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A CRITICAL REVIEW ON ANTIOXIDANT AND ANTIMICROBIAL PROPERTIES OF *ALOE VERA* L.

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ABSTRACT: Medicinal plants form the backbone of traditional system of medicine in India. Biotechnological and Pharmacological studies have acknowledged the value of medicinal plants as potential source of bioactive compounds. Phytochemicals from medicinal plants serve as lead compounds in drug discovery and design. Medicinal plants are rich source of novel drugs that forms the ingredients in traditional systems of medicine, modern medicines, nutraceuticals, food supplements, folk medicines, pharmaceutical intermediates, bioactive principles and lead compounds in synthetic drugs. *Aloe* is a genus containing about four hundred species of flowering succulent plants belonging to *Liliaceae* family. *Aloe vera* is as old as civilization and through history it has been used as a popular folk medicine. It is present in the arid regions of India. *Aloe vera* has valuable medicinal properties and is commercially used in pharmaceuticals, cosmetics and food industries. Since ancient time *Aloe vera* L. are using in many herbal preparations. The *Aloe vera* plant contains the important antioxidant components such as vitamins (A, C and E), B (thiamine), niacin, B2 (riboflavin), B12, choline and folic acid, carotenoids, polyphenolic compounds and flavonoids, which prevent damages caused by free radical, reducing risk of chronic diseases. Antioxidants are the component which works against oxidative stress. Oxidative stress depicts the existence of products as free radicals and reactive oxygen species (ROS), which are formed under normal physiological conditions but become deleterious when not being eliminated by the endogenous systems. On the other hand microbial resistance to antibiotics is increasingly becoming a concern to public health. The leaf pulp and liquid fraction of *Aloe vera* act against various microorganisms as well.

INTRODUCTION: Oxidative stress depicts the existence of products as free radicals and reactive oxygen species (ROS), which are formed under normal physiological conditions but become deleterious when not being eliminated by the endogenous systems.

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In fact, oxidative stress results from an imbalance between the generation of reactive oxygen species and endogenous antioxidant systems.

ROS are major sources of primary catalysts that initiate oxidation *in vivo* and *in vitro* and create oxidative stress which results in numerous diseases and disorders [1-2] such as cancer [3], cardiovascular disease [4], neural disorders [5], Alzheimer's disease [6] mild cognitive impairment [7], Parkinson's disease [8], alcohol induced liver disease [9], ulcerative colitis [10], ageing [11], atherosclerosis [12].

As well as, microbial resistance to antibiotics is also increasingly becoming a concern to public health. Currently used antibiotic agents are failing to bring an end to many microbial infections due to super resistant strains. For this reason the search is ongoing for new antimicrobial agents, either by the design and synthesis of new agents or through the search of natural sources for as yet undiscovered antimicrobial agents.

Herbal medications in particular have seen a revival of interest due to a perception that there is a lower incidence of adverse reactions to plant preparations compared to synthetic pharmaceuticals. Coupled with the reduced costs of plant preparations, this makes the search for natural therapeutics an attractive option.

Aloe is a genus containing about four hundred species of flowering succulent plants belonging to *Liliaceae* family [13], which includes garlic, onion and turnip. *Aloe vera* looks like cactus but it is not. *Aloe's* relationship to the lily family is evident from the tubular yellow flowers produced annually in the spring that resemble those of the Easter lily. The name was derived from the Arabic 'alloeh' meaning 'bitter' because of bitter liquid found in the leaves. It is also known as 'lily of the desert' the plant of immortality and medicine plant with qualities to serve as alternate medicine [14].

Aloe vera L. (syn.: *Aloe barbadensis* Miller) is a large succulent perennial plant growing up to 1.5 meters in height, with a strong fibrous root and at-large stem supporting a rosette of narrow lance late leaves. The leaves are whitish green on both sides and bear spiny teeth on the margins. The plant is made of turgid green leaves joined at the stem base in the rosette pattern. Mature plants can grow as tall as 2 and a half inches to 4 feet with the average being around 28 to 36 inches in length. Each plant usually has 12-16 leaves that, when mature, may weigh up to three pounds.

The plants can be harvested every 6 to 8 weeks by removing 3 to 4 leaves per plant. Inside the leaf there is a jelly-like substance. The yellow to orange drooping flowers grow in along raceme at the top of the flower stalk. The fruit is a triangular capsule containing numerous seeds [15]**.** *Aloe vera* has medicinal and cosmetic properties [16].

Each leaf consists of two parts: an outer green rind (skin) and an inner clear pulp (gel). The plant contains a large amount of phenolic compounds. Its thick leaves contain the water supply for the plant to survive long periods of drought [17].

The leaves have a high capacity of retaining water also in very warm dry climates and therefore this plant can survive very harsh circumstances where most other vegetation disappears. When a leaf is been cut, an orange- yellow sap drips from the open end. When the green skin of a leaf is removed a clear mucilaginous substance appears that contains fibres, water and the ingredient to retain the water in the leaf. This is called the gel. *Aloe vera* gel consists of 99.3% water. The remaining 0.7% is made up of solids with glucose and mannose constituting for a large part [18].

Medicinal plants form the backbone of traditional system of medicine in India. Biotechnological and Pharmacological studies have acknowledged the value of medicinal plants as potential source of bioactive compounds. Phytochemicals from medicinal plants serve as lead compounds in drug discovery and design. Medicinal plants are rich source of novel drugs that forms the ingredients in traditional systems of medicine, modern medicines, nutraceuticals, food supplements, folk medicines, pharmaceutical intermediates, bioactive principles and lead compounds in synthetic drugs [19]. *Aloe vera* has been used for medicinal purposes in several cultures for millennia: Greece, Egypt, India, Mexico, Japan, and China [20].

Aloe contains mixture of glucosides collectively called 'aloin' which is the active constituent of various drugs. Indian *Aloe* (*Aloe barbadensis*) is a rich source of over 200 naturally occurring nutrients such as vitamins, minerals, sugars, amino acids, enzymes and acids, which helps in the digestion. The products prepared from *Aloe* leaves have multiple properties such as emollient, purgative, antibacterial, antioxidant, antifungal, antiseptic and cosmetic. The Food and Drug Administration of the USA has approved the developmental study of *Aloe vera* for the treatment of cancer and AIDS. This is attributed to the antiviral and immune modulating properties of acemannan. Traditionally *Aloe* is extensively used in treating urine related problems, pimples and ulcers etc.

It is also used in gerontology and rejuvenation of aging skin. The juice of *Aloe vera* leaves is used as stomachic tonic and purgative. Scientific evidence for the cosmetic and therapeutic effectiveness of *Aloe vera* is limited and when present is frequently contradictory [21-22].

Despite this, the cosmetic and alternative medicine industries regularly make claims regarding the soothing, moisturizing, and healing properties of *Aloe vera*, especially *via* internet advertising [23-24].

The bioactive compounds are used as astringent, haemostatic, antidiabetic, antiulcer, antiseptic, antibacterial, anti-inflammatory, antioxidant and anticancer agent also, effective in treating stomach ailments, gastrointestinal problems, skin diseases, constipation, radiation injury, wound healing, burns, dysentery, diarrhoea and in the treatment of skin diseases [25].

It is used in ayurvedic formulations as appetite-stimulant, purgative, emmenogogue and antihelminthic, for treating cough, colds, piles, debility, arthritis, dyspnoea, asthma and jaundice [26].

Recently, natural plants have received much attention as sources of biological active substances including antioxidants. Numerous studies have been carried out on some plants, vegetables and fruits because they are rich sources of antioxidants, such as vitamin A, vitamin C, Vitamin E, carotenoids, polyphenolic compounds and flavonoids [27].

The *Aloe vera* plant contains the important antioxidant vitamins (A, C and E), B (thiamine), niacin, B2 (riboflavin), B12, choline and folic acid [28], which prevent damages caused by free radical, reducing risk of chronic diseases. Thus, the consumption of dietary antioxidants from these sources is beneficial in preventing cardiovascular disease [29].

The search for newer natural antioxidants, especially of plant origin has ever since increased. There has been an upsurge of interest in the therapeutic potential of medicinal plants as antioxidants properties in reducing such free radical induced damages rather than looking for synthetic ones [30].

Aloe barbadensis Miller (*Aloe vera* L.) has a long history of use as a therapeutic agent with many reported medicinal properties. Amongst its therapeutic properties, it has been shown to have anti-inflammatory activity [31-32], immunostimulatory activity [33] and cell growth stimulatory activity [34-35].

Aloe mucopolysaccharides have direct anti-bacterial, anti-viral, anti-fungal/yeast and anti-parasite effects, so that in combination we can say it has antimicrobial effect. Chronic yeast growth can be controlled so the normal, healthy flora can then thrive more easily. Furthermore, the macrophages, monocytes, antibodies and T-cells are stimulated. Phagocytosis (when large white blood cells engulf particles) is dramatically increased to ingest foreign proteins, such as the HIV virus. *Aloe* mucopolysaccharides increase the number and intensity of all immune cells in the body [36].

Free Radicals and Oxidative Stress: The production of oxygen free radicals is a natural consequence of aerobic metabolism, with these molecules being constantly generated in the body by normal metabolic processes [37]. Most atoms and molecules remain reasonably stable when placed in contact with living cells. However, free radicals are group of particles that are considered to be less benign. Free radicals are unstable, highly reactive molecules characterised by the presence of unpaired electrons in their outermost shells [38].

Free radical is a chemical compound which contains an unpaired electron spinning on the peripheral layer around the nucleus. Any free radical involving oxygen can be referred to as ROS (Reactive Oxygen Species) or ROS is the family of free radicals generated from the oxygen. Molecular oxygen is required by living organisms and biological systems to survive and is depended upon heavily, whereas, any free radical involving oxygen (ROS) causes damage to other molecules by extracting electrons from them in order to attain stability. ROS are ions, atoms or molecules that have the ability to oxidize reduced molecules. ROS are various forms of activated oxygen, including free radicals such as superoxide anion radicals ($^{\cdot}O_2$) and hydroxyl radicals ($OH^{\cdot}$), as well as non-free radicals (H_2O_2) and singlet oxygen [39].

Oxygen derived free radicals such as superoxide anions; hydroxyl radicals and hydrogen peroxide are cytotoxic and give rise to tissue injuries [40]. Excessive amount of ROS is harmful because they initiate bimolecular oxidation which leads to cell death and creates oxidative stress. In addition, oxidative stress causes inadvertent enzyme activation and oxidative damage to cellular system [41].

In the body, free radicals are derived from two sources: endogenous sources, e.g. nutrient metabolism, ageing process etc and exogenous sources e.g. tobacco smoke, ionizing radiation, air pollution, organic solvents, pesticides, etc. [42].

Superoxide Radical: Superoxide (O_2^-) is generated by multiple enzymatic and non-enzymatic pathways and is often at the start of the oxidative stress cascade. A major source is via the cellular electron transport chains, such as those of mitochondria, chloroplasts and the endoplasmic reticulum [43] where some electrons passing through the chain "leak" directly from the intermediate electron carriers onto O_2. Since oxygen accepts one electron at a time, O_2^- is formed [44].

Superoxide anions are generated enzymatically by a number of oxidases, such as xanthine oxidase and the oxidase that is found in the plasmalemma of phagocytic cells [45]. Activated phagocytic cells (such as monocytes, neutrophils, eosinophils and macrophages including microglia) also produce superoxide, which plays an important part in the mechanism by which bacteria are engulfed and destroyed [46]. Thus excessive activation of phagocytic cells (as in chronic inflammation) can lead to free radical damage. The toxicity of superoxide is seen in its ability to inhibit certain enzymes and thereby attenuate vital metabolic pathways, as well as in its effects on other major classes of biological molecules [47].

Hydroxyl Radical: The $OH^{\bullet}$ radical is probably the most reactive of the ROS species [48- 49], as it can react with almost all molecules in living cells [50]. Hydroxyl radicals are short-lived and can be formed from O_2^- and H_2O_2 through the Haber-Weiss reaction or through the interaction of metals such as iron or copper and H_2O_2, through the Fenton reaction [51- 52], as shown in the equations below;

$$O_2^- + H_2O_2 \longrightarrow H_2O + OH^- + OH^{\bullet} \quad \text{Haber-Weiss Reaction (1)}$$

$$Fe^{3+} + O_2^- \longrightarrow Fe^{2+} + O_2$$

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + OH^{\bullet} + OH^- \quad \text{Fenton Reaction (2)}$$

The hydroxyl radical has been implicated in damage to proteins, carbohydrates, DNA, and lipids [45, 49, 53]. Action on DNA results in strand breakage and chemical alterations of the deoxyribose and of the purine and pyrimidine bases. A main physiological target of free radicals is the polyunsaturated fatty acids of cell membranes and the resultant degradation causes alterations in membrane structure and function [54].

Nitric oxide: Nitric oxide (NO) is a free radical released by several cell types, especially vascular endothelial cells and phagocytes. NO is formed by nitric oxide synthase (NOS). The process involves the conversion of L-arginine to L-citrulline [55]. Neurons produce NO mainly by a calcium-dependent activation of neuronal NOS (nNOS) [56].

NO has been suggested to be involved in both the normal functioning of excitatory amino acids such as glutamate and in the damaging effects produced by their generation in excess [57].

Peroxynitrite: The interaction of NO with superoxide radical leads to formation of peroxynitrite (ONOO-), a reaction that occurs at a threefold faster rate than that of the dismutation of superoxide by SOD [58].

$$O_2^- + NO^{\cdot} \longrightarrow ONOO^- + H^+ \qquad (3)$$

Therefore the formation of peroxynitrite depends on the concentration of superoxide and NO in the cell.

At physiological pH, peroxynitrite may be able to diffuse over several cell diameters to produce cell damage by oxidising lipids, proteins and DNA [59].

Figure 1 depicts the generation of oxygen free radicals which is an important contributing factor in several chronic human diseases, including atherosclerosis and related vascular diseases, mutagenesis and cancer, neurodegeneration, immunologic disorders, and even the ageing process.

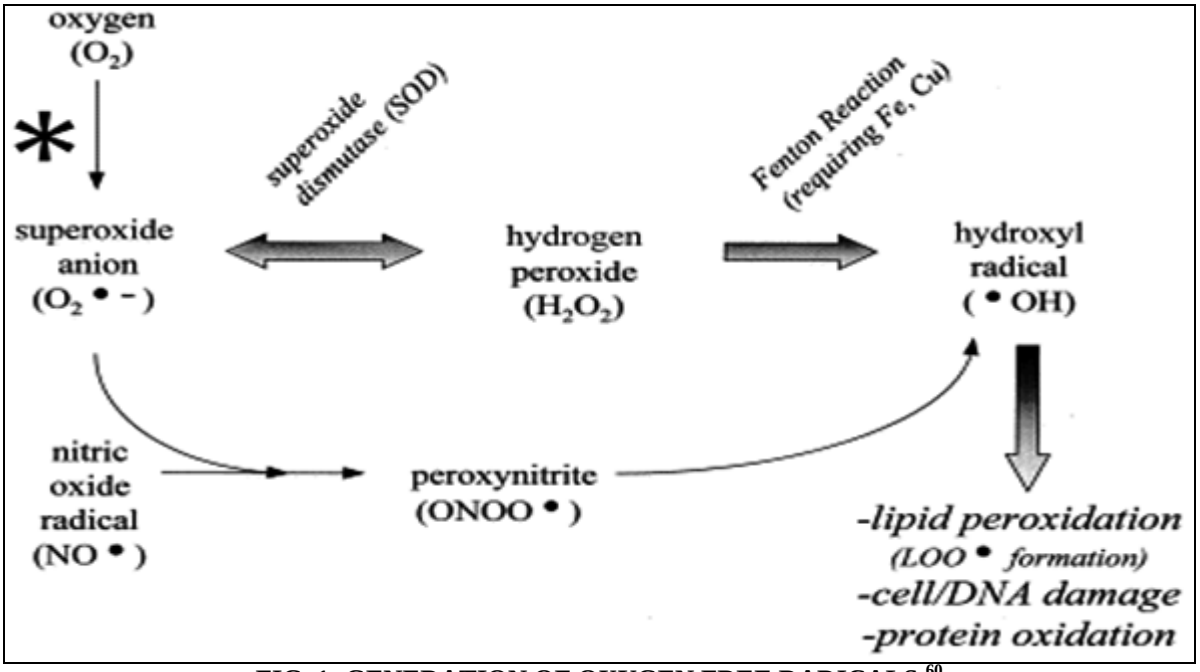

FIG. 1: GENERATION OF OXYGEN FREE RADICALS [60]

Effect of free radical and oxidative stress on ageing: Ageing is a universal process and yet it is a remarkably difficult phenomenon to define. One widely accepted definition of ageing is "the process(s) that occur during life which culminate in changes that decrease an individual's ability to handle biological challenges." Although the process cannot be stopped there are many physiological factors that can either advance or slow the ageing process. One of the most prevalent theories in aging research is the "free radical theory of aging", which was first proposed in the 1950s by Denham Harman. The basis of this theory is that oxidative damage accumulates in cells and tissues over time and contributes to the decline in physiologic function with age [61].

Effect of free radical and oxidative stress on Apoptosis: The term apoptosis was first used by Kerr *et al* in 1972 and is Greek in origin, meaning "dropping off" of petals or leaves from plants or trees [62]. Apoptosis or "programmed cell death" is a process by which cells undergo physiological cell death in response to diverse stimuli and is essential for normal biological processes such as morphogenesis, tissue homeostasis, and the elimination of damaged or virally infected cells, and may play a role in various pathologic and toxicological process [63].

Apoptosis differs from necrosis in the fact that apoptosis is an active process of cell destruction, characterized by intact plasma membranes, cell shrinkage and the formation of apoptotic bodies whereas necrotic cell death is often characterized by loss of membrane integrity, cell swelling and lyses [64].

The apoptotic process is caused by a cascade of events in which a family of cysteine proteases known as caspases are activated [65-66]. These proteins cleave key cellular substrates that are required for normal cellular function including structural proteins in the cytoskeleton and nuclear proteins such as DNA repair enzymes. The caspases also activate other degradative enzymes such as DNases, which begin to cleave the DNA in the nucleus [67]. The prominent molecular hallmark of apoptosis consists of nuclear fragmentation from chromatin condensation and internucleosomal DNA breakdown. **Figure 2** represents the deleterious events occurring in apoptosis.

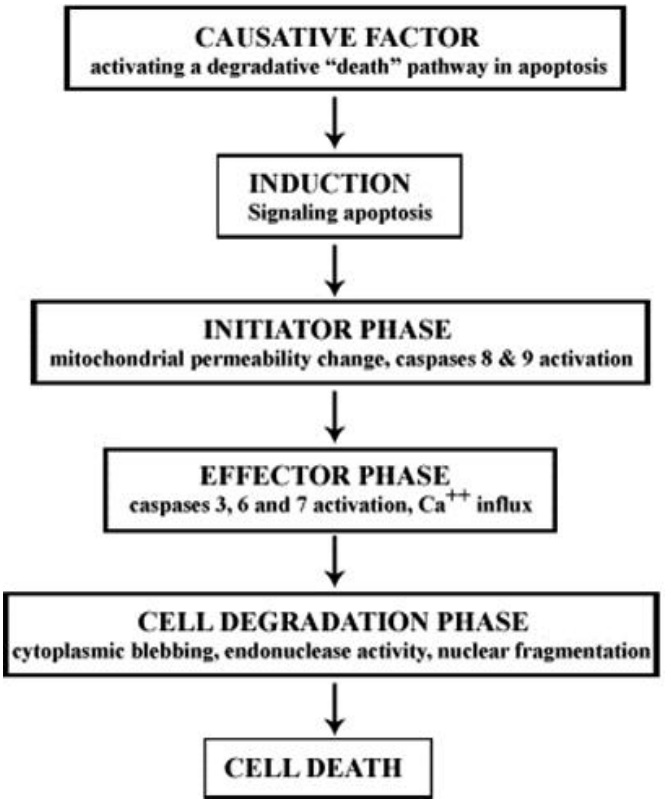

FIG. 2: PATHWAY REPRESENTING THE EVENTS IN APOPTOSIS [64]

Mitochondria have the ability to promote apoptosis through the release of proapoptotic factors such as cytochrome c, apoptosis-inducing factor (AIF), caspase -2 and -9 located in the intermembrane space of the mitochondria or in their matrix. These mediators lead to the activation of a caspase cascade and finally apoptotic death [64].

Mitochondria also contribute to apoptosis signaling via the overproduction of free radicals [68]. These reactive oxygen species can indirectly induce apoptosis by changing cellular redox potentials, depleting reduced glutathione, reducing ATP levels and these changes can accelerate the formation of permeability transition pores, leading to the subsequent release of cytochrome c.

Many *in vitro* and *in vivo* studies indicate the presence of apoptotic cell death in most of the neurodegenerative disorders such as Alzheimer's, Parkinson's and Huntington's diseases and amyotrophic lateral sclerosis (ALS). Apoptosis appears to be one of the mechanisms leading to the reduction in neurons in the substantia nigra of Parkinson's patients [69]. Dopamine was shown to induce apoptosis in several cell cultures, including chick sympathetic neurons [70] and human neuroblastoma cell line SH-SY5Y [71].

Selective degeneration of dopaminergic neurons of the SN, as well as DNA fragmentation, was reported in an MPTP-induced PD mouse model [72].

***Aloe vera* l.; a Natural Antioxidant:** Medicinal plants are an important source of antioxidants [73]. Natural antioxidants increase the antioxidant capacity of the plasma and reduce the risk of certain diseases such as cancer, heart diseases and stroke [74]. The secondary metabolites like phenolics and flavonoids from plants have been reported to be potent free radical scavengers. They are found in all parts of plants such as leaves, fruits, seeds, roots, etc. [75]. There are many synthetic antioxidants in use. It is reported, however, they have several side effects [76], such as risk of liver damage and carcinogenesis in laboratory animals [77-79].

There is therefore, a need for more effective, less toxic and cost effective antioxidants. Medicinal plants appear to have these desired comparative advantages. Therefore, there is a considerable interest in finding new and safe antioxidants from natural sources to replace these synthetic antioxidants [80].

Phytochemicals in *Aloe vera* L.: An analysis of *Aloe vera* reveals some magic behind its miraculous healing powers. The plant contains a multitude of essential vitamins and minerals such as: vitamins A, B1, B2, B3, B6, B12, C, E, folic acid, choline, calcium, phosphorous, potassium, iron, sodium, magnesium, manganese, copper, chromium, and zinc. *Aloe* also contains a wealth of amino acids: isoleucine, leucine, lysine, methionine, phenylalanine, threonine, valine, aspartic acid, glutamic acid, alanine, arginine, cystine, glycine, histidine, hydroxyproline, proline, serine, and tyrosine [81].

Free monosaccharides consisted of D-mannose and D-glucose in a molar ratio of 5:4 and trace amounts of xylose, rhamnose, galactose and either arabinose or fucose. Mannose 6 phosphate is a major sugar component in *Aloe vera* [26]. *Aloe vera* contains 75 potentially active constituents: vitamins, enzymes, minerals, sugars, lignin, saponins, salicylic acids and amino acids [82]. Additional minerals found in *Aloe vera* include copper (important for red blood cells, skin and hair pigment), iron (involved in oxygen transportation and making of hemoglobin in red blood cells), potassium (helps in fluid

balance), phosphorus (helps in building bones and teeth, assists in metabolism and maintains body pH) and sodium (regulates body liquids, helps in nerve and muscle performance, and helps in delivering nutrients to body cells). *Aloe vera* also contains the trace minerals rhodium and iridium used in cancer and tumor research experiments [83].

Another component of *Aloe vera* consists of the lignins, a major structural material of cellulose content that is helpful for penetrative properties and beneficial for skin problems such as eczema and psoriasis. The *Aloe* plant also contains flavonoids, terpenoids, lectins [24, 84], fatty acids, cholesterol, anthraquinones, chromones (8-*C*glucosyl- 7-*O*-methylAlodiol, 8-*C*-glucosyl-noreugenin, iso Aloeresin-D, iso-rabaichromone, neoAloesin-A) [85], mono and polysaccharides (pectins, hemi-celluloses, glucomannan, acemannan and mannose derivatives) [86-87], tannins, sterols (lupeol, campesterol and β - sitosterol), salicylic acid, organic acids, enzymes, saponins, vitamins, minerals [88], aloin, Aloeemodin (3-hydroxyl methylchrysazin), Aloetinic acid, choline and choline salicylate, complex mucopolysaccharides similar to hyaluronic acid, sapogenins and enzymes such as catalase, amylase, cellulase and alliinase.

Aloe vera leaves contain a range of biologically active compounds, the best-studied being acetylated mannans, polymannans, anthraquinone C-glycosides, anthrones and anthraquinones, and various lectins [24, 84, 89]. The ten main areas of chemical constituents of *Aloe vera* include: amino acids, anthraquinones, enzymes, minerals, vitamins, lignins, monosaccharide, poly-saccharides, salicylic acid, saponins, and sterols [83].

It is also reported that the main enzymes found in *Aloe vera* include amylase (breaks down sugars and starches), bradykinase (stimulates immune system, analgesic, antiinflammatory), catalase (prevents accumulation of water in the body), cellulase (aids cellulose digestion), lipase (aids fat digestion), oxidase, alkaline phosphatase, proteolytiase (hydrolyses proteins into their constituent elements), creatine phosphokinase (aids metabolism), and carboxypeptidase [83, 90]. Other constituents of *Aloe vera* would include prostaglandins, tannins, magnesium lactate, resins, mannins and proteins such as lectins, monosulfonic acid and gibberellins [83].

Anti-cancer actions: One of the common experimental cancer models is sarcoma-180. When *Aloe* was administered to mice bearing S-180 tumors, the tumor growth was inhibited [91-92]. Similarly, Alexin B, a specific molecule species derived from *Aloe*, was shown to possess anti-cancer activity against lymphocytic leukemia [92].

Additional investigations revealed that another molecular species derived from *Aloe*, Aloctin-A, had anti-tumor activity, but the action was to bolster the immune system rather than a direct anti-tumor activity [93].

The many studies carried out by Russian scientists have done more to establish a respectable place in modern medicine for *Aloe* than any other group of investigators. Whole leaf *Aloe* juice can reduce tumor mass and the frequency of metastases in rats [94].

Immune enhancing effects of whole leaf *Aloe vera* L.: Galactomannans are a class of long chain sugars derived from plants. It has been discovered that the *Aloe barbadensis* plant contains the greatest concentration of acetylated mannan which is also the most active form of mannans. This "acemannan" has been shown to have many effects in the body, mostly impacting on the gastrointestinal and immune systems.

The most striking commonality found in individuals suffering with immuno-depressive conditions (Epstein-Barr virus, Chronic Fatigue Syndrome, systemic candidiasis, HIV infection and others) is their high incidence of digestive dysfunction and maldigestion. This has several effects that contribute to stress on the immune system and therefore it's weakening.

Maldigestion means that the consumed food is not properly broken down into the elemental building blocks needed for the body to rebuild itself and to generate energy for metabolism. This results in a type of starvation at the cellular level, with all tissue suffering malnourishment and therefore decreased effectiveness of all internal chemical processes. These processes include breakdown and transport of toxins out of the cell, movement of nutrients into the cell, and energy production for cell functioning.

This affects all cells in the body, including those of the immune system such as white blood cells, (macrophages, monocytes, and lymphocytes) and red blood cells which carry oxygen.

However, it is not this cellular starvation alone that causes the immune depression. Maldigestion also results in partially digested food remnants which can be involved in several pathological reactions. First, these remnants become irritants and cause inflammation of the mucosal wall of the intestines. Many powerful enzymes and damaging chemicals are released, injuring the intestinal wall causing increased intestinal mucosal permeability. The foreign proteins of the digested food can then leak across the mucosa into the lymphatic channels of the intestinal wall and from there gain access to the circulation.

Here, these absorbed proteins are recognized as foreign and attacked by cells of the immune system. Antibodies bind to the protein and then call in macrophages and monocytes. T-cells arrive later, releasing enzymes and using oxygen to drive the metabolic breakdown of the foreign protein. The total result is that the immune system is constantly turned off and draining down like a battery. As these allergic reactions to food breakdown products continue, the cells of the immune system wear out faster, run out of fuel and aren't reproduced in sufficient numbers.

In addition to this chronic hyper immune state, undigested food remnants provide fuel for the overgrowth of fermentative fungal organisms such as Candida albicans as well as several types of parasites. Overgrowth of Candida in the intestine has significant effects throughout the body due to the absorption of toxic by-products of its metabolism. This can result in worsening of food allergies, hypoglycemia, digestive disturbances, excessive mucus, bloating, flatulence, skin rashes, and extreme fatigue. This chronic infection further drains the immune system and complicates the picture.

Further, damage is inflicted on all cell membranes from the effects of the generalized inflammation occurring as a result of maldigestion. These metabolic reactions utilize large amounts of oxygen and produce oxidative free radicals as waste by-products.

These negatively charged oxygen molecules are desperately trying to balance their electrical charge and immediately begin to chop holes in cell membranes as they grab positive charges. The result here is further damage to the intestinal mucosa and ever worsening of the increased permeability.

All these processes work together in a vicious sequence of events leading to progressive weakening of the immune system. It is clear that many mechanisms are at play in orchestrating these processes. Without definitive therapy directed at each component of immune system pathology, this is a downward spiral to death. Fortunately, a thorough multidimensional treatment protocol addressing each component has been shown to reverse these processes. Also, *Aloe* appears to play a key role on many different levels in boosting immune function.

As the biologic activities of Aloe derived acemannan have been elucidated, it has been shown to have a remarkable ability to normalize all of these damaging processes and therefore contribute significantly to the enhancement of immune system function. At the intestinal level, acemannan acts as a potent anti-inflammatory agent, neutralizing many of the enzymes responsible for damaging the mucosal wall; in effect, quenching the fire. This results in decreased leakiness of the intestinal wall and less absorption of allergic stimulating foreign protein.

Acemannan has direct virucidal, bactericidal, and fungicidal properties which can help control Candida overgrowth so that normal gastrointestinal bacterial flora can be restored. Acemannan also stimulates intestinal motility, helping to move allergenic proteins from the small intestine into the colon. All these processes help to normalize gastrointestinal wall structure and function and therefore stop the vicious cycle of immune system damage. Acemannan also has direct effects on the cells of the immune system, activating and stimulating macrophages, monocytes, antibodies and T-cells. It has been shown in laboratory studies to act as a bridge between foreign proteins (such as virus particles) and macrophages, facilitating phago-cytosis (ingestion of the protein by the macro-phage). This receptor site activation is a key component in boosting cell-mediated immunity

which is deficient in HIV infection. It increases the number and intensity of action of macrophages, killer T-cells, and monocytes, as well as increasing the number of antibody forming B-cells in the spleen. Acemannan also protects the bone marrow from damage by toxic chemicals and drugs such as AZT.

These various effects while seemingly widespread and unrelated, are in fact due to one simple process at the cell membrane level. Acemannan, a mucopolysaccharide, is a long chain sugar which interjects itself into all cell membranes. This results in an increase in the fluidity and permeability of the membrane allowing toxins to flow out of the cell more easily and nutrients to enter the cell. This results in improved cellular metabolism throughout the body and an overall boost in energy production. The vicious cycle of maldigestion and cellular starvation is finally broken as the acemannan normalizes absorption of nutrients and increases tolerance for allergenic foods**.** The immune system is now stronger, under control, and better prepared for any new threat.

As humans living in the late twentieth century, our bodies' metabolic and detoxification systems are under ever-increasing stress from foreign chemicals, nutrient depleted food, and immune damaging infectious agents. In order to control and prevent the inevitable progression of immune system destruction that these stresses cause, therapy must be multifactorial involving all levels of health, diet, and lifestyle. These different areas consist of destruction of pathogenic organisms, metabolic detoxification, intestinal cleansing, increasing cellular metabolism, antioxidant agents to combat free radicals, and direct stimulation of immune system cells.

Because of these versatile and comprehensive characteristics that concentrated whole leaf *Aloe vera* juice is strongly recommended in the treatment of immune deficiency disorders**.** It plays a prominent role along with other therapies, nutritional supplements, and medications in the multidimensional treatment of these illnesses. The healing powers of *Aloe* have been known for centuries, but now researchers have the scientific foundation that allows appreciation of this amazing plant and its important role in restoring and maintaining human health [36].

Management of diabetes & its complications: Diabetes is a prevalent systemic disease affecting a significant proportion of the population worldwide. The effects of diabetes are devastating and well documented. There is increasing evidence that in certain pathologic states, especially chronic diseases, the increased production and/or ineffective scavenging of reactive oxygen species (ROS) may play a critical role. High reactivity of ROS determines chemical changes in virtually all cellular components, leading to lipid peroxidation.

Production of ROS and disturbed capacity of antioxidant defense in diabetic subjects have been reported. It has been suggested that enhanced production of free radicals and oxidative stress is central event to the development of diabetic complications. This suggestion has been supported by demonstration of increased levels of indicators of oxidative stress in diabetic individuals suffering from complications. Therefore, it seems reasonable that antioxidants can play an important role in the improvement of diabetes [95].

Due to high prevalence, morbidity and mortality of diabetes, it is becoming the third leading cause of death worldwide after cancer and cardiovascular diseases. Chronic hyperglycemia often leads to complications such as renal failure, coronary artery disorder, cerebro-vascular disease, neurological complications, blindness, limb amputation, long term damage, dysfunctions and failure of various organs and eventually premature death.

Disease management includes lifestyle modifications, diet, exercise, and long term use of oral hypoglycemic agents or insulin therapy. Currently available synthetic antidiabetic drugs used in clinical practice have characteristic profiles of adverse side effects. Plant based drugs are considered to be less toxic and free from adverse effects in comparison to modern allopathic medicines.

Report of ethnobotany suggested that about 800 medicinal plants possess hypoglycemic or antidiabetic potential and the bioactive compounds such as glycosides, alkaloids, terpenoids, carotenoids and floavonoids are effective drugs both in preclinical and clinical studies [96].

Diabetes mellitus (DM), both insulin-dependent DM (IDDM) and non-insulin dependent DM (NIDDM) is a common and serious metabolic disorder throughout the world [97]. Diabetes mellitus is a very prevalent disease affecting the citizens of both developed and developing countries. It is estimated that 25% of the world population is affected by this disease. Diabetes mellitus is caused by the abnormality of carbohydrate metabolism which is linked to low blood insulin level or insensitivity of target organs to insulin [98].

It has been estimated that Indian people are more genetically prone to diabetes accounting about 30 to 33 million and would go up to 40 million by the end of 2010 which further will reach to maximum of 74 million by 2025 [99]. Despite considerable progress in the treatment of diabetes by oral hypoglycemic agents, search for newer drugs continues because the existing synthetic drugs have several limitations. The herbal drugs with antidiabetic activity are yet to be commercially formulated as modern medicines, even though they have been acclaimed for their therapeutic properties in the traditional systems of medicine [100].

Aloe vera gel at 200 mg/kg 1possesses significant antidiabetic, cardioprotective activity, reduces the increased TBARS (Thiobarbituric acid reactive substances), maintains the Superoxide dismutase and Catalase activity up to the normal level and increases reduced glutathione by four times in diabetic rats [101]. The leaf pulp extract showed hypoglycemic activity on IDDM and NIDDM rats, the effectiveness being enhanced for type II diabetes in comparison with glibenclamide [102]. So that herbal drugs are gaining popularity in the treatment of diabetic mellitus [103]. The major advantages of herbal medicine seem to be their efficacy, low incidence of side effects, and low cost.

***Aloe vera* l.; its Antimicrobial properties:** The leaf pulp and liquid fraction of *Aloe vera* act against various microorganisms [104]. The Chinese describe aloe's skin and the inner lining of its leaves as a cold, bitter remedy which is downward draining and used to clear constipation due to accumulation of heat; the gel is considered cool and moist. In Ayurvedic medicine of India, *Aloe* is used internally as a laxative, antihelminthic, hemorrhoid remedy and uterine stimulant (menstrual regulator); in combination with licorice root, to treat eczema or psoriasis [105]. Furthermore, activity against a variety of infectious agents has been attributed to *Aloe vera*; for instance, antibacterial [106], antiviral [107] and anti-fungal [108].

Despite the therapeutic possibilities of this plant, there have been limited reports on the antimicrobial effects of isolated *Aloe vera* components. *Aloe vera* leaf gel can inhibit the growth of the two Gram-positive bacteria *Shigella flexneri* and *Streptococcus pyogenes* [106].

Specific plant compounds such as anthraquinones [109-110] and dihydroxyanthraquinones [111], as well as saponins[112], have been proposed to have direct antimicrobial activity. Acemannan, a polysaccharide component from whole plant material, has been proposed to have indirect antimicrobial activity through its ability to stimulate phagocytic leukocytes [113]. Effect of the anthraquinone aloe emodin on arylamine N-acetyl transferase activity in *Helicobacter pylori* have also been reported, showing its antimicrobial activity [114].

CONCLUSION: There has been an increase in demand for the phytopharmaceuticals all over the world. The information shared in this review update on *Aloe vera* leaf gel might be fruitful for better understanding in the direction for search of plant origin drugs either as antioxidant which helps to fight from so many problems as discussed in detail in this review or as antimicrobial. After looking on the fact that most of microbial strains are continuously being resistant to most of the synthetic/allopathic drugs, there is a necessity of the search for the drug of natural or herbal origin. *Aloe vera* might be a wonder herb as antioxidant and antimicrobial.

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