

A Mini-Review: Possible Mechanisms of Hepatoprotective Effect of Aloe Vera Gel

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Abstract

Protective agent for hepatotoxicity is still a great challenge in the management of liver diseases. Aloe vera is a beneficial plant that has been studied for food supplements, cosmetic and herbal medicine. Aloe vera contains many compounds which have a role in body health including polysaccharides, phenolic, flavonoid, terpenoid, amino acid, and several minerals. There have been compelling evidences that natural phytochemicals and their derivatives have hepatoprotective activities. Information of the aloe vera and its mechanism of action for possible hepatoprotective activities, including *in silico*, *in vitro*, and *in vivo* studies were obtained from Pubmed, Science Direct, Scopus, and Google scholar search engines. This current review was focusing on the possible contribution of compounds inside aloe vera gel and the suggestion of its mechanism on protective effect, especially for liver. The complexity of monosaccharides composition, backbone structures, acetyl group, and molecular weight of aloe polysaccharides have possible correlations with its hepatoprotective effect. Most of the hepatoprotective mechanisms of aloe compounds are related to their protective effect against inflammation and oxidative stress. Several compounds may have combination effects or several targets lead to synergistic effects.

Keywords: *Aloe vera, food supplement, hepatoprotective, liver disease, mechanism of action.*

INTRODUCTION

Aloe vera is a beneficial plant that has been studied for food supplements, cosmetics, and medicine (Hamman, 2008; Kumar, *et al.*, 2019). Recently, the growing popularity of herbal, cosmetic, food, and beverages containing aloe gel create a big demand within the global market for aloe vera. In 2019, the global aloe vera market reached a value

of US\$ 602 Million and it is projected to grow at a CAGR of 8.40% during the forecast period (2020-2025) (IMARC Group, 2020). The rising shift of consumers from chemical-based products towards

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herbal ingredients is further driving the market growth. The ancient herbal treatments in India and China using aloe vera are one of the reasons why the market for aloe vera has been rocketing in Asia. Moreover, the health benefits from aloe vera have been approved by researchers, medical professionals, and doctors around the world also another significant reason (IMARC Group, 2020; Research and Markets, 2021; Transparency Market Research, 2021). This article was focusing on the possible contributions of compounds inside aloe vera gel and the suggestion of its mechanism on protective effect, especially for liver.

Aloe vera is a perennial green herb belonging to Liliaceae family that is native to southern and eastern Africa. Aloe vera was introduced into northern Africa and even cultivated in warm climatic areas of Asia, Europe, and America (Ahlawat and Khatkar, 2011; Sánchez, *et al.*, 2020). Aloe vera is also cultivated in Indonesia. The biggest aloe vera cultivation in Indonesia was found in Pontianak, West Kalimantan (Susanty, *et al.*, 2020). Nevertheless, many other areas in Indonesia also cultivate it including in Gunungkidul, Yogyakarta. Aloe vera has green leaves covered by a thick rind, under which is a thin vascular layer covering an inner clear pulp (Boudreau and Beland, 2006). Aloe vera is a spiky cactus-like xerophyte with fleshy leaves arising in a rosette from a short stem. In young plants, the leaves appear at ground level, but the stem can grow up to 25 cm long in older plants. The plant matures after 4 years old and has a life span until 12 years, thick fibrous roots which produce large basal leaves, usually up to 12-16 per plant, and weighing up to 1.5 kg (Liu, *et al.*, 2013).

Physicochemical and Nutrition of Aloe Gel

Aloe vera is a high-water content plant, ranging from 99% to 99.5% and the rest of 0.5–1.0% is solid material which contains several potential active compounds (Hamman, 2008). Many investigators have identified partially acetylated mannan (aloeverose or acemannan) as the primary

polysaccharide of the gel (Liu, *et al.*, 2019; Lobo, *et al.*, 2010; Metcalfe, 2019). Other polysaccharides such as arabinan, arabinorhamnogalactan, galactogalacturan, glucogalactomannan, galactoglucoarabinomannan, galactan, and glucuronic acid-containing polysaccharides have been isolated from the Aloe vera inner leaf gel part (Hamman, 2008). Acemannan, a β -(1,4)-acetylated soluble polymanose from aloe vera, induces collagen synthesis to lead to wound healing of fibroblast cells (Jettanacheawchankit, *et al.*, 2009). Pectins, biocompatible and versatile polysaccharides, are also found in aloe vera gel. Pectin is recently used for drug delivery systems and coatings of different biomaterials (Gentilini, *et al.*, 2014).

On a minor scale, other compounds are found in aloe gel including simple and complex polysaccharides, phenolic compounds, vitamins, minerals, enzymes, and organic acids (Hamman, 2008). Phenolic compounds are suggested to have a role in antioxidant and antibacterial activities of aloe gel extracts (Nejatzadeh-Barandozi, 2013). Several flavonoids are presented in the aloe gel including naringenin, apigenin, quercetin, kaempferol, and its derivatives (Añibarro-Ortega, *et al.*, 2019; Choi, *et al.*, 2019; Quispe, *et al.*, 2018). Aloe gel can be a preservative agent for mango nectar strongly due to its flavonoid compounds (Elbandy, *et al.*, 2014). Sterols that are present in aloe are kaempferol, β -sitosterol, lophenol, cycloartenol, and lupeol (Salehi, *et al.*, 2018; Tanaka, *et al.*, 2016). Several studies confirmed that aloe sterol improves skin moisture and elasticity (Kaminaka, *et al.*, 2020; Tanaka, *et al.*, 2016). Magnesium, zinc, iron, calcium, glucose, vitamins A, C, E, lignins, saponins, and amino acids are also found in aloe gel (Hamman, 2008; Rajasekaran, *et al.*, 2005). The bioavailability of vitamin C was 3 times higher when administered with the aloe gel by oral, while bioavailability of vitamin E was 3.7 times higher as compared to control (Hamman, 2008). The presence of various inorganic trace elements in the aloe gel possibly had a role in its hypoglycemic effect (Rajasekaran, *et al.*, 2005).

Possible Hepatoprotective Mechanism of Aloe Vera

Free radicals are the most reason for hepatotoxicity cases. Most of the hepatotoxic chemicals including alcohol, virus, and drugs cause damage to the liver cells by lipid peroxidation leads to oxidative damage (Padmanabhan and Jangle, 2014). In several ways, those hepatotoxic chemicals also leads to induce hepatocellular carcinoma (Pan, *et al.*, 2021). Acetaminophen is one example of drug that induces significant hepatotoxicity and causes acute liver failure. Toxicity of acetaminophen was started while a minor percentage of this drug is metabolized by the cytochrome P450 system to form a reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI) in kidney and amplifies the mitochondrial oxidant stress lead to mitochondrial dysfunction with subsequent hepatocyte necrosis (Ramachandran and Jaeschke, 2020). Management of liver diseases including hepatotoxicity are still a great

challenge in this current medicine (Padmanabhan and Jangle, 2014). Hepatoprotective mechanisms prevent hepatotoxic compounds to harm the liver and protect this organ from diseases including hepatotoxicity and cancer.

Aloe vera has organs protective effect especially for liver (Gupta, *et al.*, 2019; Kim, *et al.*, 2009; Kumar, *et al.*, 2019; Padmanabhan and Jangle, 2014). Several phytochemicals and nutrition, which are also found on aloe vera, have a role in hepatoprotective effect with several mechanisms (Table 1). Polysaccharides, as major compounds of aloe vera, have antioxidant efficiency through decreasing oxidative stress MDA and increasing GSH and SOD *in vivo* in chronic alcohol-induced hepatotoxicity in mice (Cui, *et al.*, 2014). Those phytochemicals and nutrition are also contained in aloe gel and possibly drive to synergistic hepatoprotective effect. A standardized blend of herbal medicine containing polysaccharides and aloesin of aloe

Table 1. Phytochemical and nutrition that also contained in aloe vera and its potential mechanism on hepatoprotective effect.

Class	Compounds	Mechanism	References
Polysaccharides	Aloe Polysaccharides	Decreasing oxidative stress MDA and increasing GSH and SOD <i>in vivo</i>	(Cui, <i>et al.</i> , 2014)
	Acemannan	Increasing GST activity	(Liu, <i>et al.</i> , 2019)
	Galactomannan	Signaling cascade of MyD88 and IκBα	(Wu, <i>et al.</i> , 2019)
Flavonoid	Quercetin	Inhibition of hepatocyte apoptosis and suppression of inflammatory cytokines through the IKK/NF-κB and MAPK signaling pathways	(Peng, <i>et al.</i> , 2017)
	Naringenin	1. Inhibition of MAPK, TLR, and TGF-β non-canonical pathways 2. Reducing ROS, increasing SOD, GSH 3. Has a good affinity with IAK-2, ZAP-70 Kinase, Angio-II-Type 1, TGFBR1, Kaep1, EGFR, VEGFR-2, and FGFR1	(Hernández-Aquino and Muriel, 2018; Shine, <i>et al.</i> , 2018; Zaidun, <i>et al.</i> , 2018)
	Kaempferol	1. Activating SIRT1 leads to decreasing the acetylation of a list of SIRT1 targets including PARP1, p53, NF-κB, FOXO-1, and p53 2. Protection against oxidative stress	(BinMowyna and AlFaris, 2021; Rajendran, <i>et al.</i> , 2021)
Sterol	Lupeol	Suppressing inflammation and oxidative stress through TGFβ1-Nrf2 signal pathway	(Huang, <i>et al.</i> , 2021)
Chromone	Aloesin	Antioxidant activity	(Yimam, <i>et al.</i> , 2016)
Mineral	Zinc	Suppressing inflammation and hepatocyte apoptosis via decreasing of IL-1β and IL-6 and upregulation of Cpt1a, PPARα, and ApoB mRNA expression	(Zhang, <i>et al.</i> , 2020)
	Magnesium	Reducing of SGOT, SGPT level on Wistar rat <i>in vivo</i>	(Koudria, <i>et al.</i> , 2020)

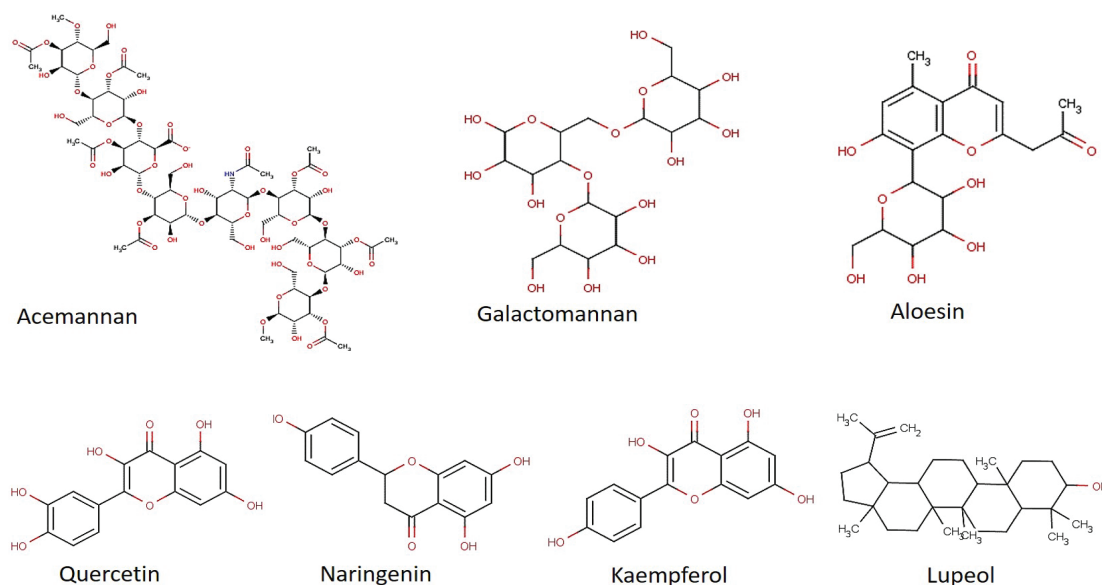


Figure 1. Chemical structure of compounds inside of Aloe vera that possibly contributes to its protective mechanism.

vera extract has shown hepatoprotective activity suggesting via its antioxidant mechanism (Yimam, *et al.*, 2016). Mixing of several constituents in aloe gel drives to show combination effect rather than its single compound (Hamman, 2008).

Qu, *et al.* (2020) described several mechanisms that have a role in protective effects on our body including the hepatoprotective effect. Several compounds have been studied for its protective mechanism. This review compiled several compounds inside aloe gel that possibly contribute to the protective mechanism (Figure 1 and Table 1).

1. Inhibition of Inflammation

Some proteins such as TNF- α , PI3K, JAK/STAT, TGF- β , and NF κ B are involved in inflammation mechanism (Kadioglu, *et al.*, 2015). Unprocessed aloe vera gel homogenate in preventing tissue damage and in the downregulation of TNF- α and Cox-2 gene expressions for the immune-modulation of inflammatory arthritis condition (Paul, *et al.*, 2021). Polysaccharide acemannan shows high binding affinity with TLR5, increases NF κ B-DNA binding expression followed by inducing IL-6/-8

expression. The immunomodulatory effect of acemannan possibly occurs through those mechanisms (Thunyakitpisal, *et al.*, 2017). Galactomannan decreased toll-like-receptor-4-mediated inflammation through the signaling cascade of MyD88 and I κ B α , leading to decreasing cytokine production (Wu, *et al.*, 2019). Lupeol is a kind of sterol that has a role in downregulation of TNF- α and IL-6 mRNA expression through suppression of the IRAK-mediated TLR4 signaling pathway (Kim, *et al.*, 2014). A flavonoid named naringenin, which is also found in aloe vera (Quispe, *et al.*, 2018), inhibits transforming growth factor- β (TGF- β) pathway (Hernández-Aquino and Muriel, 2018). Kaempferol, a flavonoid that is also present on aloe gel, inhibits NF κ B activity, NF- κ B-DNA interaction, and nuclear translocation of NF- κ B p65 (Kadioglu, *et al.*, 2015). Supplementation of zinc suppresses inflammation and hepatocyte apoptosis via decreasing interleukin (IL)-1 β and IL-6 mRNA expression (Zhang, *et al.*, 2020). Aloe vera also contains those compounds that have a role in suppressing inflammation. We suggest that aloe vera also has anti-inflammation activity through similar mechanisms.

2. Protection against oxidative stress

Liver is susceptible to injury and produces reactive oxygen species (ROS) and hydroxyl radicals (OH) lead to oxidative stress (Yimam, *et al.*, 2016). Protection against oxidative stress in the liver is a very essential process for health. Lupeol effectively reduces oxidative stress through prevention of ROS generation and mitochondrial depolarization (Kumari and Kakkar, 2012). Naringenin reduces the free radical like ROS and enhances the antioxidants activity such as superoxide dismutase (SOD), catalase, glutathione (GSH) in chronic diseases (Zaidun, *et al.*, 2018). Lupeol suppresses oxidative stress through TGF β 1-Nrf2 signaling pathway (Huang, *et al.*, 2021). Kaempferol inhibits oxidative stress via PI3K/Akt-mediated Nrf2 signaling pathway (Rajendran, *et al.*, 2021). Aloe vera also has those kinds of compounds that possibly have a protective mechanism against oxidative stress via those mechanisms.

3. Inhibition of Apoptosis

Lupeol enhances the mitochondrial antioxidant and redox status and inhibited DNA damage and cell death (Kumari and Kakkar, 2012). Quercetin inhibits hepatocyte apoptosis and suppresses inflammatory cytokines through the IKK/NF- κ B and MAPK signaling pathways (Peng, *et al.*, 2017). Another flavonoid, namely kaempferol, prevents liver damage through activation of SIRT1 lead to decreasing the acetylation of all SIRT1 targets including PARP1, NF- κ B, FOXO-1, and p53 (BinMowyna and AlFaris, 2021). Kaempferol also inhibits apoptosis via augmenting the phosphorylation of PI3K and Akt (Rajendran, *et al.*, 2021). While naringenin protects from hepatocellular carcinoma (HCC) through inhibiting TGF- β and vascular endothelial growth factor (VEGF), and regulating MAPK pathways (Hernández-Aquino and Muriel, 2018). *In silico* study also found that naringenin has good affinities with human therapeutic protein targets such as JAK-2, ZAP-70 Kinase, Angio-II-Type 1, TGFBR1, Kaep1, EGFR,

VEGFR-2, and FGFR1 and possibly inhibit the progression of liver fibrosis compared to its standard drugs (Shine, *et al.*, 2018). Furthermore, dietary zinc addition inhibits hepatocyte apoptosis through upregulation of carnitine palmitoyltransferase 1a (Cpt1a), peroxisome proliferator-activated receptor (PPAR) α , and apolipoprotein B (ApoB) mRNA expression (Zhang, *et al.*, 2020). On the other hand, *in vivo* studies revealed that supplementation of zinc and magnesium reduce toxicity level on Wistar rats caused by cadmium (Cd) by reducing SGOT, SGPT level, and liver histological alterations (Djemli, *et al.*, 2020; Kouadria, *et al.*, 2019). Apoptosis modulation may also play an important role in aloe vera hepatoprotective mechanism.

There are some possible relationships between the structure of polysaccharides as the major compound of aloe gel and its mechanism of hepatoprotective activity. The complexity of monosaccharide composition is mainly associated with better hepatoprotective activities (Qu, *et al.*, 2020). Acemaman from aloe gel has complex monosaccharide compositions. Acemannan is consists of three monosaccharides compounds namely mannose, glucose, and galactose (Liu, *et al.*, 2019). The higher distribution of branched units of backbone structure of the polysaccharide also has a role in their hepatoprotective activity (Qu, *et al.*, 2020). Then, the backbone structure of acemannan has a high distribution of branch units. Acemannan is composed of β -(1,4)-linked highly acetylated mannoses, β -(1,4)-linked glucose, and α -(1,6)-linked galactose (Liu, *et al.*, 2019). Structural modification such as sulfation, phosphorylation, acetylation, hydroxymethylation, selenization, and complexation with zinc or iron are affects the hepatoprotective activity of polysaccharides (Qu, *et al.*, 2020). Acemannan has several acetyl groups at the C-2, C-3, and C-6 of mannose residues with an acetyl/mannose ratio of approximately 1:1 (Liu, *et al.*, 2019). The last, molecular weight of polysaccharides also has a role in its hepatoprotective activity (Qu, *et*

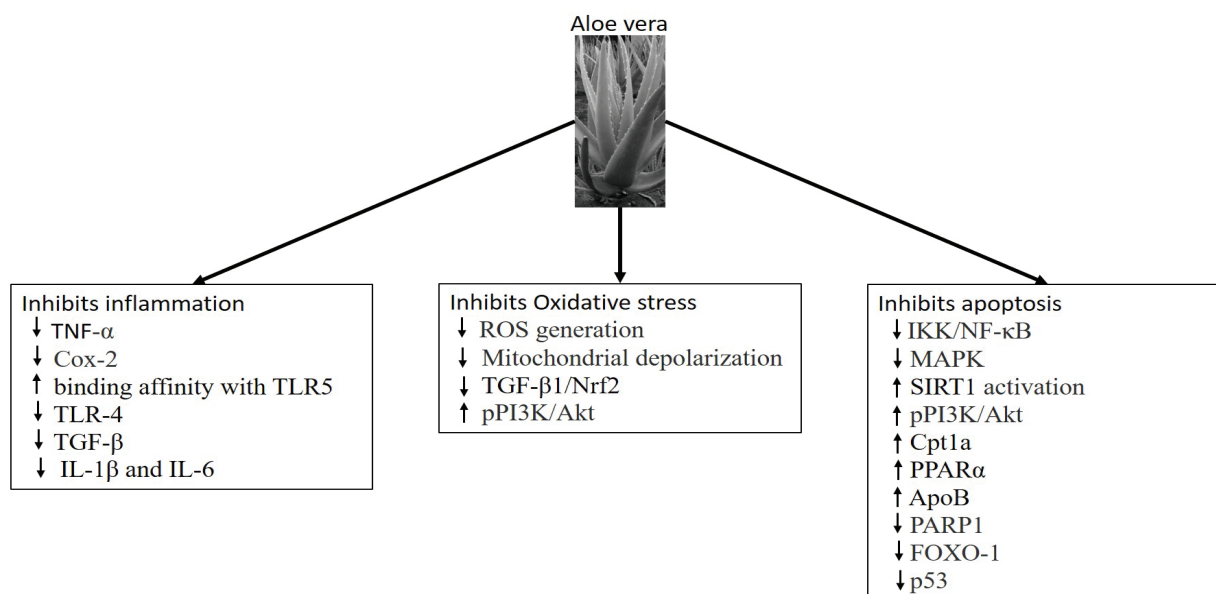


Figure 2. Possible hepatoprotective mechanisms of aloe vera.

al., 2020). Two polysaccharides isolated from *Sophora tonkinensis* namely STRP1 and STRP2 had different potential protective effects against APAP-induced liver injury in mice. The STRP1 with a molecular weight of 1.3×10^4 g/mol has a stronger hepatoprotective effect than STRP2 with a molecular weight of 1.98×10^5 g/mol (Cai, *et al.*, 2018). The molecular weight of acemannan is smaller than STRP1 *i.e.* 1.69×10^3 g/mol. If the smaller molecular weight of polysaccharide possibly has a stronger hepatoprotective effect, one of the possible reasons for the hepatoprotective effect of acemannan might correlated with its small molecular weight. Then, the complexity of monosaccharides composition, backbone structures, acetyl group, and molecular weight of aloe polysaccharides have possible correlations with its hepatoprotective effect.

Toxicity of Aloe Vera

Along with its activity, the safety of aloe products is important to be assured especially for human consumption. Several studies warn to avoid contamination of aloin on aloe product due to its carcinogenic effect (Ahlawat and Khatkar, 2011; Boudreau, *et al.*, 2013; Guo and Mei, 2016). More-

over, several heavy metals are detected on whole aloe leaves (Pawar and Kamble, 2015). The chemical composition of plants depends on the local geographical condition, type of soil and the soil composition (Derbe and Yilma, 2015). Then, aloe raw material for supplement and functional food should be ensured to be planted in geographical conditions and soil composition that are not contaminated with heavy metals. Even though aloe vera gel is safe, aloe should not be used internally during pregnancy, lactation, or childhood and by persons suffering from abdominal pain (Ahlawat and Khatkar, 2011). All of the aloe products should be prepared based on the guidance of good manufacturing practice (GMP) to ensure its safety and benefit.

CONCLUSION

Aloe vera is a plant with several benefits effect for our body. Aloe vera products can be found as functional food, medicine, and cosmetics. Aloin needs to be separated from aloe product for oral given. Aloe vera is one of prospective candidates as a hepatoprotective agent with several mechanisms of action (Figure 2). Nevertheless, studies of the

mechanism of hepatoprotective effect of aloe vera and its active compounds are limited. Then, several studies of hepatoprotective effect of aloe vera including its mechanism of action and clinical study will be a benefit to strengthen the scientific evidence of natural products for a healthy life.

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