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Aloe Vera as Penetration Enhancer

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Abstract:
Skin penetration enhancers are the most commonly used approach for enhancing drug penetration into the skin through transdermal drug delivery system or topical administration. These skin penetration enhancers are molecules which reversibly remove the barrier resistance of the stratum corneum and allow drugs to penetrate more readily to the viable tissues and thus enter the systemic circulation. The purpose of this review was to present penetration enhancing potential of *Aloe Vera*. *A. vera* gel increased the *in vitro* skin penetration of compounds depending on their molecular weights, with an apparent inverse correlation between enhancement ratio and molecular weight of the compound. Some constituents of the *A. vera* gel itself also penetrated the skin and this was interestingly dependent on the molecular weight of the co-applied compounds. Thus the penetration enhancement effect of the aloe gel was explained by a probable pull effect of complexes formed between the compound and the enhancing agent within the aloe gel, but it was stated that the proposed mechanism of action has to be further investigated and confirmed.

Keywords: *Aloe Vera*; Transdermal drug delivery system; Permeation; Penetration enhancer; Permeation enhancer.

1. Introduction

In recent years the potential of using skin as an alternative route for administering systemically active drugs has received considerable interest and the best way to administer drugs through skin is transdermal patch. Now a day's transdermal delivery is becoming more popular and research has focused on improving the absorption of such drugs, as delivery rates tend to be below therapeutic levels due to the barrier function of the skin[1].

Transdermal delivery of drugs promises many advantages over oral or intravenous administration, though human skin provides an effective barrier to the permeation of most drugs in the form of stratum corneum. Success of the transdermal route depends on the ability of drugs to breach this barrier and permeate the skin at a rate sufficient to attain effective plasma concentration. There are many approaches which are employed to enhance the skin permeation rate of active moieties. However, the most convenient and widely implemented approach is the use of chemical penetration enhancers such as DMSO, DMF, azone, ionic surfactants, but their use are also associated with unpleasant and toxic side effects. In recent years there has been a search for natural compounds as permeation enhancers to improve drug permeation that also exhibit low toxicity while maintaining their enhancing activity [2].

The natural absorption promoters documented so far include essential oils, terpenes, terpenoids, fatty acid esters, fatty acid glycols, and herbal extracts. The essential oils are nontoxic, non-allergic, and compatible with drug and excipients have received much attention of researchers and found one of the promising groups of candidates

to be employed as clinically acceptable penetration enhancers. Essential oils present a large range of chemically acceptable and relatively safe penetration enhancers to aid percutaneous drug delivery and are considered as GRAS (generally regarded as safe) compounds for medicinal use. They have been reported to use for permeation enhancement of both hydrophilic and lipophilic drugs. They cause no skin toxicity or if any, only mild irritation.

In particular, herbal penetration enhancers which have received much attention and an enhancement system based upon a product is '*Aloe Vera'*, which appears as an attractive prospect due to its purported skin friendly and humectant properties [3].

The semi-tropical plant, *Aloe Vera*, has a long and illustrious history dating from biblical times. It has been mentioned throughout recorded history and given a high ranking as an all-purpose herbal plant. Aloe's thick, tapered, spiny leaves grow from a short stalk near ground level. It is not a cactus, but a member of the tree lily family. *Aloe* is related to other members of the Lily family such as the onion, garlic and turnip families. Its relationship to the lily family is evident from the tubular yellow flowers produced annually in the spring that resemble those of the Easter lily.

There are over 250 species of *Aloe* grown around the world. However, only two species are grown today commercially, with *Aloe barbadensis Miller* and *Aloe aborescens. Aloe barbadensis Miller (Aloe vera Linne)* is the most widely used both commercially and for its therapeutic properties. This plant is having various medicinal, cosmetic and nutraceutical purposes [4], with topical applications features is the source of two main products. The first is a yellow exudate from the cut leaf base which contains a high concentration of anthraquinone compounds and when dried is used as a potent cathartic and for medicinal purges. The second product, *Aloe Vera*, is pressed from the whole leaf and is a clear mucilaginous gel that has been used since ancient times to treat burns and other wounds where it is thought to increase the rate of healing and reduce the risk of infection, along with these diverse properties, it also posses skin penetrative property [5].

At present there is minimal literature evidence to suggest that Aloe Vera has any skin penetration enhancement properties, although one paper mentions its use as a vehicle for other substances [6]. However, two recent United States patents have been filed which claim that *Aloe Vera* is responsible for increased skin penetration of co-formulated drugs.

2. ALOE VERA LEAF COMPOSITION

The *Aloe* leaf can be divided into two major parts, namely the outer green rind, including the vascular bundles, and the inner colorless parenchyma containing the aloe gel. Description of the inner central part of the aloe leaf may sometimes be confusing, due to the different terms that are used interchangeably such as inner pulp, mucilage tissue, mucilaginous gel, mucilaginous jelly, inner gel and leaf parenchyma tissue. Technically, the term, pulp "or 'parenchyma tissue" refers to the intact fleshy inner part of the leaf including the cell walls and organelles, while gel" or mucilage, refers to the viscous clear liquid within the parenchyma cell [7].

The three structural components of the *Aloe vera* pulp are the cell walls, the degenerated organelles and the viscous liquid contained within the cells. These three components of the inner leaf

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pulp have been shown to be distinctive from each other both in terms of morphology and sugar composition. The raw pulp of *A. vera* contains approximately 98.5% water, while the mucilage or gel consists of about 99.5% water. The remaining 0.5 – 1% solid material consists of a range of compounds including water-soluble and fat-soluble vitamins, minerals, enzymes, polysaccharides, phenolic compounds and organic acids as shown in figure no. 1. It has been hypothesized that this heterogenous composition of the *Aloe vera* pulp may contribute to the diverse pharmacological and therapeutic activities which have been observed for aloe gel products.

Many compounds with diverse structures have been isolated from both the central parenchyma tissue of *A. vera* leaves and the exudate arising from the cells adjacent to the vascular bundles. The bitter yellow exudate contains 1,8 dihydroxyanthraquinone derivatives and their glycosides, which are mainly used for their cathartic effects. The aloe parenchyma tissue or pulp has been shown to contain proteins, lipids, amino acids, vitamins, enzymes, inorganic compounds and small organic compounds in addition to the different carbohydrates. Some evidence of chemotaxonomic variation in the polysaccharide composition of aloes exists.

The large fluctuations in polysaccharide composition of *A. vera* fillet as found in the literature has been explained by the fact that the mannosyl residues are contained in a reserve polysaccharide with a significant seasonal influence, as well as large variations between cultivars in terms of the quantities of mannose-containing polysaccharides within the parenchyma cells [8].

3. ALOE VERA GEL

Aloe (often called *Aloe vera*) produces two substances, gel and latex, which are used for medicines. Aloe gel is the clear, jelly-like substance found in the inner part of the aloe plant leaf. Aloe latex comes from just under the plant's skin and is yellow in color.

Aloe Vera Gel is the viscous, transparent and colourless mucilaginous gel obtained from the parenchymatous cells in the fresh leaves of *Aloe vera*. It is succulent, almost sessile perennial herb; leaves 30–50 cm long and 10cm broad at the base; colour pea-green (when young spotted with white); bright yellow tubular flowers 25–35 cm in length arranged in a slender loose spike; stamens frequently project beyond the perianth tube.

Major constituents

Aloe Vera Gel consists primarily of water and polysaccharides (pectins, hemicelluloses, glucomannan, acemannan, and mannose derivatives). It also contains amino acids, lipids, sterols (lupeol, campesterol, and β-sitosterol), tannins, and enzymes. Mannose 6-phosphate is a major sugar component.

At present no commercial preparation has been proved to be stable. Because many of the active ingredients in the gel appear to deteriorate on storage, the use of fresh gel is recommended. Preparation of fresh gel: harvest leaves and wash them with water and a mild chlorine solution. Remove the outer layers of the leaf including the pericyclic cells, leaving a "fillet" of gel. Care should be taken not to tear the green rind which can contaminate the fillet with leaf exudate. The gel may be stabilized by pasteurization at 75–80°C for less than 3 minutes. Higher temperatures held for

longer times may alter the chemical composition of the gel [9].

Uses described in pharmacopoeias and in traditional systems of medicine

Aloe Vera Gel is widely used for the external treatment of minor wounds and inflammatory skin disorders. The gel is used in the treatment of minor skin irritations, including burns, bruises, and abrasions. The gel is further used in the cosmetics industry as a hydrating ingredient in liquids, creams, sun lotions, shaving creams, lip balms, healing ointments, and face packs.

Aloe Vera Gel has been traditionally used as a natural remedy for burns. *Aloe Vera* Gel has been effectively used in the treatment of first- and second-degree thermal burns and radiation burns. Both thermal and radiation burns healed faster with less necrosis when treated with preparations containing *Aloe Vera* Gel. In most cases the gel must be freshly prepared because of its sensitivity to enzymatic, oxidative, or microbial degradation. *Aloe Vera* Gel is not approved as an internal medication, and internal administration of the gel has not been shown to exert any consistent therapeutic effect [10].

Uses described in folk medicine, not supported by experimental or clinical data

The treatment of acne, haemorrhoids, psoriasis, anaemia, glaucoma, petit ulcer, tuberculosis, blindness, seborrhoeic dermatitis, and fungal infections.

Pharmacology

Wound healing

Clinical investigations suggest that *Aloe Vera* Gel preparations accelerate wound healing. *In vivo* studies have demonstrated that *Aloe Vera* Gel promotes wound healing by directly stimulating the activity of macrophages and fibroblasts. Fibroblast activation by *Aloe Vera* Gel has been reported to increase collagen and proteoglycan synthesis, thereby promoting tissue repair. Some of the active principles appear to be polysaccharides composed of several monosaccharides, predominantly mannose. It has been suggested that mannose 6-phosphate, the principal sugar component of *Aloe Vera* Gel, may be partly responsible for the wound healing properties of the gel. Mannose 6-phosphate can bind to the growth factor receptors on the surface of the fibroblasts and thereby enhance their activity [11].

Furthermore, acemannan, a complex carbohydrate isolated from *Aloe* leaves, has been shown to accelerate wound healing and reduce radiation induced skin reactions. The mechanism of action of acemannan appears to be twofold. First, acemannan is a potent macrophage-activating agent and therefore may stimulate the release of fibrogenic cytokines. Second, growth factors may directly bind to acemannan, promoting their stability and prolonging their stimulation of granulation tissue.

The therapeutic effects of *Aloe Vera* Gel also include prevention of progressive dermal ischaemia caused by burns, frostbite, electrical injury and intra-arterial drug abuse. *In vivo* analysis of these injuries demonstrates that *Aloe Vera* Gel acts as an inhibitor of thromboxane A2, a mediator of progressive tissue damage. Several other mechanisms have been proposed to explain the activity of *Aloe Vera* Gel, including stimulation of the complement linked to polysaccharides, as well as the hydrating, insulating, and protective properties of the gel.

Because many of the active ingredients appear to deteriorate on storage, the use of fresh gel is recommended. Studies of the growth of normal human cells *in vitro* demonstrated that cell growth

and attachment were promoted by exposure to fresh *Aloe vera* leaves, whereas a stabilized *Aloe Vera* Gel preparation was shown to be cytotoxic to both normal and tumour cells. The cytotoxic effects of the stabilized gel were thought to be due to the addition of other substances to the gel during processing.

Anti-inflammatory

The anti-inflammatory activity of *Aloe Vera* Gel has been revealed by a number of *in vitro* and *in vivo* studies. Fresh *Aloe Vera* Gel significantly reduced acute inflammation in rats (carrageenin-induced paw oedema), although no effect on chronic inflammation was observed. *Aloe Vera* Gel appears to exert its anti-inflammatory activity through bradykinase activity and thromboxane B2 and prostaglandin F2 inhibition. Furthermore, three plant sterols in Aloe Vera Gel reduced inflammation by up to 37% in croton oil-induced oedema in mice. Lupeol, one of the sterol compounds found in *Aloe vera*, was the most active and reduced inflammation in a dosedependent manner. These data suggest that specific plant sterols may also contribute to the anti-inflammatory activity of *Aloe Vera* Gel [12].

Burn treatment

Aloe Vera Gel has been used for the treatment of radiation burns. Healing of radiation ulcers was observed in patients treated with *Aloe vera* cream, although the fresh gel was more effective than the cream. Complete healing was observed, after treatment with fresh *Aloe Vera* Gel, in patients with radiation burns. The *Aloe Vera* Gel-treated lesions healed faster than the burns treated with petroleum jelly gauze, a difference that is statistically significant.

4. CHEMICAL COMPOSITION

Many compounds with diverse structures have been isolated from both the central parenchyma tissue of *Aloe vera* leaves and the exudate arising from the cells adjacent to the vascular bundles as shown in figure 1. The bitter yellow exudate contains 1,8 dihydroxyanthraquinone derivatives and their glycosides, which are mainly used for their cathartic effects. The aloe parenchyma tissue or pulp has been shown to contain proteins, lipids, amino acids, vitamins, enzymes, inorganic compounds and small organic compounds in addition to the different carbohydrates. Some evidence of chemotaxonomic variation in the polysaccharide composition of aloes exists.

The large fluctuations in polysaccharide composition of *A. vera* fillet as found in the literature has been explained by the fact that the mannosyl residues are contained in a reserve polysaccharide with a significant seasonal influence, as well as large variations between cultivars in terms of the quantities of mannose-containing polysaccharides within the parenchyma cells [13]. The chemical constituents of A. vera leaves including the pulp and exudate are given in Table 1.

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Table 1: Summary of the chemical composition of A. vera leaf pulp and exudate.

Class	Compounds
Anthraquinones / anthrones	Aloe-emodin, aloetic-acid, anthranol, aloin A and B (or collectively known as barbaloin), isobarbaloin, emodin, ester of cinnamic acid
Carbohydrates	Pure mannan, acetylated mannan, acetylated glucomannan, glucogalactomannan, galactan, galactogalacturan, arabinogalactan, galactoglucoarabinomannan, pectic substance, xylan, cellulose
Chromones	8-C-glucosyl-(2'-O-cinnamoyl)-7-O-methylaloediol A, 8-C-glucosyl-(S)-aloesol, 8-C-glucosyl-7-O-methyl-(S)-aloesol, 8-C-glucosyl-7-O-methylaloediol,8-C-glucosyl-noreugenin, isoaloeresin D, isorabaichromone, neoaloesin A
Enzymes	Alkaline phosphatase, amylase, carboxypeptidase, catalase, cyclooxidase, cyclooxygenase, lipase, oxidase, phosphoenolpyruvate carboxylase, superoxide dismutase
Inorganic compounds	Calcium, chlorine, chromium, copper, iron, magnesium, manganese, potassium, phosphorous, sodium, zinc
Miscellaneous including organic compounds and lipids	Arachidonic acid, γ-linolenic acid, steroids (campestrol, cholesterol, β-sitosterol), triglicerides, triterpenoid, gibberillin, lignins, potassium sorbate, salicylic acid, uric acid
Non-essential and essential amino acids	Alanine, arginine, aspartic acid, glutamic acid, glycine, histidine, hydroxyproline, isoleucine, leucine, lysine, methionine, phenylalanine, proline, threonine, tyrosine, valine
Proteins	Lectins, lectin-like substance
Saccharides	Mannose, glucose, L-rhamnose, aldopentose
Vitamins	B1, B2, B6, C, β-carotene, choline, folic acid, a-tocopherol

Mucopolysaccharides – a secret Aloe's weapon

Polysaccharides make up most of the dry matter of the *A. vera* parenchyma. A storage polysaccharide, acetylated glucomannan, is located within the protoplast of the parenchyma cells and a variety of polysaccharides are present in the cell wall matrix. An overall carbohydrate analysis of the alcohol insoluble residues showed that the cell walls in the fillet of the aloe leaf hold mainly mannosecontaining polysaccharides, cellulose and pectic polysaccharides whereas the skin of the leaf contains in addition significant quantities of xylose-containing polysaccharides.

Many investigators have identified partially acetylated mannan (or acemannan) as the primary polysaccharide of the gel, while others found pectic substance as the primary polysaccharide. As mentioned before, this discrepancy in polysaccharide composition was initially explained by differences in geographical locations of the plants and seasonal changes but later it was found that extraction and processing of the parenchyma tissue are also very important variables that contribute to the differences in the results. Other polysaccharides such asarabinan, arabinorhamnogalactan, galactan, galactogalacturan, lucogalactomannan, galacto glucoarabinomannan and glucuronic acidcontaining polysaccharides have been isolated from the *Aloe vera* inner leaf gel part[14] .

Mannan

In general, mannans play a structural role in plants by acting as hemicelluloses that bind cellulose. They also fulfil a storage function as non-starch carbohydrate reserves in seeds and vegetative tissues. In addition, evidence was found that it may act as a signalling molecule in plant growth and development. Linear mannans arehomopolysaccharides that are composed of linear chains of β-(1→4)-D-mannopyranosyl residues with less than 5% galactose.

Although different results on the composition of polysaccharides in aloe pulp have been described in the literature, the consensus among most authors is that acetylated glucomannan molecules are mainly responsible for the thick, mucilage like properties of the raw aloe gel.

Acemannan found in *A.vera* gel is also known as carrysin and has a backbone of β-(1→4)-D-mannosyl residues acetylated at the C-2 and C-3 positions that exhibit a mannose monomer:acetyl ratio of approximately 1:1 and contains some side chains of mainly galactose attached to C-6. The molecular weights of these polysaccharides range from 30-40 kDa or greater and is usually as high as 1000 kDa in fresh aloe leaf material. The repeating units of glucose and mannose exist in a ratio of 1:3, but other ratios of 1:6, 1:15 and 1:22 have also been reported. These discrepancies in glucose to mannose ratios have been explained by differences between species as well as due to sample processing and treatment. In a study where the linkages between monomers in acemannan were analysed, the acemannan was treated with the enzyme endo-β-D-mannanase and the C-4 and C-6 resonances of the fractions were scrutinised using 13C-NMR.

The β -(1→4)-glycosidic bond configuration of acemannan is an important consideration in terms of the therapeutic effects of *A. vera* gel, since humans lack the ability to enzymatically break down these bonds.

The acemannan found in aloe is structurally unique that makes it a characteristic compound of aloe species amongst other well known plant mannans (which have distinct side-chains or are unacetylated and insoluble). Plant galactomannans are made up of β-(1→4)-D-mannopyranosyl residues containing side chains of single α-(1→6)-D-galactopyranosyl groups. True galactomannans are represented by those mannans that contain more than 5% by weight of D-galactose residues. The physiological function of plant galactomannans is to retain water by solvation, especially to prevent complete drying of seeds in regions with high temperatures.

Glucomannans are polysaccharides that contain chains of randomly arranged β-(1→4)-D-manose and β-(1→4)-D-glucose residues in a ratio of 3:1. The backbone of galactoglucomannans consists of β -(1→4)-D-mannopyranosyl and β-((1→4)-D-glucopyranosyl residues with a α-(1→6)-D-galactopyranosyl and *O*-acetyl groups.

Maloyl glucans

Three malic acid acylated carbohydrates were isolated from *A. vera* gel and characterised as 6-*O*- (1-L-maloyl)-α-, β -D-Glc*p*(termed veracylglucan A), α-d-Glcp-(1→4)-6-*O*-(1-L-maloyl)-α-, β -D-Glc*p*termedveracylglucon α-D.Glcp-(1→4)-tetra-[6-*O*-(1-L-maloyl)-α-D-Glc*p*-(1→4)]-6-*O*-(1-Lmaloyl)- α-, β -D-Glc*p* (termed veracylglucan C).

Veracylglucan A (C10H16O10), with a molecular weight of 296 Da was only detected in very small quantities in the *A. vera* gel and was very unstable with hydrolysis of the ester group [6-*O*-(1-Lmaloyl)- Glc*p*-] that occurred after only one week at a temperature of 7 °C. Veracylglucan B (C16H26O15) has a molecular weight of 458 Da andpH of 3.8, while veracylglucan (C56H18O51) molecular weight of 1570 Da and a pH of 4.7 [15].

Pectic substance

Pectic substance is a term that refers to a group of closely related polysaccharides including pectin, pectic acid and arabinogalactan. Pectin is a polysaccharide consisting of α-(1→4) linked poly galacturonic acid with intra-chain rhamnose insertion, neutral sugar side-chains and methyl esterification

Arabinan and arabinogalactan

Arabinogalactan contains mainly arabinose and galactose, but also other sugars including glucuronic acid and/or galacturonic acid. Certain arabinans and arabinogalactans sometimes form the neutral side chains of pectins.

Arabinogalactan is present in a much lower concentration in aloe gel compared to acemannan.

Other polysaccharides

Aloeride is a polysaccharide that comprises only 0.015% of the crude *A. vera* juice material (dry weight). It has a molecular weight between 4 and 7 million Da with its glycosyl components containing glucose (37.2%), galactose (23.9%), mannose (19.5%) and arabinose (10.3%). Polyuronide has a molecular weight between 275 and 374 kDa, while that of aloeferon is 70 kDa. Another biologically active polysaccharide with a molecular weight between 420 and 520 kDa was isolated from aloe gel that comprises equal amounts of glucose and mannose [16].

5. BIOLOGICAL ACTIVITY

Skin penetration enhancement

A. vera gel increased the *in vitro* skin penetration of compounds depending on their molecular weights, with an apparent inverse correlation between enhancement ratio and molecular weight of the compound. This penetration enhancement effect of the aloe gel was explained by a probable pull effect of complexes formed between the compound and the enhancing agent within the aloe gel, but it was stated that the proposed mechanism of action has to be further investigated and confirmed. Some constituents of the *A. vera* gel itself also penetrated the skin and this was interestingly dependent on the molecular weight of the co-applied compounds. The higher the molecular weight of the co-applied compound, the less of the gel components were transported across the skin. This was explained by the probable displacement of *A. vera* components from the penetration pathways and thereby it inhibits permeation of the gel components more effectively than the smaller compounds. Similar to the discussion for intestinal drug absorption enhancement, *A. vera* gel could potentially be used as a penetration enhancement agent for the transdermal delivery of drugs if proven to be effective and safe [17].

Aloe seems to increase penetration of drugs as:

- it penetrates very deeply into the deep layers of the epidermis
- it regulates the acid-alkaline ph levels of the skin
- it inhibits the multiplication of bacteria, viruses, and fungi
- it works as an anti-inflammatory agent and astringent
- it relieves pain and itching
- it moisturizes the skin
- it dilates blood vessels under the skin and accelerates the blood circulation
- it stimulates cell division and accelerates tissue regeneration

Aloe Vera has an element called "Lignin" which helps it to penetrate right down to the cellular level. It also has another element called "Saponin" which works as a natural cleansing agent. Both these elements working in conjunction reach the cellular level of the skin. In addition to this, it also nourishes the skin and replenishes it with the much needed nutrition that it requires.

Effect of *Aloe vera* gel on biological membrane permeation

Intestinal drug absorption enhancement

The effect of *A. vera* gel and whole leaf extract on the oral bioavailability of vitamins C and E was investigated in humans in a randomised, double-blind, cross-over clinical trial. Both the gel and whole leaf extract decreased the rate of vitamin

C absorption, but the overall bioavailability (area-undercurve) of vitamin C was 3 times higher when administered with the aloe gel as compared to the control and the gel kept the level of this vitamin significantly higher ($p \leq 0.05$) than the baseline even after 24 hours. The bioavailability of vitamin C administered in conjunction with the whole leaf extract was only 80 % compared to the control and the level returned to baseline after 24 hours. For vitamin E, the bioavailability was 3.7 times higher when administered with aloe gel and 2 times higher with the aloe whole leaf extract. The mechanism of action of the aloe products to improve the bioavailability of the vitamins was explained to be a possible protection effect against the degradation of the vitamins in the intestinal tract as well as binding of the polysaccharides to the vitamins and thereby slowing down the absorption rate [18].

It is well known that polysaccharides of natural origin such as chitosan are capable of enhancing the intestinal absorption of co-administered drugs by means of a transient opening of the tight junctions between adjacent epithelial cells to allow for paracellular transport across the intestinal epithelium. In a recent *in vitro* study it was shown that both *A. vera* gel and whole leaf extract could decrease the transepithelial electrical resistance of intestinal epithelial cell monolayers (Caco-2), thereby indicating opening of the tight junctions between adjacent epithelial cells. The *A. vera* gel and whole leaf extract were also able to significantly increase the transport of the macromolecular peptide drug, insulin, across the Caco-2 cell monolayers.

Many potential therapeutic agents face the disadvantage of low bioavailability after oral administration due to poor membrane permeability. Drug absorption enhancers are compounds capable of reversibly removing the resistance of the outer layers in the body with minimum tissue damage, thus allowing the drug to enter the blood circulation in sufficient quantities. Although many compounds have been investigated for their drug absorption enhancing properties, some have been associated with cytotoxic effects and others were not efficient enough to ensure that therapeutic levels of poorly absorbable drugs are achieved. Only limited information is currently available on the drug absorption enhancement activities of *A. vera* gel, but if it proves to be a safe and effective absorption enhancer *in vivo*, it could be used in novel dosage forms for the oral delivery of poorly absorbable drugs that are administered by means of injections [19].

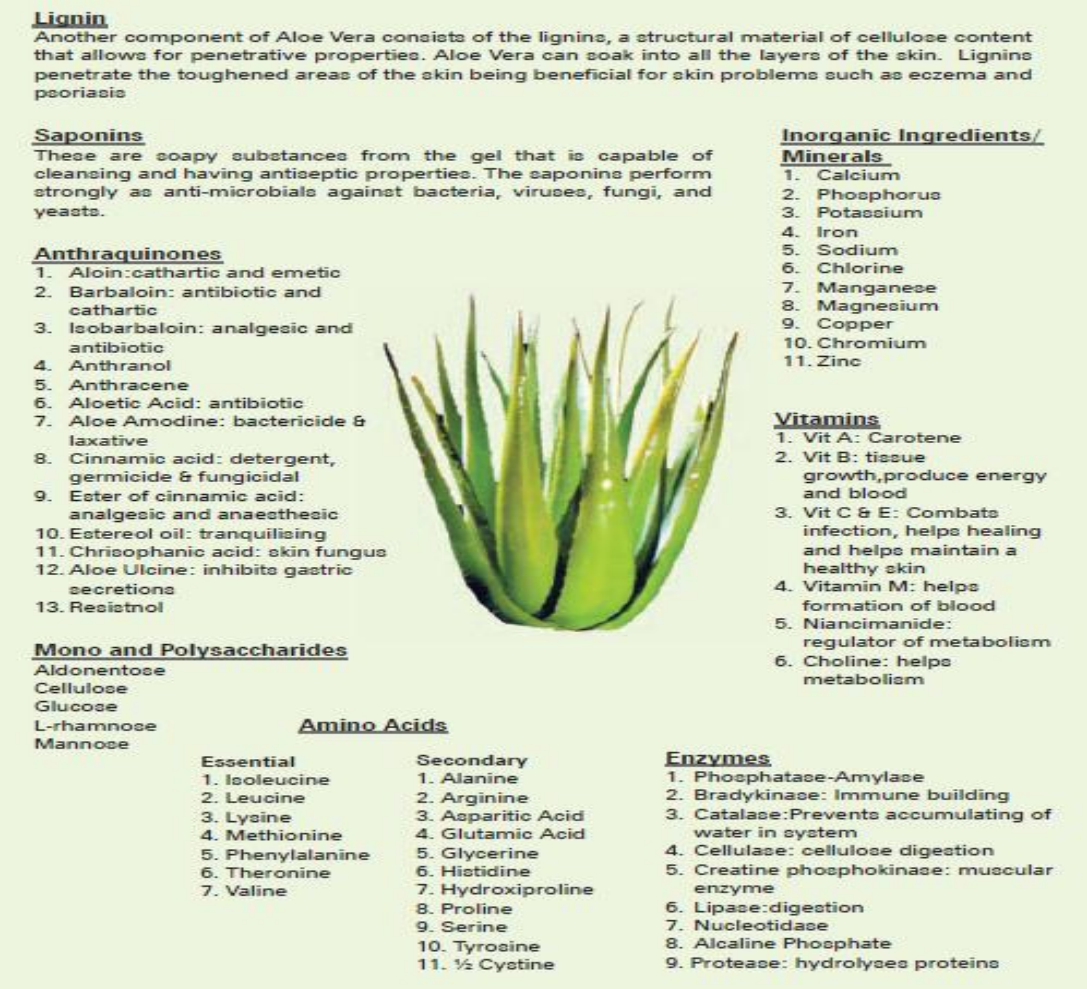
6. ALOE VERA LEAF GEL AS AN EXCIPIENT

A. vera has a long history as a medicinal plant with diverse therapeutic applications. Although it was claimed that some of the biological activities of this plant can be attributed to the polysaccharides found in the leaf gel, it is a daunting task to link individual polysaccharides to specific therapeutic properties. Differences in plant composition due to geographic location as well as differences in gel extraction methods and sample preparation techniques have contributed to discrepancies in the results obtained from many studies in terms of the chemical composition and biological activities of *A. vera* leaf gel. Although some indications were found that a particular polysaccharide is effective when tested for a specific biological activity, it seems as if it is rather a combination of

compounds that account for the health benefits of *A. vera* leaf gel. With technological developments in the field of analytical chemistry it has become easier to isolate and characterize the chemical components of the leaf gel and it is expected that more information in this regard will become available in the future at a faster rate .

Gums and mucilages from natural origin that contain complex polysaccharides have found a wide range of pharmaceutical applications such as functional excipients in dosage forms, which include binders, disintegrants, emulsifiers, suspending agents, gelling agents and sustaining agents in modified release tablets. Furthermore, some natural gums and mucilages have been reported to modify the release of drugs from modified release dosage forms such as matrix type tablets [20].

Figure 1: *Aloe Vera* gel main chemical constituents.



7. MECHANISM OF ACTIONS

1. Skin penetration properties: Penetration enhancers work by means of two possible mechanisms: (1) the penetration enhancer increases the solubility of the drug within the SC by altering the partitioning of the drug into the SC and/or (2) the penetration enhancer influences the diffusion of the drug across the SC by disrupting the ordered nature of the skin lipids. Lignins as structural material of cellulose content allows for penetration properties. Aloe Vera can soak into all the layers of the skin and this may be helpful in increasing the penetration of certain

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drug molecules across the skin, as lignins can penetrate the toughened areas of the skin [21].

2. Healing properties: Glucomannan, a mannose-rich polysaccharide, and gibberellin, a growth hormone, interacts with growth factor receptors on the fibroblast, thereby stimulating its activity and proliferation, which in turn significantly increases collagen synthesis after topical and oral *Aloe vera*. Aloe gel not only increased collagen content of the wound but also changed collagen composition (more type III) and increased the degree of collagen cross linking. Due to this, it accelerated wound contraction and increased the breaking strength of resulting scar tissue. An increased synthesis of hyaluronic acid and dermatan sulfate in the granulation tissue of a healing wound following oral or topical treatment has been reported [22].

3. Effects on skin exposure to UV and gamma radiation: *Aloe vera* gel has been reported to have a protective effect against radiation damage to the skin. Exact role is not known, but following the administration of *Aloe vera* gel, an antioxidant protein, metallothionein, is generated in the skin, which scavenges hydroxyl radicals and prevents suppression of superoxide dismutase and glutathione peroxidase in the skin. It reduces the production and release of skin keratinocyte-derived immunosuppressive cytokines such as interleukin-10 (IL-10) and hence prevents UV-induced suppression of delayed type hypersensitivity [23].

4. Anti-inflammatory action: *Aloe vera* inhibits the cyclooxygenase pathway and reduces prostaglandin E2 production from arachidonic acid. Recently, the novel anti-inflammatory compound called C-glucosyl chromone was isolated from gel extracts [24].

5. Effects on the immune system: Alprogen inhibit calcium influx into mast cells, thereby inhibiting the antigen-antibody-mediated release of histamine and leukotriene from mast cells. In a study on mice that had previously been implanted with murine sarcoma cells, acemannan stimulates the synthesis and release of interleukin-1 (IL-1) and tumor necrosis factor from macrophages in mice, which in turn initiated an immune attack that resulted in necrosis and regression of the cancerous cells. Several low-molecular-weight compounds are also capable of inhibiting the release of reactive oxygen free radicals from activated human neutrophils [25].

6. Laxative effects: Anthraquinones present in latex are a potent laxative. It increases intestinal water content, stimulates mucus secretion and increases intestinal peristalsis [26].

7. Antiviral and antitumor activity: These actions may be due to indirect or direct effects. Indirect effect is due to stimulation of the immune system and direct effect is due to anthraquinones. The anthraquinone aloin inactivates various enveloped viruses such as herpes simplex, varicella zoster and influenza. In recent studies, a polysaccharide fraction has shown to inhibit the binding of benzopyrene to primary rat hepatocytes, thereby preventing the formation of potentially cancer-initiating benzopyrene-DNA adducts. An induction of glutathione S-transferase and an inhibition of the tumor-promoting effects of phorbol myristic acetate has also been reported which suggest a possible benefit of using aloe gel in cancer chemoprevention.

8. Moisturizing and anti-aging effect: Mucopolysaccharides help in binding moisture into the skin. Aloe stimulates fibroblast which produces the collagen and elastin fibers

making the skin more elastic and less wrinkled. It also has cohesive effects on the superficial flaking epidermal cells by sticking them together, which softens the skin. The amino acids also soften hardened skin cells and zinc acts as an astringent to tighten pores. Its moisturizing effects has also been studied in treatment of dry skin associated with occupational exposure where *Aloe vera* gel gloves improved the skin integrity, decreases appearance of fine wrinkle and decreases erythema. It also has anti-acne effect [27].

9. Antiseptic effect: *Aloe vera* contains 6 antiseptic agents: Lupeol, salicylic acid, urea nitrogen, cinnamonic acid, phenols and sulfur. They all have inhibitory action on fungi, bacteria and viruses [28].

Conclusion

Alternative routes of drug administration (such as the transdermal route) are less desirable and feasible compare to the most convenient drug intake methods (i.e. the oral route) because of the skin offering a formidable barrier to molecular transport due to the nature of the SC. Therefore, penetration enhancers can be employed to improve the movement of drugs across the skin. *Aloe vera* seems to enhance the penetration for certain drugs molecules across the skin along with skin hydrating and anti-inflammatory effects. Since the external use of aloe on intact skin is not associated with adverse reactions and is generally regarded as safe, the use of this natural resource as a penetration enhancer is promising.

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