Original Article

LITERATURE REVIEW OF NEEM TREE (*Azadirachta indica*) AND ALOVERA (*Aloe barbadensis miller*)

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Abstract

Azadirachta indica (neem tree) grows up to almost the all over around the asia. It is abundant in Pakistan too and having many medicinal and other beneficial uses. A total of 135 structural compounds have been extracted and identified and they are classified as Isoprenoids and non-isoprenoids. Most important ingredient is nimbin and azadirachtin. From the ancient time, neem tree and its all part have ethenomedicinal importance. The active constituents in the neem posses most of the therapeutic effect on kidney, liver, heart disorder. It also improves the immune system and gives antitumor effect. The neem constituents help to improve all the skin condition. *Aloe barbadensis miller* (alovera) is a juicy and fleshy plant and grows in hot and tropical climate. It also gives beneficial effect as it is anti inflammatory, anti acne, anti diabetic and also helps to improve the skin condition. Along all these therapeutic effect, these both plants use in pharmaceutical and cosmaceutical industry for making of exicipent or use in liquid syrup, creams, ointments, gel, spray and lotions etcs.

Keywords: Nimbin, azadiradione, succulent, aloe, ethenomedicinal, perennial**.**

OBJECTIVE:

To descriptive study of neem tree (*Azadirachta indica*) and alovera (*Aloe barbadensis miller*) along with its major and essential constituents and their phyto and pharmaceutical importance. The aim to study these both plant is to identify the major action in acne vulgaris.

METHODOLOGY:

More than 70 articles search from the google scholar engine then reviewed and rewrite the detailed overview of literature about neem and alovera plant.

NEEM TREE

Introduction:

Neem tree have potential height of 20m is long lasting remain green plant throughout the year. The leaves are alternating, with 8–19 leaves per leaflet, and may grow in March–April. They have a bitter flavor. (1) It can survive in semi-arid conditions and thrives and bears up to 50°C. It's height up to 15 m tall and lifespan of about 200-300 years. Small, white blooms with a fragrant, jasmine-like aroma make up its blossoms. Its edible fruit has white kernels and is approximately 3/4 of an inch long (2 cm). (2)

Neem tree with its parts:

Figure 1 Images includes neem tree, leaves, flower, bark, twig, fruit and seed.

<table>
<tr>
<td rowspan="2"> 
(3)Neem Tree</td>
<td> 
(4) Neem Leaves</td>
<td> 
(5) Neem Flower</td>
<td> 
(6) Neem Seed</td>
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<td> 
(7) Neem Fruit</td>
<td> 
(8) Neem Bark</td>
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(9) Neem Twig</td>
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Taxanomical Data:

Table 1: An updated taxonomy of Neem plant. (10, 11)

Biological/ Scientific Name	*Azadirachta indica*
Domain	Eukaryotae
Kingdom	Plantae
Phylum	Spermatophyta
Subphylum	Angiospermae
Class	Dicotyledonae
Order	Rutales
Suborder	Rutinae
Family	Meliaceae
Sub Family	Melioideae
Tribe	Melieae
Genus	*Azadirachta*
Species	*indica*
Common Name	Neem tree
Trade/ Brand Name	neem
Other Biological Name	Antelaea canescens Cels ex Heynh. Antelaea javanica Gaertn. Azadirachta indica subsp. Vartakii Azadirachta indica var. minor Valeton Azadirachta indica var. siamensis Valeton Melia azadirachta L. Melia indica Brandis
Native	Abundantly in tropical and semitropical regions of India, Bangladesh, Pakistan, and Nepal and in Northern part of Nigeria.

Major types of constituents:

Table 2: Neem major chemical constituents (11)

From various portions of the Neem tree, a total of 135 structural compounds have been extracted and identified and they are classified as Isoprenoids and non-isoprenoids	
Isoprenoids	Consist of limonoids, protomeliacins, gedunin, azadirone, vilasinin and C-secomeliacins like salanin, nimbin and azadirachtin
Non-Isoprenoids	Consist of amino acids, polysaccharides, polyphenolics like flavonoids, sulphurous compounds, dihydrochalcone, glycosides, tannins, coumarin and aliphatic compounds.

Constituents of Neem tree:

Numerous chemical constituents have therapeutic effect and found in different parts of the plant, in which Azadirachtin is the most active chemical ingredient.

Leaves contain nimbin, nimbanene, nimbandiol, ascorbic acid, 6-desaacetylnimbinene, nimbolide, n-hexacosanol and amino acid, 7-desaacetyl-7- benzoylgedunin, 7-desaacetyl-7-benzoylazadiradione, 17-hydroxyazadiradione, nimbiol, quercetin and Beta-sitosterol.

Seeds contain gedunin and azadirachta and limonoids, triacylglycerols of oleic, strearic, linoleic, and palmitic acids and Margosa oil also salanin and nimbin, nimbolide, gedunin, mahmoodin.

Stem bark contains bioactive compounds as tannins such as tricyclic diterpenoids, NB-II peptidoglycan, gallic acid, epigallocatehin, gallocatehin, catechin, epicatechin, margolone, Margolonone and isomargolonone. Polysaccharides G1A, G1B and Polysaccharides G2A.

Constituents 1: Major bio active constituents in different parts of neem plant. (12) (13)

Chemical structure of Neem constituents:

Figure 2: Chemical Structure of Azadirachtin and Nimbin (14)

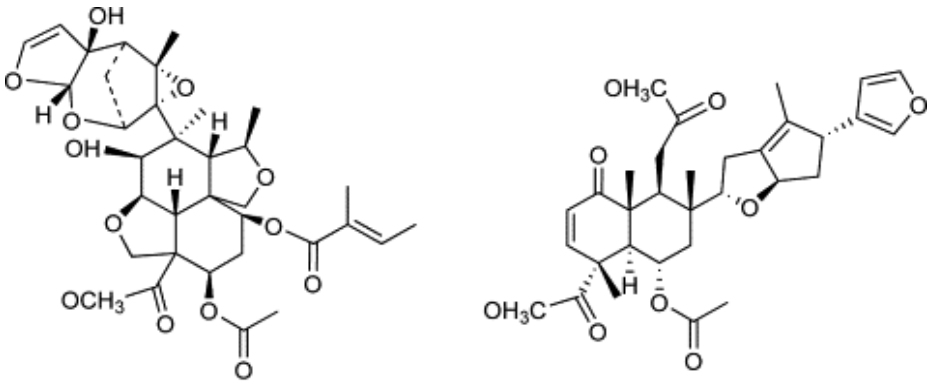
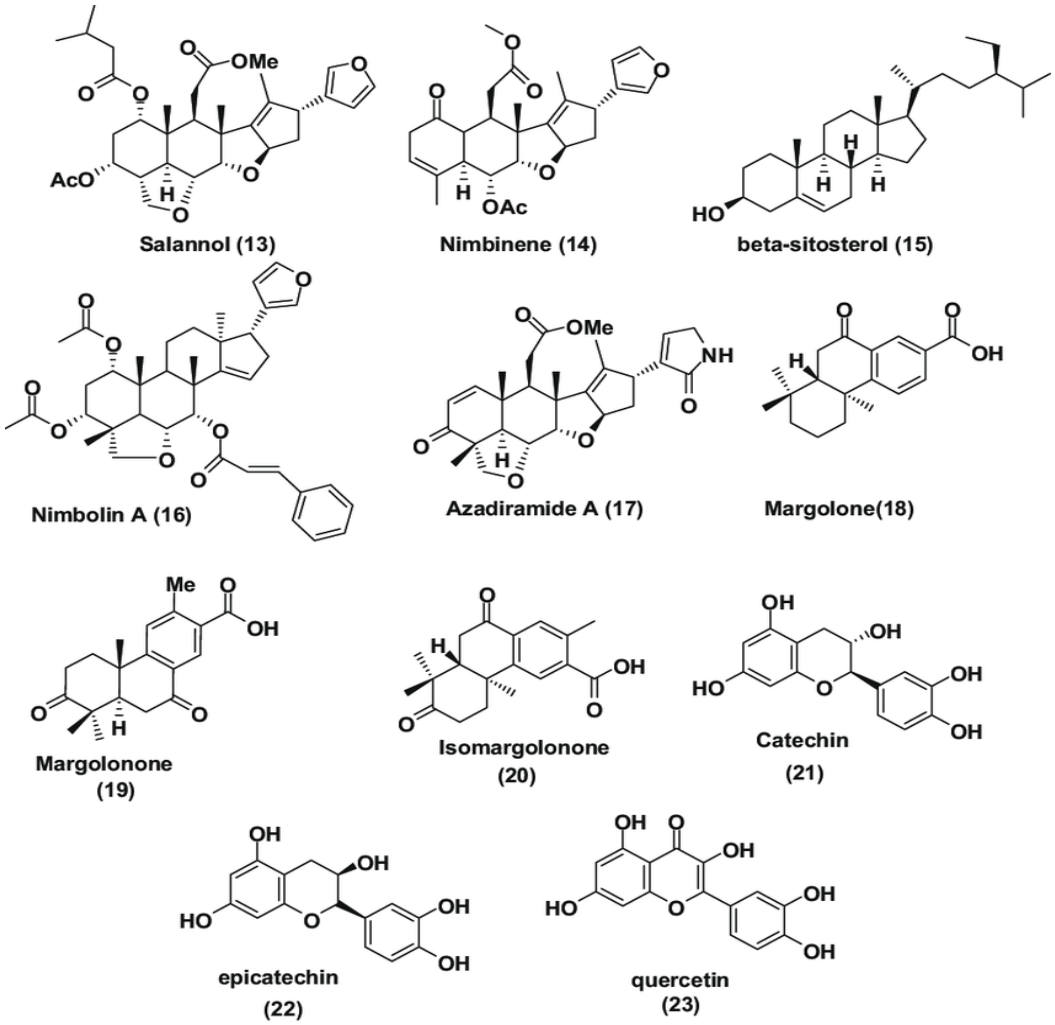


Figure 3: The most active other chemical structure (15)



Therapeutic applications:

Since ancient times, neem has been employed for therapeutic and ethnomedical purposes. Neem plant parts, including the leaf, bark, root, seed, and flowers, demonstrate a function in the control of illness through the regulation of diverse biological processes. Many individuals have been able to gain benefits from this powerful plant because of how easily and affordably it is available.

1. Anticancer and antitumor:

- It influence intracellular signaling pathways which involved in managing of cancer and alter the environment around tumor by various mechanisms like reducing angiogenesis and enhancing cell toxicity. (16)
- It changes genes involved in cellular development and activity, and it also reduces the stimulatory action of vascular endothelial growth factor. (17)
- The use of gedunin as a preventative and therapeutic drug for breast cancer. (17)
- 35 limonoids from neem seed extracts have been proven to be cytotoxic. This neem chemical has a dose- and time-dependent cytotoxic effect, having a significant impact on cancer cells and a limited impact on healthy fibroblasts. (17)
- p53, pTEN, NF-B, PI3K/Akt, Bcl-2, and VEGF are just few of molecular pathways that neem and its components have been shown to modulate in antitumor control in studies using animal models.(17)
- The growth of Ehrlich ascites carcinoma cell lines is reduced by both acidic and neutral extract from leaves and seeds (18)
- At least 50% a dose of 100 μg/ml gives therapeutic effect of desire aliment. (19)

2. Action on immune system:

- Mitogenic or antigenic stimulation done by activating cell-mediated immune system. (11)
- It mediates non specific cell and hormonal mediated immunological response of immunologic condition like cytotoxic and phagocytic activity of macrophage. (11)
- It enhances the antibody titer growth performance and also elicits the cell mediated immune mechanism in response to selective mitogens. (19)
- Its leaves has potential immunostimulant action by acting on serum interleukin -2 (IL-2) and glucosamine. (20)
- It is a natural growth booster and immunological stimulant that promotes body weight, feed conversion ratio, gross return, death rates, and antibodies titer versus infectious bursal illness (IBD). Neem seed oil use in the prophylaxis of paw edema.(21)

3. Antidiabetic action:

- The roots and bark extract in 70% ethanol gives anti diabetic effect. (11)
- Terpenoid, flavonoid, and glycoside is responsible for hypoglycemic properties.(9)
- Oral glucose tolerance test (OGTT) is use to analyze hypoglycemic effect of neem (roots) with reference of Glibenclamide medicine and observed the significant reduction in blood sugar level. (22)

- Human pancreatic -amylase (HPA) inhibitors are an efficient way to regulate starch digestion and minimize postprandial hyperglycemia. Limonoids from *Azadirachta indica* have ability to inhibit pancreatic -amylase, a well-known anti-diabetic target. (23)

- Nimbidin shows delay in the peak rise of blood sugar soon after glucose administration as it binds to receptor sites especially the peroxisome proliferator which is the chief regulators of glucose metabolism. (24)

- Orally ingestion of Nimbidin shows reduces in blood sugar level. (25)

- The limonoids, azadiradione and gedunin is potent inhibitors of human pancreatic amylase and treat postprandial hyperglycemia. (26)

4. Coronary heart disease:

- When compared to Vitamin E, neem extract has comparable cardioprotective properties. (19)

- Neem leaf extract dilates blood arteries in diabetics, and its seed oil lowers the need for insulin. (20)

- Blood glucose, urea, total cholesterol, and creatinine levels in the blood have all been shown to be reduced by neem leaf extract and it may prevent the progression of CHD. (20) (21)

5. Anti-viral activity:

- The neem bark extract had a direct anti-HSV-1 capability by blocking its enterance when preincubated with virus.(10)

- Neem leaf extract have anti-coxsackievirus B-4 action and Interference observed early in the replication cycle. (11)

- Aqueous extract of neem leaf and neem oil have suppress HIV and Polio viruses.(18)

- The leaves extract of neem show significant inhibition against Dengue virus type -2. (25)

- Neem seed kernel alcohol extracts exhibit antiviral properties against the virus that causes duck plague (DPV). Neem leaf aqueous extract has strong therapeutic potential against HSV, polio, smallpox, and fowlpox.(27)

6. Anti-malarial activity:

- Neem leaf and stem bark extracts suppressed parasitaemia levels in infected mice by 51-80% and 56-87%, respectively.(11)

- Nimbolide poses anti-malarial activity against *Plasmodium falciparum*.(25)

- The constituents in the neem plant helps to protect against the marlaria transmission like its crude extract form of neem leaves and seed kernel rich in gedunin which is potent anti malaria. According to studies the aqueous and acetone water extract of neem leaves inhibit the growth and further development of *P. falciparum*.(28)

7. Anti-fungal activity:

- The seed oil extraction showed the potent inhibitory effect against *Fructicola, Penicillium expansum, Trichothecium roseum,* and *Alternaria* pathogens. Nimonol at the concentration of 5, 10, 15, and 20% suppressed human infections *Aspergillus flavus, Aspergillus fumigatus, Aspergillus niger, Aspergillus terreus, Candida albicans* and *Microsporum gypseum*. (11)

- Neem leaves in aqeous and ethanolic extract shows potent inhibitory effect against *Rhizopus* and *Aspergillus, Tinea rubrum* and *Mycobacterium tuberculosi, Candida albicans*. (25)

- It has wide antimicrobial action and has antifungal and antiviral efficacy against *Candida albicans* and Polio virus replication.(29)

8. Antibacterial activity:

- It gives antibacterial activity against pathogen *V. vulnificus*, and nontoxic human lymphocyte in minimal concentrations.(21)

- It is effective against dangerous bacteria including *Staphylococcus aureus* , *Salmonella typhi*, *E. coli* and *Pseudomonas aeruginosa*. (29)

- Potent antibacterial activity is due to azadirachtin, gallic acid, epicatechin, catechin, margolone, nimbin,nimbolide, nimbidin which is abundantly found in the neem plant. (30)

9. Antifertility activity:

- Neem seed oil is a potent spermicidal that inhibits spermatogenesis considerably. It causes sperm motility a nd count to decrease, as well as the discontinuation of fertility. It possesses abortifacient and antiimplantation effects. (11)

- A unique approach to contraception. Praneem (pure neem extract) causes infertility in baboons and bonnet monkeys when administered orally. Neem oil appears to have a non-hormonal mode of action, which is most likely mediated by its spermicidal activity, and may be less harmful than steroidal contraceptives.(12)

- The neem flower alcoholic extract show its potent therapeutic effect on mensurational cycle, fertility and ovulation cycle also the fetal morphology. It significant lowers the shed of ova in the morning of estrus, also block of spermatogenesis without affecting testosterone production.(19)

- Raw neem oil is spermicidal with no change in hormonal parameters, while an aqueous extract of old and tender leaves exhibits 100% sperm mortality without changing its morphology (head, midpiece and tail).(25)

- A single intrauterine application of neem oil appears to trigger a long-term and reversible pre-implantation restriction in fertility.(31)

10. Central nervous system disorder:

- A significant decrease in motor coordination and motor nerve velocity conduction and behavioral changes. It is also use in the treatment of allodynia , hyperalgesia and peripheral neuropathy which is induce by partial sciatic nerve ligation. (19)

- Different degree of depressive activity can be treated with neem leave extract because of its direct significant CNS action.(21)

11. Insect repellent:

- The combination of neem cake extract with banana corm or pseudostem wetness, as well as its extracted powder of seed, leaves, and oil, may disturb the settlement response, egg production, and larva eating of Cosmopolites sordidus, also known as The Banana Corm Borer.(25)

- It is grown in most tropical and subtropical areas of the world provide shade, reforestation, and in making of raw materials for manufacturing of natural insecticides and medicines, also decrease the detoxifying enzymatic level. Actually it causes obstruction in the protein synthesis so it is most effective pesticide which affects insect strains. (32)

- The insecticidal preparation of neem act as (i) partially or completely inhibit fecundity or egg hatchability (ii) decrease in life span (iii) oviposition repellence (iv) immediate ovicidal effects (v) antifeedant impacts against larvae (or nymphs) and adults (vi) creation of permanent larvae (vii) inhibit growth and produce larval-pupal, nymphal-pupal, nymphal-adult, pupal-adult, crippled. (33)

- The tetranortriterpenoid azadirachtin are the most important insecticidal constituents in Neem seed kernels. Insecticides made from crude Neem formulations, mostly seed kernel extracts or powders, are used by farmers.(33)

- Neem products also elicit the juvenile hormones. Azadirachtin penetrates the larva's body and inhibits the activity of ecdysone, causing the larva to fail to moult and remain in the larval stage. It also prevents the synthesis of chitin, which is the insect's hard portion covering, forcing the larva to expire. Crops treated with a neem product cause an antiperistaltic wave in the alimentary canal, causing the insect to vomit due to the presence of azadirachtin, salanin, and melandriol.(34)

12. Biofertilizer:

- The residue after neem oil extraction from its seeds act as fertilizer neem cake and give nourishment to the plant and also increase the crop yield, thus overall it is a good biofertilizer. It also contain good amount of organic matter like phosphorus, nitrogen, potassium, calcium and magnesium which is essential for soil fertility. (25)

- It is a beneficial fertilizer for both cash and food crops. It is used as insect and pest control and repellent as well and also used as manure to fertilize the land and improve the soil fertility and promote the growth of plant.(34)

13. Cosmaceutical use:

- Nimbidin therapy useful in skin diseases like eczema, furunculosis, arsenical dermatitis, scabies and seborrhebic dermatitis. Neemoids are just a loose pale brown to yellowish brown powder obtained from cold-pressed Neem seed and are employed in cosmetic formulations such as creams, lotions, hand and body washes, shampoos, oil, and other similar items.(12, 13)

- Limonoids containing neem oil azadirachtin are used in making of hair care products due to its anti-head lice, anti-dandruff, and antifungal properties. It is also use as lubricant in the industrial preparation and as emulsions, ointments, poultices and liniments. It has generally been used as a skin emollient and replenishing lotion to treat dandruff, dry, itchy scalps, and broken hairs.(30)

14. Dentistry action:

- Twigs of neem used as toothbrushes and gum relateetd inflammations and disorder.(11)

- Its antioxidant property helps to boostup the immune response in gum and tissue of mouth result in curing the ulcers of mouth, tooth decay and pain reliever in all tootache problem. Neem contains mouthwashes, fluoride and toothpaste is a remedy for all oral infection and gives the protection against the bleeding and sore gums. It inhibited *Streptococcus mutans* and *Streptococcus salivarius* . It stops streptococci to form colony in tooth surfaces. Mucoadhesive dental gel is useful in minimizing the plaque index and salivary bacterial count.(30)

15. Hepatoprotective:

- Neem constituent is primilary used in hepatic related disorders as it lowers the necrotic cellby both histologically and macroscopically. The significant decrese in the raised level of AST and ALT and reversence the damage of hepatic cell due to antitubercular drugs.(19)

- It aids in the improvement and maintenance of serum glutamate oxaloacetate transaminase (SGOT), serum glutamate pyruvate transaminase (SGPT), alkaline phosphatase (ALP), serum bilirubin, and total protein levels.(25)

- It protects the liver and purifies the blood. It also preserves the serum enzyme and increases antioxidant levels (vitamin A, E, and natural carotenoids), eliminating free radicals and reducing liver damage.(34)

16. Antioxidant activity:

- High antioxidant activity is found in the different extracts from leaf, flower, roots and stem bark. The methanolic extract of the roots have potent flavonids that have strong free radical-scavenging properties as well as the ethonolic extraction of flower and seed oil. (19)

17. Anti-ulcer activity:

- At a dose of 600mg/kg, neem leaf aqueous extract shows significant antiulcer action by suppressing stomach lesions that are caused by apoptosis, and acid secretion. It inhibits H+K + ATPase activity in a concentration-dependent manner.(11)

- Neem bark extract eliminates manual stomach acid hypersecretion, gastro-esophageal and gastroduodenal ulcers, and provides significant pain relief while also accelerating the healing of duodenal and gastric lesions.(34)

18. Nephro protective activity:

- Sodium Nimbidinate as a diuretic agent. It shows diuresis after the administration and thus prevents the renal tubules from damage by chemical formulation and increases the volume and flow of urine thus eliminating the harmful urinary causative organism from the body and reduces the kidney related problems. (25)

19. Analgesic and antipyretic effect:

- In comparing to morphine, neem seed oil at a dose of 2ml/kg body weight provides a stronger analgesic effect than morphine at a dose of 1mg/kg body weight.(25)

- A decrease in fever observed after the administration of ethanolic extract of neem leaves.(25)

20. Margosa oil:

- Margosa Oil is an extract of the neem seed extensively use foe topical application. (35)

21. Anti acne effect:

- Neem oil is rich lecithin in its colloid form that has a sustained effect and provides adequate antibacterial action on acne-causing microorganisms. Solid lipid nanoparticles are widespread in neem oil. As a consequence, neem oil has long been employed to effectively treat acne.(36)

- It is use in making makeup base, concealer and camouflage blemish and to improve inperfection. It is also use in making bb cream , foundation, cream and moisturizing gel and lotions.at the concentrations of upto 25 %w/w neem oil was give antibacterial action.(37)

Contraindication:

Its leaves extract may worsen the condition of ventricular fibrillation and cardiac arrest. It is use in caution with hypoglycemic patient as it because lowering of blood sugar level. Its oil and leaves not given in pregnancy, breastfeeding mothers and children under 12 year. It is also reported that ingestion of neem leaves and fruits cause allergic reaction that sometimes become worse.(26)

Toxicity:

- Pharmacotoxic symptoms were noted with dose related toxicity and target the lungs and CNS.(37)
- Neem oil is readily available locally, and use of it results in acidosis, seizures, altered sensory abilities, and a high rise in blood transaminases, which lead to liver damage and fatty liver degeneration.(38)
- Margosa Oil, a neem seed extract used mostly for exterior treatments, is frequently and cautiously given orally to fetuses and infants. Particularly in babies and young children, it produces toxic encephalopathy, that is followed by vomiting, lethargy, tachypnea, and frequent generalised seizures.(35)
- Potential causes of the neuro-metabolic crisis associated with glutaric aciduria type II include stress carried on by neem oil intoxication, which also impacts mitochondrial oxidative phosphorylation.(39)

ALOVERA

Introduction:

Since olden history, alovera has been employed for multiple medical, therapeutic, and cosmetic purposes. The Arabic term ‘alloeh’and ‘vera’ which mean ‘truth’and ‘shining bitter substance’respectively. It is a succulent plant that survives well in unfavourable conditions and only needs a small bit of water. The creeping rhizomes of this alovera spread from base offshoots to dominate a large region. The plant bears fruits with many seeds, yellow tubular blooms, and triangle, fleshy leaves with serrated edges. Each leaf is represented by three layers: 1) A 99% water internal clear gel composed of glucomannans, amino acids, lipids, sterols, and vitamins. 2) The anthraquinones and glycosides present in the acidic yellow sap of the middle layer of latex. 3) The rind is a strong, outer layer of 15 to 20 cells that acts as a protective covering also while generating proteins and carbohydrates. Vascular bundles within the rind are in charge of driving elements like as water (xylem) and starch (phloem).(42-44)

Alovera plant, gel and flower.

Figure 4: Inages of Alovera plant , gel along with flower.

(40)Alovera plant

(41)Alovera gel

(42)Alovera flower

Taxonomical importance:

Table 3: An updated taxonomical review of Alovera plant

Taxonomic	
Biological/ Scientific Name	*Aloe barbadensis miller.*
Domain	Eukaryota
Kingdom	Planta
Phylum	Spermatophyta
Subphylum	Angiospermae
Class	Monocotyledonae
Order	Asparagales
Family	Liliaceae or Asphodelaceae.
Genus	Aloe Linn.

1. **Vitamins***:* It contains vitamins A (beta-carotene), C and E, vitamin B12, folic acid, and choline.
2. **Enzymes***:* It contains 8 enzymes: aliiase, alkaline phosphates, amylase, bradykinase, carboxypeptidase, catalase, cellulose, lipase, and peroxidase that help in digestion by breaking down fats and sugars. Carboxy peptidases and bradykinases produce an anti inflammatory effect by inactivating bradykinins. Lectins give anti tumor effects.
3. **Minerals***:* It provides calcium, chromium, copper, selenium, magnesium, manganese, potassium, sodium and zinc.
4. **Sugars***:* It provides monosaccharide (glucose and fructose) and polysaccharides: (glucomannans/polymannose). These are derived from the mucilage layer of the plant and are known as mucopolysaccharides. The most prominent monosaccharide is mannose-6-phosphate, and the most common polysaccharides are called glucomannans [beta-(1, 4)-acetylated mannan]. Acemannan, a prominent glucomannan has also been found. Recently, a glycoprotein with anti allergic properties, called alprogen and novel anti-inflammatory compound, C-glucosyl chromone, has been isolated from Aloe Vera gel.
5. **Anthraquinones***:* Barbaloin, aloeemodin-9-anthrone, lsobarbaloin, Anthrone-C-glycosides and chromones. It provides 12 anthraquinones, which are phenolic compounds traditionally known as laxatives. Aloin and emodin act as analgesics, antibacterial and antivirals. The main active constituent of alovera plant extract is aloine, an anthraquinone heteroside.
6. **Fatty acids:** It provides 4 plant steroids; cholesterol, campesterol, β-sisosterol and lupeol. . All these have anti-inflammatory action and lupeol also possesses antiseptic and analgesic properties.
7. **Hormones***:* Auxins and gibberellins that help in wound healing and have anti-inflammatory action.

Others:

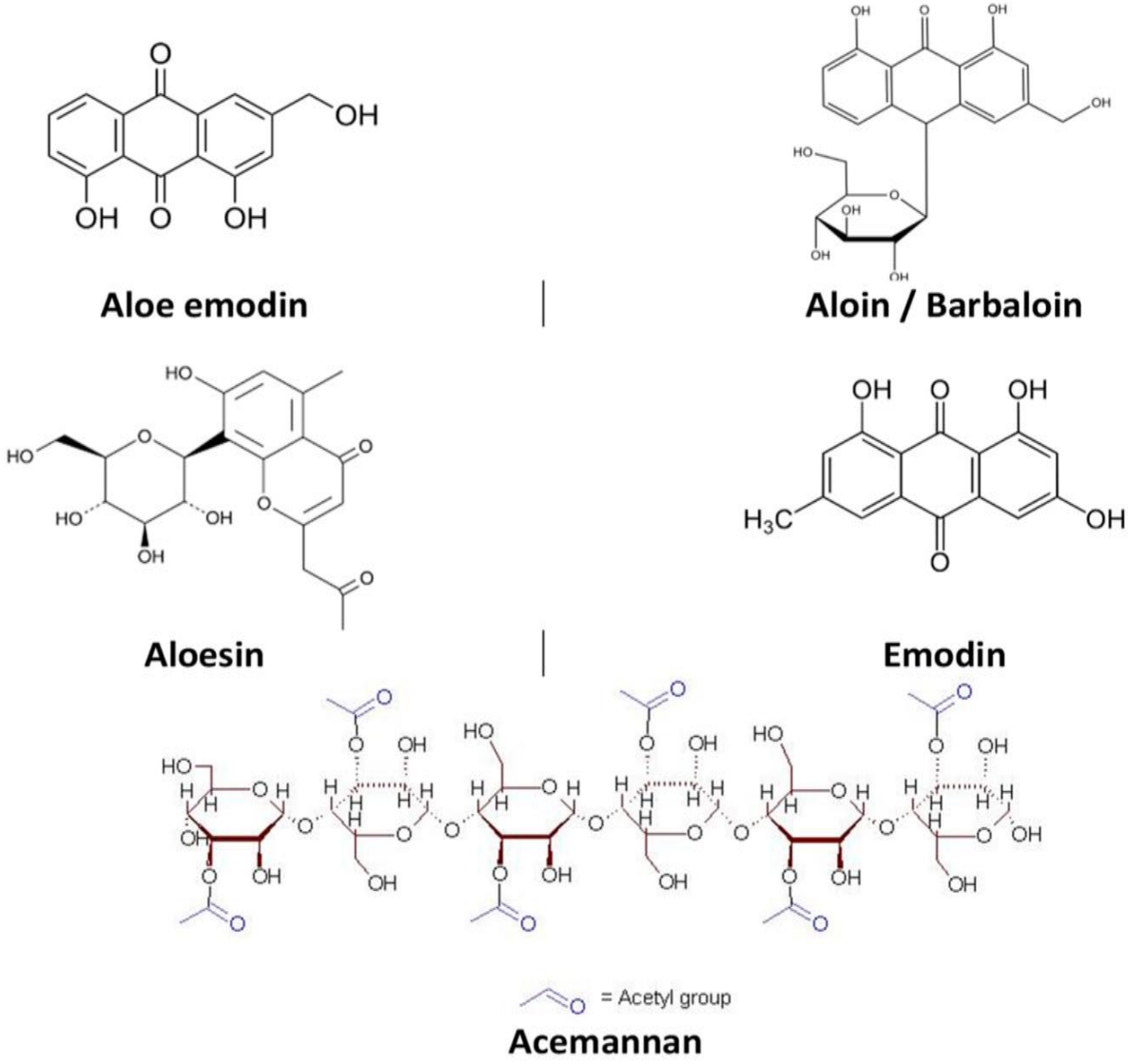
- It provides 20 of the 22 human required *amino acids* and 7 of the 8 essential amino acids.
- It also contains salicylic acid that possesses anti-inflammatory and antibacterial properties.
- Lignin, an inert substance, when included in topical preparations, enhances penetrative effect of the other ingredients into the skin.
- Saponins that are the soapy substances form about 3% of the gel and have cleansing and antiseptic properties.

Chemical constituents of Alovera:

Constituents 2: Summarized description of bio active molecule found in Alovera (43-45)

Chemical structure of Alovera constituents:

Figure 5: chemical structure of aloe emodin, barbaloin, aloesin, emodin and acemannan (46)



Therapeutical applications:

1. Wound healing properties:

- Alovera increases the cross-linkage development of collagen, which changes the composition of collagen and causes it to form quickly. The alovera gel also induces a wound to contract and accelerate the threshold, causing scar tissue to form. In the granulation tissue of a treating wound, antioxidant properties of aloe gel stimulated the synthesis of hyaluronic acid and dermatan sulphate.(44)

- Wound healing process further elicits by Auxins, and gibberellin present in alovera. (47)

- Gibberellins (growth hormone) and glucomannan (a mannose-rich polysaccharide) engage with fibroblast growth factor receptors to stimulate fibroblast activity and proliferation, resulting in an improvement in collagen synthesis.(44)

- The high content of water present in alovera helps to faster healing process. (48)

- Alovera covers a range of amino acid residues as well as extrinsic electrolytes such as iron, potassium, and magnesium, which aid in wound healing. It also helps wound healing and scar prevention by enhancing growth factors, which promote cell production and support the regeneration process in the deepest layers of the skin. It also softens superficial epidermal cells, which aids them adhere together.(49)

- Alovera quickly heal the burns or minor wounds within 10-15 days because of the presence of saponins.(50)

- Aloe vera accelerates wound healing in both acute and chronic wounds including lacerations, surgical incisions, and burns, infected wounds, arterial and venous ulcers. It can also be used in wound dressing to facilitate faster wound healing.(51)

- The alovera extract containing glycoprotein causes proliferation of cell and improve the blood supply and oxygen to the wounded area and accelerates the wound healing process (52)

2. Antioxidant properties:

- Metallothionein (antioxidant protein) in alovera extract mimic the scavenges of hydroxyl radicals and prevents the suppression of superoxide dismutase and glutathione peroxidase in the skin, thus inhibits the production and release of skin keratinocyte-derived immunosuppressive cytokines like interleukin-10 (IL-10), preventing UV-induced suppression of delayed type hypersensitivity and delivering anti-acne effects.(44)

- It has a broad range of topical formulations, including astringent, moisturizing, humidifier, hydrating lotion, and cleanser. It also helps to treat acne, spots, measles, psoriasis, eczema, skin disorders, red spots, mycosis, fever blisters, skin irritation, and is appropriate for sunburns, fragile skin, and the removal and restoration of dead the skin's outer layers.(48)

- It limits free radicals and boosts cellular thiol levels, contributing in antioxidant activity. Due to the inclusion of antioxidant such as -tocopherol, carotenoids, and ascorbic acid, this also enhances glutathione-S-transferase enzymatic activity and delivers beneficial effects in a dose-dependent way for a range of of disease. It is also found that alovera polysaccharide can reduce hydrochloride-induced oxidative stress and cell death in kidney epithelial cells.(49)

- Lesions healed with aloe gel recovered faster as burns treated with paraffin jelly gauze. When compared to its cream, its fresh gel has a greater impact on wound healing. In a placebo-controlled research, patients with partial thickness burns were treated with Aloe gel. Its fresh juice assists in the smooth operation of the body's mechanism. It also controls cell damage triggered by stress and physiochemical changes within the body.(52)

- Alovera's antioxidant action is due to glutathione peroxidase enzymes, superoxide dismutase enzymes and a phenolic anti-oxidant. It increases blood quality by efficiently oxygen transport, blood and give nourishment to the body's cells.(43)

3. Anti-inflammatory action:

- It gives anti inflammatory effect by inhibiting the cycloxygenase and prostaglandin E2 pathway. C-glucosyl chromone that was recovered from its gel extracts has a potent new anti-inflammatory action, while lupeol has antibacterial and analgesic effects. When alovera is administered topically, bradykinase aids in the suppression of excessive inflammation.(44)

- It contains 12 essential nutrients which helps to suppress the inflammatory process and improves joint and muscle mobility cause by arthritis.(48)

- It absorbs into the skin to soothe and ease symptoms via direct application. It is also used to relieve tendinitis and injury-related pain, as well as to avoid the cause of arthritis via daily use. (43)

- Daily consumption of fresh alovera juice for about 15days helps to relief from the symptoms of inflammation of eyes , ears and joint pains.(53)

4. Action on immune system:

- Alprogen in alovera restricts calcium influx into mast cells, allowing them to release antigen-antibody-mediated histamine leukotrien and acemannan encourages the synthesis and release of interleukin-1 (IL-1) and tumour necrosis factor from macrophages, resulting in an immune attack in response to necrosis and tumour cell regression.(44)

5. Laxative effects*:*

- Anthraquinones (1,8-dihydroxyanthracene glycosides) present in alovera do have laxative effect and raise intestinal water content by boosting mucus secretion and gastrointestinal muscular contractions.(23) (44)

- After the oral administration of aloin A and B, the gut bacteria hydrolyzed them and reduce them to the active metabolites (aloe-emodin9-anthrone) and these metabolite gives stimulating and irritant activity to the gut system.(52)

6. Antiviral activity:

- Due to anthraquinones, the indirect effect of alovera is to improve the immune system, whereas the direct effect is to inactivate numerous encapsulated viruses including such herpes simplex, varicella zoster, and influenza.(44)

- Anthraquinones, lectin and emodin have antiviral properties and help to prevent CMV replication also efficient against a variety of infectious viruses, including the herpes simplex virus. (49)

7. Antitumor activity:

- Alovera gives anti mutagenic activity through glycoprotein and acemannan (polysaccharides). The combination treatment of alovera gives suppression of genotoxicity by direct acting mutagen. The formation of benzo[α]pyrene- DNA adducts alovera shows anti-genotoxic and chemo protective action. It induce glutathione converting enzyme and inhibit cancer promoting effect of phorbol myristic acetate. (43)

- The polysaccharides in alovera inhibit benzopyrene binding to primary rat hepatocytes, reducing the development of cancer-initiating benzopyrene-DNA adduct. Inhibiting phorbol myristic acetate's tumor-promoting effects and inducing glutathione S-transferase has a beneficial effect in cancer prevention.(44)

- It activate macrophages and demonstrate antineoplastic .(47)

- It stimulate the immune system in the body resulting in tumor associated disorder.(48)

8. Antiulcer activity:

- Alovera cure and protect the gastric ulcer as it is anti-inflammatory and stimulate the healing process and regulate the gastric secretion. Further alovera stimulate the mucus secretion into the gut. Alovera contain lectin which inhibit the aminopyrine which is responsible for up taking and inhibit the gastric acid secretion and smoothen them.(43)

- Its ingestion aids in stomach ulcers by different methods. It heals cutaneous ulcers, particularly mouth ulcers around 80% and reduces erythema, exudation, and ulcer size. (27)

- Alovera juice provides relief in all kinds of digestion disorders like heart and acid reflux; it also stabilizes the alkaline acid in the body. This will protect the symptoms associated with irritable bowel syndrome and relief from constipation. Therefore it is a excellent cure for ulcers, Celiac and Crohn's diseases.(53)

9. Antiseptic effect:

Lupeol, salicylic acid, urea nitrogen, cinnamonic acid, phenols and sulfur are responsible for the antibacterial effect and also give inhibitory effect on virus and fungi.(43, 44)

10. Antiacene effect:

- The combination of different oil with alovera oil give significant effect against mild to moderate acne vulgaris (54)

- Alovera gel combination with ocimum oil results in potent anti acne effect in comparison with 1% clindamycin gel.(55)

- Alovera inhibit many bacteria causing acne and thus have efficient effect in the acne treatment.(56)

11. **Cardioprotective activity**:

- Alovera helps to suppress the risk of heart attack and stroke and also lowers the disease associated with high cholesterol level.(48)

- Alovera lowers the risk of cardio vascular disease and hypercholestermia. It will help in diminish nephropathy progression by alteration of lipid and decrease the renal oxidative stress.(49)

- It also prevents the heart attack and stroke attack by purifying the blood quality and makes it thinner and less sticky. It helps to regulate the blood supply by prevent them to stick together and form clumping. It helps to balance blood chemistry by enhancing the blood viscosity and maintain the triglycerides and cholesterol level for better heart function. It regulates bp and reduce stickiness of blood cell making good circulatory blood flow throughout the body , overall smooth blood flow makes heart to pump better and maintain blood pressure.(53)

12. Nephroprotective action:

- It flushed all the excessive waste and water from the body thus help in preventing from oxalates stones formation of urine in the kidney and gives protection from type 2 diabetics.(53)

- Studies shows that single dose of 100–200 mg orally of alovera leaf in aqeous extract of gives protective effects in gentamicin and cisplatin-induced nephrotoxicity . The inherent antioxidant and freeradical properties of alovera contribute to its nephroprotective action.(57)

13. Aloe vera benefits for beauty:

- Alovera's mucopolysaccharides aid in moistening the skin by penetrating into skin deeply. It stimulates fibroblasts therefore collagen and elastic fibers is produced thus minimize the wrinkles. (49)

- It is useful in making variety of cosmetics including creams and toiletries or gel.(51)

- It boosts skin tone and moisture by removing dead cells and maintaining the skin smooth, and shining. They remove dark spots, pigmentation, dry flaky skin, and freckles, giving the face a healthy glow. Its anti-inflammatory properties aid in preventing the occurrence of acne and pimples even while effectively curing lesions and acne scars. It promotes collagen and elastic formation, resulting in skin renewal and the reduction of wrinkles and fine lines. It removes suntan and provides a glowing, even complexion free of dark spots. It definitely works on stretch marks by eliminating their remnants. A good massage with alovera on fragile nails aids in strengthening and restore their sheen.(53)

14. Hepatoprotective activity:

- Alovera shows potential therapeutic activity against liver toxicity and its damage and also treat sepsis.(47)

- It show significant prevention in scarring of liver and improve the hepatic juice secretion which further enhance the liver function. it act as antidote for excessive consumotion of alcohol.(48)

15. Antidiabetic activity:

- The stimulation of insulin is elicited by alovera which can decrease down the blood glucose level in mice. (48)

- In diabetic induced rats there is significant decrease of creatinine, serum urea and oxidative stress observed also the oxidative enzyme activity and glutathione level has been raised. At the dose of 300mg/kg showed reduction in oxidative stress. Due to ant oxidative and hypoglycemic properties of alovera , a significant imorvement of behavioral deficit is observed and it also protect the hippocampus neurons.(49)

- Phytosterols in alovera is lophenol, 24-methyllophenol, 24-ethyl-lophenol, cycloartanol and 24-methylenecycloartanol showed anti-diabetic effects diabectic type-2 diabetic. Because it has polysaccharides which increases the insulin level.(52)

- The major symptoms of diabetic peripheral neuropathylike numbness in hands and legs has been prevented by improving the overall circulatory health.(53)

- One tablespoon full of alovera fresh juice will decrease the blood sugar level of diabetic patient if taken twice a day for atleast 2 week.(58)

- The secretion of insulin from pancreatic islets is increased by alovera by significantly inhibiting the pancreatic α-amylase activity. This will decreases the breakdown of starch and control the postprandial glucose. (59, 60)

16. Antifungal activity:

- In *Cytomegalovirus* the inhibition of growth is done by lectin in alovera as it interfere its protein synthesis.(43)

- Alovera fresh leaves extract shows antifungal activity against mycelia growth of *B.gladiolorum, F. oxysporum, F.spgladioli* due to its hydro alcoholic content.(45)

- Due to polar constituents present in the alovera plant exhibits the potent anti fungal activity in its methanolic and ethanolic extract.(47)

- It inhibit the growth of many bacteria which spoil the food and also it lowers the growth of C*andida albicans*.(49)

- Topical application of alovera gives relief from genital herpes virus. (53)

- Alovera can inhibit the growth of *Alternaria alternata, Aspergillus flavus, Aspergillus niger, Botrytis gladiolorum, Candida albicans, Colletotrichum coccodes, Crytococcus neoformans, Drechslera hawaiensis, Fusarium oxysporum, Heterosporium pruneti, Microsporium canis, Penicillium gladioli, Penicillium maneffei, Penicillum migitatum, Phythium Sp., Rhizoctonia solani, Trichophyton mentagraphytes* and *Trichophyton schoenleini*.(61)

- High zone of inhibition against candida species observed in ethanolic extract of alovera.(62)

- Silver nanoparticles using aqueous alovera leaf extract shows antifungal activity against plant pathogenic fungus.(63)

- It gives potent antifungal activity against *aspergillus flavus* and *aspergillus niger*.The antifungal activity reported in acetone extract than aqueous extract and ethanol extract(64)

17. Antibacterial activity:

- It shows activity against *Mycobacterium smegmatis, Klebisella pneumoniae, Enterococcus faecalis, Micrococcus luteus, Candida albicans* and *Bacillus sphricus* and it can inhibit both gram positive and gram negative bacteria. It is also effective against gram positive bacteria *Shigella flexneri* and *Streptococcus progenes* .(62)

- Aloe vera also effective against *Staphylococcus aureus, Streptococcus pyogenes, Pseudomonas aeruginosa* and *Escherichia coli*. Alovera acetone extract have greater efficacy against bacteria. Alovera major constituent like anthraquinones and dihhydroxyanthraquinones as well as saponins has direct antimicrobial activity.(64)

18. Commodities:

- Alovera now use as moisturizer and also as anti irritant by direct application on the facial tissue. It can also be use into nose by giving them protection from hayfever or cold. Alovera is used in many cosmaceutical industries for making of cosmaceutical product like sunscreen, soaps , makeup, tissues, wipes, shaving cream, shampoos.(60)

- The extracts of alovera uses for the semen dilution in artificial fertilization of sheep. It is also use as fresh food preservative. Biofuels from seeds of alovera useful in making gelling agents.(53)

19. Dental health:

- Alovera associated in toothpaste helps to strengthening the gums and also gives the prevention from bad breath. Others benefits also can be achieved by massaging alovera around the teeths and gums.(53)

- It is very useful in plaque associated disease as it is antiplaque and inhibits the bacterial growth which harms the gums and teeth. (65)

- Alovera is used in dentistry to treat eczema planus, oral submucous fibrosis, chronic mouth ulcer aphthous, stomachache, alveolar osteitis, and periodontitis.(66)

20. Pharmaceutical applications:

- Alovera in powdered form use as excipient for sustained release dosage forms.(67)

- Alovera gel powder with the rational combination of different excipient gives the lowest lag time with high drug release in the period of 4h. Invivo study reported that the combination with gallic acid and alovera give 75% ulcer inhibition with comparison to alone gallic acid which inhibit only 57%. Alovera use for making the bilayer floating tablets in ulcer associated disease.(68)

- The gums and mucilage present in the alovera have complex polysaccharide structure which gives widest application in the pharmaceutical manufacturing like binder, disintegrations , suspending agents, gelling agent and emulsifying agent and also useful in sustain and modified release tablet processing. (69)

Toxicity:

- Anthraquinones in which aloin and barbaloin are more prone to cause allergic reaction. It is better to apply upon a smaller region of skin for test of allergy. Prolonged use cause colorectal cancer. Ingestion of alovera is not allow in pregnancy because of uterine contraction and lactating mother because of GI distress in infants.(43, 49).

- When there's a recognised allergy to liliaceae family. Alovera should not be used by anyone experiencing cramps or colic discomfort, hemorrhoid, nephropathy, or any unidentified gastrointestinal symptoms like pain, nausea, or vomiting. Anyone with inflammatory bowel disorders such appendicitis, Crohn's disease, ulcerative colitis, irritable bowel syndrome should not take aloe, but neither should patients less than 10 years old.(52)

Interactions:

- The drastic decline in the effectiveness of digoxin and digitoxin with accelerated adverse effect has been reported. Alovera may also increase the absorption of steroids in the skin therefore given with cautions. The increases potassium depletion has been reported with combined use of furosemide with alovera. Alovera lowers the blood sugar level therefore it is not good to give with hypoglycemic drug and insulin.(43, 70)

- Excessive alovera consumption can result in toxicity such as diarrhea, electrolyte imbalance, and kidney dysfunction, while topical treatment might result in contact dermatitis, erythema, or photo toxicity. (52)

Conclusion:

Acne vulgaris is a persistent skin disorder that is highly frequent among adolescents. This disorder is caused by *Propionobacterium acnes* and *Staphylococcus epidermidis*. The neem extract and aloveras essential improve their combined anti-acne effect since they are both anti-inflammatory, antibacterial, and antioxidant, which not only block the growth of germs that cause acne but also provide skin a radiant glow and protection, leaving clear consequences. Acne combo preparations can be manufactured in the form of gel, spray, creams, and ointments that can be applied topically to the affected area.

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