European Journal of Medicinal Plants

33(6): 23-43, 2022; Article no.EJMP.87187
ISSN: 2231-0894, NLM ID: 101583475

A Review on Pharmacological and Therapeutic Potential of *Aloe barbadensis* Miller

Deepak Sharma [a], Naimish Purohit [a], Shiwa Chaubey [b], Mohan Tiwari [a], Mradu Bhadauriya [a], Mohit [c,d], Nilam Bhasker [e] and Dharmendra Kumar [f*]

[a] School of Studies in Biochemistry, Jiwaji University, Gwalior - 474011, India.
[b] CSIR- Phytochemistry Division, National Botanical Research Institute, Lucknow - 226001, India.
[c] Department of Prosthodontics, Faculty of Dental Sciences, King George's Medical University, Lucknow - 226003, India.
[d] Center for Advance Research, Faculty of Medicine, King George's Medical University, Lucknow - 226003, India.
[e] Department of Pathology, Employee State Insurance Corporation hospital, Lucknow - 226023, India.
[f] Department of Orthopedic Surgery, Faculty of Medicine, King George's Medical University, Lucknow - 226003, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript and equally contributed.

Article Information

DOI: 10.9734/EJMP/2022/v33i630471

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/87187

Review Article

Received 08 March 2022
Accepted 17 May 2022
Published 28 May 2022

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.

**Corresponding author: E-mail: dharmendra00715@gmail.com;*

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).

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. No	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]

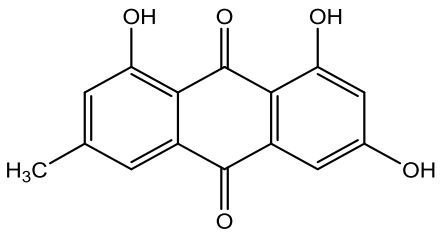
3.10 Phenylpropanoids and Coumarins

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

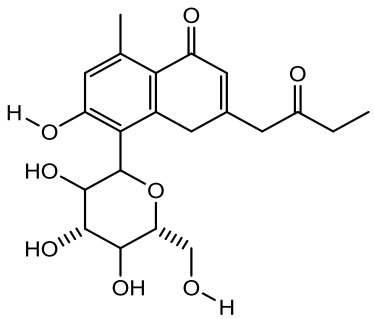
3.11 Others

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.

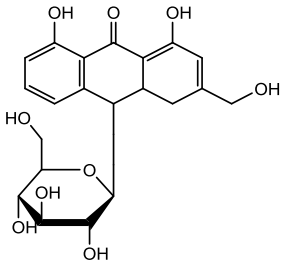
Moisture, ash, fibre, amino acids, fats, organic acids, free sugars, and some polysaccharides were revealed during a chemical analysis of *Aloe vera* leaves and the main free sugars were monosaccharides like fructose and glucose. Some important organic acids include isocitric, fumaric acid, lactone,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



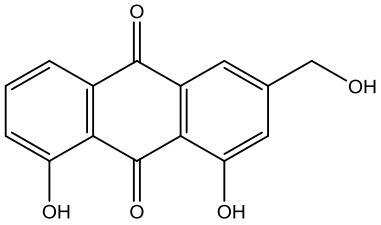
Emodin



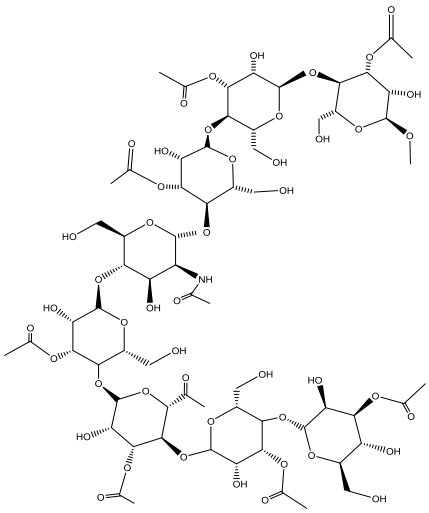
Aloe resin



Aloin



Aloe emodin



Acemannan

Fig. 1. Major chemical constituents present in *Aloe vera* (drawn at Chemdraw)

Table 3. Anthraquinone and their derivatives

S. No	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	$C_{42}H_{42}O_{18}$	

S. No	Compound	Formula	Reference
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	$C_{15}H_{8}O_{6}$	[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. No	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	$C_{9}H_{10}O_{5}$	[28]
4	Gallic acid	$C_{7}H_{6}O_{5}$	
5	Gentisic acid	$C_{7}H_{6}O_{4}$	
6	Ascorbic acid	$C_{6}H_{8}O_{6}$	
7	Vanillic acid	$C_{8}H_{8}O_{4}$	
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	$C_{7}H_{8}O$	
12	P-anisaldehyde	$C_{8}H_{8}O_{2}$	
13	1-(2,4-dihydroxy-6-methylphenyl) ethanone	$C_{9}H_{10}O_{3}$	
14	Salicylaldehyde	$C_{7}H_{6}O_{2}$	

Table 5. Phytosterols and others

S. No	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. No	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. No	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]

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 led 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 defense. 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 signaling 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 vascularization, 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 randomized 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 chemo preventative 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 in diabetic rats that the liver necrosis 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 localized 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 hemoglobin, 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 emodin. 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.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENT

Mohit is recipient of a Senior Research Fellowship (Fellowship ID: 2020-3690) from the Indian Council of Medical Research, New Delhi, Government of India.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Vickers A, Zollman C, Lee R. Herbal medicine. The Western Journal of Medicine. 2001;175:125-128.
2. Vogler BK, Ernst E. *Aloe vera*: A systematic review of its clinical effectiveness, The British Journal of General Practice: The Journal of the Royal College of General Practitioners. 1999;49: 823-828.
3. Zhang Y, Bao Z, Ye X, Xie Z, He K, Mergens B, Li W, Yatcilla M, Zheng Q. Chemical Investigation of Major Constituents in *Aloe vera* Leaves and Several Commercial Aloe Juice Powders. J. AOAC Int. 2018;101:1741-1751.
4. Nejatzadeh-Barandozi F. Antibacterial activities and anti-oxidant capacity of *Aloe vera*, Org Med Chem Lett. 2013;3:5-5.
5. Baumann L. Anti-Inflammatory Agents, in: Cosmeceuticals and Cosmetic Ingredients, McGraw-Hill Education, New York, NY; 2015.
6. Hamman JH. Composition and Applications of *Aloe vera* leaf gel. Molecules. 2008;13.
7. Chantarawaratit P, Sangvanich P, Banlunara W, Soontornvipart K, Thunyakitpisal P. Acemannan sponges stimulate alveolar bone, cementum and periodontal ligament regeneration in a canine class II furcation defect model. J. Periodontal Res. 2013;49:164-178.
8. King G, Yates K, Greenlee P, Pierce K, Ford CR, Mcanalley B, Tizard I. The effect of Acemannan Immunostimulant in combination with surgery and radiation therapy on spontaneous canine and feline fibrosarcomas, J. Am. Anim. Hosp. Assoc. 1995;31(5):439-447.
9. Jettanacheawchankit S, Sasithanasate S, Sangvanich P, Banlunara W, Thunyakitpisal P. Acemannan stimulates

gingival fibroblast proliferation; Expressions of Keratinocyte Growth Factor-1, Vascular Endothelial Growth Factor, and Type I Collagen; and Wound Healing, J. Pharmacol. Sci. 2009;109:525-531.
10. Grindlay D, Reynolds T. The *Aloe vera* phenomenon: A review of the properties and modern uses of the leaf parenchyma gel. J. Ethnopharmacol. 1986;16:117-151.
11. Lee KY, Weintraub ST, Yu BP. Isolation and identification of a phenolic anti-oxidant from Aloe barbadensis. Free Radic. Biol. Med. 2000;28:261-265.
12. Reynolds T, Dweck AC. *Aloe vera* leaf gel: a review update. J. Ethnopharmacol. 1999;68:3-37.
13. Surjushe A, Vasani R, Saple DG. *Aloe vera*: A short review. Indian J. Dermatol. 2008;53;163-166.
14. Sheikh FA, Singh RPP, Singh JB, Lehana P. Effect of microwaves on the resistance of *Aloe vera* leaves, in, 2013.
15. Ermias D, Daniel B, Alvaro V, Ben-Erik Van W. Chemistry of Aloe Species, Current Organic Chemistry. 2000;4:1055-1078.
16. Javed S, Atta ur R. Chapter 9 - *Aloe Vera* Gel in Food, Health Products, and Cosmetics Industry, in: R. Atta ur (Ed.) Studies in Natural Products Chemistry. Elsevier. 2014;41:261-285.
17. Ro JY, Lee BC, Kim JY, Chung YJ, Chung MH, Lee SK, Jo TH, Kim KH, Park YI. Inhibitory Mechanism of Aloe Single Component (Alprogen) on Mediator Release in Guinea Pig Lung Mast Cells Activated with Specific Antigen-Antibody Reactions. J. Pharmacol. Exp. Ther. 2000;292:114.
18. Pegu A, Sharma M. Review on *Aloe vera*. International Journal of Trend in Scientific Research and Development. 2019;3:35-40.
19. Lee S, Do SG, Kim S, Kim J, Jin Y, Lee C. Mass spectrometry-based metabolite profiling and anti-oxidant activity of *Aloe vera* (*Aloe barbadensis* Miller) in Different Growth Stages, J. Agric. Food Chem. 2012;60.
20. Okamura N, Hine N, Tateyama Y, Nakazawa M, Fujioka T, Mirmhi K, Yagi A. Three chromones of *Aloe vera* leaves. Phytochemistry. 1997;45:1511-1513.
21. Okamura N, Hine N, Tateyama Y, Nakazawa M, Fujioka T, Mihashi K, Yagi A. Five chromones from *Aloe Vera* leaves. Phytochemistry. 1998;49:219-223.
22. lv L, Yang QY, Zhao Y, Yao CS, Sun Y, Yang EJ, Song KS, Mook-Jung I, Fang W. BACE1 (β-Secretase) Inhibitory Chromone Glycosides from *Aloe vera* and Aloe nobilis, Planta Med. 2008;74:540-545.
23. Zhong JS, Huang YY, Zhang TH, Liu YP, Ding WJ, Wu XF, Xie ZY, Luo HB, Wan JZ. Natural phosphodiesterase-4 inhibitors from the leaf skin of Aloe barbadensis Miller, Fitoterapia. 2015;100:68-74.
24. Rehman N, Al-Riyami S, Hussain H, Ali A, Khan A, Al-Harrasi A. Secondary metabolites from the resins of *Aloe vera* and Commiphora mukul mitigate lipid peroxidation, Acta. Pharm. 2019;69:433-441.
25. Li FF, Xu XL. Extraction and purification of anthraquinones derivatives from *Aloe vera* L. using alcohol/salt aqueous two-phase system. Bioprocess and Biosystems Engineering. 2012;36.
26. Yang M, Li L, Heo SM, Soh Y. Aloe-Emodin Induces Chondrogenic Differentiation of ATDC5 Cells via MAP Kinases and BMP-2 Signaling Pathways, Biomol. Ther. (Seoul). 2016;24:395-401.
27. Rehman NU, Al-Riyami SA, Hussain H, Ali A, Khan AL, Al-Harrasi A. Secondary metabolites from the resins of and mitigate lipid peroxidation, Acta Pharmaceutica. 2019;69:433-441.
28. López A, De Tangil MS, Vega-Orellana O, Ramírez AS, Rico M. Phenolic constituents, anti-oxidant and preliminary antimycoplasmic activities of Leaf Skin and Flowers of *Aloe vera* (L.) Burm. f. (syn. A. barbadensis Mill.) from the Canary Islands (Spain), Molecules. 2013;18.
29. Tanaka M, Misawa E, Ito Y, Habara N, Nomaguchi K, Yamada M, Toida T, Hayasawa H, Takase M, Inagaki M, Higuchi R. Identification of Five Phytosterols from *Aloe Vera* Gel as Anti-diabetic Compounds, Biol. Pharm. Bull. 2006;29:1418-1422.
30. Keyhanian S, Stahl-Biskup E. Phenolic Constituents in Dried Flowers of *Aloe vera* (Aloe barbadensis) and their in vitro Antioxidative Capacity, Planta Med. 2007;73:599-602.
31. Kahramanoğlu İ, Chen C, Chen J, Wan C. Chemical Constituents, Antimicrobial Activity, and Food Preservative Characteristics of *Aloe vera* Gel, Agronomy. 2019;9.
32. Pizzino G, Irrera N, Cucinotta M, Pallio G, Mannino F, Arcoraci V, Squadrito F,

Altavilla D, Bitto A. Oxidative stress: Harms and Benefits for Human Health, Oxid. Med. Cell. Longev. 2017;8416763.
33. Sato H, Shibata M, Shimizu T, Shibata S, Toriumi H, Ebine T, et al. Differential cellular localization of anti-oxidant enzymes in the trigeminal ganglion. Neuroscience. 2013;248:345-358.
34. Wu JQ, Kosten TR, Zhang XY. Free radicals, anti-oxidant defense systems, and schizophrenia, Prog. Neuropsychopharmacol. Biol. Psychiatry. 2013;46:200-206.
35. Wang H, Brumaghim J. Polyphenol compounds as anti-oxidants for disease prevention: Reactive Oxygen Species Scavenging, Enzyme Regulation, and Metal Chelation Mechanisms in *E. coli* and Human Cells; 2011.
36. Xu DP, Li Y, Meng X, Zhou T, Zhou Y, Zheng J, et al. Natural anti-oxidants in foods and medicinal plants: Extraction, assessment and resources. Int J Mol Sci. 2017;18:96.
37. Marmitt DJ, Bitencourt S, da Silva GR, Rempel C, Goettert MI. Traditional plants with anti-oxidant properties in clinical trials—A systematic review. Phytother. Res. n/a; 2021.
38. Sultana B, Anwar F, Ashraf M. Effect of extraction solvent/technique on the anti-oxidant activity of selected medicinal plant extracts, Molecules (Basel, Switzerland). 2009;14:2167-2180.
39. Naqvi S, Ullah MF, Hadi SM. DNA degradation by aqueous extract of *Aloe vera* in the presence of copper ions, Indian J. Biochem. Biophys. 2010;47:161-165.
40. Loots DT, van der Westhuizen FH, Botes L. Aloe ferox Leaf Gel Phytochemical Content, Anti-oxidant Capacity, and Possible Health Benefits. J. Agric. Food Chem. 2007;55:6891-6896.
41. Hęś M, Dziedzic K, Górecka D, Jędrusek-Golińska A, Gujska E. *Aloe vera* (L.) Webb.: Natural Sources of Anti-oxidants – A Review, Plant Foods Hum. Nutr. 2019;74:255-265.
42. Anilakumar K, Sudarshanakrishna K, Chandramohan G, Ilaiyaraja N, Khanum F, Bawa A. Effect of *Aloe vera* gel extract on anti-oxidant enzymes and azoxymethane-induced oxidative stress in rats. Indian J. Exp. Biol. 2010;48:837-842.
43. Esteban A, Zapata JM, Casano L, Martín M, Sabater B. Peroxidase Activity in Aloe barbadensis Commercial Gel: Probable Role in Skin Protection, Planta Med. 2000;66:724-727.
44. Bendjedid S, Lekmine S, Tadjine A, Djelloul R, Bensouici C. Analysis of phytochemical constituents, antibacterial, anti-oxidant, photoprotective activities and cytotoxic effect of leaves extracts and fractions of *Aloe vera*, Biocatalysis and Agricultural Biotechnology. 2021;33: 101991.
45. Saini DK, Saini MR. Evaluation of radioprotective efficacy and possible mechanism of action of Aloe gel, Environ. Toxicol. Pharmacol. 2011;31:427-435.
46. Subbiah R, Sivagnanam K, Subramanian S. Modulatory effects of *Aloe vera* leaf gel extract on oxidative stress in rats treated with streptozotocin, The Journal of pharmacy and Pharmacology. 2005;57: 241-246.
47. Lordan R, Tsoupras A, Zabetakis I. Chapter 2 - Inflammation, in: I. Zabetakis, R. Lordan, A. Tsoupras (Eds.) The Impact of Nutrition and Statins on Cardiovascular Diseases, Academic Press. 2019;23-51.
48. Paul S, Modak D, Chattaraj S, Nandi D, Sarkar A, Roy J. et al. *Aloe vera* gel homogenate shows anti-inflammatory activity through lysosomal membrane stabilization and downregulation of TNF-α and Cox-2 gene expressions in inflammatory arthritic animals. Future Journal of Pharmaceutical Sciences. 2021;7:12.
49. Ma Y, Tang T, Sheng L, Wang Z, Tao H, Zhang Q, Zhang Y, Qi Z. Aloin suppresses lipopolysaccharide‐induced inflammation by inhibiting JAK1‐STAT1/3 activation and ROS production in RAW264.7 cells. Int. J. Mol. Med. 2018;42:1925-1934.
50. Li CY, Suzuki K, Hung YL, Yang MS, Yu CP, Lin SP, Hou YC, Fang SH. Aloe Metabolites Prevent LPS-Induced Sepsis and Inflammatory Response by Inhibiting Mitogen-Activated Protein Kinase Activation. The American Journal of Chinese Medicine. 2017;45:847-861.
51. Thunyakitpisal P, Ruangpornvisuti V, Kengkwasing P, Chokboribal J, Sangvanich P. Acemannan increases NF-κB/DNA binding and IL-6/-8 expression by selectively binding Toll-like receptor-5 in human gingival fibroblasts. Carbohydrate Polymers. 2017;161:149-157.
52. Na HS, Song YR, Kim S, Heo JY, Chung HY, Chung J. Aloin Inhibits Interleukin (IL)-

4²-Stimulated IL-8 Production in KB Cells, J. Periodontol. 2016;87(6):e108-115.
53. Ahluwalia B, Magnusson MK, Isaksson S, Larsson F, Öhman L. Effects of Aloe barbadensis Mill. extract (AVH200®) on human blood T cell activity *in vitro*. J. Ethnopharmacol. 2016;179:301-309.
54. Davis RH, Donato JJ, Hartman GM, Haas RC. Anti-inflammatory and wound healing activity of a growth substance in *Aloe vera*, J. Am. Podiatr. Med. Assoc. 1994;84:77-81.
55. Hutter JA, Salman M, Stavinoha WB, Satsangi N, Williams RF, Streeper RT, Weintraub ST. Antiinflammatory C-Glucosyl Chromone from Aloe barbadensis, J. Nat. Prod. 1996;59:541-543.
56. Prabjone R, Thong-ngam D, Wisedopas N, Chatsuwan T, Patumraj S. Anti-inflammatory effects of *Aloe vera* on leukocyte-endothelium interaction in the gastric microcirculation of Helicobacter pylori-infected rats. Clin. Hemorheol. Microcirc. 2006;35(3):359-366.
57. Kshirsagar AD, Panchal PV, Harle UN, Nanda RK, Shaikh HM. Anti-inflammatory and antiarthritic activity of anthraquinone derivatives in rodents. International Journal of Inflammation. 2014;690596.
58. Feily A, Namazi MR. *Aloe vera* in dermatology: A brief review, Giornale italiano di dermatologia e venereologia: organo ufficiale. Societa Italiana Di Dermatologia e Sifilografia. 2009;144(1): 85-91.
59. Rippon M, Perrin A, Darwood R, Ousey K. The potential benefits of using *aloe vera* in stoma patient skin care. Br. J. Nurs. 2017;26:S12-S19.
60. Saddiq A, Al-Ghamdi H. *Aloe vera* extract: A novel antimicrobial and antibiofilm against methicillin resistant *Staphylococcus aureus* strains. Pak. J. Pharm. Sci. 2018;31:2123-2130.
61. Bawankar R, Singh P, Babu S. Bioactive compounds and medicinal properties of *Aloe Vera* L.: An Update. Journal of Plant Sciences. 2014;2:102-107.
62. Bawankar R, Deepti VC, Singh P, Subashkumar R, Vivekanandhan G, Babu S. Evaluation of Bioactive potential of an *aloe vera* sterol extract. Phytother. Res. 2013;27:864-868.
63. Xiang H, Cao F, Ming D, Zheng Y, Dong X, Zhong X, Mu D, et al. Aloe-emodin inhibits Staphylococcus aureus biofilms and extracellular protein production at the initial adhesion stage of biofilm development. Appl. Microbiol. Biotechnol. 2017;101: 6671-6681.
64. Goudarzi M, Fazeli M, Azad M, Seyedjavadi SS, Mousavi R. *Aloe vera* Gel: Effective Therapeutic Agent against Multidrug-Resistant Pseudomonas aeruginosa Isolates Recovered from Burn Wound Infections, Chemotherapy Research and Practice. 2015;639806.
65. Cataldi V, Di Bartolomeo S, Di Campli E, Nostro A, Cellini L, Di Giulio M. *In vitro* activity of *Aloe vera* inner gel against microorganisms grown in planktonic and sessile phases. Int. J. Immunopathol. Pharmacol. 2015;28:595-602.
66. Karkare S, Ahire N, Khedkar S. Comparative evaluation of antimicrobial activity of hydroalcoholic extract of *Aloe vera*, garlic, and 5% sodium hypochlorite as root canal irrigants against Enterococcus faecalis: An *in vitro* study. J. Indian Soc. Pedod. Prev. Dent. 2015;33: 274-278.
67. Rezazadeh F, Moshaverinia M, Motamedifar M, Alyaseri M. Assessment of Anti HSV-1 Activity of *Aloe vera* Gel Extract: an *in vitro* Study. J Dent (Shiraz). 2016;17:49-54.
68. Sun Z, Yu C, Wang W, Yu G, Zhang T, Zhang L, Zhang J, Wei K. Aloe Polysaccharides Inhibit Influenza A Virus Infection-A Promising Natural Anti-flu Drug, Front Microbiol. 2018;9:2338-2338.
69. Kumar S, Yadav A, Yadav M, Yadav JP. Effect of climate change on phytochemical diversity, total phenolic content and in vitro anti-oxidant activity of *Aloe vera* (L.) Burm.f. BMC Res. Notes. 2017;10:60-60.
70. Quezada MP, Salinas C, Gotteland M, Cardemil L. Acemannan and Fructans from *Aloe vera* (*Aloe barbadensis* Miller) Plants as Novel Prebiotics. J. Agric. Food Chem. 2017;65:10029-10039.
71. Saroj PL, Ram C, Kumar K. Arid Horticultural Crops: Status and Opportunities under Changing Climatic Conditions. Indian Journal of Plant Genetic Resources. 2020;33:17-31.
72. Teplicki E, Ma Q, Castillo D, Zarei M, Hustad A, Chen J, Li J. The Effects of *aloe vera* on wound healing in cell proliferation, migration, and viability. Wounds: A

Compendium of Clinical Research and Practice. 2018;30:263-268.
73. Wahedi HM, Jeong M, Chae JK, Do SG, Yoon H, Kim SY. Aloesin from *Aloe vera* accelerates skin wound healing by modulating MAPK/Rho and Smad signaling pathways *in vitro* and *in vivo*. Phytomedicine. 2017;28:19-26.
74. Atiba A, Ueno H, Uzuka Y. The effect of *aloe vera* oral administration on cutaneous wound healing in type 2 diabetic rats. J. Vet. Med. Sci. 2011;73:583-589.
75. Femenia A, Sánchez ES, Simal S, Rosselló C. Compositional features of polysaccharides from *Aloe vera* (Aloe barbadensis Miller) plant tissues, Carbohydrate Polymers. 1999;39:109-117.
76. Chithra P, Sajithlal GB, Chandrakasan G. Influence of *Aloe vera* on collagen characteristics in healing dermal wounds in rats, Mol. Cell. Biochem. 1998;181:71-76.
77. Chithra P, Sajithlal GB, Chandrakasan G. Influence of *Aloe vera* on the glycosaminoglycans in the matrix of healing dermal wounds in rats. J. Ethnopharmacol. 1998;59:179-186.
78. Sari Y, Purnawan I, Kurniawan DW, Sutrisna E. A Comparative Study of the Effects of Nigella sativa Oil Gel and *Aloe Vera* Gel on Wound Healing in Diabetic Rats. J Evid Based Integr Med. 2018;23: 2515690X18772804-12515690X18772804.
79. Chantarawaratit P, Sangvanich P, Banlunara W, Soontornvipart K, Thunyakitpisal P. Acemannan sponges stimulate alveolar bone, cementum and periodontal ligament regeneration in a canine class II furcation defect model. J. Periodontal Res. 2014;49:164-178.
80. Leng H, Pu L, Xu L, Shi X, Ji J, Chen K. Effects of aloe polysaccharide, a polysaccharide extracted from *Aloe vera*, on TNF‐α‐induced HaCaT cell proliferation and the underlying mechanism in psoriasis. Mol Med Rep. 2018;18:3537-3543.
81. Hekmatpou D, Mehrabi F, Rahzani K, Aminiyan A. The effect of *aloe vera* clinical trials on prevention and healing of skin wound: A systematic review. Iran J Med Sci. 2019;44:1-9.
82. Burusapat C, Supawan M, Pruksapong C, Pitiseree A, Suwantemee C. Topical *Aloe Vera* Gel for Accelerated Wound Healing of Split-Thickness Skin Graft Donor Sites: A Double-Blind, Randomized, Controlled Trial and Systematic Review, Plast. Reconstr. Surg. 2018;142.
83. Hoopfer D, Holloway C, Gabos Z, Alidrisi M, Chafe S, Krause B, et al. Three-Arm Randomized Phase III Trial: Quality Aloe and Placebo Cream Versus Powder as Skin Treatment During Breast Cancer Radiation Therapy, Clin. Breast Cancer. 2015;15:181-190.e184.
84. Nandal U, Bhardwaj RL. *Aloe vera*: A valuable wonder plant for food, medicine and cosmetic use - a review, International Journal of Pharmaceutical Sciences Review and Research. 2012;13:59-67.
85. Noor A, Gunasekaran S, Vijayalakshmi MA. Improvement of Insulin Secretion and Pancreatic β-cell Function in Streptozotocin-induced Diabetic Rats Treated with *Aloe vera* Extract, Pharmacognosy Res. 2017;9:S99-S104.
86. Subbiah R, Kasiappan R, Sivagnanam K, Subramanian S. Beneficial effects of *Aloe vera* leaf gel extract on lipid profile status in rats with STZ diabetes, Clinical and Experimental Pharmacology & Physiology. 2006;33;232-237.
87. Kumar R, Sharma B, Tomar NR, Roy P, Gupta AK, Kumar A. *In vivo* evalution of hypoglycemic activity of Aloe spp. and Identification of Its Mode of Action on GLUT-4 Gene Expression *in vitro.* Appl. Biochem. Biotechnol. 2011;164:1246-1256.
88. Devaraj S, Jialal R, Jialal I, Rockwood J. A pilot randomized placebo controlled trial of 2 *Aloe vera* supplements in patients with pre-diabetes/metabolic syndrome. Planta Med. 2008;74:SL77.
89. Shin E, Shim KS, Kong H, Lee S, Shin S, Kwon J, et al. Dietary Aloe Improves Insulin Sensitivity via the Suppression of Obesity-induced Inflammation in Obese Mice, Immune Netw. 2011;11:59-67.
90. Rahimifard M, Navaei-Nigjeh M, Mahroui N, Mirzaei S, Siahpoosh Z, P. D, A. Nili-Ahmadabadi, A. Mohammadirad, M. Baeeri, R. Hajiaghaie, M. Abdollahi. Improvement in The Function of Isolated Rat Pancreatic Islets through Reduction of Oxidative Stress Using Traditional Iranian Medicine, Cell J. 2014;16:147-163.
91. Kim K, Chung MH, Park S, Cha J, Baek JH, Lee SY, Choi SY. ER stress attenuation by Aloe-derived polysaccharides in the protection of pancreatic β-cells from free fatty acid-

induced lipotoxicity. Biochem. Biophys. Res. Commun. 2018;500:797-803.
92. Alshatwi AA, Subash-Babu P. Aloe-Emodin Protects RIN-5F (Pancreatic β-cell) Cell from Glucotoxicity via Regulation of Pro-Inflammatory Cytokine and Downregulation of Bax and Caspase 3, Biomol. Ther. (Seoul). 2016;24:49-56.
93. Kim K, Kim H, Kwon J, Lee S, Kong H, Im SA, et al. Hypoglycemic and hypolipidemic effects of processed *Aloe vera* gel in a mouse model of non-insulin-dependent diabetes mellitus. Phytomedicine. 2009;16: 856-863.
94. Chandrasekar R, Sivagami B, Babu M. A Pharmacoeconomic Focus on Medicinal Plants with Anticancer Activity, Research Journal of Pharmacognosy and Phytochemistry. 2018;10:91.
95. Greenwell M, Rahman PKSM. Medicinal Plants: Their Use in Anticancer Treatment. Int J Pharm Sci Res. 2015;6:4103-4112.
96. Hussain A, Sharma C, Khan S, Shah K, Haque S. *Aloe vera* Inhibits Proliferation of Human Breast and Cervical Cancer Cells and Acts Synergistically with Cisplatin, Asian Pacific Journal of Cancer Prevention: APJCP. 2015;16:2939-2946.
97. Trybus W, KrÓL T, Trybus EWA, Stachurska A, Kopacz-Bednarska A, KrÓL G. Induction of Mitotic Catastrophe in Human Cervical Cancer Cells After Administration of Aloe-emodin, Anticancer Res. 2018;38:2037.
98. Hamiza OO, Rehman MU, Khan R, Tahir M, Khan AQ, Lateef A, Sultana S. Chemopreventive effects of aloin against 1,2-dimethylhydrazine-induced preneoplastic lesions in the colon of Wistar rats, Hum. Exp. Toxicol. 2013;33:148-163.
99. Pan Q, Pan H, Lou H, Xu Y, Tian L. Inhibition of the angiogenesis and growth of Aloin in human colorectal cancer *in vitro* and in vivo, Cancer Cell Int. 2013;13:69-69.
100. Das S, Mishra B, Gill K, Ashraf MS, Singh AK, Sinha M, Sharma S, et al. Isolation and characterization of novel protein with anti-fungal and anti-inflammatory properties from *Aloe vera* leaf gel. Int. J. Biol. Macromol. 2011;48:38-43.
101. Shalabi M, Khilo K, Zakaria MM, Elsebaei MG, Abdo W, Awadin W. Anticancer activity of *Aloe vera* and Calligonum comosum extracts separetely on hepatocellular carcinoma cells, Asian Pacific Journal of Tropical Biomedicine. 2015;5:375-381.
102. Tong X, Li M, Li D, Lao C, Chen J, Xu W, et al. *Aloe vera* gel extract: Safety evaluation for acute and chronic oral administration in Sprague-Dawley rats and anticancer activity in breast and lung cancer cells, J. Ethnopharmacol. 2021; 280:114434.
103. Shirali S, Barari A, Hosseini S, Khodadi E. Effects of six weeks endurance training and *Aloe vera* supplementation on COX-2 and VEGF Levels in Mice with Breast Cancer. Asian Pacific Journal of Cancer Prevention : APJCP. 2017;18:31-36.
104. Hamman J. Composition and applications of *Aloe vera* leaf gel, Molecules (Basel, Switzerland). 2008;13:1599-1616.
105. Sharma B, Siddiqui S, Guru G, Chaudhary M, Sharma G. Hypoglycemic and hepatoprotective effects of processed *Aloe vera* gel in a mice model of alloxan induced diabetes mellitus. Journal Diabetes Metab. 2013;04.
106. Misawa E, Tanaka M, Nomaguchi K, Nabeshima K, Yamada M, Toida T, Iwatsuki K. Oral ingestion of *Aloe vera* phytosterols alters hepatic gene expression profiles and ameliorates obesity-associated metabolic disorders in zucker diabetic fatty rats. J. Agric. Food Chem. 2012;60:2799-2806.
107. Saeed M, Deng Y, Dai R. Attenuation of biochemical parameters in streptozotocin-induced diabetic rats by oral administration of extracts and fractions of *Cephalotaxus sinensis*. J. Clin. Biochem. Nutr. 2008;42: 21-28.
108. Joseph B, Jini D. Antidiabetic effects of Momordica charantia (bitter melon) and its medicinal potency. Asian Pac J Trop Dis. 2013;3:93-102.
109. Racherla P, Rodda R, Pande M, Tirlangi T, Dadannagari S, Rathod P, Ramarapu R, Chidrawar V, Rao U. Evaluation of hepatoprotective activity of alchoholoic extract of *aloe vera* polysaccharides in experimentally induced liver injury. 2014;3: 80.
110. Zhang L, Tizard IR. Activation of a mouse macrophage cell line by acemannan: The major carbohydrate fraction from *Aloe vera* gel, Immunopharmacology. 1996;35:119-128.
111. Budai M, Varga A, Milesz S, Tözsér J, Benko S. *Aloe vera* downregulates LPS-induced inflammatory cytokine production

and expression of NLRP3 inflammasome in human macrophages. Mol. Immunol. 2013;56:471-479.
112. Halder S, Mehta AK, Mediratta PK. Augmented humoral immune response and decreased cell-mediated immunity by *Aloe vera* in rats. Inflammopharmacology. 2012;20:343-346.
113. Wu C, Liu Y, Yang Y, Zhang P, Zhong W, Wang Y, et al. Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods, Acta Pharmaceutica Sinica B. 2020;10: 766-788.
114. Azer SA. COVID-19: Pathophysiology, diagnosis, complications and investigational therapeutics, New Microbes and New Infections. 2020; 37:100738.
115. Mpiana PT, Ngbolua KTN, Tshibangu DST, Kilembe JT, Gbolo BZ, et al. Identification of potential inhibitors of SARS-CoV-2 main protease from *Aloe vera* compounds: A molecular docking study, Chem. Phys. Lett. 2020;754: 137751.
116. Sharuk K, Siddiqui F. Beta-sitosterol: As immunostimulant, anti-oxidant and inhibitor of SARS-CoV-2 Spike Glycoprotein. 2020;2:12-16.
117. López Z, Femenia A, Núñez-Jinez G, Zúñiga M, Cano ME, Espino T, Knauth P. *In vitro* immunomodulatory effect of food supplement from *Aloe vera*, Evid. Based Complement. Alternat. Med. 2019;1-9.
118. Madhyastha R, Madhyastha H, Pengjam Y, Nurrahmah QI, Nakajima Y, Maruyama M. The pivotal role of microRNA-21 in osteoclastogenesis inhibition by anthracycline glycoside aloin. J. Nat. Med. 2019;73:59-66.
119. Eftekhar S, Keshavarzi Z, Hajzadeh MAR. Neuroprotective effects of pine bark and *Aloe vera* on the Locomotor Activity in Focal Cerebral Ischemia: Possible Anti-oxidant Mechanisms. Journal of Biomedical Engineering and Medical Devices. 2016;01.
120. Sánchez M, González-Burgos E, Iglesias I, Gómez-Serranillos MP. Pharmacological update properties of *Aloe Vera* and its major active constituents, Molecules (Basel, Switzerland). 2020;25: 1324.
121. Rath M, Bhattacharya A, Rath K, Santra S, Ghosh G, Nanda B. A Comprehensive study of the neuropharmacological profile of methanol leaf extract of *Aloe vera* and identification of associated neuroprotective compounds through gas chromatography-mass spectrometry analysis. Indian J. Pharm. Sci. 2020;82.
122. Şahin H, Yener A, Karaboga I, Şehitoğlu H, Dogu T, Altinisik H, Altınışık U, Simsek T. Protective effect of gel form of gastric gavage applicated *aloe vera* on ischemia reperfusion injury in renal and lung tissue. Cell. Mol. Biol. 2017;63:34.
123. Zhang P, Liu X, Huang G, Bai C, Zhang Z, Li H. Barbaloin pretreatment attenuates myocardial ischemia-reperfusion injury via activation of AMPK, Biochem. Biophys. Res. Commun. 2017; 490:1215-1220.
124. Esmat AY, Said MM, Khalil SA. Aloin: A natural antitumor anthraquinone glycoside with iron chelating and non-atherogenic activities. Pharm. Biol. 2015;53:138-146.
125. Park MK, Park JH, Shin YG, Kim WY, Lee JH, Kim KH. Neoaloesin A: A New C-Glucofuranosyl Chromone from Aloe barbadensis. Planta Med. 1996;62:363-365.
126. Kim JH, Yoon JY, Yang SY, Choi SK, Kwon SJ, Cho IS, et al. Tyrosinase inhibitory components from *Aloe vera* and their antiviral activity. J. Enzyme Inhib. Med. Chem. 2017;32:78-83.
127. Borges-Argáez R, Chan-Balan R, Cetina-Montejo L, Ayora-Talavera G, Sansores-Peraza P, Gómez-Carballo J, Cáceres-Farfán M. *In vitro* evaluation of anthraquinones from *Aloe vera* (Aloe barbadensis Miller) roots and several derivatives against strains of influenza virus. Ind Crops Prod. 2019;132:468-475.
128. Epifano F, Fiorito S, Locatelli M, Taddeo VA, Genovese S. Screening for novel plant sources of prenyloxyanthraquinones: *Senna alexandrina* Mill. and *Aloe vera* (L.) Burm. F, Natural Product Research. 2015;29:180-184.
129. Tan ZJ, Li FF, Xu Xl. Extraction and purification of anthraquinones derivatives from *Aloe vera* L. using alcohol/salt aqueous two-phase system. Bioprocess and Biosystems Engineering. 2013;36: 1105-1113.
130. Speranza G, Dadá G, Lunazzi L, Gramatica P, Manitto P. Aloenin B, a New Diglucosylated 6-Phenyl-2-pyrone from

Kenya Aloe. J. Nat. Prod. 1986;49:800-805.

131. Yang QY, Yao CS, Fang W. A new triglucosylated naphthalene glycoside from *Aloe vera* L. Fitoterapia. 2009;81: 59-62.

132. Lawrence R, Tripathi P, Jeyakumar E. Isolation, Purification and evaluation of antibacterial agents from *Aloe vera*. Brazilian Journal of Microbiology: [Publication of the Brazilian Society for Microbiology]. 2009;40:906-915.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/87187