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Exploring the therapeutic efficacy of *Aloe vera*: A pharmacological perspective

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Abstract
Plants are a great source of pharmaceuticals because they are the source of many of the treatments that are now on the market. Nevertheless, the healthcare system in poorer nations depends heavily on plants and the products derived from them. Around the world, aloe vera, one of the most well-known medicinal plants, is used to cure or prevent skin conditions, metabolic and cardiovascular diseases, and cancer. Aloe leaf's polysaccharide content has been demonstrated in numerous studies to possess a variety of properties, including as immunomodulation, antibacterial, antiviral, anti-cancer, and anti-inflammatory properties. Because aloe vera is grown all over the world, its precise origin is hard to pinpoint. The Madeira Islands, Algeria, Morocco, Tunisia, and the Canary Islands have all been proposed as sites for the species' naturalised stands. Habitats show that humans dispersed it over the Mediterranean region, which includes parts of southern Australia, eastern and southern Africa, the Mediterranean Sea region of Europe, and the United States. Aloe possesses a wide range of pharmacological properties, including Anti-oxidant activity, Anti-microbial, Anti-aging, Anti-cancer activity, Cardiovascular activity, Ulcer-protective property, Laxative, Skin protection properties. Various compounds have been reported to be purified or identified from Aloe. These identified phytochemicals have reported significant pharmacological effects. This review can widen the understanding regarding phytochemistry, geographical distribution and pharmacological activities of Aloe.

Keywords: Aloe vera, cardiovascular diseases, cancer, phytochemicals, pharmacological activities

1. Introduction
Many of the medications currently on the market have their origins in plants, which makes them a wonderful source of drugs. In developing countries, plants and the products made from them are nevertheless essential to the healthcare system. Modern pharmaceuticals derived from plants include digitalis, aspirin, anti-malarials, and anti-cancer therapies. Protective qualities against infections, inflammation, blood disorders, brain disorders, cardiovascular illnesses, oxidative stress, immune system dysfunction, reproductive disorders, and cancer chemotherapy are found in plants and phytochemicals. Most prescription drugs created in the world are derived from plants [1, 2]. Medicinal herbs, which are old enough to be regarded as true natural treatments, can be taken either whole or as an extract. People have been using plants, plant parts, and phytochemical extracts as remedies and preventative measures for a wide range of ailments since ancient times [3, 4]. More than 25% of all prescribed pharmaceuticals are derived from plants, and about 80% of India's rural population receives their medical care through traditional systems or herbal remedies. Most medicines came from plant sources two or three decades ago. Herbal medicines are gaining popularity in both developed and developing countries due to their reduced side effects. According to the World Health Organisation (WHO), more than 21,000 plants are used medicinally worldwide [5]. One of the most well-known medical plants, aloe vera is used all over the world to prevent or treat cancer, metabolic disorders, cardiovascular disorders, and skin ailments. Due to the existence of polysaccharides, aloe leaf has been shown in multiple studies to have a wide range of capabilities, including immunomodulation, antibacterial, antiviral, anti-cancer, and anti-inflammatory effects [6-8]. Numerous modifications to polysaccharide function can result from polysaccharide acetylation [9]. The main bioactive polysaccharide of Aloe vera, from which gel and skin are derived, is acemannan, a β-(1,4)-acetylated soluble polymannose [10]. Acemannan has been shown to have numerous pharmacological and biological uses in medical and industrial domains in recent decades, including metabolic, cardiovascular, and tumour illnesses [11, 12]. Recent studies on acemannan have concentrated on wound healing and dentistry.

According to US Food and Drug Administration (FDA)-approved protocols, acemannan has been used to treat wounds and alveolar osteitis [13]. More significantly, an increasing number of studies are focussing on the use of acemannan in medication administration and novel materials [14].

2. Methodology
Data on aloe's ethno-pharmacological applications, phytochemical constituents, and *in vivo* and *in vitro* biological activity were collected from around 65 published articles that were retrieved from several pertinent sources. A variety of online scientific databases, including PubMed, SciFinder, Web of Science, Science Direct, Wiley Online, ResearchGate, Google Scholar, and Scopus, were checked in addition to other search engines in order to find pertinent publications, research, and studies. Search terms including "Aloe vera," "Aloe," "phytochemicals," "ethno-pharmacology," and "traditional uses" were used to find the information needed about this plant species.

3. Morphology
This perennial plant is succulent and evergreen, with thick, sword-shaped leaves that can reach a height of one metre. With thorny edges, the leaves are green, closely packed, and arranged radially in two or three rings. Open tubular flowers, bright yellow, in a spike. Larger and oldest leaves are found near the base of the rosette arrangement, with younger, smaller leaves positioned in its centre. Upon reaching maturity, leaves may have a base 2-4 cm thick and a width 6-7 cm, tapering progressively to the tip at the apex. The upper surface of the leaf is flat or somewhat dish-shaped, while the lower surface is spherical and both are smooth to the touch. Conversely, the margins of the leaf are furnished with triangle-shaped, 2-4 mm long, hard, spreading teeth. Hanging from the unbranched flower stem are yellow tubular blooms. A spike that can grow up to 90 cm tall bears blooms in the summer. Each pendulous bloom has a 1-2 cm (0.8-1.2 in) long golden tubular corolla [15, 16].

4. Distribution
It is difficult to determine the exact origin of aloe vera due to its widespread global cultivation (Fig no.1). The Canary Islands, the Madeira Islands, Algeria, Morocco, and Tunisia have all been suggested as locations for the species naturalised stands. Habitats indicate that people spread it over the Mediterranean region, which encompasses parts of the United States, Southern Australia, eastern and southern Africa, and the region of Europe surrounding the Mediterranean Sea. Its closest cousins, however, are found in Arabia, indicating that this is most likely where it originated. It is situated on the lower slopes of the coastal mountains. The species was introduced to China, India, Pakistan, and a few areas of southern Europe in the seventeenth century. The plant is mainly found in desert regions of India, such as Rajasthan. It grows around Mumbai, Gujarat, and the coast of South India [17].

Fig 1: (A) Cultivation of Aloe, (B) Aloe leaf & gel, (C) Aloe flower

5. Phytochemistry
A. vera leaves are mostly made of three layers. The thick outer layer, known as the rind, is made up of 15-20 cells that produce proteins and carbohydrates. Vascular bundles like xylem and phloem are found inside the rind [18]. The chemical components of A. vera are complicated. Eleven categories can be used to group the primary chemical components of aloes: anthraquinones, carbohydrates, chromones, enzymes, inorganic compounds, vitamins, essential and non-essential amino acids, sugar, fatty acids, and other chemicals (Table 1).

Table 1: List of phytoconstituents with their property

S. No.	Constituents	Compounds	Activity and property	Ref
1	Anthraquinones/ anthrones	Aloe-emodin, aloetic-acid, anthranol, barbaloin, isobarbaloin, emodin, ester of cinnamic acid.	Aloin and emodin acts as analgesics, antibacterials and antivirals.	[18]
2	Carbohydrates	Pure mannan, acetylated mannan, acetylated galactan, xylan, cellulose, glucomannan, glucogalactomannan, galactogalacturan, arabinogalactan, galactoglucoarabino mannan, pectic substance	A glycoprotein with anti allergic properties, called alprogen and novel antiinflammatory compou	[19]
3	Chromones	8-C-glusoly-(2'-O-cinnamoly) -7-O Methylaloediol A,8-C-glucosyl-(S)- aloesol,8-C-glucosyl-7-O methylaloediol A, 8-C-glucosyl-7-0-methylaloediol, 8-Cglucosyl-noreugenin, isoaloeresin D, iso rabai chromone, neoalosin A	The novel anti-inflammatory commands.	[20]
4	Enzymes	Alkaline phosphatese, amylase, brady kinase, carboxy-peptidase, catalase, cyclo-oxidase, lipase, oxidase, cyclooxygenase, phosphoenol pyruvate, carboxylase, superoxide dismutase.	Brady kinase helps to reduce excessive inflammation when applied to the skin topically, while others help in the breakdown of sugars and fats	[21]
5	Inorganic compounds	Calcium, Sodium, Chiorine, Manganese, Zinc, Chromiurm, Potassium sorbate, Copper, Magnesium, lron, Selenium	They are essental for the proper functioning of various enzyme systems in different metabolic pathways and few are antioxidants.	[22, 23]
6	Vitamins	A, B1, B2, B6, B12, Choline, Folic acid, C, a-focopheral, B- carotene.	Antioxidant, neutralizes free radicals	[24, 25]
7	Essential amino acids	Lysine, Threonine, Valine, Leucine, Isoleucine, Phenylalanine, Methionine.	Provides the basic building blocks of proteins in the production of muscle, tissue etc.	[26, 27]
8	Non-essential amino acids	Histidine, Arginine, Hydroxyproline, Aspartic acid, Glutamic acid, Proline, Glycine, Alanine, Tyrosi	Provides the basic building blocks of proteins in the production of muscle, tissue etc.	[27, 28]
9	Sugars	Glucose, Galactose, Mannose, L-thamnose, Aldopentose, Glucuronic acid, Celluose, C-glucosyl chromone	Anti-inflammatory action, anfi viral, immune modulated achvity.	[29, 30]
10	Fatty acids	Cholesterol, B-sitosterol, Campestrol, Lupeol	Anti-inflammatory action and lupeol possesses antiseptic and analgesic action.	[31, 32]
11	Miscellaneous	Lignins, Uric acid, Auxins, Gibberelins, Salicylic acid, Arachidonic acid, Saponins.	Lignin, an inert substance enhances penetrative effect of the other ingredients into the skin. Auxins and gibberelins help in wound healing and have anti-inflammatory action. Salicylic acid that possesses anti-inflammatory and anti-bacterial properties Saponins that are the soapy substances have cleansing and antisepic properties.	[33-35]

6. Traditional uses

Aloes have long been used to treat a variety of illnesses, especially those relating to the digestive system; they have also been used to treat burns, wounds, and skin issues. The dried juice that emerges from the transversely sliced bases of the leaves is what aloes are known for. It is the ideal herbal solution to support the body's health and healing processes because it doesn't cure; instead, it nourishes the body's systems so they may operate at their optimum and stay healthy.

Pharmacologically, it detoxifies the body and increases immunity. To get rid of drug-induced gastritis and other side effects, it is advised in adjuvant therapy with antibiotics, NSAIDs (Nonsteroidal Anti-Inflammatory Drugs), and chemotherapy [24]. Useful for a number of illnesses, including ulcers, spleen enlargement, type II diabetes, arthritis, eye problems, tumours, liver complaints, vomiting, bronchitis, asthma, and jaundice. Assists with non-ulcer dyspepsia, gastric and duodenal ulcers, inflammatory bowel disorders, constipation relief, and maintaining a healthy stomach pH. A nutritional supplement for postmenopausal women, patients before and after surgery, and people with osteoporosis [36].

7. Pharmacological activities

7.1 Anti-oxidant activity

Dietary supplements frequently contain antioxidants, which are chemicals that prevent other molecules from oxidizing. Antioxidant activity is the antioxidants' overall ability to get rid of free radicals in food and cells. Aloe vera has a powerful antioxidant impact, according to Sharma Priyanka *et al.* (2014). A. vera gel was discovered to have glutathione peroxidase activity, superoxide dismutase enzymes, and a phenolic antioxidant, which may be the cause of these antioxidant properties [37]. Additionally, some other researchers also evaluated Glutathione peroxidise activity, superoxide dismutase enzymes and a phenolic anti-oxidant were found to be present in Aloe Vera gel [38]. Aloe vera improves blood quality, most likely by making it possible for the blood to carry nutrients and oxygen to the body's cells more efficiently [39] and it contains aloe barbendol, aloe emodin, barbaloin A which possess antioxidant activity [40].

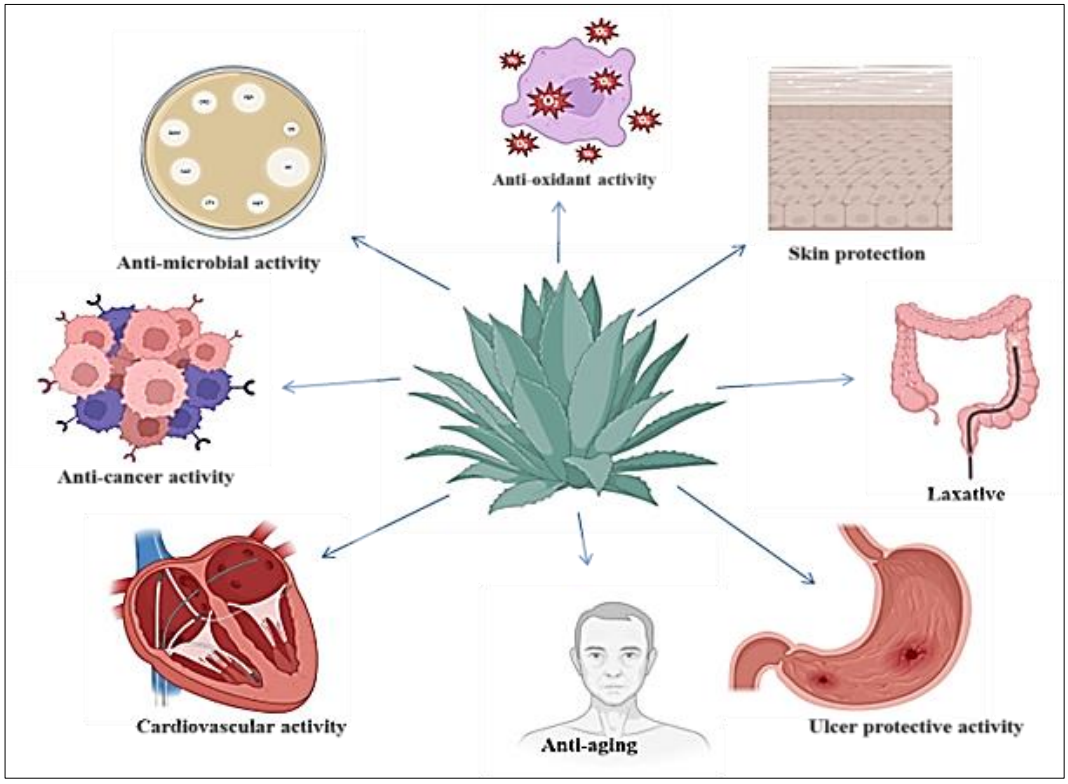

Fig 2: Aloe vera's various pharmacological activities

7.2 Anti-microbial

An antimicrobial agent kills microorganisms or inhibits their growth. Antimicrobial agents may be antibacterial, which work against bacteria; antifungal, against fungi; microbiocides, which kill microbes; or microbiostatic, growth inhibitors of microbes**.**According to the Sharma Priyanka *et al*., 2014,The antibacterial action of Aloe vera gel enhances the wound healing process by its anti-inflammatory action [41]. The anthraquinone derivatives of Aloe leaf have shown virucidal effects on enveloped viruses [42]. In particular, aloe vera inhibits the growth of Gram-positive bacteria that cause food poisoning or infections in humans and animals, such as Streptococcus pyogenes, Shigella flexneri, and Klebsiella sp [43]. However, other researchers have calculated the antifungal activity of the leaf pulp and liquid portion of Aloe vera, which demonstrated an inhibitory effect on the mycellium development of Rhizoctonia solani, Fusarium oxysporum, and Colletotrichum coccodes. Along with other oral pathogens isolated from patients with periapical and periodontal abscesses, such as Actinobacillus actin mycetemcomitans, Aloe vera aqueous extract inhibited the growth and biofilm formation of methicillin-resistant Staphylococcus aureus [44].

7.3 Anti-aging

Many people believe that as people age, their bodies' physiological systems deteriorate, making them more susceptible to age-related illnesses. Age is a major risk factor for neurological illnesses as well. The relationship between degenerative diseases and aging indicates that aging is a key factor in the pathophysiology of many conditions. Many researchers evaluate anti-aging effectivity of aloe-vera, It increases the skin's capacity to retain moisture and aids in the elimination of dead skin cells that produce collagen and elastin fibers, increasing the skin's suppleness and decreasing wrinkles, therefore reversing the degenerative changes in the skin (SaleemAisha *et al*.2022) [45]. Additionally, some other researchers also indicated, Aloe increases the production of collagen and elastin fibers by stimulating fibroblasts, which makes the skin less wrinkled and more elastic [46]. There are unrealistic moisturizing qualities to it. It helps remove dead skin cells and enhances the skin's capacity to moisturize itself. By generating collagen and elastin fibers, it reverses the degenerative changes in the skin and makes it more elastic and less wrinkled [47].

7.4 Anti-cancer activity

Anticancer activity: Refers to the ability of a substance or compound to inhibit the growth of cancer cells, induce apoptosis (programmed cell death), or otherwise interfere with the processes that allow cancer to develop and spread. Research suggests that various components of Aloe vera, such as polysaccharides, anthraquinones, glycoproteins, and certain enzymes, may exhibit anti-cancer properties through different mechanisms. In a study it has been observed that, the impact of aloin on cell viability was investigated by using Jurkat T cells. Aloin treatment resulted in a dose-dependent decrease in cell size, impaired membrane integrity, and loss of mitochondrial membrane potential. Furthermore, the cell cycle was altered as a result of aloin therapy. A decrease of mitochondrial membrane potential precedes the loss of cell membrane integrity, indicating a mitochondrial-dependent mechanism for aloin-induced apoptosis [48]. On the other hand, in a research on adult drosophila, Stanic S. et. Al found that, the co-treatment of Aloe vera was beneficial in lowering the genotoxicity of the direct-acting mutagen [49]. The polysaccharide fragment of Aloe gel prevented the production of benzo[α]pyrene-DNA adducts, exhibiting chemo preventive and antigenotoxic effects [37]. It is suspected that, Acemannan as a biological response modulator and a strong stimulator of murine B- and T-cells, may improve antigen recognition by causing tumour cell cytotoxicity in murine peritoneal macrophage cells [50]. Also, by triggering apoptosis in the mitochondria and endoplasmic reticulum and preventing metastatic oxidative stress, the isolated chemical

aloe-emodin has proven to be a potent anticancer drug against both MCF-7 cells and HeLa cells [51-54]. While promising, much of the evidence is preclinical, and further research is required to establish safety and efficacy in humans.

7.5 Cardiovascular activity

Aloe vera has been studied for various potential health benefits, including its cardioprotective properties. According to a study by Zhang P. *et al*. when aloin (20 mg/kg/day, 5 days) was given intragastrical to Sprague Dawley rats suffering from myocardial ischemia/reperfusion damage, it enhanced AMPK signalling and decreased myocardial oxidative stress and inflammatory response [55]. This compound's non-atherogenic action and iron chelating qualities were shown by Esmat *et al*. [56] when it was injected intramuscularly at a dose of 50 mg/kg body weight, twice weekly for two weeks. In another study, the hypotensive effects of bisbenzopyran, elgonica dimer A, aloeemodin, and aloin A from A. barbadensis is examined. In recent pharmacological studies, aloe emodin has been shown to be a strong hypotensive agent, lowering mean arterial blood pressure in rats [57]. However, while these potential benefits are promising, more clinical research is needed to fully establish the extent and mechanisms of aloe vera's cardioprotective effects.

7.6 Ulcer-protective property

Aloe vera is also recognized for its potential ulcer-protective activity, particularly in the gastrointestinal tract. It can prevent or treat stomach ulcers. Several potential processes, including as A. vera's anti-inflammatory qualities, healing benefits, mucus production stimulation, modulation of stomach secretions, and presence of lectins, have been linked to its anti-ulcer properties. Parietal cells' absorption of aminopyrines is inhibited by the lectins. Thus, the unusual capacity of the extract to prevent the production of gastric acid may be due to direct action on the cells that produce acid [38, 42]. Several studies have shown the potential of aloe vera in reducing ulcer size and promoting healing, but more clinical trials are needed to fully confirm its efficacy and understand the mechanisms involved.

7.7 Laxative

Anthraquinones, especially aloin, are the chemicals that give aloe vera its inherent laxative qualities. Anthraquinones promote intestinal peristaliasis, raise intestinal water content, and stimulate water secretion [58]. The yellowish material called latex, which is found just beneath the aloe vera leaf's epidermis, contains several chemicals.Blumenthal *et al*. found that, gut bacteria break down the anthraquinones, which are poorly absorbed from the GIT, to create aloe-emodin, which is more easily absorbed and gives these preparations their purgative qualities [59]. Considering these factors, aloe vera exhibits potential as a natural laxative; nonetheless, further study is required to confirm its effectiveness, establish appropriate dose recommendations, and completely comprehend its long-term health impacts.

7.8 Skin protection

Aloe vera is widely recognized for its potential benefits in skin care, particularly its soothing, moisturizing, and healing properties. Liu FW *et al*. investigated that, by lowering lipid peroxidation, ROS formation, DNA damage, and IL-8 production while raising GSH and SOD activity, aloin provided skin protection [60]. Furthermore, several studies found that, aloe vera enhanced fibroblasts' production of TFG_1, bFGF, and Vegf-A and boosted keratinocyte proliferation and differentiation by lysosomal membrane stability [61-65]. All things taken into account, aloe vera shows promise for a number of skin protection uses; nevertheless, more thorough study is required to confirm these advantages and determine the best doses and formulations for its application in skincare products.

8. Conclusion

The current study summarises the distribution, phytochemistry, pharmacological aspects of Aloe vera and critically evaluates the results that have been published. Current research indicates that aloe vera had significant therapeutic advantages. The majority of published research has focused on the wide range of pharmacological activities of crude plant extracts. This plant's phytochemicals have a variety of properties, such as antibacterial, antioxidant, and anticancer properties. Therefore, the focus of future studies should be on the biological and pharmacological effects of plant extracts as well as analyses of the bioactive compounds that underlie the activity. Future dosages for treating a range of ailments could be created using these findings. Recent pharmacological research indicates that aloe vera possesses a wide range of pharmacological qualities, such as Anti-oxidant activity, Anti-microbial, Anti-aging, Anti-cancer activity, Cardiovascular activity, Ulcer-protective property, Laxative, Skin protection. To further explore its possible practical applications, more *in vivo* pharmacological activity and toxicity research of aloe vera and their chemical constituents are recommended.

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