induce the incidence of alveolar epithelial cell apoptosis and pulmonary vascular endothelial cells by suppressing Bcl2 protein expression through inhibition of the release of cytochrome C from mitochondria.[12,13]

We did a study on experimental animals by exposing the rats with cigarette smoke and administered *Aloe barbadensis* Miller gel for 42 days. After that, the lungs of mice were taken for later examinations, which are a number of macrophage observation, macrophage phagocytosis test, as well as immunohistochemistry with an anti-Bcl2 antibody. It prove that exposure to cigarette smoke can increase the number of macrophages in the lungs and *Aloe barbadensis* Miller gel can prevent the process of the increment. The results due to the presence of vitamin C and sterols in Aloe gel that is known as an antioxidant and anti-inflammatory by inhibiting acute inflammatory processes.[12,13,14]

Our previous study showed that the group given exposure to cigarette smoke without *Aloe barbadensis* Miller gel administration have a lower alveolar macrophage phagocytosis activity than the control group.

Interestingly, the group given the Aloe gel had higher macrophage activity than the control group. These results explained the presence of long chain polysaccharide molecules in Aloe gel that could modulate the immune system by increasing the production and improving macrophage activity (Figure 2). [12,13,14]

The content of beta-sitosterol in *Aloe barbadensis* Miller gel can increase the expression of Bcl2, which will suppress the occurrence of cell apoptotic process in alveolar. Thus, the administration of Aloe gel is expected to decrease the incidence of cell apoptosis in lung induced by cigarette smoke.[12,15]

The cardiomyocytes protection of Aloe barbadensis Miller *gel*

Cardiomyopathy is a pathological condition in the heart, especially myocardium that causes the heart cannot function optimally. Cellular damage to the heart muscle can be induced by various causes, for instance, exposure to cigarette smoke. The toxins content in cigarette smoke not only inhibit the flow of oxygen in the blood but also carried to the heart so that the metabolic processes and respiration of cardiomyocytes are disrupted, which could lead to the occurrence of hypoxic conditions in myocardium.[16]

We have researched to prove the effect of *Aloe barbadensis* Miller as cardiomyocytes protector agent against free radical molecules caused by exposure to cigarette smoke on experimental animals. *Aloe barbadensis* Miller gel extract is proven to reduce the incidence of fibrosis in the myocardium. That findings demonstrated the group of mice treated with Aloe gel extracts have smaller amount of fibroblasts in the myocardium than the untreated group. Hence, this clearly concludes that the antioxidant present in Aloe gel can prevent the increase of free radical in the blood due to exposure to cigarette smoke, followed by the decrease of the amount of cell damage in the myocardium. It knows that the number of damaged cells could affect to fibroblasts stimulation.[17,18,19]

In addition to inducing cell death and increasing the formation of fibroblasts in the myocardium, exposure to cigarette smoke can also decrease the expression of vascular endothelial growth factor-A (VEGF-A). However, these factors function in the regulation of growth and improvement of the endothelial through its bond with the VEGF type-2 receptor (VEGFR2). Such interaction will stimulate proliferation, migration, and tubular formation in cardiac endothelial cells. The antioxidant present in *Aloe barbadensis* Miller gel may increase VEGF-A expression in myocardial cells (Figure 3).[17, 20,21]

The antibacterial effect of Aloe barbadensis Miller

Aloe barbadensis Miller has been used by the pharmaceutical industry because of its several effects including laxative, anti-inflammatory, immunostimulant, antiseptic, wound healing, antiulcer, antitumor and antidiabetic. *Aloe barbadensis* Miller also has antibacterial activity by inhibiting the growth of *Shigella flexneri* and *Streptococcus pyogenes*. Other bacteria such as *Staphylococcus aureus, Pseudomonas aeruginosa, Escherichia coli, Propionibacterium acne, Helicobacter pylori and Salmonella typhii* were reported eliminated or significantly reduced by the antimicrobial agent of Aloe gel.[22,23] Anthraquinones, dihydroxyanthraquinones and saponins are proposed to have direct antimicrobial activity. Another component such as polysaccharides has antibacterial activity through stimulation of bacterial phagocytosis by leukocyte. Pyrocatechol that is also present in *Aloe barbadensis* Miller has a toxic effect on bacteria by proteins denaturation and cell membranes disruption. This hydroxylated phenol also acts as a disinfectant and antituberculocidal agent. Cinnamic acid in Aloe gel has antibacterial activity by inhibiting glucose uptake and ATP production in resting cell of bacteria. P-coumaric acid observed in Aloe gel increases the microorganism lag phase and inhibit microorganism enzymatic activity. Antibacterial activity of ascorbic acid originates from interfering with the cell membrane, enzymatic activity or genetic mechanisms.[22] In dentistry, Gutta percha (GP) is used as important

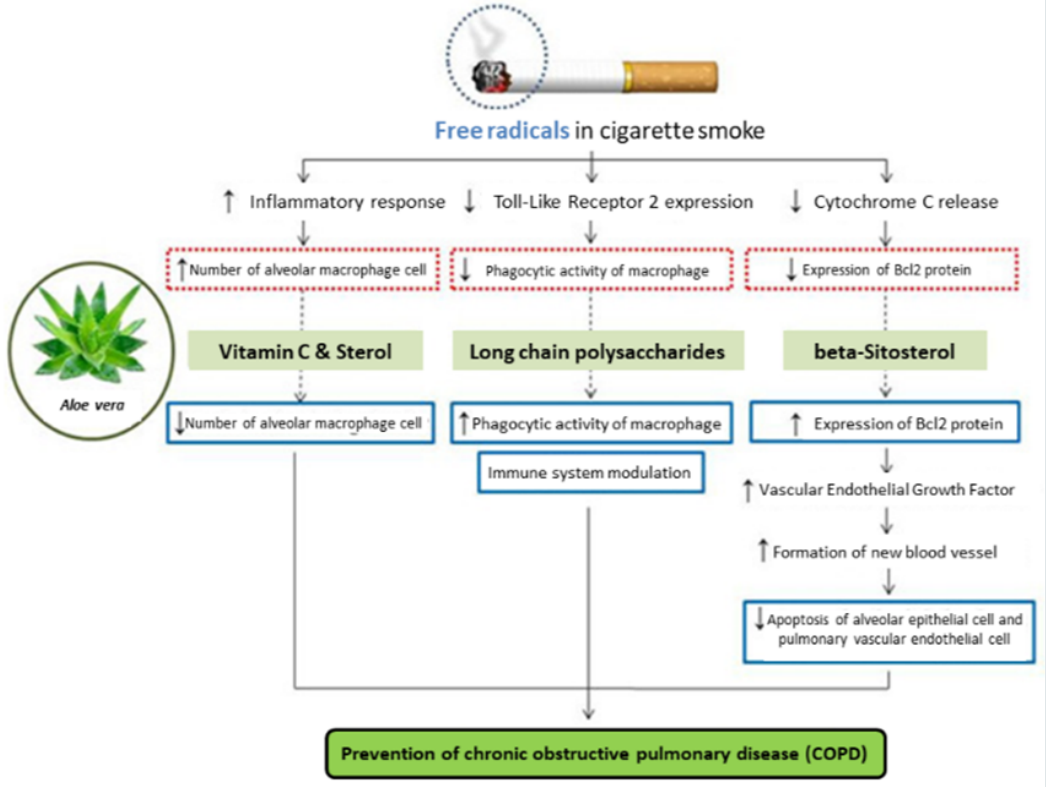

Figure 2: The molecular mechanism of *Aloe vera* (*Aloe barbadensis* Miller) in the prevention of COPD from cigarette smoke consumption.

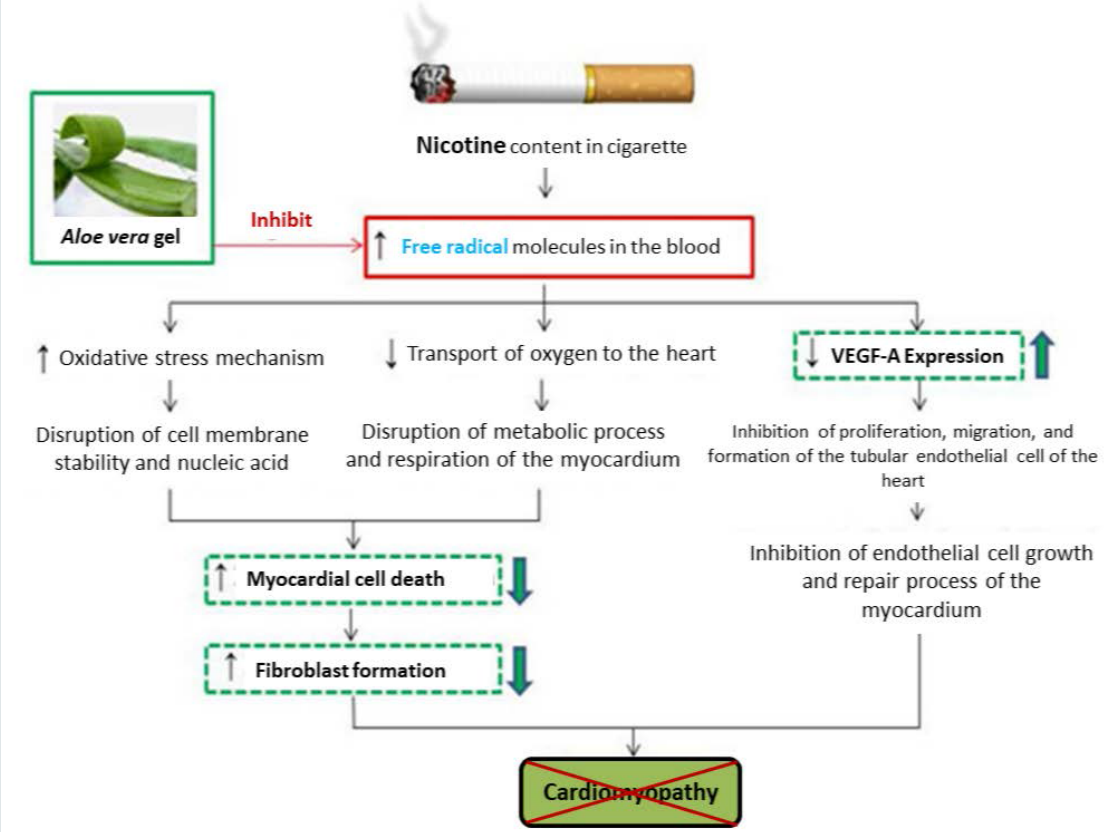

Figure 3: The molecular mechanism of *Aloe vera* (*Aloe barbadensis* Miller) in the prevention of cardiomyopathy from cigarette smoke consumption.

dental material and as the prime root canal filling. GP is an extract of palaquiam of the blanco genus of Sapotaceae family. Before obturation, commercial GP is not usually sterilized or decontaminated. Several compounds have used for GP decontamination such as hydrogen peroxide, chlorhexidine, ethyl alcohol, polyvinylpyrrolidone iodine, and quaternary ammonium. However, none of these compounds are fully effective. As previously described, Aloe gel has antibacterial effect for many bacteria. It reported that Aloe gel could be used effectively for decontaminating GP cones within a short duration.[24]

The antidiabetic effect of Aloe barbadensis Miller

Diabetes mellitus (DM) is one of the highest metabolic diseases worldwide.[25] The prevalence of DM was 285 million people worldwide and rose to 382 million people in 2013. There are two types of diabetes mellitus, namely DM type-1 and type-2. DM type-2 occurs when the body cannot utilize the produced insulin to take glucose into the cell.[25,26]

In human, *Aloe barbadensis* Miller juice has shown antidiabetic effect in combination with glibenclamide.[27] Other study, using *Aloe barbadensis* Miller high molecular weight fraction (AHM) showed that administration of AHM 3 times daily for 12 weeks simultaneously with oral hypoglycaemic drug resulted in significant reduction of fasting blood glucose. AHM also acts as thromboxane A2 inhibitor that can stimulate vasodilation. This effect can maintain the perfusion to surrounding tissue in diabetic patient.[28] In mouse model of diabetes, processed Aloe gel (PAG) exerts antidiabetic activity. When PAG gave, fasting blood glucose level decreased to normal level. PAG also reduced plasma insulin level concentration in the fasted state by decreasing blood glucose and insulin level. Plasma lipid levels and hepatic triacylglyceride concentration reduced after oral administration of PAG. It was speculated that these reductions caused by PAG ameliorated insulin resistance. Expression of the adipogenic genes SREBP-1a, FAS, and GPAT was suppressed by PAG, suggesting that reduction of lipid toxic effect by PAG in the liver could improve insulin resistance. However, the component of PAG that is responsible for antidiabetic effect have not been identified.[29]

The effect of Aloe barbadensis Miller *on Bone Marrow Stromal Cells (BMSCs) proliferation, differentiation and bone formation*

As previously discussed, *Aloe barbadensis* Miller affects on wound healing. This plant also affects on bone formation in tooth extraction model. There are three overlapping phases in socket healing: blood clot formation, bone formation, and bone remodeling. Osteoprogenitor cells migrate, proliferate and differentiate to osteoblast on wound site when bone formation phase occurred. BMSCs are the source of osteoprogenitor cell. Acemannan, the b-(1–4)- acetylated polymannose, which is the major polysaccharide from Aloe gel, accelerated oral wound healing and reparative dentin formation. In bone formation, BMSCs proliferation was stimulated by acemannan. Acemannan stimulated BMSCs proliferation and bone formation by upregulating VEGF, BMP-2, extracellular matrix synthesis and mineral deposition. Acemannan also increases bone mineral density. Histologically, osteoblast and osteocyte found higher when treated with acemannan.[30]

The antibacterial, antiulcer and cytoprotective effect of Aloe barbadensis Miller *on peptic ulcer disease*

In the world's population, peptic ulcer disease has become a significant threat. This disease has high morbidity and mortality. It results from an imbalance between gastric acid and defensive mucosal barrier function.[31] Etiology of this disease is numerous, for example, *Helicobacter pylori* infection, drugs, acid hypersecretion state, tumors, Crohn's disease, andsystemic mastocytosis. There are several factors

contributed to ulcer formation such as smoking, excessive alcohol use, NSAIDs, emotional stress and psychological factors. The pathogenesis of this disease is complex and multifactorial.[31-35]

Helicobacter pylori infection has a robust association with the peptic ulcer (gastric and duodenal ulcer). These bacteria colonize the gastric epithelium.[31,36,37] The infection caused by these bacteria impair the negative feedback regulation of gastrin release and acid secretion. These bacteria can produce alkaline ammonia to protect themselves and disrupt the ability of D cell in sensing acidity. This disruption leads to a reduction of somatostatin secretion and increase of gastrin secretion.[31,38,39] Eventually, causing excessive acid secretion. *H. pylori* also inhibit neural antral inhibitory complex, causing an increase of acid secretion by the parietal cell. *H. pylori* induced inflammation in gastric mucosa. This inflammation reaction induces Interleukin (IL) 8 and IL 1B. This process leads to an influx of neutrophil and macrophage with the release of lysosomal enzymes, leukotrienes, and reactive oxygen species that can impair mucosal defense and cause ulceration.[31] Another etiology of peptic ulcer is NSAIDs. NSAID, especially the non-selective COX-2 group supress prostaglandin production by inhibiting both COX-2 and gastric COX-1. Cyclooxygenase-1 (COX-1) is an important enzyme for the production of gastric prostaglandin. The inhibition of COX-1 may impair the gastric mucosal lining protection, which leads to ulceration.[31,40]

Aloe barbadensis Miller has been used to treat peptic ulcer. As previously described, this plant has an antibacterial effect to *H. pylori*.[22,23] With this effect, the growth of *H. pylori* in gastric or duodenal mucosa can be suppressed. Consequently, it can reduce the infection and inflammation of gastric mucosa caused by *H. pylori*. *Aloe barbadensis* Miller has a cytoprotective effect on gastric mucosa. It hypothesized that there are several mechanisms of this cytoprotective effect, such as increased mucus synthesis, bicarbonate secretion, increased mucosal blood flow, and increased phospholipid mucosal coating. The neovascularization effect is also suggested to play a role in gastric protection by improving the re-epithelialization process. *Aloe barbadensis* Miller also has an antiulcer effect by its acid reducing properties. The acid reducing properties presumably exists due to lecithin content in this plant. Lecithin is a glycoprotein that can recognize and bind to carbohydrate moieties. It can inhibit aminopyrine uptake by parietal cells. *Aloe barbadensis* Miller also inhibits the effect of histamine in augmenting acid secretion by interacting with H2-receptors on the parietal cell. Therefore, the mechanism of acid reducing properties possibly generated from the direct inhibition of parietal cells and the inhibition effect of histamine.[41]

The antitumor effect of Aloe barbadensis Miller

Many plants studied as anti-cancer agents. *Aloe barbadensis* is one of them. This plant has various bioactive components that have chemopreventive potentials such as lectin, aloin aloe-emodin and aloesin. They showed immune potential, anti-mutagenic, anti-proliferative, inducing apoptosis of tumor cells, antioxidant and anti-metastasis effect.[42,46,47] These effects are mediated via targeting many receptors such as ER-A, STAT3 protein, STAT3-regulated anti-apoptotic (Bcl-xl), MMP-2, urokinase plasminogen activator (u-PA), VEGF receptor (VEGFR), c-MYC, and VEGF.[42-45] Moreover, *Aloe barbadensis* Miller active compounds such as aloe-emodin, barbaloin and aloesin also enhance antioxidant enzyme activities.[42,46,47] In vivo studies reported that there is increase of glutathione S-transferase (GST) and Superoxide Dismutase (SOD) activities in Ehrlich ascites carcinoma cell (EACC) tumor cells after treated with *Aloe barbadensis* Miller compound.[47] Several studies also reported that *Aloe barbadensis* Miller can reduce the intensity of radiation-induced inflammation.[43,49,50]

In vitro study in human breast (MCF-7) and cervical (HeLa) cancer cells after treated with *Aloe barbadensis* Miller crude extract (ACE) demonstrated a decrease of the viability of these cells in dose and time-dependent manner.[42] *Aloe barbadensis* Miller also have unique properties towards the proliferation of the cells. On the contrary from cancer cells, the viability of normal lymphocytes treated with ACE was not reduced significantly. These results demonstrated that *Aloe barbadensis* Miller significantly reduced the proliferation of cancer cells but not toxic to the normal cells. Treatment of the MCF-7 and HeLa cells with ACE resulted in significant changes in cellular morphology. The cells are rounding off, shrinking and detached from the matrix. They characterized with chromatic condensation and fragmentation along with the appearance of intensified apoptotic bodies with increasing time of exposure to ACE. From cycle analysis, it reported that there is increase proportion of cells in the sub-G0/G1 phase after treatment with ACE. This shown that ACE induces cell death via apoptosis. Apoptosis induced the effect of *Aloe barbadensis* Miller also correlated from the enhancement of bax gene by this plant. The anti-proliferative effect of *Aloe barbadensis* Miller correlated from the expression of cyclin D1 and p21. This study found decreased expression of cyclin D1 and increase expression of p21 when these cancer cells treated with ACE. *Aloe barbadensis* Miller due to its many mechanisms towards cancer cells and less side effect possibly prove to future studies to be an agent for human cancer[42]

The effect of *Aloe barbadensis* Miller to corneal healing

The cornea is the outermost layer of the eye. The cornea is transparent and has no blood vessels. Cornea also plays an important role in vision by focusing light entering the eye. Corneal injury is one of the major presentation of eye trauma. Corneal injury can potentially be threatening vision.[51,52] Every year, there are 2.5 million cases of eye trauma reported and 50.000 people permanently lose some or all of their vision.[53] Treatment of corneal injury is critical because incomplete healing of corneal injury can affect vision. The treatment must be done immediately to maintain corneal integrity, restore visual function, and avoid complications that may occur.[54]

In many countries, *Aloe barbadensis* Miller has been used for many years for medical purposes. As previously mentioned, it has many compounds that possess effects in wound healing, antibacterial, antiulcer, antioxidant, antitumor and cardioprotective. In Indonesia, *Aloe barbadensis* Miller can thrive on peatlands due to the tropical climate. It has many compounds such as bradykinase, lignin, aloctin, campestrol, β-sitosterol, and glucomannan that show anti-inflammatory effect (Figure 4). Furthermore, there are many compounds that have antiseptic and antibacterial effect such as lupeol, phenol, sulfur and anthraquinone. Because of these effects, this plant can accelerate the wound healing process. No toxic effects were observed in the cornea after treated with Aloe gel.

In vivo study showed that there was slower growth of corneal fibroblast when treated with *Aloe barbadensis* Miller in comparison with control. The mechanism is still unknown, probably because the active components of this plant induce apoptosis and inhibit proliferation. This effect creates a better visual outcome because increasing number of corneal fibroblast can cause corneal scarring. Corneal wound healing is a complex process that requires the involvement of many tissues, growth factor and cytokines. Re-epithelialization is an important process during corneal wound healing. In in vivo study using diabetic rats that undergo delayed corneal re-epithelialization, topical application of *Aloe barbadensis* Miller accelerates the corneal epithelial wound closure. It is also shown in this study that there is an increase in epithelial wound closure whether the rats were diabetic or not. The mechanism of re-epithelialization is affected by several biochemical factors such as epidermal growth factor, insulin-like growth factor 1 (IGF-1), platelet-derived growth factor, transforming growth factor (TGF-β), and basic fibroblast growth factor (bFGF). The study reported

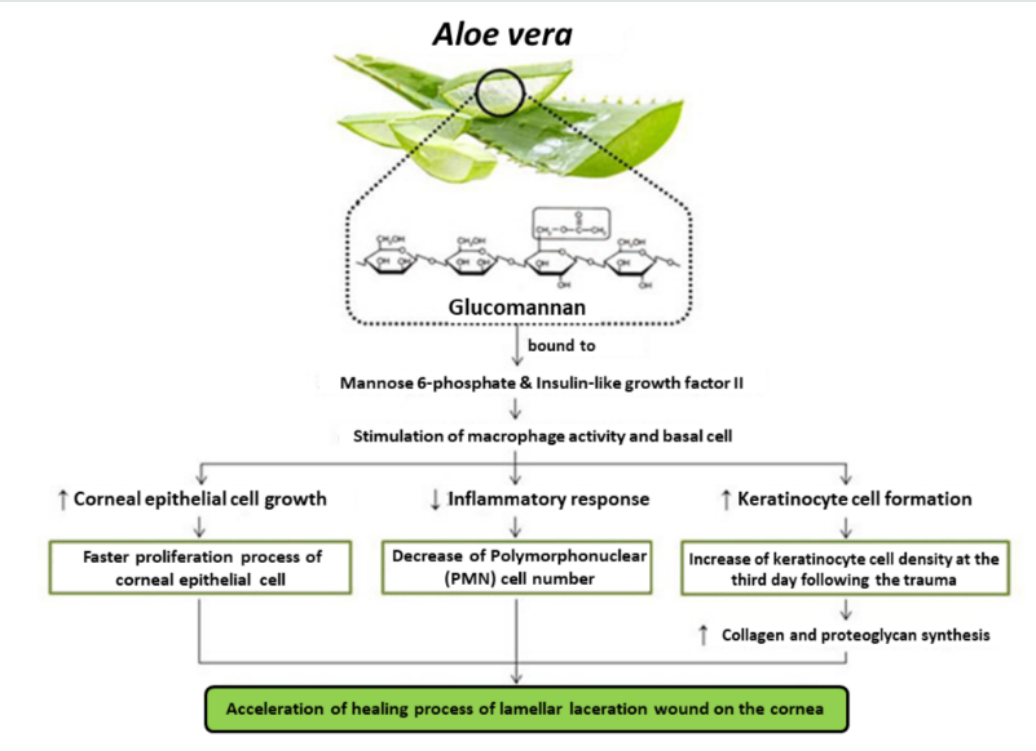

Figure 4: The molecular mechanism of *Aloe vera* (*Aloe barbadensis* Miller) in the corneal wound healing process.

Table 1: Summary of *Aloe barbadensis* Miller type of study.

No.	Effect	Type of study	Reference(s)
1.	Effects of *Aloe barbadensis* Miller gel on wound healing	In vivo (animal study)	7-11
2.	Protective effects of *Aloe barbadensis* Miller gel on lungs of cigarette smoker	In vitro, In vivo (animal study)	12-15
3.	Cardiomyocytes protection of *Aloe barbadensis* Miller gel	In vitro, in vivo (animal study)	16-21
4.	Antibacterial effect of *Aloe barbadensis* Miller	In vitro	22-24
5.	Antidiabetic effect of *Aloe barbadensis* Miller	In Vivo (RCT), in vivo (animal study)	25-29
6.	Effect of *Aloe barbadensis* Miller on bone marrow stromal cells	In vitro	30
7.	Effect of *Aloe barbadensis* Miller on peptic ulcer disease	In vitro, In vivo (animal study)	22,23,40
8.	Antitumor effect of *Aloe barbadensis* Miller	In vivo (animal study), in vitro	41-49
9.	Effect of *Aloe barbadensis* Miller to corneal healing	In vivo (animal study)	51-57

that there were increase in TGF and bFGF expressions that accelerated skin wound healing and increased epithelialization. *Aloe barbadensis* Miller also inhibits the inflammatory process by decreasing the level of pro-inflammatory cytokine, reducing adhesion and infiltration of leukocyte.[55] All of the study types regarding the effects of *Aloe barbadensis* Miller are presented in Table 1.

CONCLUSION

The present review highlights molecular mechanisms of bioactive compounds present in *Aloe barbadensis* Miller as a promising candidate for herbal medicine. These bioactive compounds yield various pharmacological effects including acceleration in the wound healing process, protection on the lung of a cigarette smoker, protection on cardiomyocytes, antibacterial effect, antidiabetic effect, bone formation, cytoprotection on ulcer disease, antitumor effect, and corneal healing effect. Therefore, these scientifically proven data indicate that this plant has high value in the community for its health promoting benefits. Various bioactive compounds in *Aloe barbadensis* Miller are also still considered a great opportunity for future research related with the possibility of their new health promoting benefits other than discussed in this review. Eventually, more complete and systematic studies towards phytochemical and pharmacological properties of *Aloe* barbadensis are Miller desirable to establish the utilization of this plant as herbal medicine more convincing.

ACKNOWLEDGEMENT

The authors thank the DIKTI grant and USAID through Sustainable Higher Education Research Alliances (SHERA)-Centre for Collaborative Research on Acute Respiratory Infections (CCR-ARI) Program.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ABBREVIATIONS

ACE: *Aloe vera* crude extract; **AHM**: *Aloe vera* high molecular weight fraction; **ATP**: adenosine triphosphate; **BALT**: broncho-alveolar lymphoid tissue; **Bcl2**: B-cell lymphoma 2; **bFGF**: basic fibroblast growth factor; **BMP-2**: bone morphogenetic protein 2; **BMSCs**: bone

marrow stromal cells; **CAM**: chorio-allantoic membrane; **COPD**: chronic obstructive pulmonary disease; **CTGF**: connective tissue growth factor; **DM**: diabetes mellitus; **EACC**: Ehrlich ascites carcinoma cell; **EGF**: epithelial growth factor; **FAS**: fatty acid synthase; **GP**: gutta percha; **GPAT**: glycerol 3-phosphate acyltransferase; **GST**: glutathione S-transferase; **HUVEC**: human umbilical vein endothelial cell; **IGF-1**: insulin-like growth factor 1; **IGF-2**: insulin-like growth factor 2; **IL**: interleukin; **MMP-2**: matrix metalloproteinase 2; **NSAID**: nonsteroidal anti-inflammatory drug; **PAG**: processed *Aloe vera* gel; **PDGF**: platelet-derived growth factor; **SOD**: superoxide dismutase; **SREBP-1a**: sterol regulatory element binding protein 1a; **STAT3**: signal transducer and activator of transcription 3; **TGF-α**: transforming growth factor alpha; **TGF-ß**: transforming growth factor beta; **TLR2**: Toll-like receptor 2; **u-PA**: urokinase plasminogen activator; **VEGF**: vascular endothelial growth factor; **VEGF-A**: vascular endothelial growth factor-A; **VEGFR**: vascular endothelial growth receptor.

REFERENCES

1. who.int [Internet]. Geneva: World Health Organization, Global Health Observatory (GHO) data; c2019 [cited 2019 Apr 9]. Available from: https://www.who.int/gho/ncd/mortality_morbidity/en/
2. Hughes BB, Kuhn R, Peterson CM, Rothman DS, Solórzano JR, Mathers CD, *et al.* Projections of global health outcomes from 2005 to 2060 using the International Futures integrated forecasting model. Bulletin of the World Health Organization. 2011 Jul;89(7):478-86.
3. Pan SY, Zhou SF, Gao SH, Yu ZL, Zhang SF, Tang MK, *et al.* New perspectives on how to discover drugs from herbal medicines: cam's outstanding contribution to modern therapeutics. Evid Based Complement Alternat Med. 2013;2013:627375.
4. Bent S. Herbal medicine in the United States: review of efficacy, safety, and regulation: grand rounds at University of California, San Francisco Medical Center. J Gen Intern Med. 2008;23(6):854–859.
5. Chrysant SG, Chrysant GS. Herbs used for the treatment of hypertension and their mechanism of action. Curr Hypertens Rep. 2017;19:77.
6. Ekor M. The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. Front Pharmacol. 2014;4:177.
7. Atik N, Rahman JI. Perbedaan efek pemberian topikal gel lidah buaya (aloe vera l.) Dengan solusio povidone iodine terhadap penyembuhan luka sayat pada kulit mencit (*Mus musculus*). Majalah Kedokteran Bandung. 2009 Jun 25;41(2).
8. Vogt PM. PVP-iodine in hydrosome and hydrogel – a novel concept in wound therapy leads to enhanced epithelialization and reduced loss of skin grafts. Burns. 2006 Sep;32(6):698-705.
9. Wang Z, Gao Z, Shi Y, Sun Y, Lin Z, Jiang H, *et al.* Inhibition of Smad3 expression decreases collagen synthesis in keloid disease fibroblasts. J Plastic, Reconstuctive & Aesthetic Surgery. 2007; 60:1193-9.
10. Roy H, Bhardwaj S, Herttuala SY. Biology of vascular endothelial growth factors. FEBS Letters. 2006; 580: 2879-87.
11. Scrementi ME, Ferreira AM, Zender C, DiPietro LA. Site-spesific production of TGF-beta in oral mucosal and cutaneous wounds. Wound Repair Regen. 2008;16(1):80-6.
12. Atik N, Avriyanti E, Indrati AR. Pengaruh lidah buaya (Aloe vera L.) pada paru-paru tikus yang diinduksi asap rokok. Majalah Kedokteran Bandung. 2012 Sep 28;44(3):159-64.
13. World Health Organization, International Agency for Research on Cancer. IARC MONOGRAPH, Some Drugs and Herbal Products. vol. 108. Lyon, France: The Association; 2016.p.37-71
14. Williamson G, Coppens P, Serra-Majem L, Dew T. Review of the effcacy of green tea, isoflavones and aloe vera supplements based on randomised controlled trials. Food Funct. 2011;2(12):753-9.
15. Liu SK, Chen P, Chen JB. Apoptosis of alveolar epithelial cells and pulmonary vascular endothelial cells in chronic obstructive pulmonary disease. Zhonghua Jie He He Hu Xi Za Zhi. 2008 Aug;31(8):581-5.
16. Leone A, Biadi O, Balbarini A. Smoking and cardiovascular system: cellular features of the damage. Current pharmaceutical design. 2008 Jun 1;14(18):1771-7.
17. Atik N, Nanua NK, Avriyanti E. The aloe vera effect on cardiomyocytes and vegf-a expression in rats after cigarette smoke exposure. Advanced Science Letters. 2017 Jul 1;23(7):6658-61.
18. Michaud SÉ, Dussault S, Groleau J, Haddad P, Rivard A. Cigarette smoke exposure impairs VEGF-induced endothelial cell migration: role of NO and reactive oxygen species. J Mol Cell Cardiol. 2006 Aug;41(2):275-84.
19. Ushio–Fukai M. VEGF signaling through NADPH oxidase-derived ROS. Antioxidants & redox signaling. 2007 Jun 1;9(6):731-9.
20. Edirisinghe I, Rahman I. Cigarette smoke–mediated oxidative stress, shear stress, and endothelial dysfunction: role of VEGFR2. Ann N Y Acad Sci. 2010 Aug;1203:66-72.
21. Edirisinghe I, Arunachalam G, Wong C, Yao H, Rahman A, Phipps RP, *et al.* Cigarette smoke–induced oxidative/nitrosative stress impairs vegf-and fluid shear stress–mediated signaling in endothelial cells. Antioxid Redox Signal. 2010 Jun 15;12(12):1355-69.
22. Lawrence R, Tripathi P, Jeyakumar E. Isolation, purification and evaluation of antibacterial agents from Aloe vera. Braz J Microbiol. 2009; 40(4):906-15.
23. Nejatzadeh-Barandozi, Fatemeh. Antibacterial activities and antioxidant capacity of Aloe vera. Org Med Chem Lett. 2013; 3: 5.
24. Athiban PP, Borthakur BJ, Ganesan S, Swathika B. Evaluation of antimicrobial efficacy of Aloe vera and its effectiveness in decontaminating gutta percha cones. J Conserv Dent. 2012; 15(3):246-8.
25. Zarrintan A, Mobasseri, M, Zarrintan A, Ostadrahimi A. Effects of Aloe vera supplements on blood glucose level and lipid profile markers in type 2 diabetic patients-a randomized clinical trial. Pharmaceutical Sciences. 2015; 21(2):65.
26. Lynn M, Dorcas E, Bilal J. Prevalence of Diabetes in Zambuk General Hospital. Rep Opinion. 2012; 4:54-57.
27. Bunyapraphatsara N, Yongchaiyudha S, Rungpitarangsi V, Chokechaijaroenporn O. Antidiabetic activity of Aloe vera L. juice II. Clinical trial in diabetes mellitus patients in combination with glibenclamide. Phytomedicine. 1996; 3(3):245-248.
28. A Yagi A, Hegazy S, Kabbash A, Wahab EA. Possible hypoglycemic effect of Aloe vera L. high molecular weight fractions on type 2 diabetic patients. Saudi Pharm J. 2009; 17(3):209-15.
29. Kim K, Kim H, Kwon J, Lee S, Kong H, Im SA, *et al.* Hypoglycemic and hypolipidemic effects of processed Aloe vera gel in a mouse model of non-insulin-dependent diabetes mellitus. Phytomedicine. 2009;16(9):856-63.
30. Boonyagul S, Banlunara W, Sangvanich P, Thunyakitpisal P. Effect of acemannan, an extracted polysaccharide from Aloe vera, on BMSCs proliferation, differentiation, extracellular matrix synthesis, mineralization, and bone formation in a tooth extraction model. Odontology. 2014; 102(2):310-317.
31. Malfertheiner P, Chan FK, McColl KE. Peptic ulcer disease. The Lancet. 2009; 374(9699):1449-1461.
32. Osefo N, Ito T, Jensen RT. Gastric acid hypersecretory states: recent insights and advances. Curr Gastroenterol Rep. 2009;11(6):433-41.
33. Callaghan J, Brown S, Battcock T, Parry S, Snook J. Aggressive Helicobacter pylori-negative peptic ulceration as the initial manifestation of Crohn's disease. Frontline Gastroenterol. 2012;3(3):201-205.
34. Hull DH, Beale PJ. Cigarette smoking and duodenal ulcer. Gut. 1985;26(12):1333-7.
35. Lee YB, Yu J, Choi HH, Jeon BS, Kim HK, Kim SW, *et al.* The association between peptic ulcer diseases and mental health problems: A population-based study: a STROBE compliant article. Medicine (Baltimore). 2017;96(34):e7828.
36. Rauws EAJ, Tytgat GNJ. Cure of duodenal ulcer associated with eradication of Helicobacter pylori. Lancet. 1990; 335: 1233–35.
37. Malfertheiner P, Leodolter A, Peitz U. Cure of Helicobacter pylori- associated ulcer disease through eradication. Baillieres Best Pract Res Clin Gastroenterol. 2000; 14:119-32.
38. Moss SF, Calam J, Legon S, Bishop AE, Polak JM. Effect of Helicobacter pylori on gastric somatostatin in duodenal ulcer disease. Lancet. 1992; 340:930-32.
39. Odum L, Petersen HD, Andersen IB, Hansen BF, Rehfeld JF. Gastrin and somatostatin in Helicobacter pylori infected antral mucosa. Gut. 1994; 35:615-18.
40. Wallace JL. Prostaglandins, NSAIDs, and gastric mucosal protection: why doesn't the stomach digest itself? Physiol Rev. 2008; 88: 1547–65.
41. Yusuf S, Agunu A, Diana M. The effect of Aloe vera A. Berger (Liliaceae) on gastric acid secretion and acute gastric mucosal injury in rats. Journal of ethnopharmacology. 2004: 93(1):33-37.
42. Hussain A, Sharma C, Saniyah K, Kruti S, Shafiul H. Aloe vera inhibits proliferation of human breast and cervical cancer cells and acts synergistically with cisplatin. Asian Pacific Journal of Cancer Prevention. 2015; 16(7):2939-2946.
43. Chen YY, Chiang SY, Lin JG, Ma YS, Liao CL, Weng SW, *et al.* Emodin, aloe-emodin and rhein inhibit migration and invasion in human tongue cancer SCC-4 cells through the inhibition of gene expression of matrix metalloproteinase-9. Int J Oncol. 2010; 36:1113-20.
44. Huang PH, Huang CY, Chen MC, Lee YT, Yue CH, Wang HY, *et al.* Emodin and Aloe-Emodin Suppress Breast Cancer Cell Proliferation through ER α Inhibition. Evid Based Complement Alternat Med. 2013;376123.
45. Pan Q, Pan H, Lou H, Xu Y. Inhibition of the angiogenesis and growth of Aloin in human colorectal cancer in vitro and in vivo. Cancer Cell Int. 2013; 13:69.

46. Choi S, Chung, MH. A review on the relationship between Aloe vera components and their biologic effects. Semin Integr Med. 2003; 1:53-62.
47. Akev N, Turkay G, Can A, Gurel A, Yildiz F, Yardibi H, *et al*. Tumour preventive effect of Aloe vera leaf pulp lectin (Aloctin I) on Ehrlich ascites tumours in mice. Phytother Res. 2007; 21:1070-5.
48. El-Shemy HA1, Aboul-Soud MA, Nassr-Allah AA, Aboul-Enein KM, Kabash A, Yagi A. Antitumor properties and modulation of antioxidant enzymes' activity by Aloe vera leaf active principles isolated via supercritical carbon dioxide extraction. Current medicinal chemistry 2010; 17(2):129-138.
49. Ahmadi A. Potential prevention: Aloe vera mouthwash may reduce radiation-induced oral mucositis in head and neck cancer patients. Chin J Integr Med. 2012; 18:635-40.
50. Haddad P, Amouzgar-Hashemi F, Samsami S, Chinichian S, Oghabian MA. Aloe vera for prevention of radiation- induced dermatitis: a self-controlled clinical trial. Curr Oncol. 2013; 20:345-8.
51. Remington LA. Clinical anatomy and physiology of the visual system. 3rd ed. St.Louis: Elsevier; 2012. p. 10-35.,
52. Mescher AL. Junqueiras's Basic Histology Text and Atlas. 13th ed. Mc Graw Hill; 2013. p. 479-83.
53. Willmann D, Melanson SW. Corneal injury. In: StatPearls. Treasure Island (FL): StatPearls Publishing [Internet]. 2018 Jan [Updated 2018 Oct 27; cited 2019 Apr 9]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK459283/
54. Owens PL, Mutter R. Statistical Brief Related to Eye Injuries. Journal of Healthcare Cost and Utilization Project. 2011;31(1):1-10.
55. Vora GK, Haddadin R, Chodosh J. International Ophthalmology Clinics. vol 53. Lippincott Williams & Wilkins; 2013;53(4):1-10.
56. Lee S. Management of Corneal wounds: Some Practical Tips. Nepalese Journal of Ophthalmology. 2009;1(2):146-50.
57. Atiba A, Wasfy T, Abdo W, Ghoneim A, Kamal T, Shukry M. Aloe vera gel facilitates re-epithelialization of corneal alkali burn in normal and diabetic rats. Clin Ophthalmol. 2015; 9:2019-26.