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Aloe vera– botanical variants, pharmacological constituents, mode of working and commercial preparations

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Abstract
There is increasing awareness for medicinal plants and herbal products as safe alternatives to synthetic chemicals. A medicinal plant that has been in use in folk medicine for centuries as cure for various health disorders is *Aloe vera*. The plant boosts immune system too and does have both nutraceutical and cosmeceutical values. Consequent to the proven health benefits of the plant, aloe industry is booming up with products like hand sanitizers, hair creams and health drinks. Pharmacologically active constituents of the plant include unusual polysaccharides, glycoproteins, enzymes, lipids and hundreds of phenolic compounds such as anthraquinones, flavonoids, chromones and coumarins. This paper describes the plant's botanical variants, medicinal, nutraceutical and cosmeceutical values, phytochemical constituents and their working at molecular level.

Keywords: aloe vera gel, antioxidants, acemannan, phenolics, green pharmacy

Introduction
Use of medicinal plants for herbal products for use in medicine, nutrition and cosmetics is increasing steadily, principally to ward off the accompanying ill effects of synthetic chemicals. Additionally, many among them strengthen body's immune system, the significance of which was realized more since the breakdown of SARS-CoV-2 (Covid-19) pandemic in early 2020. One such plant that has been in use in folk medicine across the globe even before the days of alchemy is *Aloe vera* (AV, Alloeh in Arabic for 'shining bitter substance', vera in Greek for 'true') referred as Ghritakumari and Gwarpatha in northern India. Consequent to the plethora of constituents with wide ranging pharmacological significance and increased public awareness for herbal products, aloe industry is booming up and new players with diverse products ranging from hand sanitizers to hair vitalizers to health drinks are lining up in the market. It is an opportune time to know more about this plant, its benefits, chemistry, biochemical working and thrust areas for future research.

Aloe Vera Plant
Aloe vera, a native of Cape of Good Hope in South Africa, belongs to the Family Aloaceae (Order: Liliales, Class: Liliopsida, Division: Magnoliophyta). There are close to 550 species under the genus Aloe of which the most commercialized one is *Aloe vera* L. *(*syn. *Aloe barbadensis* Mill.). Few others of lesser significance are *A. arborescens* Mill, *A. vulgaris* Lam, *ferox* Mill, *A. perryi* Baker, *A. chinensis* Steud, *A. inermis* Forssk, *A. officinalis* Forssk, *A. tomentosa* Deflers, *A. maculata* Forssk and *A. littoralis* Baker. The plant (60 to 100 cm tall, ~ 10 cm wide) is a pea-green succulent monocot xerophytic cactus like shrubby or arborescent perennial (~ 12 years) and develops water storage tissue in the leaves. Triangular 12 to 16 fleshy turgid leaves with serrated edges and white flecks on the upper and lower areas emerge from the short stems in a rosette pattern. Leaves, most pharmaceutically significant part of the plant, weigh ~ 3 pounds and are composed of three layers viz. a translucent slippery astringent gel made of large thin-walled mucilaginous parenchyma cells as the inner layer, a yellow-brown sticky bitter taste latex as the central layer and a rind of 15 to 20 cells rich in polysaccharides and proteins imparting protective function as the outer layer. The pulp and the rind account for 70 to 80 and 10 to 20% of the leaf weight, respectively. Bright yellow ~ 2 to 3 cm long flowers with tubular corolla are arranged in a loose spike. The plant matures in 4 years. The gel is principally water (98%) and contains ~ 0.66% total solids of which ~ 0.56% is soluble solids and is used for preparing 'ready to use' aloe based commercial products. The latex too finds limited use.

Pharmacologically Significant Constituents
Aloe vera gel (AVG), the most medicinally significant fraction of the plant, is acidic (pH ~ 4.5) with polysaccharides as their most abundant constituent (55% of dry matter) followed by sugars (17%), minerals (16%), proteins inclusive of enzymes (7%), lipids (4%), traces of free amino acids, organic acids, vitamins and minerals, a range of secondary metabolites, and many diverse organic constituents. Some of the individual constituents of these broad classes of metabolites are unique to AVG contributing to its medicinal, antimicrobial, nutrient and cosmetic values. Table 1 depicts some of the primary metabolites of AVG and their significance.

Table 1: Primary Metabolites in AVG

Class	Description	Medicinal significance/health
		Benefits
Saccharides	i) Polysaccharides are the major components accounting for 0.2 to 0.6% of fresh gel weight depending upon the plant's maturity, season, and cultivar. Average molecular weight is ~ 2x106 Da. Monomers of the polysaccharides are mannose, glucose and galactose. Many are structural, reserve and mucopolysaccharides, largely linear biopolymers and derived from the mucilage layers of the leaves. Acemannan, the major polysaccharide, is few hundred to several thousand β1, 4-linked acetylated mannose (> 60%, cetylation at 3 and occasionally at 2 positions of the sugar) with sporadic glucose (~ 20%) and galactose (< 10%) residues. The liner and branch linkages linking mannose with glucose and galactose are β-1, 4 and α-1,6 glycosidic linkages, respectively. Polysaccharides present in traces and unique to AVG are aloeride made of mannose, glucose, galactose and arabinose, and polyuronide. Polymannose, arabinan, galactan, glucogalactomannan, arabinorhamnogalactan, galactogalacturan, galactoglucoarabinomannan and pectic substances are other polysaccharides of significance. Among monosaccharides, mannose-6-phosphate and glucose are present in significant amounts.	Polysaccharides present in unique proportions contribute to majority health benefits. Some among them exhibit free radical scavenging property with potent antioxidant activity during oxidative stress. Some can hold water molecules in the intermolecular space, contributing to the humectant, emollient and moisturizing property, thermostability and gelatinous nature of AVG. Acemannan is anti- diabetic, wound healing, hepatoprotective and immunomodulatory through macrophage activation and cytokines production. Both aloeride and polyuronide have significant pharmacological
		Value. The two monosaccharides are wound healing, antidiabetic, and anti-inflammatory and possess much nutraceutical value.
Proteins	Some polysaccharides get attached to proteins forming glycoproteins with medicinal value viz. alprogen and lectins (aloctin A and B).	y glycoproteins are wound healing. Alprogen exhibits antiallergic and immunity boosting property. Aloctins have strong carbohydrate binding domains and are immunomodulatory and wound healing through angiogenesis.
Enzymes	Bradykinase, cyclooxygenase, superoxide dismutase (SOD), peroxidase (POD), catalase (CAT) and alkaline phosphatase.	Bradykinase and cyclooxygenase help reduce inflammation. Others are concerned with healthy functioning of the body.
Lipids	Triterpenoid phytosterols (nonsaponifiable lipids) e.g., campesterol, β-sitosterol and lupenol. Among other phytosterols, cycloartenol, methylene cycloartenol and lophenol are significant. Fatty acids e.g., arachidonic acid (20 C ω-6 fatty acid) and γ-linolenic acid (18 C, prostaglandins precursor).	i) Campesterol, β-sitosterol and lupenol lower cholesterol, are concerned with healthy functioning of the heart, and have analgesic properties,
		Respectively. ii) AVG fatty acids are polyunsaturated, prevent thickening of the arteries and improve coronary functioning.
Vitamins, minerals and others	1. Vitamin C and E. 2. Selenium 3. Magnesium lactate 4. Salicylic acid 5. Auxins and gibberellins	1. Vitamin C is a biochemical reducing agent. Vitamin E is an antioxidant, scavenger of free radicals and prevents them from causing any damage to the tissues. Constituent of selenoenzymes which play crucial roles in reproduction, thyroid metabolism, DNA synthesis, immunity and Protection from oxidative damage. 2. anti-itching 3. vi) antimicrobial 4. v) wound healing

Table 2: Major Phenolic Classes in *Aloe vera*

Class	Important constituents in AVG	Pharmacological significance
Anthraquinones	Most abundant of all the phenolic classes in AV. Content is more in yellow-brown latex than AVG. Barbaloin, isobarbaloin, *O*- glycosides of the two, chrysophanol (chrysophanic acid), aloin A & B (diasteromers) and their acetyl and hydroxy derivatives and glucosides, emodin and physcion. Some of them act as both anti- and prooxidants depending upon concentration.	Analgesic, antibacterial, antiviral, laxative and UV radiation protectant.
Chromones	Aloesin, neoaloesin A, aloeresin A, E and F, isoaloeresin D, and aloeveraside A and B. Majority occur as glucosides or in methylated forms. Like anthraquinones, some chromones act as both anti- and prooxidant depending upon concentration.	Antimelanogenic due to competitive inhibition of the enzyme tyrosinase, anti-inflammatory due to free radical scavenging property and antidiabetic.
Flavonoids	Isoorientin, isoquercitrin, isovitexin, catechin, apigenin, saponarin, luteolin, naringenin, and myricetin are important among flavonoids inclusive of flavones, flavonols and flavan-3-ols. Occur mostly as glycosides.	Antioxidants, anti-inflammatory, inhibitory on blood platelet aggregation and improve liver functioning.
Phenylpropanoids	3-(4-Hydroxyphenyl) propionic acid and its methyl ester, chlorogenic acid and its 5-feruloyl derivative and caffeoylshikimic acid.	Hypoglycemic, hypolipidemic, antioxidant and anti-inflammatory.
Phenylpyrones	Aloenin A and B and feroxidine	Promotes hair growth, recuperative effect on skin and antitumor.
Phenol derivatives	Anisal- and salicyl-aldehyde, cresol, pyrocatechol, and gallic, syringic and vanillic acid. Majority are low molecular weight compounds.	Gastroprotective, antioxidant, antimicrobial, antimutagenic and antiangiogenic.
Coumarins	Coumarins- benzopyrone derivatives - contribute to the bitter	Antioxidant, antimicrobial, antifungal, antihypertensive, antihyperglycemic,
	Taste of AV. Feralolide, dihydroisocoumarin, 7- demethylsiderin and coumaroylquinic acid.	neuroprotective and stimulatory for macrophages for fluid reabsorption in persons suffering from edema.

Major Uses and Mode of Working

Aloe vera has been in use for centuries in folk medicine for treating various health hazards and eloquently referred in various superlative descriptions e.g., 'plant of immortality', 'universal panacea' and 'wand of heaven'. Historical records mention that the Greek philosopher Aristotle was driven by the plant's benefits to persuade Alexander to conquer Socotra Island in Africa for aloe to be in booty to be used for wound healing of soldiers. Some of the major uses of *Aloe vera* are described.

Wound healing

AVG proves soothing for wounds, provides rapid cure for injuries resulting from cuts, bruises, burns, sunburns, frost bite and psoriasis, and prevents infection of the exposed areas of the injury. For wound healing, aloe is often used in as tincture benzoin (aloe 2% with benzoin 10%, storax 8% and Tolu balsam 4% in 95% ethanol).

Skin protection

AVG protects skin by virtue of its moisturizing property. Also, it inhibits undesirable skin eruptions like boils, corns, warts and acne because of its antimicrobial and tissue regeneration property.

Hair care

Both AVG and water extract of the dry leaves strengthen root hair, arrest premature hair fall and impart a glossy look of the hair, thus making it an ingredient in many hair care products.

Food preservation

Perishable postharvest edible materials such as fruits and vegetables like tomato destined for export are added a longer in-hand time by providing edible AVG coatings. The coating, accomplished by dipping, brushing or spraying, acts as a mechanical barrier for atmospheric gases, moisture and pathogens to find entry to the produce and helps in maintaining/improving quality attributes e.g., retention of garden fresh colour, texture, appearance, firmness, freshness, brightness and weight reduction (external quality attributes), soluble solids concentration, titratable acidity, volatile aroma biosynthesis, sugar contents, ethylene production and nutritional value (internal quality attributes). Shelf life and consumer acceptability of the farm produce are thus enhanced and at the same time, a safe alternative to postharvest chemical treatment of an edible produce is opened. Correct rate of the coating material depends upon the method followed for coating (dipping, spraying etc) and nature of the shell of the fruits e.g., < 25, 25 to 50 and > 50% AVG (blended with 2% glycerol as plasticizer) for thin- (grape, papaya, cherry), medium- (mango, guava, apple) and thick-shelled (pineapple, lichi, pomegranate) fruits.

Drug delivery

Many drugs and some vitamins when taken orally are very poorly absorbed making them poorly effective. In many such cases, AVG preparations such as tablets used as excipients make the drug delivery process more effective due to sustainable and controlled release and absorption of the active constituents over an extended period of time.

Food products

AV extracts, gel and latex are used as bitter flavouring agents in health and soft drinks, yoghurts, instant tea powders, ice creams, candies, jams and alcoholic beverages and also as dietary supplements for strength and rejuvenation.

Ayurveda

In Ayurveda, the traditional Indian system of medicine, AV preparations taken orally are in use for multiple health disorders ranging from cosmic to cosmetic e.g., laxatives, gastro protectives for abdominal bloating and stomach

ulcers, hemorrhoid remedies, anthelmintics, high blood sugar and hypertension lowering agents, skin toners, and for preventing and dissolving renal stones. When used topically, AV proves effective for skin eczema and canker sores. In veterinary, crude AVG is used as laxative and for udder disinfection.

Table 3 depicts the mode of working of the AV constituents at biochemical level for some of its major functions.

Table 3: Mode of Working of AV Constituents for its Major Functions

Function	Mode of Working
Wound healing	Glucomannan, acemannan and gibberellins execute increased collagen synthesis in the wound zone through their interaction with the growth factor receptors, and favourably alter its composition and cross linking with other biopolymers. This causes contraction of the wound and increases breaking strength of the scar tissue. Besides, synthesis of hyaluronic acid, a mucopolysaccharide intimately involved in wound healing process, is increased. Mannose-6-phosphate, a sugar phosphate, also contributes to the wound healing process.
Skin protection	The concerned active ingredients regulate the epidermal skin protein involucrin by activation of target enzymes and modulation of hyaluronic acid synthesis.
Antiinflammation	Anti-inflammatory constituents inhibit the enzyme cyclooxygenase 2 (COX-2) as also done by many synthetic nonsteroidal anti-inflammatory drugs (NSAID). COX-2 catalyzes the rate limiting step of the conversion of arachidonic acid to prostaglandins, especially PGE2, which cause inflammation, mild to moderate pain and fever.
Moisturizing action	Some mucopolysaccharides help binding moisture to the skin. Aloe stimulates fibroblasts for increased collagen and elastin fibres synthesis for making the skin more elastic and less wrinkled. Also, skin is softened due to cohesive effects on the superficial flaking epidermal cells by sticking them together.
Laxative property	Laxative and cathartic property leading to free defecation by some AV constituents e.g., 1, 8-dihydroxyanthraquinone are due to increased amount of water in the intestine that in turn stimulates mucous secretion and enhanced peristaltic movement.
Strengthening immunity	Some glycoproteins retard calcium influx into mast cells inhibiting antigen-antibody mediated histamine and leukotriene release from such cells. Acemannan stimulates the synthesis and release of interleukin-1 (IL-1) and tumor necrosis factor from macrophages causing regression of cancerous cells. Some low molecular weight compounds inhibit release of reactive free radicals of oxygen like superoxide anion (O2-) from activated neutrophils adding more teeth to body's immune system for assault against infecting microbes. Also, some among them direct macrophage cells to generate nitric oxide, secrete cytokines and stimulate the lymphocytes for antigenic response.
Antioxidant activity	Antioxidants in AV which confer many of its medicinal, nutraceutical and cosmeceutical functions act as scavengers of highly reactive free radicals that otherwise may cause biochemical damage leading to disrupted functioning of cellular organelles and their membranes. Antioxidant activity is largely due to the phenolic constituents that are distributed more in the peel rather than the gel or latex suggesting that the waste material of AV processing plants can be more effectively utilized and can no longer be treated as waste suitable for use only as a manure.
Skin protection against radiation	Synthesis of proteins like metallothionein which scavenge hydroxyl radicals and prevent suppression of SOD and glutathione peroxidase in the skin is induced. Besides, the production and release of skin keratinocyte derived immunosuppressive cytokines are reduced, a process that in turn prevents damage of the exposed skin by UV radiation.
Antisepsis	AV Constituents like lupeol, salicylic acid, cinnamic acid, p-coumaric acid, and several substituted phenols inhibit the growth of bacteria, fungi and protozoa that find entry to the body's inside through cuts and bruises and may later cause sepsis. Interference in solute transport systems of the microbes through the membranes is one among the several ways for such inhibition.
Anti-ageing	Several AV constituents make fibroblast more active, producing more structural proteins e.g., collagen and elastin. Skin thus gets more elastic and less wrinkled. Cohesive effects mentioned in moisturization also

Processing and Commercial Formulations

Consequent to the high market demand for diverse kinds of pharmaceutical uses and nutritional and cosmetic value of *Aloe vera*, processing of the plant's leaf pulp is now a fast growing industry. For preparing value added commercial products, the plant is used in two forms viz. the clear viscous gel obtained from the mucilaginous cells of the leaves and the bitter yellow latex of the pericyclic tubular cells called juice or simply aloe. For preparing AVG, the leaves are washed with mild chlorine solution and the outer layers are removed. Pasteurization of the product at 70 to 800C for 3 min inactivates enzymatic activities. One kg fresh leaf forms ~ 0.43 kg gel. Gel concentrates are prepared by vacuum distillation of the filtered, decolourised and decontaminated gel. The gel and the juice have markedly different chemical compositions and pharmaceutical uses and so are used differently.

The gel is rich in acemannan, glucomannan and anthraquinones and is therefore more widely used in medicinal, cosmetic and personal care products. Many ready to use AV preparations are now available in different formulations viz. simple liquids, suspensions, creams, lotions, ointments, sprays, powders, tablets, pills, capsules and balm. In cosmetic and personal hygiene, the products of these formulations include hand sanitizers, soaps, shampoos, skin toners, moisturizing gels, facial cleansers, shaving creams, after shave lotions, sun blocks, antiseptic soothing creams, emollients, lip balms, mouth wash, and hair creams, oils and vitalizers. Also, there are many over the counter general medicines based on AV e.g., AV gel cream for relief from post defecation pain due to anal fissures. In food industry, aloe is used as an ingredient in health drinks and beverages, general nourishment tablets and syrups and as a source of functional food.

Thrust Areas of Research

1. The bioactive constituent/s responsible for many of the properties that are still uncertain are to be identified for executing structure activity variations for arriving at more potent bioactive synthetic derivatives.
2. The peel and husk of aloe industry treated largely as waste are to be utilized for making pharmaceutically and nutritionally effective preparations.

3. Molecular level mechanisms for the working of AV coatings for effective fruits and vegetables preservation involving enzymes like CAT, SOD and POD are to be studied.
4. Early research results indicated the presence of many pharmacologically active constituents in *Aloe vera* flowers. More research is therefore required on the medicinal use of flowers for potential curative and therapeutic purposes.
5. Present harvest rate of 3 to 5 leaves from each plant at 6 to 8 weeks intervals is inadequate to meet the demand of aloe industry. This warrants genetic modifications in the plant for higher number of leaves and faster growth.

Summary

Aloe vera does have pharmacologically effective constituents effective for a myriad of benefits viz. wound healing, anti-inflammatory, antidiabetic, antihypertensive, antiseptic, skin protection against short wavelength radiation, laxative and cosmetic uses. The plant thus has been in use in folk medicine across the world for centuries and treated much like a green pharmacy at home. Some of the polysaccharides, proteins, enzymes and lipids with medicinal values are unique to the plant. The plant is also a rich source of phenolics with diverse kinds of pharmaceutical applications. Both awareness and market demand of *Aloe vera* based products are now high and justifiably, Aloe industry is booming up with wide ranging pharmaceutical and general health and hygiene products such as hand sanitizers, hair vitalizers, skin care products, laxatives and health drinks are lining up in the market. It is an appropriate time to know more about the plant, go for its cultivation and fix priority research areas for further harnessing of the plant's potential.

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