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Phytochemical profiles, biological activities and medicinal importance of *Aloe vera* L.: A review

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ABSTRACT

Aloe vera (Av) is revered in Ayurveda as the "wand of heaven" or "heaven's blessing" and precisely the "silent healer". This herbaceous plant belongs to Asphodelaceae family, previously classified as Liliaceae. In Traditional Chinese Medicine (TCM), Av is acknowledged for its abundant bioactive substances that have considerable therapeutic value. Therefore, the objective of this review is to analyze Av's bioactive compounds, highlighting its medicinal potential in drug development. An extensive literature review is performed utilizing databases such as PubMed, Web of Science, SpringerLink, and more until October 2024. The research investigates the bioactive compounds of Av and their *in vivo*, *in vitro*, and *in silico* effects on infections (bacterial, fungal, viral, and protozoan infections), along with their medicinal properties and significance in drug development. The most investigated active constituents of Av are aloin, emodin, acemannan, and aloesin. Av contains more than 100 potentially active components from six different classes: anthraquinone, chromone, phenylpropanoids, coumarins, phenylpyrone, and phytosterols, focusing on its anti-infective, anti-cancer, anti-diabetic, anti-oxidant, anti-inflammatory, immuno-modulatory activity and impact on neural diseases as well, based on peer-reviewed scientific data. By deepening the understanding of Av's medicinal value, this study may provide a reference for its future research and the development of new bioactive drug molecules from Av.

1. Introduction

Aloe vera (L.) Burm. f. (*Aloe vera* Ghritakumari in Bengali) is a succulent, perennial, drought-resistant, herbaceous plant that is widely distributed in hot and dry regions of North Africa, the Middle East, Asia, the Southern Mediterranean, and the Canary Islands.[1] The name "*Aloe vera*" is derived from the Arabic word "Allaeh" (meaning "shining bitter substances") and the Latin word "Vera" (meaning "true").[1,2] According to the World Health Organization, *Aloe vera* (Av) is considered the most potent bioactive plant among the 420 species of *Aloe*.[3] The growing therapeutic recognition of Av is supported by emerging scientific evidence demonstrating its potential benefits in treating a range of diseases, including Parkinson's disease, asthma, rheumatism, cancer, diabetes, burns, and infections.[4] In India, the whole leaves, exudates, and fresh gel of Av are used as a stomachic, emmenagogue, cathartic, and anthelmintic.[1] The colorless, transparent mucilaginous gel from Av leaves is extensively used for its medicinal, antioxidant, anti-inflammatory, anti-aging, anticancer, antidiabetic, sunburn relief, and antifungal properties.[1,5,6] Traditionally, the active constituents in Av extracts include anthraquinones, chromones, and their glycoside derivatives, as well as flavonoids, coumarins, phenylpyrone derivatives, phenylpropanoids, phytosterols, lipids, and vitamins.[7,8] Av, is a well-known medicinal plant with a wide range of therapeutic properties in Traditional Chinese Medicine (TCM).[9] According to the Traditional Chinese Medicine Information Database (TCMID), (https://bidd.group/TCMID/herb.php?herb=TCMH1343), Av is commonly used to purge the bowels, neutralize heat in the liver, and expel worms.[10] In China, the authentic growing regions for Av include Guangdong Province, Hong Kong, and Macao.[11] As an integral part of TCM, Av has been used in various formulations for centuries.[12] It is traditionally believed to clear heat, cool the liver, kill parasites, alleviate chronic constipation, reduce fever, and drain excess heat. One well-known TCM formula, Bu Dai Wan, also known as the "cloth sack pill", contains Av as one of its key ingredients (https://www.meandqi.com/herb-database/aloe-vera). This formulation is used to expel roundworms (ascariasis), treat parasitic infestations, and address malnutrition and childhood nutritional impairments. Another herbal formula, Dang Gui Long Hui Wan, also includes Av and is used to clear heat, purge toxins, and cool the liver and

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gallbladder (https://www.tcm-pro.com/Plants-and-Formulas). Av is listed in the pharmacopoeia of the People's Republic of China (2020) as a traditional medicinal plant. It has historically been utilized in TCM for addressing wound healing, dyspepsia, and anorexia.[13] As the most widely farmed *Aloe* species in the food sector, Av serves as a component for functional foods, including gel-based health drinks and beverages.[14,15] In the pharmaceutical field, it is used for making gels, ointments, along with capsules and tablets.[15,16] Av has been acknowledged for its therapeutic properties in addressing numerous health concerns in individuals. This research seeks to improve our knowledge of the therapeutic properties of Av, offering perspectives that may inform future studies and the creation of novel bioactive drug compounds for health-related uses. The investigation centered on keywords associated with Av's antibacterial, antifungal, antiviral, antiprotozoal, antioxidant, immunomodulatory, anti-diabetic, neuroprotective, and anticancer characteristics. The analysis also evaluated bioactive substances, along with *in vivo*, *in vitro*, and *in silico* investigations, in addition to safety and toxicity measures. Furthermore, the review examines its therapeutic possibilities, backed by TCM, and emphasizes the bioactivity of its plant compounds. An extensive literature review was performed utilizing multiple online databases up to October 2024, such as PubMed, Web of Science, SpringerLink, ScienceDirect, ResearchGate, Scopus, and Google Scholar. We also analyzed Chinese databases for medicinal formulations incorporating Av. Through this comprehensive overview, we aim to contribute to the growing body of knowledge that will support the development of effective, safe, and novel therapeutic agents derived from Av.

2. Botanical description

Av is a succulent perennial green herb with thick, short and somewhat divided stem (30–69 cm high). Its leaves are triangular in shape, glaucous green in color, crowded, sessile, erect spreading rather than concave, lanceolate and spiny toothed at margin, generally about 10 cm broad, 30–60 cm long, 1.8 cm thick.[17–20] The leaf can be divided into two major parts, namely the outer green rind, including the vascular bundles, and the inner parenchyma containing transparent white gel.[21] The term pulp or parenchyma tissue refers to the fleshy interior part of the leaf including the cell walls and organelles, while gel or mucilage refers to the viscous transparent liquid within the parenchyma cells.[22] The plant's complete life cycle is 12 years.[20] There are various species of *Aloe* such as Av, *A. gilbertii*, *A. eleganis*, *A. elegans*, *A. pulcherrima* Gilbert and *A. turkanensis*.[23]

3. Chemical constituents

The bioactive constituents of *Aloe* sp. are divided into two major types: namely, nutritive and non-nutritive compounds. The nutritive compounds include carbohydrates, enzymes, vitamins, protein and amino acids, minerals and trace elements, whereas the non-nutritive constituents include organic compounds, phytosterols, phenolics and other bioactive compounds.[24,25] Av plants primarily comprise 99%–99.5% high water content, with the remaining 0.5%–1.0% of solid matter containing various bioactive compounds.[26] The diverse range of compounds found in Av can be categorized into three principal groups. The first group, complex sugars, located in the gel (or mucilage) of the leaf, possesses immune-enhancing properties.[21] The second group, anthraquinones, is found in the outer pulp of leaves, known as the latex or exudate.[26] The raw pulp of Av contains about 98.5% water, while the gel consists of nearly 99.5% water.[14] The third group comprises the epidermis, or rind, which constitutes the outer thick layer of the plant.[19] This rind includes lignin, pectin, polysaccharides, cellulose and hemicellulose.[8] Furthermore, the rind also contains several substances with a wide array of actions, such as minerals, essential, semi-essential, and non-essential amino acids, organic acids, phospholipids, enzymes, lignin and saponins, salicylic acid, vitamins, anthraquinones, such as aloesin, acemannan, aloin and emodin.[5,27] The Av root equally contains aloesin, whereas the flowers have ascorbic acid and volatile compounds.[5,8] Table 1 provides a summary of the diverse phytochemical components found in Av. Fig. 1 depicts the structures of some bioactive compounds found in different parts of the Av plant, including the leaf, gel, and root.

4. Bioactivity and medicinal property

4.1. Anti-infective efficacy and mechanism of action

4.1.1. Antibacterial property

Substances that kill or inhibit the growth of bacteria are known as antibacterial agents.[42] In plants, secondary metabolites (flavonoids, alkaloids, glycosides, tannins, and coumarins) are used as part of the plant's defense mechanism against pathogens.[43] Since, antibacterial activity of these bioactive substances is promising, they are highly effective for treatment of bacterial infections.[44] Several studies have suggested that Av gel acts as a potential antibacterial agent. Av contains hydroxylated phenolic compounds, such as pyrocatechol, known to its high toxic effect on bacteria.[45] It also contains anthraquinones, a category of potent bioactive compounds, which are structural analogs of tetracycline. Like tetracycline, anthraquinones inhibit bacterial protein synthesis by blocking the ribosomal A site, preventing the entry of aminoacylated tRNA, and for which bacteria cannot grow in culture media containing Av exudates.[45–47] Furthermore, polysaccharides in Av gel, have been found to kill bacteria by stimulating phagocytic leucocytes.[48] Av containing inner gel showed antibacterial activity against the

Table 1
Phytochemical composition of *Aloe vera*.

Class	Compounds	Reference
Chromone and its glycoside components	Aloesin (also called aloeresin B), aloeresin A, aloeveraside B, isoaloeresin D and aloeresin E	28–30 29 30
Other flavonoids	Flavone, flavonol and flavan-3-ol	33
Anthraquinone and its glycoside compounds	Aloin (aloin A and aloin B), anthraquinone glucosides, aloe-emodin and emodin, chrysophanol, physcione	31,32
Phenylpyrone derivatives and coumarins	Aloveroside A, 1-methyltetralin derivative, feroxidin, 7-demethylsiderin, feralolide, dihydrocoumarin, dihydrocoumarin ethyl ester	34–36
Phenylpropanoids and phenol derivatives	Phenylpropanoid acids and their ester derivatives, phenol derivatives	34 33
Phytosterols	Cycloartanol, 24-methylene-cycloartanol, lophenol, 24-methyl-lophenol, and 24-ethyl-lophenol	37
Enzymes	Alkaline phosphatase, amylase, bradykinase, catalase, cyclooxidase, cyclooxygenase, oxidase, lipase, phosphoenolpyruvate, carboxylase, superoxide enzymes	22,38,39
Hormones	Auxin and gibberellin	5
Other proteins	Lectin and lectin-like substance	22
Saccharides	Mannose and glucose (polymannans), pure mannan, acetylated glucomannan, acetylated mannan, glucogalactomannan, galactan, arabinogalactan, galactogalacturan, galactoglucoarabinomannan, pectic substance, xylan, cellulose, glucose, mannose, aldopentose	4,27,38,39,41
Vitamins	Vitamin A, C, E, B1, B2, B12, choline and folic acid	5
Fatty acids	Campesterol and lupeol	5,19
Other organic compounds and lipids	γ-Linolenic acid, steroids (campesterol, cholesterol), triterpenioid, trigyycerides, arachidonic acid, gibberellin, lignin, salicylic acid, sorbate and uric acid	40
Inorganic compounds	Calcium, chloride, copper, magnesium, iron, potassium, sodium, zinc and phosphorus	5

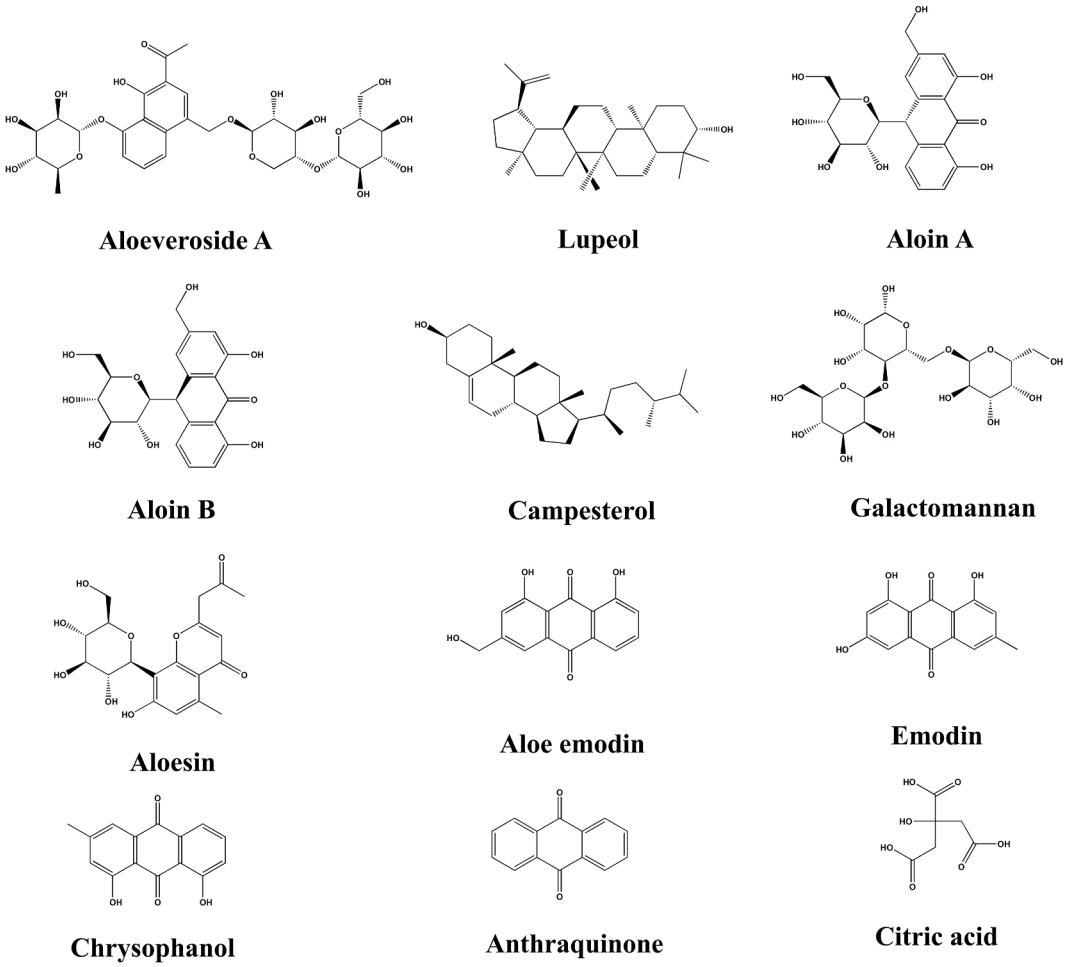

Fig. 1. Chemical structures of representative bioactive compounds found in *Aloe vera*.

H. pylori pathogenic strain, and combat gastric infections caused by this bacterium.[49] Av leaf extract is also reported to act against *Staphylococcus aureus* (*S. aureus*), *Salmonella* sp., *Escherichia coli*.[50]

Additionally, aloesin, in Av root extract, displayed robust antibacterial efficacy against *Agrobacterium tumefaciens*, *Shigella* sp., *Enterococcus faecalis* (*E. faecalis*), *Streptococcus pyogenes* (*S. pyogenes*), *Pseudomonas aeruginosa* (*P. aeruginosa*), and *S. aureus*.[5,50,51] Previous studies have also highlighted the excellent antibacterial efficacy of Av leaf extract against both gram-positive and gram-negative bacteria.[51] Antibacterial property and mechanism of actions of different components of Av as reviewed,[45–47] are depicted in Fig. 2. Antimicrobial activity of various parts of the Av plant against both gram-positive and gram-negative bacteria is shown in Table 2.

4.1.2. Antiviral activity

Av is widely acknowledged for its antiviral benefits. Previous reports have suggested that Av exudate has an excellent antiviral property that prevents viral attachment, or entry to the host cell.[56] Several anthraquinones have shown virucidal effects on viruses.[57] Three bioactive anthraquinones, aloe-emodin, emodin, and chrysophanol from Av reportedly showed antiviral activity against novel influenza A H7N9.[58] Specifically, aloe-emodin inhibits the replication of influenza A in Madin-Darby Canine Kidney (MDCK) cells and upregulates galectin-3, which is responsible for inhibition of viral replication process.[58] Furthermore, the intake of Av gel has been shown to play a crucial role in HIV-positive individuals by improving the immunity strength through the increase of CD4 count.[58,59] Additionally, Av has the capability to express human cytokine interferon-alpha-2 (IFNα2), which may help in enhancing the immune system function.[60] Two new anthraquinone compounds, aloesaponarin I and aloesaponarin II, extracted from Av root, were evaluated for antiviral activity against MDCK cell lines. These compounds exhibited antiviral effects by inhibiting viral replication, specifically against the influenza A H1N1 virus.[61] Another study investigated the antiviral activity of polysaccharides derived from Av leaves against the influenza PR8 (H1N1) virus. The results demonstrated a marked reduction in viral replication during the adsorption phase, resulting in a significant decrease in viral load and mortality.[62] In addition, the anti-hepatitis B activity of anthraquinones (aloe-emodin, aloin B, and chrysophanol) from Av was evaluated using both *in vitro* and *in silico* methods. The experiments indicated that aloe-emodin exhibited the most potent anti-hepatitis B activity.[63] Antiviral efficacy and mechanism of action of various compounds of Av as reviewed,[58] are shown in Fig. 2.

4.1.3. Antifungal actions

Av has exhibited antifungal activity against several pathogenic fungi. Av's ethanolic leaf and root extract has shown excellent antifungal activity against *Aspergillus niger* (*A. niger*), *Fusarium oxysporum* (*F. oxysporum*), *A. fumigatus* and *Candida albicans* (*C. albicans*).[51] Additionally, a protein (14 kDa) isolated from Av gel also exhibited antifungal effects against *C. albicans C. krusei* and *C. parapsilosis*.[45] Saniasiaya et al.[64] reported that Av ethanolic extract had antifungal

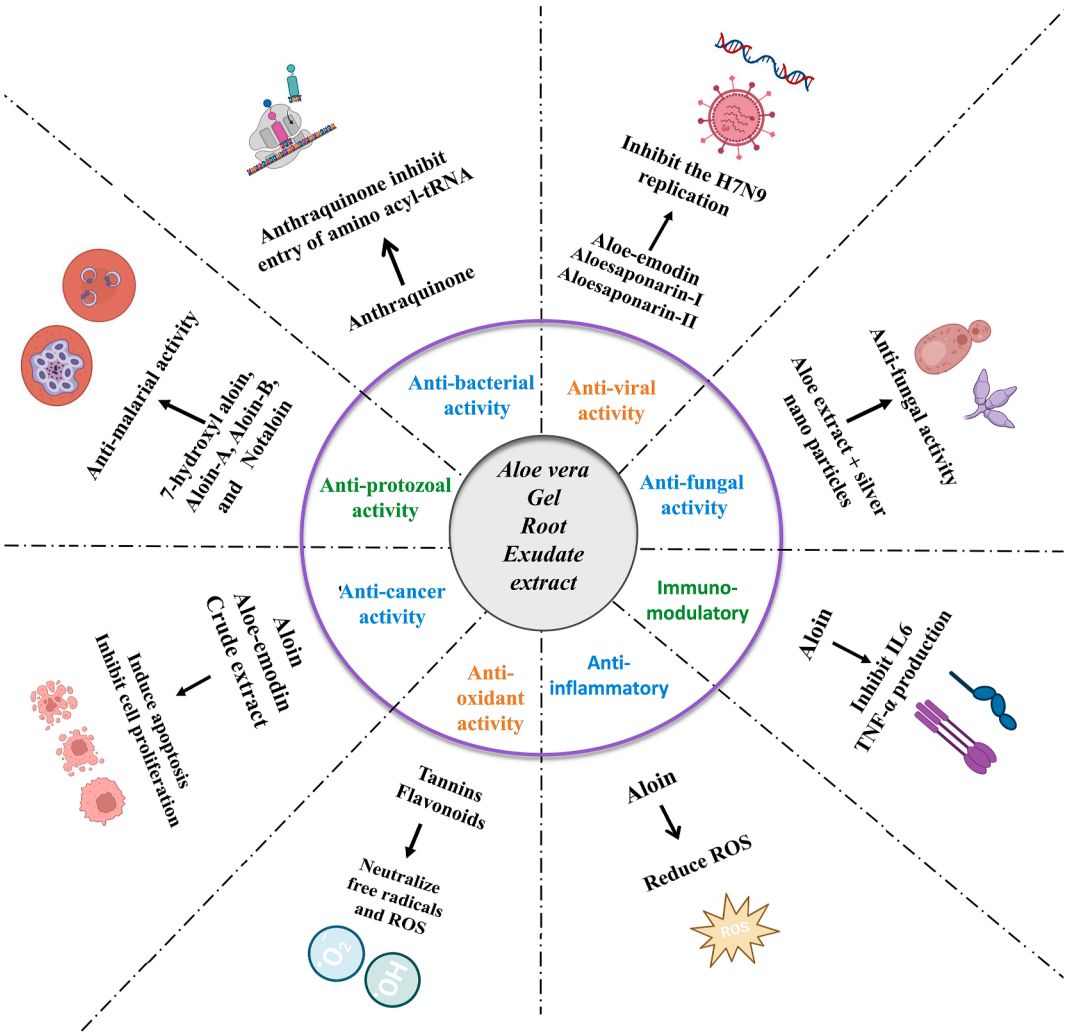

Fig. 2. Anti-infective and bioactive properties of different components of Av along with their mode of actions: Anthraquinone inhibits entry of amino acyl-tRNA, subsequently inhibits the protein synthesis; 7-hydroxy aloin, aloin-A/B and notaloin induce the killing process of malarial parasite; Av extract with silver nanoparticles showed anti-fungal activity; Aloin reduces the production of ROS, and inhibits the production of pro-inflammatory cytokines IL-6 and TNF-α) and acts as an anti-inflammatory agents; aloe-emodin and Aloesaponin-I/II directly inhibit the replication process of influenza A N7N9; Aloin, Aloe-emodin and Av Crude extract helps to induce apoptosis; Tannins, flavonoids, neutralize the free radicals. This illustration was created by the first and second authors using webtools available at: BioRender.com and https://app.diagrams.net/, (details are available in the text).

activity against *A. niger* and *C. albicans.* An additional study found that Av ethanol extract demonstrated antifungal properties against *C. albicans*, showing a zone diameter of inhibition (ZDI) between 12.45 and 17.225 mm in disc diffusion assays at four varying concentrations.[65] Moreover, research utilizing silver nanoparticles derived from Av extract indicated potent antifungal effects on *C. albicans.*[66] In another investigation, Bernardes et al.[67] found that a glycolic extract of Av leaves inhibited the growth and germ tube formation of *C. albicans*. Notably, a 10% v/v concentration of Av extract inhibited up to 90%–100% of fungal growth, suggesting its potential as a promising antifungal agent. Fig. 2 depicts the antifungal efficacy of Av.[65,66]

4.1.4. Anti-protozoan activity

Due to the presence of various bioactive constituents, plants have long been considered as an important resource in both traditional and modern medicine.[68] Particularly in herbal remedies, Av plays an important role in the treatment of infectious disorders like malaria.[69] A number of *Aloe* sp. leaf exudates and latex demonstrated antimalarial activity, particularly latex-derived compounds homonataloin A/B exert antimalarial activity.[70] Av gel has demonstrated anti-cryptosporidium activity against dexamethasone immunosuppressed mice.[71] Additionally, chromone, anthrone (from leaf latex) and two bioactive compounds aloin A and B have shown antimalarial activity.[72,73] The anti-protozoan efficacy of Av is shown in Fig. 2.

4.2. Antioxidant activity

Plant-derived natural antioxidants serve as essential agents which support the body's defensive response to oxidative stress from free radicals.[74] The oxidative stress induced tissue damage leads to the formation of serious chronic diseases including neurological, cardiovascular, liver diseases and cancer.[75] Natural dietary antioxidants derived from plants aid in safeguarding the body by counteracting free radicals, such as damaging reactive oxygen species (ROS).[76,77] *Aloe* sp. demonstrates high contents of vitamins and enzymes along with bioactive substances that possess powerful antioxidant properties. The Av contains vitamins (vitamin B6, B12 and C) along with minerals (manganese and copper), enzyme (superoxide dismutase) and amino acid (cysteine).[20] Av includes many secondary metabolites like tannins, flavonoids and carotenoids, which work together to enhance its antioxidant properties.[26] Table 3 summarizes the antioxidant activity of compounds from Av, and Fig. 2 illustrates the antioxidant properties of

Table 2
Antibacterial efficacy of *Aloe vera*.

Plant part	Phytochemicals	Target bacteria	Reference
Av leaf extract	Anthraquinone, aloisin, isoaloisin,	Gram-negative bacteria (*Shigella* sp., *Escherichia coli*, and *Salmonella* sp.) and Gram-positive bacteria (*Staphylococcus aureus*)	49,50
Av root extract	Aloisin	*Escherichia coli*, *Shigella* sp., *Staphylococcus aureus*, *Agrobacterium tumefacins*	5,50,51
Av gel	Campesterol, cholesterol, citric acid, isoaloisin	*Staphylococcus aureus, Escherichia coli, Enterococcus faecalis*	34,52
	Aloisin, isoaloisin	*Bacillus cereus, Bacillus subtilis, Streptococcus pyogenes*	5,53
Av hydrogel	*d*-Tartaric acid, aloisin, isoaloisin, campesterol, cholesterol	*Staphylococcus aureus* (ATCC 25923), *Pseudomonas aeruginosa* (ATCC 27853)	54,55

Table 3
Anti-oxidant activity of *Aloe vera*.

Active substances	Anti-oxidant activity	Reference
Isorabaichromone, feruloylaloesin, *p*-coumaroylaloesin, emodin, anthraquinone	Shows anti-oxidant activity by DPPH (2,2-diphenyl-1-picrylhydrazyl) assay	1,2
Manganese	Slows down the aging process and makes cells stronger in the fight against the negative effects of broad-spectrum radiation and oxygen	20
Vitamin B12	Takes part in complex cellular metabolic processes by being an indispensable regulator together with glutathione reductase, as part of the process of maintaining stable levels of glutathione, a highly active anti-free radical.	20
Vitamin B6	Plays a vital role in the metabolism of tryptophan, an essential amino acid, involved in protein synthesis and is a strong antioxidant.	20
Vitamin C	Limits the damage caused through the oxidation of free radicals to the white blood cells.	20
Vitamin E	Interacts in cellular energy production processes, plays a vital role in nervous system and immune system illnesses.	20
Copper	Limits the damaging effects of free radicals, mainly by the ceruloplasmin protein	78
Superoxide dismutase	Prevents rancidity of polyunsaturated fatty acids as well as keeps the cell membranes, strong. Produces anticancer property.	79
Cysteine	Plays a vital role for our health and longevity by de-activating free radicals through its sulphurous function group by protecting and strengthening cellular membranes from external attacks.	80
Polysaccharide	Showed a protective effect against 2,2′-azobis(2-amidinopropane) dihydrochloride-induced oxidative stress.	81

Av components.

4.3. Immuno-modulatory and anti-inflammatory activity

The immune system is a self-defence mechanism which plays a crucial role to fight against infections and diseases.[82,83] Several auto-immune diseases like rheumatoid arthritis, lupus erythematosus, bowel inflammation occur due to an imbalance of immune regulation system.[84] Immuno-modulators (compounds that suppress immune responses) might also be used to control autoimmune diseases.[85] Inflammation is a biological response of the host defence mechanisms to harmful stimuli, including pathogen-induced infections and cellular injuries.[86] The release of inflammatory mediators including chemokines, cytokines, and prostaglandins is largely mediated by various signalling pathways.[86–88] Av exhibits marked anti-inflammatory activity, especially in the murine macrophage RAW264.7 cells, which have been proved to possess bioactive compounds with anti-inflammatory activity against LPS-induced inflammation.[89] The anti-inflammatory effects of aloin are attributed to its ability to reduce ROS production, decrease iNOS expression, and inhibit the release of pro-inflammatory cytokines like interleukin (IL)-1β, IL-6, and tumor necrosis factor-α (TNF- α).[89] Aloe-emodin sulfates and glucuronides (0.5 μM) also inhibited the production of pro-inflammatory cytokines, nitric oxide, MAPK phosphorylation, and iNOS expression.[90] In another study, acemannan increased the expression of IL-6 and IL-8, as well as NF-κB/DNA binding in human gingival fibroblasts.[91] Additionally, Na et al.[92] demonstrated the anti-inflammatory properties of aloin in human oral KB epithelial cells. Av gel has also been investigated in an acetaminophen-induced hepatitis (inflammatory condition of the liver) in the mice model. The results of this study revealed that Av (150 mg/kg) reduced hepatic injury by decreasing malondialdehyde, IL-12, IL-18 and transaminase level, and increasing hepatic glutathione content.[93] Previous study revealed that emodin induces LPS/IFN and IL4 responsive genes by inhibiting two pathways NFκB/IRF5/STAT1 and IRF4/STAT6. This inhibitory activity modulates the macrophage phagocytosis, migration and NO production and helps in the suppression of excessive response of macrophages.[94] As indicated in the earlier study, Aloe-emodin and aloin demonstrated dose dependent (5–40 mM) inhibition of the inducible nitric oxide synthase (iNOS) mRNA, nitric oxide (NO) production and cyclooxygenase-2 (COX-2) and thereby supressed the inflammatory responses.[95] Recent evidence exhibits that polysaccharide, derived from Av gel, directly inhibits allergic responses through direct suppression of type 2 helper T cells and reduces the serum pro-inflammatory cytokines such as IL4, IL-5, IL-13, as well as histamine, mast cell protease-1 (MCP-1) and IgE.[96] Earlier research demonstrated that Av derived extract AVH200®, dose dependently suppressed human blood T-cell proliferation, reduced CD28 receptor on $CD3^+$ T cells, also reduced the secretion of IL-2, IFN-γ and IL-17A in peripheral blood mononuclear cells.[97] The anti-inflammatory and immunomodulatory activities of various Av compositions are summarized in Table 4, and are also illustrated in Fig. 2 along with their mechanism of actions.[89]

4.4. Anticancer property

Cancer is a life-threatening disease characterized by the uncontrolled proliferation and differentiation of normal cells, with major health crisis.[103] Common treatment options like tumor removal and chemotherapy involve alkylating agents, topoisomerase inhibitors and mitotic arrest by tubulin polymerization inhibition.[104,105] Though, chemotherapy is widely applied, yet various side effects including cytotoxicity to healthy tissues still pose a threat.[105,106] An ideal cancer drug would specifically target cancer cells without causing damage to healthy cells or inducing other toxic side effects.[107] In contrast, plant-derived phytochemicals have demonstrated significant anticancer activity against various cancer cell lines, selectively targeting cancer cells with high efficacy.[108] These plant compounds and their derivatives show promising potential as anticancer agents. In our study, Av, known for its rich array of bioactive compounds, has been identified as a plant with

Table 4
Anti-inflammatory and immunomodulatory activity of *Aloe* vera.

Aloe vera part/ composition	Anti-inflammatory and immune-modulatory effect	Mechanism of action	Reference
Av leaves	Methanolic extracts of dried Av leaves have inhibitory action against cyclooxigenase-1	Cyclooxigenase-1 is one of the key enzymes in the prostaglandins biosynthesis that are implicated in inflammatory processes	98
Av gel polysaccharide	Attenuate the reperfusion injury and cerebral ischemia in severe traumatic–hemorrhagic rats	Inhibiting systemic inflammatory response and lipid peroxidation as well as leukocyte aggregation in the brain	99
Av gel polysaccharide	Av polysaccharides are immune stimulants	Displaying adjuvant activity on specific antibody production; enhancing the release of interleukin-1 (IL-1), interleukin-6 (IL-6), tumour necrosis factor-α (TNF-α) and interferon-γ (INF-γ)	100
Av gel acemannan	Human gingival fibroblast	Increased IL-6 and IL-8 expression and NF-κB/DNA binding	91
Av gel emodin sulfates/ glucuronides	LPS-induced septic mice	Decrease NO level	90
Barbaloin	BALB/c mice LPS-induced acute lung injury	Histological analysis revealed certain protective effect	101
Av extract	Anti-inflammatory action on male ICR strain mice and acetaminophen-induced hepatitis	Decreased hepatic MDA, IL-12 and IL-18; decreased ALT transaminase	93
Av	Wistar albino rats	Decrease NF-κβ and nNOS expressions and inflammatory cell migration	102
Av latex aloin	Anti-inflammatory action on κβ cells	Decreased IL-8 production	92
Av latex aloin	Action on RAW 264.7 cells	Decreased iNOS expression; decreased IL-1β, IL-6, TNF-α and JAK1-STAT1/3 activation; decreased ROS production; decreased STAT1/3 nuclear translocation	89

notable anticancer properties. Due to its diverse chemical constituents, Av is gaining attention as a valuable resource for cancer treatment. One of the main active compounds in Av, the anthraquinone aloin, has shown significant anticancer potential. Research has shown that aloin provides chemoprotective benefits against preneoplastic lesions caused by 1, 2-dimethylhydrazine in the colons of Wistar rats.[109] Furthermore, aloin therapy has been found to reduce the secretion of VEGF (vascular endothelial growth factor) in cancer cells, which is crucial for tumor angiogenesis.[110] Another anthraquinone derivative from Av, aloe-emodin, has been thoroughly researched for its anticancer properties. Aloe-emodin has been demonstrated to exhibit various biological activities, including properties that fight cancer.[111] It boosts the transamidation activity of transglutaminase while inhibiting cell proliferation in metastatic human melanoma cell lines.[112] Additionally, aloe-emodin decreases AKT and ERK phosphorylation and reduces the number of cells during the S phase of the cell cycle.[113] Av crude extract has been observed to induce apoptosis in cancer cells, such as MCF-7 and HeLa cells, by elevating levels of pro-apoptotic proteins like Bax, p21, Cyclin D1, and CYAP1A1, along with activating CYP1A2.[114] Another component from Av, termed aloesin, has shown the potential to diminish cancer cell invasion, halt cell cycle progression in the S phase, reduce cell viability, and stimulate apoptosis in SKOV3 cells.[115] As per a previous study, aloe-emodin increases the endoplasmic reticulum stress that eventually induces apoptosis in H460 cells through caspease-3 apoptotic pathway. Further aloe-emodin plays a crucial role in decreasing the intracellular ATP level as well as mitochondrial injury.[116] Another study also suggests that aloe-emodin induces photodynamic activity on human gastric cells (SGC-7901) through dose dependent and energy dependent manner to inhibit the cell proliferation of cancer gastric cells by upregulation of caspase-9 and caspase-3.[117] Aloe-emodin induces phototoxicity of lung cancer cells which results in disruption of cytoskeleton, expression of α-actinin and mitogen-activated protein (MAP) kinase, thereby eventually creating rapid opening of the mitochondrial membrane permeability transition pore, and expression of apoptosis related proteins, which mediate the lung cancer cell (H460) death.[118] The anticancer activities of various Av constituents are summarized in Table 5, and are also illustrated in Fig. 2 along with their mechanism of actions.

4.5. Antidiabetic activity

Diabetes mellitus is a fatal metabolic disorder characterized by either insufficient production of insulin or peripheral tissues' inability to respond to insulin, causing an increase in blood glucose levels.[123,124] Type 1 diabetes is due to a deficiency of insulin and type 2 is due to the incapability of the body to effectively use of insulin.[124,125] Av gel caused a significant decrease in fasting blood glucose level, plasma cholesterol, phospholipids and liver transaminases, and also a striking increase in plasma insulin levels by oral administration in diabetic rats.[126] Clinical studies have further supported Av gel's potential as a safe anti-hypercholesterolemic and antihyperglycemic agent for type 2 diabetes patients.[127] Both *in vivo* and *in vitro* studies showed that the water-soluble fraction of Av can reduce blood glucose level and modulate the expression of GLUT-4 mRNA, a key factor in glucose uptake.[128] A notable improvement in pancreatic function was noticed by Av treatment in isolated rat pancreatic islets, where it enhanced cell survival and insulin secretion as well as reduced reactive oxygen species production.[129] Moreover, Av was used in a randomization of controlled trials on many participants to manage non-treated diabetes mellitus and prediabetes conditions. This study revealed that Av supplementation might significantly decrease the blood sugar levels, triglycerides, low density lipoproteins and total cholesterol levels.[130] Another study showed the administration of Av skin extract enriched with polyphenolic and flavonoid compounds, notably reduced the serum glucose level and cholesterol level up to 25% and 69% respectively.[131] Additionally, an oral administration trail of Av gel on 72 diabetic female patients showed a significant reduction of fasting glucose level and triglyceride.[132] Further, a clinical trial of Av gel capsule on 30 hyperlipidemic type 2 diabetic patients up to 2 months, revealed anti-hyperglycemic and anti-hypercholeteraemic activity of Av gel capsules as reduced fasting blood glucose levels without significant effects on liver and kidney.[133]

4.6. Action against neural diseases

Av is known for its antioxidant properties, which have been shown to offer protective effects against cerebral ischemia/reperfusion injury in rats.[134,135] Studies have demonstrated significant changes in sciatic nerve tissue, including alterations in nuclear respiratory factor-1 (NRF1) levels, malondialdehyde (MDA) concentrations, and enzyme activities of superoxide dismutase in response to Av treatment.[135] Additionally, a study on the hydroalcoholic extract of Av gel revealed its positive impact on histological and histomorphometric parameters in the sciatic nerve tissue of aged rats, suggesting that it could ameliorate some degenerative processes.[136] In earlier studies, the *Aloe* polymannose multinutrient complex (APMC) showed practically significant improvement in Alzheimer's patients as large reductions were seen in vascular endothelial growth factor (VEGF), tumor necrosis factor (TNF), and IL-2 and IL-4.[137] Another study highlighted Av's potentials of attacking Alzheimer's disease, the bioactive compounds in Av being the natural β-secretase 1 (BACE 1) inhibitors which can prevent the formation of amyloid β plaques that are characteristic of Alzheimer's disease. Through β-secretase

Table 5
Anticancer activity of *Aloe vera*.

Aloe vera composition	Target cells	Mechanism of action	Reference
Av crude extract	MCF-7 cells and HeLa cells	Decreased Cyclin D1, CYP1A1 and CYP1A2 expression Decreased cell viability and apoptosis induction Decreased Bax and p21 expression	114
Aloe-aloesin	SKOV3 cells	Decreased cell viability and cell clonality Decreased cell cycle at S-phase Increased Apoptosis Decreased migration and invasion cancer	115
Aloe-emodin	Metastatic human melanoma cell lines	Increased transamidating activity of transglutaminase Decreased cell proliferation	112
	TE1 cancer cells	Decreased AKT and ERK phosphorylation Decreased the number of cells in S phase	113
	MCF-7 cells	Decreased adhesion, migration and invasion of cells	119
	HUVECs cells	Decreased adhesion, migration and invasion of cells Apoptosis: mitochondrial death pathways	120
	HeLa cells	Decreased cell proliferation G2/M and S phase cell cycle arrest Decreased radiosensitivity Increased Cyclin B and γ-H2AX expression Increased ALP activity	121
	KB cells	Decreased cell proliferation Increased Caspase-3 upregulation Increased Bax protein levels Decreased Bcl-2 protein levels	122

inhibition by Av, therefore, dementia progression could tend to descend while deriving some neuroprotective support.[138,139] Chromone glycosides, such as aloeresin D and C-2′-decoumaroyl-aloesin G, present in *Aloe*, have shown remarkable inhibitory activity against BACE1 with IC_{50} values of 39.0 and 20.5 μM, respectively.[140] Av targeted Parkinson's disease, a neurodegenerative disorder marked by motor impairments and non-motor symptoms like anxiety, depression, and sleep disturbances. Av extract was probed for its potential to open avenues for the treatment of Parkinson's disease, focusing primarily on the inhibition of acetylcholinesterase and monoamine oxidase, which are synergistic in neurodegeneration.[141] Besides the neuroprotective agents, Av is also noted for being high in hyaluronan (HA); HA is a polysaccharide having important roles in tissue protection, embryonic development, inflammation, wound healing, and cancer, constituting an integral part in treatments for arthritis and osteoarthritis. Putri et al.[142] explained that HA accumulates just under the waxy cuticle of Av's rind, where HA-producing bacteria, such as Streptococci, are normally associated. This discovery indicates that the rind of Av has significant potential for high HA content, further enhancing its medicinal value. The effectiveness of different bioactive compounds of Av against neural diseases and their mode actions are outlined in Fig. 3.

5. Safety and toxicity

The profiles of safety and toxicity of drug compounds are essential in finding effective therapies.[143] Herbal plants, abundant in bioactive compounds, are gaining recognition for their healing properties. Nonetheless, comprehending the safety and toxicity of these substances is crucial to prevent harmful effects.[144,145] Av, a commonly utilized medicinal herb, comprises various bioactive components that possess both advantageous and harmful effects. As per the Traditional Chinese Medicine Information Database (TCMID), (https://bidd.group/TCMID/herb.php?herb=TCMH1343), the bioactive compounds from Av displayed considerable drug-likeness characteristics according to Lipinski's rule of five (Table 6).

Studies indicate that the water extract of Av leaves provides considerable defense against pesticide-induced harm in rat tissues, implying that *Aloe*'s natural elements might serve as therapeutic aids to alleviate cytotoxicity and oxidative stress from xenobiotics.[78] Aloin, an important component in Av, has been demonstrated to mitigate aluminum sulfate toxicity in rats.[146] Av gel is frequently used externally to address an array of skin issues, such as burns, sunburns, surgical injuries, skin ulcers, oral ulcers, rashes, genital herpes, cold sores, psoriasis, eczema, and pressure sores.[147] In addition to its surface advantages, Av gel enhances skin cell turnover and includes UV-protective ingredients and antioxidants that assist in preventing photoaging and long-lasting skin harm.[148] Furthermore, Av contributes to alleviating constipation and reducing blood sugar levels in people with diabetes.[149,150] Nonetheless, the scientific community is still split on the safety of Av products. One set of specialists claims that Av is typically safe for human intake, whereas another set cautions against its use because of possible contamination with aloin, a substance present in the yellow secretion of the plant.

Aloin has been reported to be DNA-damaging and potentially carcinogenic.[151] Certain *Aloe* sp. like *A. ferox*, are recognized as toxic, whereas most *Aloe* sp. is safe; however, a handful can be extremely toxic, highlighting the necessity of assessing possible negative impacts prior to using medicinal plants.[152,153] Reports have also emphasized allergic responses and hypersensitivity to Av products.[154] Prolonged or high-dose consumption of Av juice or latex can disturb electrolyte balance and such imbalances may lead to signs like muscle weakness, exhaustion, cognitive disorientation, weight reduction, and kidney issues.[155] Av should be refrained from during pregnancy, nursing, and childhood, as well as by those experiencing abdominal discomfort, intestinal blockage, or appendicitis.[153] Frequent adverse effects of oral Av consist of nausea, diarrhea, stomach pains, and vomiting.[156] At greater doses, Av can trigger drug-induced hepatitis and sudden kidney failure.[156,157]

6. Discussion

In the development of human civilization medicinal plants play a very essential role to combat diseases.[4] Most of the medicinal plants and their hidden activity were obscured, just because of a lack of proper investigations.[14,42] As a medicinal plant Av contains an array of potential bioactive compounds which have medicinal effects.[13]

The current review elucidates the major bioactive compounds of Av and their roles in curing various diseases.[24–26] The three major parts of Av include Av gel, leaf exudate and root extract, which enriched with various bioactive molecules like anthraquinone, aloesin, campastrol,

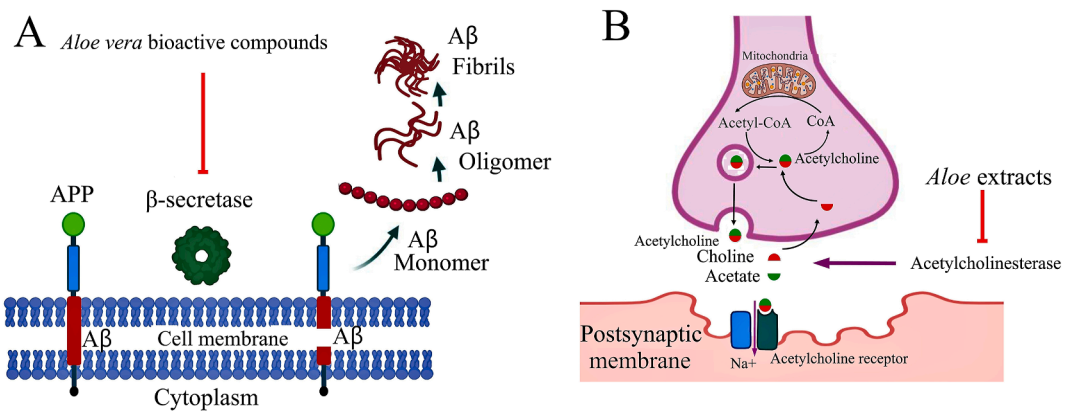

Fig. 3. (A) Inhibition of β-secretase 1 (BACE1) by bioactive compounds derived from Av, leads to prevention of the formation of amyloid plaque (Aβ fibrils) in Alzheimer's disease.[138,139] (B) Inhibition of acetylcholinesterase by Av-extract, leads to decrease of the acetylcholinesterase enzyme activity, which helps to maintain acetylcholine imbalance in Parkinson's disease.[140] This illustration was created by the first and second authors using webtools available at: BioRender.com and https://app.diagrams.net/.

Table 6
Bioactive compounds present in *Aloe vera* obtained from TCMID database.

No.	ID	Chemical formula	Compounds name	Molecular weight	Lipinski's rule of 5 violation
1	TCMC24	$C_{15}H_{14}O_6$	(+)-Epicatechin	290.08	0
2	TCMC3	$C_{15}H_{14}O_6$	(−)-Catechin	290.08	0
3	TCMC663	$C_{15}H_{10}O_5$	Aloe-emodin	270.00	0
4	TCMC3609	$C_{19}H_{22}O_{10}$	Aloenin	410.00	0
5	TCMC4586	$C_{28}H_{28}O_{11}$	Aloeresin A	540.00	0
6	TCMC4587	$C_{29}H_{30}O_{10}$	Aloeresin G	538.00	0
7	TCMC3573	$C_{19}H_{22}O_9$	Aloesin	394.00	0
8	TCMC4589	$C_{13}H_{12}O_4$	Aloesone	232.00	0
9	TCMC664	$C_{21}H_{22}O_9$	Aloin	418.13	1
10	TCMC665	$C_{21}H_{22}O_9$	Aloin B	418.13	1
11	TCMC666	$C_{27}H_{32}O_{13}$	Aloinoside B	564.18	2
12	TCMC710	$C_{15}H_{10}O_5$	Apigenin	270.00	0
13	TCMC847	$C_9H_8O_4$	Caffeic acid	180.04	0
14	TCMC3652	$C_{28}H_{48}O$	Campesterol	400.00	1
15	TCMC5879	$C_{15}H_{26}O$	Campherenol	222.19	0
16	TCMC880	$C_6H_6O_2$	Catechol	110.04	0
17	TCMC897	$C_{16}H_{18}O_9$	Chlorogenic acid	354.10	1
18	TCMC913	$C_{15}H_{14}O_6$	Cianidanol	290.08	0
19	TCMC916	$C_9H_8O_2$	Cinnamic acid	148.05	0
20	TCMC948	$C_9H_8O_3$	Coumaric acid	164.05	0
21	TCMC1157	$C_{10}H_{18}O$	Eucalyptol	154.14	0
22	TCMC6646	$C_{22}H_{24}O_9$	Homonataloin	432.14	1
23	TCMC1429	$C_{15}H_{10}O_6$	Kaempferol	286.05	0
24	TCMC1895	$C_5H_7NO_3$	Pidolic acid	129.04	0
25	TCMC2014	$C_{15}H_8O_6$	Rhein	284.03	0
26	TCMC1982	$C_{15}H_{10}O_7$	Quercetin	302.04	0
27	TCMC1986	$C_{21}H_{20}O_{11}$	Quercitrin	448.10	1
28	TCMC666	$C_{27}H_{32}O_{13}$	Aloinoside B	564.18	2
29	TCMC5849	$C_{19}H_{22}O_{10}$	Isoaloesin	410.12	0

and isoaloesin, exhibiting antibacterial potential against various gram-positive (*S. aureus*, *Bacillus cereus*, *E. faecalis, S. pyogenes* and *Bacillus subtilis*) and gram-negative bacteria (*E. coli*, *P. aeruginosa*, and *A. tumefaciens*) as per previous reports.[50,51] Ethanol extract of Av contributing its efficacy against clinically isolated gram-positive (*Enterococcus bovis*, and *S. aureus*) and gram-negative (*P. aeruginosa*, *Morganella morganii*, *Proteus mirabilis*, and *Proteus vulgaris*) bacteria.[45] Many experimental studies suggest that Av's ethanolic and glycolic extract exhibited significant anti-fungal activity.[51] As per a previous report, Av derived bioactive compounds such as anthraquinone and its root extract indicated promising antiviral activity (inhibition of replication process and virucidal activity) against influenza virus.[58] Besides, the Av exudates and latex demonstrated antimalarial activity, particularly latex-derived compounds homonataloin A/B exert antimalarial activity.[70] Previous study revealed that isolated bioactive compound aloin dose dependently inhibited the growth of malarial parasite (*Plasmodium berghei*).[72] As per a recent study, byproducts of Av contain good source of bioactive compounds.[158] By using green extraction methods Av byproduct may be utilized as an excellent source of functional compounds.[158] Another study reported that Av parenchyma utilized as a cost effective material for scaffold preparation, was suitable for protein and engineering sector.[159] So, it is evident that Av-derived phytocompounds and extract showed excellent anti-infective action, including antibacterial, anti-fungal, antiprotozoal, anti-viral activity and potent therapeutic activity, paving to the development of effective alternative therapeutic drugs against the array of infections.

Av also showed anti-inflammatory activity, by down regulating or inhibiting inflammation mediators.[86] Furthermore, Av containing vitamin B6, B12, C, E, and amino acid cysteine, plays a pivotal role in maintaining cellular stress and gets rid of consequences from free radicals.[20,80] In addition, aloin and emodin showed anti-inflammatory activity by decreasing NO level, nNOS expression, and IL-8 production.[91,92] Moreover, aloe-emodin is also responsible for phototoxicity in lung cancer cells and induces apoptosis by creating pores in the mitochondrial membrane.[118] Hence, based upon previous studies, Av derived phytocompounds also exhibited anti-oxidant, anti-inflammatory and anti-cancer actions.

For a long time in TCM, Av and its formulations cure various diseases.[12,14] Av, as an integral part of many formulations, helps to eradicate various infections or diseases.[42] Av, widely used in TCM, for treating wound healing, anorexia, dyspepsia, acts as a functional food to address malnutrition (https://www.meandqi.com/herb-database/aloe-vera). The therapeutic finding of Av based on TCM formulation and other previously reported studies supports the fewer side effects of Av, which is one of the vital criteria to design drug molecules as well as ensure their applicability.[5,27] This current review elucidates the major bioactive compounds of Av and their roles in curing various diseases.[24–26] Addressing their mode of actions on different targets and biological activities further open up new possibilities for researchers worldwide.[5,26]

7. Conclusion

The review meticulously analyzes the different bioactivities and primary pharmacological impacts of Av, providing a comprehensive evaluation of its therapeutic attributes. For centuries, Av has been utilized traditionally, leaving a significant influence from ancient times to today. The plant exhibits diverse pharmacological effects, such as anti-

infective, immune-enhancing and anticancer characteristics and also has conventional applications for ailments like eczema, inflammation, and fever, nevertheless additional study and scientific confirmation are needed in order to create new, effective therapies. Although its therapeutic advantages have been acknowledged for centuries, pharmacological research is essential to thoroughly comprehend its mechanisms of action and to investigate its potential applications in contemporary medicine. This research will enhance the knowledge of Av's therapeutic potential in creating effective and safe medications.

CRediT authorship contribution statement

Suchhanda Nandi: Writing – review & editing, Writing – original draft, Visualization, Software, Resources, Methodology. **Golak Majumdar:** Writing – review & editing, Writing – original draft, Visualization, Software, Resources, Methodology. **Shyamapada Mandal:** Visualization, Supervision, Formal analysis, Conceptualization.

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