Review Article

A review on pharmacological and therapeutic potential of *Aloe barbadensis* Miller

Abstract:

Aloe vera, a popular succulent perennial medicinal plant with a wide range of phytochemicals that have shown various pharmacological activities including anti-oxidant, antimicrobial, antidiabetic, wound healing promotion and so on. Acemannan, aloe-emodin, aloin, aloesin, and emodin are widely investigated active constituents that show various pharmacological activities. Thus, the purpose of this review is to highlight previous pharmacological studied conducted *in vivo*, *in vitro* and human assays over the past decades. As current pharmacological research is focused on anticancer and neurological action, it would be interesting and important to study the main compounds present in *Aloe vera* for therapeutic purposes.

Keywords: *Aloe vera*, Anti-oxidant, Acemannan, Aloe-emodin, emodin

1. Introduction:

In recent years, there has been a significant increase in the recognition and study of the pharmacological, medical and economic potential of medicinal plants. However, only a substantial number of plant species have been examined. Plants have been used for therapeutic purpose since pre-historic times and are the source of many modern medicines. Digoxin, derived from *Digitalis purpurea*, morphine from *Papaver somniferum* and quinine from *Cinchona officinalis* are some examples of common herbal medicines [1]. *Aloe barbadensis* Miller, commonly known as *Aloe vera* is a perennial plant that grows in arid climatic in Africa, Asia, Europe, and America. It originally belonged to the Liliaceae family. There has been approximately 360 well known species of *Aloe vera* till now [2]. *Aloe vera* leaves have a 12-year life span and take usually 4 years to mature before being harvested

and processed for aloe product manufacturing [3]. It is an eternal pulpy xerophyte that constitutes the vacuoles in the leaves to sustain in the parched, ambiguous rainfall regions [4]. The demand of *Aloe vera* is high in the field of cosmetics and nutraceutical industries, so it is cultivated in the large quantities in the different part of the world [5]. The plant provides two specific products: yellow latex, commonly known as aloe juice, and the leaf pulp, which is the innermost component of the plant and comprises parenchyma cells whose key purpose is to store food and nutrients in the form of viscous mucilage. About 98.5% of the raw pulp comprises water, with the remaining 1.5% comprising a variety of substances including rich minerals, vitamins, phenolics and polysaccharides such as cellulose or hemicellulose, organic acids and enzymes [6]. The above polysaccharides could be completely acetylated, semi acetylated and non-acetylated. Acemannan, a β-(1, 4)-acetylated polymannose, is the most predominant polysaccharide in *Aloe vera* gel [7]. It has fairly significant therapeutic benefits, including immune-stimulating antineoplastic [8], and its wound-healing properties [9].

The *Aloe vera* plant has been used in folk medicine for nearly 2000 years, and it continues to be an essential part of holistic medicine in many modern ethnic groups, including some southeastern countries such as India, China and Japan, and parts of the Caribbean. [10]. *Aloe vera* has been grown in Western countries, primarily to offer the latex constituents of the leaf to the pharma industry [11]. Consequently, *Aloe vera* has grown in popularity as a therapeutic natural product over the last decade, promoting the development of a significant industry [12].

2. ***Aloe vera* plant anatomy and physical composition:**

The *Aloe vera* plant features triangular, juicy leaves having spiked ends along with yellow tubular blooms with fruits in the plant. Each leaf is made up of three layers 1) *Aloe vera* gel having 99% of water and rest 1% composed of amino acids, lipids, carbohydrates, sterols, and vitamins. 2) *Aloe vera* latex, which is a bitter yellow sap in the intermediate of the layer.

This sap is carried in specific tubules that seem to be part of the nutrition tubes of the vascular bundles just under the leaf's wax-covered, thick green rind and contains some important secondary metabolites such as anthraquinones and glycosides. 3) The *Aloe vera* rind, made up of 15–20 cells and serving as a protective function and a source of macromolecules including amino acids and carbohydrates. Vascular bundles are found inside the rind and its function of the transporting the water molecules in xylem and starch in phloem [13, 14].

3. Major Chemical constituents in *Aloe vera* plant:

Polysaccharides, lipids, minerals, phytosterols, organic acids, saponins, vitamins, lignins, protein, and amino acids are the main chemical constituents present in aloe leaves [6, 15, 16]. Over 100 chemicals have been discovered in latex derived from the vascular bundle, including anthraquinones, chromone, anthrones, tetrahydroanthracenones, and its glycosides derivatives.

3.1 Vitamins: An Aloe leaf comprises the ascorbic acid, vitamin A (beta-carotene) and vitamin E that functions as anti-oxidants. However, vitamin B12, folic acid, and choline are also present in the plant that has a potential to neutralize free radicals species inside the cell and act as an anti-oxidant potential [17].

3.2 Enzymes: Some important enzymes featuring *aliiase, carboxypeptidase, alkaline amylase, phosphatase, bradykinase, peroxidase, catalase, cellulase and lipase* are also found in this plant. *Bradykinase* act as an anti-inflammatory function capable of suppressing the high inflammation in the skin however, other enzymes are responsible in the metabolism of carbohydrates and lipids [17].

3.3 Minerals: Some important minerals and cofactors like chromium, calcium, selenium, magnesium, copper, manganese, zinc, sodium and potassium. These minerals are vital for the appropriate enzymatic functions in different biochemical pathways [18].

3.4 Carbohydrates: Glucose, fructose and some polysaccharides, including Glucomannans/polymannose, Mucopolysaccharide are present in the plant. The most prevalent monosaccharide is Mannose-6-phosphate, while glucomannans [beta-(1, 4)-acetylated mannan] are the most ordinary polysaccharides. Acemannan, a well-known glucomannan, was also discovered. Past study have revealed that, a specific glycoprotein component alprogen function as an anti-allergic effect and a novel anti-inflammatory molecule obtained by *Aloe vera* gel [17] **(Table 1)**.

3.5 Chromone: 29 derivates of chromone were identified from *Aloe vera*. In all of these, aloeresin A [19], Aloesin (also called as aloe resin B), isoaloeresin D [20] and aloeresin E [21] having most prominent effective compound in the plant. Three aloediols were isolated and identified from *Aloe vera*, however exact mechanism has not yet been determined [22] (**Table 2**).

3.6 Anthraquinones: Aloe vera has been used to isolate and identify 32 anthraquinones and their derivatives. The most prevalent anthraquinone major compounds are aloin A and aloin B [23]. However, the four major anthraquinone are chrysophanol, physcion [24], emodin and aloe-emodin [25]. Six anthraquinone dimers were also discovered in *Aloe vera* [23] **(Table 3)**.

3.7 Phenylpyrone and Phenol Derivatives

Aloe vera was used to isolate and identify one triglucosylated naphthalene derivative named aloveroside A [26], three phenylpyrone derivatives**,** and one 1-methyltetralin derivative feroxidin [27]. Together with these, nine types of phenol derivatives were also isolated from the plant [28] **(Table 4).**

3.8 Phytosterols and Others

The *Aloe vera* gel contained 24-methylene-cycloartanol, 24-methyl-lophenol,Cycloartanol, lophenol and 24-ethyl-lophenol [29]**(Table 5)**.

3.9 *Flavonoids:*

Aloe vera was used to isolate and identify 13 flavonoids and their glycoside derivatives, including three types: flavones, flavonols [28], and flavan-3-ol [30] **(Table 6).**

3.10 Phenylpropanoids and Coumarins

Aloe vera has been used to identify and isolate 12 phenylpropanoid acids and their ester derivatives, along with four Coumarins [27] **(Table 7).**

3.11 Others:

It comprises seven to eight essential amino acids necessary by human. Salicylic acid is also found, which has anti-inflammatory and antibacterial properties. When an inert substance like lignin is introduced to topical medicines, it promotes the other compounds to enter into the skin. Saponins roughly about 3% of the gel are also present and having antiseptic effects.

Moisture, ash, fibre, amino acids, fats, organic acids, free sugars, and some polysaccharides were revealed during a chemical analysis of *Aloe vera* leaves and the main free sugars were monosaccharides like fructose and glucose. Some important organic acids include isocitric, fumaric acid, lactone, oxalic, isocitric, lactic, L-Malic, lactone, citric, and fumaric acid **(Figure 1)** [31].

4. Pharmacological Properties of *Aloe vera*:

4.1 Anti-oxidant activity: Any disproportion in the synthesis and deposition of reactive oxygen species (ROS) in cells or tissues, causes oxidative stress [32]. Hydrogen peroxide (H_2O_2) and singlet oxygen ($^1O_2$) are some examples of ROS. They are synthesized as metabolic by-products by biological systems [33]. When ROS levels have risen inside the cell, they begin to have negative impacts on essential cellular structures such as proteins, lipids, and nucleic acids [34]. Anti-oxidant are agents that scavenge free radicals, chelate metals, and regulate enzymes to protect or delay the biomolecules oxidative damage caused by ROS [35]. It has been proposed that anti-oxidant molecules derived from nutrients present in food and medicinal plants such as vitamins E and C, flavonoids and polyphenols [36] can

minimize the deleterious impact of various pathological disorders caused by oxidative stress, that play an integral role in the pathophysiology of a wide range of disorders including neurodegenerative disorders caused by neurons diminished anti-oxidant capacity [37].

Sultana B *et al.* investigated the *Aloe vera* leaf extract anti-oxidant activity with four distinct solvents with two different extraction techniques protocol. Author's work revealed that the extracts were effective at 2,2 diphenyl-1-picryl-hydrazyl-hydrate scavenging (DPPH) assay [38]. However, similar work also been demonstrated by Naqvi S *et al.* [39] and found that the *Aloe vera* extracted in aqueous solvent, have copper ions that causes DNA degradation and a reduction of cupric to cuprous ion, as well as the concentration dependent generation of ROS species. This observation concludes that the anti-oxidant also has a pro-oxidant property.

Oxygen Radical Anti-oxidant Capacity (ORAC) assay and Ferric Reducing Ability of Plasma (FRAP) experiment analyses were performed to determine the anti-oxidant activity of *Aloe vera* [40]. The authors FRAP data reveals that based on the chemical structure of the compounds, various individual polyphenols constituent of the mixture may have more free radical neutralizing ability than reducing power or vice versa. So it can be utilized to treat or prevent disease caused by oxidative stress [41]. An anti-oxidant study performed by group lead by Anila kumar *et al.* [42] proposed that *Aloe vera* gel extract validates the property of minimizing the oxidative stress and the other present of toxic compounds in the liver.

Esteban A *et al.* [43] investigated the presence of peroxidase available in commercially available aloe gel and *Aloe vera* plant and the peroxidase enzyme present in the plant leaves may be able to scavenge H_2O_2 if applied on the skin surface.

The galvinoxyl radical (GOR) scavenging activity of extracts and fractions has been perceived in this study which suggested the increased scavenging activity of GOR linearly together with the concentration. The chloroform fractional extract had the highest activity when compared to the other extracts, but it was less than that of the anti-oxidant standards,

and it was followed by the ethyl acetate fraction [44]. *In vivo* evaluation of *Aloe vera* anti-oxidant action demonstrated that, *Aloe vera* gel not just to prevent against 8G radiation damage, and also tends to slow the onset and degree of radiation disease in mice [45]. *Aloe vera* gel ethanolic extract lowering thiobarbituric acid reactive compounds and other ROS compounds in streptozotocin (STZ)-induced diabetic rats [46]. In a nutshell, it is found that *Aloe vera* has a potential to reduce the oxidative stress and maintains cellular oxidative stress level.

4.2 Anti-Inflammatory Activity: A typical complex biological cascade process that arises in the tissue as a result of any sort of injury, infection, mechanical damage, infection, chemical irritation or toxin exposure is termed as inflammation [47]. Inflammatory processes lead to body defence. Prolonged inflammation, on the other hand, can lead to chronic diseases and substantial tissue injury. Inflammatory processes are generally classified as two types: **acute** which occurs at short-duration and **chronic** occurs in long-duration based on the time span of the inflammatory reactions in the body [48]. Recent research on *Aloe vera* anti-inflammatory potential has targeted the mode of action of isolated compounds in RAW264.7 cells of BALB/c mice derived from monocytes cells and mice exposed to Lipopolysaccharides. As a result, aloin present in *Aloe vera* is prospective anti-inflammatory impact is linked to its capacity to suppress inflammatory cytokines, ROS species generation, and the JAK-STAT signalling pathway [49]. Furthermore, different concentrations of aloe-emodin together with rhein suppressed the generation of pro-inflammatory cytokines and the phosphorylation of Mitogen Activated Protein Kinases (MAPKs) [50].

Prior study performed by Thunyakitpisal P *et al* [51] demonstrate that acemannan elevated the expression of IL- 6 & 8, along with NF-$_k$B in gingival fibroblasts (GF) of human through signalling pathway of toll-like receptor in periodontal disease. The anti-inflammatory potential of aloin [52] in human oral epithelial cell line (KB) has been cultured with saliva from the control samples. Results found that saliva samples elevated level in IL-1 triggers the

IL-8 expression in KB cells, but pretreatment with aloin has decreased the level of IL-8 production through suppressing the extracellular signal-regulated kinase and p38 pathway.

Furthermore, action of *Aloe vera* in inflammatory processes has been studied in a mouse model of acetaminophen-induced hepatitis (an inflammatory disorder in the liver). According to the findings, *Aloe vera* lowered the hepatic Malondialdehyde, IL-12 and 18 levels, as well as alkaline transferease, while increasing Glutathione (GSH) level. The effect of AVH200® which is a standardized *Aloe vera* extract containing acemannan inhibits the proliferation of T cell and decreased the level of IL-2, IL-17A and IFN-γ in a concentration-dependent manner [53].

Polysaccharides derived from the *Aloe vera* plant have anti-inflammatory properties [54]. 8-[C-beta-D-[2-O-(E)-cinnamoyl]glucopyranosyl] -2- [(R)-2-hydroxypropyl] -7-methoxychromone compound derived from *Aloe vera* were was first reported as an anti-arthritic potential [55]. *Aloe vera* plant also TNF-ά down regulating activity in *helicobacter pylori*-infected rats [56]. Apart from these discoveries, anthraquinones to be an important anti-inflammatory treatment in *Aloe vera* [57].

Regular oral ingestion in inflammatory mouse models, the region of lysosomal membrane disintegration and degradation of protein was reduced by the crude Aloe vera gel, along with modulating the expression of important pro-inflammatory cytokines such as TNF-ά and a major inflammation modulator Cox-2 *in vivo* [48].

Aloe vera plant has also been used to cure dermatitis, and certain data have supported its use in many conditions, including psoriasis and atopic dermatitis (type of chronic inflammatory skin disorder) [58]. Immune dysfunction and epidermal barrier defects in atopic dermatitis patients are caused by both environmental and genetic causes [59]. These finding suggests *aloe vera* as a promising anti-inflammatory action.

4.3 Anti-microbial property:

Numerous studies have been conducted to elucidate *Aloe vera* antagonistic activity and key constituents against fungae, viruses, and bacteria. The majority of these studies have been conducted *in vitro* and are primarily associated with anti-microbial property. The microorganisms that have drawn the greatest attention are *Pseudomonas aeruginosa* and *Staphylococcus aureus*. As a result, aqueous extract of *Aloe vera* inhibited methicillin-resistant in *S. aureus* bacterial growth and biofilm formation [60]. The effectiveness of *Aloe vera* extracted in different solvents (acetone, aqueous and ethanol) against selected clinical pathogens was examined using the agar diffusion method and it was discovered that the acetone extract had the best known anti-bacterial and anti-fungal activity against methicillin resistance *S. aureus* [61]. The sterol present in *Aloe vera* extract shown an anti-fungal and anti-bacterial effect on *Candida albicans* and *Streptomyces greseus*as compared to other ones respectively [62].

Aloe vera extract and parched latex (Aloe drug) obtained with ethyl acetate, methanol, and hexane for anti-fungal activity and the extractives were found to have a stronger inhibitory effect on *Colletotrichum* species. Aloin and aloe-emodin discovered to have anti-bacterial properties because of their efficacy against *Cladosporium cucumerinum* and *Colletotrichum gloeosporides* [61]. Aloe-emodin also inhibiting the formation of the biofilm and extracellular protein synthesis and attributed to the anti-bacterial activity against *Staphylococcus aureus* [63].

In wound infections of burnt individuals, *aloe vera* extracts inhibits the development of multi drug resistance *Pseudomonas aeruginosa* [64]. *Aloe vera* inner gel has also been shown to hinder *Pseudomonas aeruginosa* growth together with biofilm formation. *Helicobacter pylori, E. coli* and *Candida albicans,* were also inhibited by this [65]. The hydro alcoholic extract of *Aloe vera* had anti-bacterial property against *Enterococcus faecalis* (bacteria that cause the root canals in the teeth) [66].

Aloe vera's anti-viral activity has already been studied against herpes and the H1N1 influenza virus strain. The inner gel of *Aloe vera* inhibited the growth of herpes virus on *Vero cell lines* [67]. Cell based studies have suggested that the polysaccharides present in *Aloe vera* reduced the replication and viral adsorption phase of H1N1 subtype influenza virus by communicating with the influenza virus particles [68].

Anti-plasmodium falciparum action of aqueous extracts of *Aloe vera* extracted in distinct ecological conditions of India including highland, semi-arid, dry and wet region, humid subtropical environment etc and data revealed that *Aloe vera* in colder climates had the strongest anti-plasmodial efficacy and associated to the maximum aloin and aloe-emodin activity [69]. Finally, *Aloe vera* mucilage (high in acemannan) has the potential to promote gastrointestinal health by boosting short-chain fatty acids and disrupting the membrane integrity of bacteria. Furthermore, Acemannan promoted the gut microbiota growth, particularly the population of *Bifidobacterium* [70]. The inhibiting mechanism of *Aloe vera* against the several bacteria and fungi growth may be an additional advantage in the plant's medicinal role in the current pharmaceutical applications.

4.4 Wound Heal promotion:

Wound healing is a rigorous mechanism that occurs in three stages. First stage of healing is defined by inflammation, leukocyte infiltration and hyperaemia, second stage comprises the elimination of dead and unwanted tissues and third stage is proliferation, which incorporates epithelium regeneration and the development of fibrous tissue [71]. One of the most eminent characteristics of *Aloe vera* gel is to heal wounds. It speeds up the healing of various internal and exterior wounds, including peptic ulcers, cutaneous and sub dermal tissues. Prior research revealed that principal components of *Aloe vera* such as aloesin, aloin, and emodin, protect the body primarily through the anti-inflammatory and anti-oxidant mechanisms. As a result, it boost the keratinocytes expansion and differentiation by increasing the lysosomal membrane integrity and upregulating TFG1, bFGF, and expression of vascular endothelial

growth factor-A in fibroblasts[72]. Aloin protected our skin by minimizing the production of IL-8, DNA, lipid degradation and ROS production and also increases the amount Glutathione (GSH) content and activity of superoxide dismutase (SOD) enzyme. Aloesin promoted wound healing mechanism by promoting the migration of cell through Cdc42 and Rak1 phosphorylation and growth factors [73]. It has been demonstrated that oral administration of *Aloe vera* of mouse with type II diabetes enhancing the wound healing which indicates that, treatment *of Aloe vera* triggers the Vascular Endothelial Growth Factor (VEGF) expression in the wound area of the skin while Transforming Growth Factor-1 promoted fibroblast for the better repair of the extracellular matrix at the injured site of the skin [74]. *Aloe vera* also promotes collagen cross-linking, and acemannan works as a macrophage stimulant. Catecholamine's have a wound-healing action. Aloe promotes catecholamine activity which enhance the epithelialization. It also stimulate wound vascularisation, which eliminates dead tissue and restores wound health [75].

Aloe vera triggers the flow of blood in the injured area. So that, the collagen concentration and extent of collagen cross linking in the wound, resulting in increased wound contraction and scar tissue rupture [76]. In a human keratinocyte monolayer, a specific glycoprotein having 5.5 kDa isolated from *Aloe vera* increased epithelial cell motility and improved wound healing [77].

Except for healing therapeutic potential, *Aloe vera* polysaccharide has been found to be a potential agent in psoriasis, by decreasing the levels of TNF-ά and expression of IL-8, IL-12 in the human keratinocyte HaCaT *in vitro* cell lines. A study performed with other medicinal plants to investigate the efficiency of oil gel of *Nigella sativa* and *Aloe vera* gel on diabetic ulcers and it was found that *Aloe vera* was reported to be more effective in wound repair mechanism in out bred albino rats with much less inflammation, necrotic tissue, and improved re-epithelialization [78]. Polysaccharides present in *Aloe vera* stimulate the overexpression of metallopeptidase inhibitor-2 and matrix metallopeptidase (MMP)-3 genes,

which aids in the modulation of *Aloe vera* gel's wound mitigating effect and also stimulate fibroblast proliferation as well as the production of hydroxyproline and hyaluronic acid in fibroblasts, all of which are important during the wound healing process for remodeling the extracellular matrix. Acemannan promotes the cell proliferation, cartilage-derived morphogenetic protein 1, type I collagen, and enzymatic activities in primary human periodontal ligament cells [79].

Several clinical investigations on the significance of the *Aloe vera* plant on ulcers have also been undertaken in the previous decade. As a result, applying the *Aloe vera* gel on the wounds, enhances and expedited the healing process [80]. It also has been found that applying gel portion of *Aloe vera* on the sacrum, hip, and heel prevented the development of foot ulcers [81]. Furthermore, medical research investigated that *Aloe vera* gel enhanced the tissue granulation and epithelialization in burns and accelerates the healing of wounds in skin transplanted donor sites. [82].

Between 2014 and 2019, two clinical trials on radiation induced skin toxicity effect were reported. Both investigations discovered that topical *Aloe vera* gel or cream show no potential to reduce the vogue and severity of skin damage in breast cancer patients [83]. Despite the clinical evidence on *Aloe vera* skin-protective potential, clinical trials have yet to find the notable action of *Aloe vera* in mitigating the radiation-induced skin damage and other healing properties.

4.5 Anti-diabetic Activity:

Diabetes is a chronic condition in which the blood glucose level elevated due to insulin resistance or deficiency. Researchers discovered that polysaccharides from the aloe plant have the ability to manage blood sugar, increase the body's own anti-oxidant production, reduced the levels of cholesterol, glucose and tri-glycosides in diabetic people [84]. The activity of *Aloe vera* on diabetes and related problems has been primarily studied *in vivo* model of mouse produced by streptozotocin (STZ). As a result, *Aloe vera* shown the ability to

lower blood glucose levels, boost insulin production, and enhance pancreatic islet cells by number [85].

In diabetic rats, treatment with an ethanolic extract of leaf gel led to a rise in plasma levels of insulin from the residual β-cells of pancreas, which revert the glucose levels in blood back to normal. Furthermore, Cholesterol plasma lipid and triglycerides levels all decreased after treated with *aloe vera* extract. The compounds phenolics and saponins are responsible for the decrease of lipid and glucose level [86]. Both Animal and cell based model studied firmly suggests that the *Aloe vera* aqueous extract lowering the glucose level activity, and that several of its constituents influence the glucose transporter (GLUT)-4 gene expression [87]. *Aloe* gel complex also lowered the body weight in obese prediabetic and early onset diabetic individuals in a randomised controlled experiment. Furthermore, two Aloe products seems to improve the impaired glucose tolerance found in prediabetic syndrome individuals in an 8-week pilot study [88].

Although these are significant peripheral tissues impacted by insulin resistance, dietary Aloe formula was found to reduce obesity-induced glucose tolerance by decreasing the inflammatory response and inducing the anti-inflammatory cytokines in the liver and adipose tissue [89]. *Aloe vera* has also been found to increase the activity of isolated rat pancreatic β-cells by increasing the cell survival, mitochondrial activity, and insulin levels while decreasing reactive oxygen species generation [90].

In vitro study found that anti-diabetic activity of polysaccharides present in *Aloe vera* is connected to suppress the cellular apoptosis stress signalling [91]. Another investigation done on RIN-5F cell line found that the chemical aloe-emodin prevent cells from glucotoxicity via apoptotic and anti-inflammatory responses [92]. In diet-induced obesity mice, 8 weeks of oral administration of *Aloe vera* gel mitigating the blood glucose to normal levels. Processed *Aloe vera* Gel (PAG) anti-diabetic properties were validated by intraperitoneal glucose tolerance tests and also improve the insulin resistance, and mitigating the blood glucose levels. PAG

lowered the average size of adipocytes in histological investigation of the periepididymal fat pad. This data suggested the anti-diabetic and hypolipidaemic activity of processed *Aloe vera* gel [93].

4.6 Anti-cancerous Activity:

Cancer, a malignant disease caused by rapid and unregulated cell differentiation, is a globally dispersed deadly disease that is affecting an increasing number of people today. Natural compounds, particularly those derived from the plant kingdom, have traditionally been employed as chemo protective therapeutics. They are employed to control cancer all around the world due to their effective function and low cost [94]. When comparing the modern trends in plant based medicine and its complementary medicine, India may be the world's leading herbal medication manufacturer. Due to the existence of phytochemicals such as polyphenols, steroids, and other major constituents, plants have their own anti-cancer capabilities. [95].

In vitro human cervical HeLa cell lines and breast MCF-7 cell lines treated with *Aloe vera* crude extracts in different dosages at different time interval has been reported to reduce the cell cytotoxicity. MCF-7 cells role is to express the estrogen receptor while HeLa cell lines are immortal and most widely utilized as cervical cancer cell lines by inducing apoptosis through chromatin condensation and fragmentation and the appearance of apoptotic bodies in cell division and modulating the effector gene expression by increase the expression of cyclin D1, CYP1A and less expression of bax and p21 [96]. Aloe-emodin has been proven to be a potent anti-tumor medication for HeLa and MCF-7 cells by activating the Endoplasmic reticulum and mitochondrial apoptosis as well as the metastatic oxidative stress. It also shown potential photosensitive compound against the human osteosarcoma (a type of bone cancer) MG-63 cell line via the ROS/JNK signalling pathway, as indicated by a rise in caspases and cytochrome c expression while other compound aloesin inhibited the tumour growth in ovarian cancer by blocking the MAPK signalling pathway [97]. Another

anthraquinone molecule, aloin, has been studied for the alternatives treatment in cancer which shows anti-tumor properties against 1,2-dimethylhydrazine-induced preneoplastic lesions in the colon of outbreed albino mice [98]. Vascular Endothelial Growth Factor is the significant proangiogenic cytokine and is well known inducer of tumour neovascularization. Treatment with aloin may reduce VEGF release in cancer cells. Aloin administration significantly decreased the angiogenic response induced by VEGF, resulting in a suppression of endothelial cell proliferation and migration [99]. Natural emodin derivatives like rhein, aloin and chemically synthesized anthraquinone-2-sulfonic acid have reported to prevent the cell death induced by tau aggregation and beta amyloid via anti-aggregation or promoting phosphatidylinositol-3-kinase enzyme viability, This shows that anthraquinone-2-sulfonic acid might have been a novel therapeutic chemical as well as a caspase inhibitor in the brain cancer [100].

Retrospective study shown cytotoxic action of *Aloe vera* and *C. comosum* may be mediated by apoptosis regulation, and hence both extracts displayed anti-cancer activities against HepG2 cells. Both p53 and Bcl2 gene and protein expression were dramatically changed in response to extracts [101]. The expression of p53 was upregulated and Bcl2 was downregulated in a time as well as dose dependent manner in the human HepG2 cell line, which is a critical route for regulating programmed cell death [101].

A novel innovative pathway of aloe gel extract has been reported in controlling the apoptotic death of cancerous cell by altering the metabolic pathway of mitochondria. A potential application of *Aloe vera* gel extract for the treatment of malignant cancer using rat safety testing and anti-cancer research on cancer cells and non-cancer cells has also been studied [102].

Prior study found that *Aloe vera* extract had an anti-cancer impact in mouse with breast cancer by decreasing the level of COX-2 and suppressing the COX pathway and prostaglandin E2 synthesis [103]. Several investigations have found that, *Aloe vera* gel has

anti-tumor efficacy, reducing the tumour burden and shrinkage and enhanced overall survival. In addition, *Aloe vera* gel contains chemopreventative and anti-genotoxic effects on cancer cells[104]. Further studies will be necessary to conclude the anti-cancer properties of the Aloe vera plant.

4.7 Hepatoprotective activity:

Liver is the most vital organ for drug and other toxicant metabolism. The breakdown of the liver cell impairs the permeability of the liver cell membrane, causing tissue contents to flow into the bloodstream [105].Phytosterols like lophenol and cycloartanol isolated from *Aloe vera* have the ability to down regulate the lipid biosynthesis and an increase in fatty acid oxidation in the liver. Besides this, metabolic syndrome-related problems and hepatic steatosis were reduced in the Aloe-sterol-treated Zucker diabetic fatty rats [106].

It has been observed that, In diabetic rats, the liver necrotizes, resulting in increased activity of aspartate aminotransferase (SGOT) and alanine aminotransferase (SGPT) enzymes when they release from the liver cell cytosol into the bloodstream. The high level of these enzymes were significantly reduced after 21 days of oral ingestion of *Aloe vera* doses [107]. Moreover, the improvement of liver damage by *Aloe vera* oral administration might also be substantiated by investigating their effects on serum bilirubin levels. Bilirubin maintains a balance between pigment production and elimination, the reduction in bilirubin levels in treated rats indicates that *Aloe vera* can heal liver injury [108].

Aloe vera doses of 250 and 500mg/kg replaced the total thiols lost by Paracetamol (PCT). The total thiol concentration of liver tissue includes protein-bound thiols as well as glutathione. As a result, *Aloe vera*'s anti-oxidant activity is most likely responsible for its hepatoprotective action [109]. *Aloe vera* compounds also lowering the levels of proinflammatory cytokines, liver cell receptors and 11-hydroxysteroid dehydrogenase 1, while increasing the anti-inflammatory cytokines in the liver [90].

4.8 Immunomodulatory activity:

Aloe vera gel has the most potent immunomodulatory action, owing to components like aloctin A and acemannan. *In vitro* studied on mouse macrophage RAW 264.7 cell lines was performed to deciphering the immunomodulatory activity of acemannan, it was found that acemannan enhances the production of macrophage cytokine generation, surface molecule expression, and cell morphologic alterations [110]. In human macrophages, *Aloe vera* gel exhibits strong immunomodulatory effect, as it reduces Lipopolysaccharides-induced inflammatory response and expression of the several inflammasome proteins [111].

Retrospective research evaluated the influence of aqueous extract of the burn plant on parameters of humoral and cell-mediated immunity, and it was discovered that *Aloe vera* significantly improved the secondary humoral immune response [112].

4.8.1 Potential effect on Covid-19 medication: A Severe Acute Respiratory Syndrome abbreviated as SARS-CoV-2 or COVID-19 is caused by the coronavirus that was first reported in 2019 in china. It is an RNA virus with four known structural proteins: Membrane protein, Envelope protein, Nucleocapsid and Spike protein [113]. To facilitate attachment and fusion with the host cell, the virus spike protein attached to human lung cells angiotensin-converting enzyme 2 (ACE2) receptors on the surface of the respiratory tract. The virus subsequently inserts itself inside the host cell, replicates, and causing inflammation and eventually cause acute respiratory distress [114].

Because of the numerous components present in the medicinal plants contain like *Aloe vera*, it is being investigated as target medications in the therapy of novel corona virus outbreak. *In silico* findings have revealed that anthraquinones (aloe emodin, aloin, 9-dihydroxyl-2-O-(z)-cinnamoyl-7-methoxy-aloesin, and isoaloeresin) might be possible covid-19 inhibitors [115]. Furthermore, one more *in silico* Molecular docking data revealed that β-sitosterol significantly interacts with the receptor-binding region of the virus spike protein and blocking viral passage into the host cell and helps to strengthen the immune system [116].

Furthermore, the plant's anti-inflammatory characteristics can help to inhibit the production of pro-inflammatory markers, which increase inflammation and, as a result, acute breathing difficulties, and the major cause of mortality in covid-19 patients [117].

4.9 Other properties:

Aloin component has been shown to be effective in the treatment of bone related disease like osteoporosis by the reducing the receptor action of NFκ-B ligand (RankL) generated by NF_k-B inhibition in macrophage RAW 264.7 cells [118]. *In vitro* studies on *Aloe vera* constituents were conducted in order to investigate the potential preventive effect on bone pathophysiology. Aloe-emodin stimulated the chondrogenic layer development in the genetic modified mouse chondrogenic ATDC5 cells associated with bone production via activation of the BMP-2 and MAPK signalling pathways [26].

In temporary cerebral ischemia, *Aloe vera* is a powerful neuroprotectant. According to the findings, the thiol levels in *Aloe vera* were substantially higher. As a result, it might be potential compounds for improving preventative therapy of brain ischemia. Agents having the thiol group, such as bioflavonoids, also have free radical scavenging properties [119]. Some research hypothesized that flavonoid-derived substance has a preventative effect in localised ischemia by reducing motor impairment [35]. Methanolic Extract of *Aloe vera* demonstrated the potential anti-epileptic potential with increasing *Aloe vera* dosages. Hexadecanoic acid, β-caryophyllene, humulene, ά-tocopherol, hexadecanoic acid methyl ester, squalene, maltol and phytol are the bioactive constituents responsible for such activities [120]. Methanolic Extract of *Aloe vera*-derived chemicals inhibited the activation of oxidative and neuroinflammatory pathways, providing neuroprotection and modifying behavioral phenotypes in neurological disorders. As a result, the Methanolic Extract of *Aloe vera* -derived molecule could serve as an alternate treatment for neurological illnesses [121].

Ischemia-reperfusion injury *in vivo* model is frequently used for the investigation of *Aloe vera*'s cardioprotective effects. *Aloe vera* delivered via gastric gavage prior to abdominal

aorta and spinal cord ischemia improved anti-oxidative enzymatic activity and decreased the level of lipid, edema, bleeding, and inflammatory cell migration [122]. Researchers discovered that *Aloe vera* easily promotes fibroblasts, which are responsible for the formation of new tissues. When fibroblasts are activated, proteoglycans and collagens are generated, lowering the risk of cardiovascular disease and consuming *Aloe vera* gel may help to reduce the accumulation of blood lipids associated diseases [54]**.** In myocardial ischemia/reperfusion injury, Aloin reduced the oxidative stress and inflammatory response while increasing AMPK signalling [123]. Moreover, it was also notice that aloin had non-atherogenic action as well as iron chelating characteristics when injected intramuscularly. *In vitro* model of haemoglobin, aloe-emodin revealed its maximal efficacy as an anti-aggregatory agent, suggested by structural changes in the hemoglobin chain sheet and the development of chain helices[124].

5. Side effects:

It is observed that, in some cases, *Aloe vera* can elicit redness, stinging, burning, and in rare cases, cause dermatitis. Anthraquinones (aloin and barbaloin) are the most prevalent cause of allergic responses. It is important to test it in a small region initially to rule out any allergic reactions. Electrolyte imbalances may occur as a result of the laxative impact (low potassium levels) [13].

6. Conclusion:

Aloe vera plant has been traditionally used for a wide range of pharmacological purposes, including anti-oxidant, anti-bacterial, immune boosting, anti-cancer, hypoglycemia, hypolipidemic, wound healing, and anti-diabetic. *Aloe vera*'s medical benefits have been known for thousands of years, and contemporary research has confirmed many of its biological activities. However, the potential use of its gel and leaf extract in a variety of drug delivery applications has recently been discovered. In recent years, the majority of

pharmacological research has been conducted *in vitro* and *in vivo*. Anti-inflammatory, cytotoxic, anti-microbial, anti-cancer, and skin protective actions have received the greatest attention *invitro* research. Cardioprotective, anti-tumor, cytotoxic and anti-cancer properties, as well as skin protection activities, are all being investigated *in vivo*. *Aloe vera* leaves contain a wide range of phytochemical substances with a variety of biological functions, including acemannan, aloesin, aloin, aloe-emodin and amodin. However, aloin and aloe-emodin being the most extensively studies. *In vitro* studies of Aloe–emodin have shown promise as a cardioprotective, anti-diabetic, anti-bacterial, cytotoxic and bone protective and *in vivo* studies suggested anti-inflammatory and skin protective activities. However, Aloin was found to be useful *in vitro* tests of inflammatory processes and bone related diseases, as well as anti-cancerous and cardiovascular diseases in *vivo* studies. As a result, it appears to be fairly promising as a versatile therapeutic agent; nevertheless, more study is needed to isolate and determine the mode of action of mechanism of the bioactive compounds using latest sophisticated instruments. The US Food and Drug Administration have already permitted research on the use of *Aloe vera* in cancer and AIDS treatment. In the future, controlled research will be necessary to establish the effectiveness of *Aloe vera* in a variety of scenarios.

Declaration:

1. **Ethical approval and consent to participate:** Not Applicable
2. **Consent for publication:** All authors have approved the final article and consented to publication.

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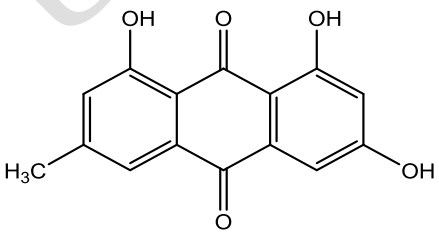
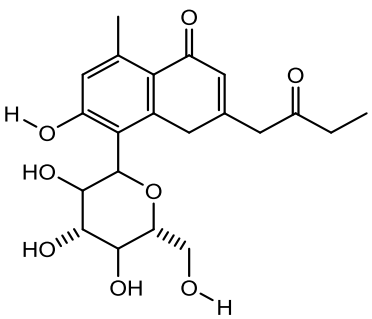
Figure legends:

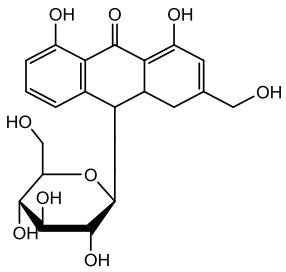
Figure1. Major chemical constituents present in *Aloe vera* (**drawn at Chemdraw**).



Emodin



Aloe resin



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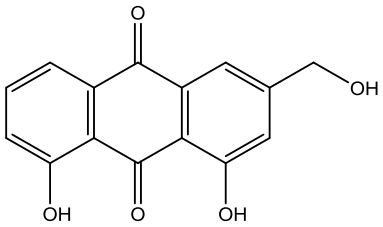
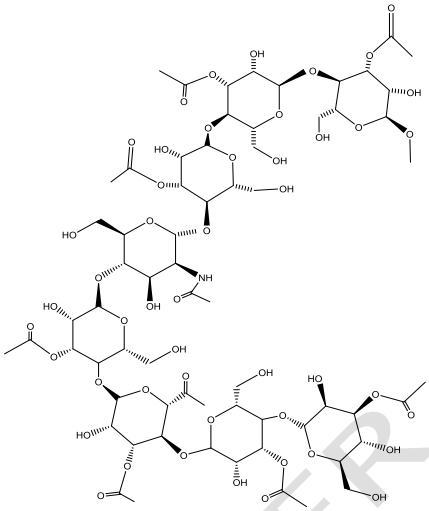


Aloe emodin



Acemannan

Table 1: Compounds in *Aloe vera*

S.No.	Class	Major Constituents	References
1.	*Vitamins*	Vitamin A (beta-carotene), vitamin C and vitamin E, vitamin B12, folic acid, and choline	[17]
2.	*Enzymes*	Carboxypeptidase, aliiase, alkaline phosphatase,	

		amylase, lipase, bradykinase, catalase, cellulaseand peroxidase	
3.	*Carbohydrates*	Glucose, Fructose and Glucomannans/polymannose, Mannose-6-phosphate, glucomannans [beta-(1, 4)-acetylated mannan], Acemannan,	
4.	*Minerals*	Sodium, calcium, magnesium, chromium, copper, selenium, potassium, manganese, and zinc	[18]
5.	*Amino acids*	Arginine, alanine, tyrosine, aspartate, histidine, glycine, isoleucine, methionine, lysine, proline, phenylalanine, valine and glutamic acid, leucine	[61]

Table 2: Chromone and their derivatives

S.N0	Compound	Formula	Reference
1	C-2’ -decoumaroyl-aloeresin G	$C_{20}H_{24}O_8$	[22]
2	Aloesin	$C_{19}H_{22}O_9$	
3	Aloeresin D	$C_{29}H_{32}O_{11}$	

4	Allo-aloeresin D	$C_{29}H_{11}O_{11}$	
5	8-C-glucosyl-7-methoxy-(R)-aloesol	$C_{20}H_{26}O_9$	
6	8-C-glucosyl-(R)-aloesol	$C_{19}H_{24}O_9$	
7	8-C-glucosyl-7-O-methylaloediol	$C_{20}H_{26}O_{10}$	
8	Rabaichromone	$C_{29}H_{32}O_{12}$	
9	Neoaloesin A	$C_{19}H_{22}O_9$	[125]
10	8-C-glucosyl-(S)-aloesol	$C_{19}H_{24}O_9$	[20]
11	Iso-rabaichromone	$C_{29}H_{32}O_{12}$	
12	8-C-glucosyl-7-methoxy-(S)-aloesol	$C_{20}H_{26}O_9$	
13	Isoaloeresin D	$C_{29}H_{32}O_{11}$	
14	Aloeresin E	$C_{29}H_{32}O_{10}$	
15	8-C-glucosyl-noreugenin	$C_{16}H_{18}O_9$	[21]
16	8-glucosyl-(2’-O-cinnamoyl)-7-O-methylaloediol B	$C_{29}H_{32}O_{12}$	
17	8-glucosyl-(2’-O-cinnamoyl)-7-O-methylaloediol A	$C_{29}H_{32}O_{12}$	
18	4’-O-glucosyl-isoaloeresin DII	$C_{35}H_{42}O_{16}$	
19	4’-O-glucosyl-isoaloeresin DI	$C_{35}H_{42}O_{16}$	
20	Glucopyranosyl]-2-[(R)-2-hydroxypropyl]-7-methoxy-5-methylchromone	$C_{29}H_{32}O_{10}$	[55]
21	Aloeresin J	$C_{30}H_{34}O_{11}$	[23]
22	Aloeresin K	$C_{31}H_{34}O_{12}$	
23	9-dihydroxyl-2’-O-(Z)-cinnamoyl-7-methoxy-aloesin	$C_{29}H_{30}O_{12}$	[126]
24	7-O-methyl-aloeresin A	$C_{29}H_{30}O_{11}$	

25	aloeveraside B	$C_{28}H_{28}O_{12}$	[27]
26	6’-O-coumaroyl-aloesin	$C_{28}H_{28}O_{12}$	
27	Aloeveraside A	$C_{29}H_{30}O_{12}$	
28	7-methoxy-6’-O-coumaroyl-aloesin	$C_{29}H_{30}O_{12}$	
29	Aloeresin A	$C_{28}H_{28}O_{11}$	[19]

Table 3: Anthraquinone and their derivatives

S.N0	Compound	Formula	Reference
1	Aloin A	$C_{21}H_{22}O_9$	[23]
2	6’-O-acetyl-aloin A	$C_{23}H_{24}O_{10}$	

3	Aloin B	$C_{21}H_{22}O_9$	
4	6’-O-acetyl-aloin B	$C_{23}H_{24}O_{10}$	
5	Aloinoside B	$C_{27}H_{32}O_{13}$	
6	Aloinoside A	$C_{27}H_{32}O_{13}$	
7	Elgonica dimer A	$C_{36}H_{30}O_{14}$	
8	Elgonica dimer B	$C_{36}H_{30}O_{14}$	
9	Aloindimer A	$C_{42}H_{42}O_{18}$	
10	Aloindimer B	$C_{42}H_{42}O_{18}$	
11	Aloindimer C	$C_{42}H_{42}O_{18}$	
12	Aloindimer D	$C_{42}H_{42}O_{18}$	
13	10-hydroxyaloins A	$C_{21}H_{22}O_{10}$	[20]
14	10-hydroxyaloins B	$C_{21}H_{22}O_{10}$	
15	Aloe-emodin-11-O-rhamnoside	$C_{21}H_{20}O_9$	[24]
16	Aloesaponarin I	$C_{17}H_{12}O_6$	[127]
17	Aloesaponarin II	$C_{15}H_{10}O_4$	
18	3-Geranyloxyemodin	$C_{24}H_{24}O_5$	[128]
19	Madagascine	$C_{20}H_{18}O_5$	
20	Rhein	$C_{15}H_8O_6$	[129]
21	Aloe-emodin	$C_{15}H_{10}O_5$	
22	Emodin	$C_{15}H_{10}O_5$	
23	Physcion	$C_{16}H_{12}O_5$	
24	Chrysophanol	$C_{15}H_{10}O_4$	[19]
25	7-hydroxyaloin A	$C_{21}H_{22}O_{10}$	
26	7-hydroxyaloin B	$C_{21}H_{22}O_{10}$	
27	Nataloeemodin	$C_{15}H_{10}O_5$	

28	7-hydroxy-8-O-methylaloin A	$C_{22}H_{24}O_{10}$	
29	7-hydroxy-8-O-methylaloin B	$C_{22}H_{24}O_{10}$	
30	Homonataloside B	$C_{28}H_{34}O_{14}$	
31	6’ –malonylnataloin A	$C_{24}H_{24}O_{12}$	
32	6’ –malonylnataloin B	$C_{24}H_{24}O_{12}$	

Table 4: Phenylpyrones derivatives

S.N0	Compound	Formula	Reference
1	Aloenin A	$C_{19}H_{22}O_{10}$	[130]

2	Aloenin B	$C_{34}H_{38}O_{17}$	
3	Syringic acid	$C_9H_{10}O_5$	[28]
4	Gallic acid	$C_7H_6O_5$	
5	Gentisic acid	$C_7H_6O_4$	
6	Ascorbic acid	$C_6H_8O_6$	
7	Vanillic acid	$C_8H_8O_4$	
8	Aloveroside A	$C_{30}H_{40}O_{17}$	[131]
9	P-coumaroylaloenin	$C_{28}H_{28}O_{12}$	
10	Feroxidin	$C_{11}H_{14}O_3$	[27]
11	P-cresol	C_7H_8O	
12	P-anisaldehyde	$C_8H_8O_2$	
13	1-(2,4-dihydroxy-6-methylphenyl) ethanone	$C_9H_{10}O_3$	
14	Salicylaldehyde	$C_7H_6O_2$	

Table 5: Phytosterols and others

S.N0	Compound	Formula	Reference

1	Lophenol	$C_{28}H_{48}O$	[29]
2	24-ethyl-lophenol	$C_{31}H_{52}O$	
3	Cycloartanol	$C_{30}H_{52}O$	
4	24-methyl-lophenol	$C_{29}H_{50}O$	
5	24-methylene-cycloartanol	$C_{31}H_{52}O$	

Table 6: Flavanoids in *Aloe vera*

S.N0	Compound	Formula	References
1	Apigenin	$C_{15}H_{10}O_5$	[28]
2	Kaempferol	$C_{15}H_{10}O_6$	
3	Catechin	$C_{15}H_{14}O_6$	
4	Rutin	$C_{27}H_{30}O_{16}$	
5	Epicatechin	$C_{15}H_{14}O_6$	
6	Quercitrin	$C_{21}H_{20}O_{11}$	
7	Myricetin	$C_{15}H_{10}O_8$	
8	Quercetin	$C_{15}H_{10}O_7$	
9	Isovitexin	$C_{21}H_{20}O_{10}$	[30]
10	Lutonarin	$C_{27}H_{30}O_{16}$	
11	Luteolin	$C_{15}H_{10}O_6$	
12	Saponarin	$C_{27}H_{30}O_{15}$	
13	Isoorientin	$C_{21}H_{20}O_{11}$	

Table 7: Phenylpropanoids and Coumarins.

S.N0	Compound	Formula	Reference
1	Cinnamic acid	$C_9H_8O_2$	[132]
2	Caffeic acid	$C_9H_8O_4$	[28]
3	Sinapic acid	$C_{11}H_{12}O_5$	
4	P-coumaric	$C_9H_8O_3$	
5	Ferulic acid	$C_{10}H_{10}O_4$	
6	5-p-coumaroylquinic	$C_{16}H_{18}O_8$	
7	Methyl 3-(4-hydroxyphenyl) propionate	$C_{10}H_{12}O_3$	[27]
8	3-(4-hydroxyphenyl) propanoic acid	$C_9H_{10}O_3$	
9	7-demethylsiderin	$C_{11}H_{10}O_4$	
10	Caffeoylshikimic	$C_{16}H_{16}O_8$	[30]
11	5-feruloylquinic	$C_{17}H_{20}O_9$	
12	5-p-cis-coumaroylquinic	$C_{16}H_{18}O_8$	
13	Feralolide	$C_{18}H_{16}O_7$	[27]