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Biomaterials based nano-applications of Aloe vera and its perspective: A review

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REVIEW ARTICLE

Biomaterials based nano-applications of Aloe vera and its perspective: A review

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Aloe vera is noted for its meritable medicinal as well as commercial usages. From the past until now, it has been using as a promising remedy for several ailments. Recently, the concept of nanotechnology has astonishingly changed its outlook for biomedical applications. Nanotechnology has revolutionized several fields with its admirable capabilities and ground-breaking innovations. In the field of medicine, nanostructured materials have introduced great range of flexibility by refashioning traditional practices and also by exploring new effective approaches. Accordingly, the usage of *Aloe vera* in the form of hydrogels, nanoparticles, nanocomposites, nanofibers and bio-inspired sponges has extended its well established application spectrum in the field of wound healing, tissue engineering and drug delivery. In addition, the growing interest in consuming and synthesizing materials based on green or eco-friendly methods also highly encourages the usage of numerous plant-based natural products including *Aloe vera*. Hence, an effort has been made to discuss the works related to recent advancements made in the use of *Aloe vera,* especially in the form of biomaterial-based nanostructures. This will encourage the scientists to explore the unplumbed abilities of *Aloe vera*. Moreover, it will also help the industry players to recognise its immense potential and bring significant aloe products to the market.

1. Introduction

Centuries ago, humans depended on several natural products which cuddles rich nutrition as well as medicinal content. They used these products to satisfy all their basic needs such as food, shelter, medications, etc. Over the course of time, with the development of civilization and the evolution of new technologies, humans began to modernise their lifestyle which leads to the loss of information about numerous natural products. But there are still some plants which are currently used for several of the purposes as they were in ancient days. *Aloe vera* is one such plant which has many applications, even in this modern world. *Aloe vera* belongs to the genus called *Aloe,* which is reported to have approximately 420 species [1] and it comes under the *Liliaceae* family. The botanical name of *Aloe vera* is *Aloe barbadensis miller*. Basically, it is a short-stemmed, perennial, drought-resisting, succulent plant which is evenly distributed across warm areas of the world [2]. The geographical origin of *Aloe vera* is reported to be the Sudan, but it subsequently spread to Mediterranean regions and now it exists in various countries across the world. *Aloe vera* is believed to have been used in medical practice from the early days of the human race and hence it is thought to have a longer history of relations with humans than any other flora.

The first authentic record about the usage of *Aloe vera* for healing purposes is mentioned in the Mesopotamian clay tablet dated 2100 BC. Later a document in "Egyptian medical papyrus of herbal knowledge" dated 1550 BC is reported to have the detailed depiction of its medicinal value and abilities to cure both external and internal ailments. The Egyptians had quoted *Aloe vera* as the "Plant of Immortality". Further, the "Greek Herbal of Dioscorides" dated 70 AD contains a detailed insight about *Aloe vera* flora and its vital role in treating wounds [3, 4]. Since biblical times *Aloe vera* has been comprehensively used by the Egyptians, Assyrians and Mediterranean civilizations as remedies for hair loss, genital ulcers haemorrhoids, wounds and various skin disorders [2]. At the start of the 18th century, *Aloe vera* was officially recommended by the U.S. pharmacopoeia as an effective purgative and skin protectant. Moreover, the first clinical use of *Aloe vera* for the treatment of radiotherapy burns and mucous membranes was reported in 1930. From the early ages of the human race until now, *Aloe vera* has been exploited for various health related applications in traditional medical methods of countries like India, China, Malaysia, West Indies, South Africa, and Japan [2, 5-7]

[a] *Address here.*
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Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

The bioactive compounds present in *Aloe vera,* especially those in *Aloe vera* gel, have been exploited for various applications which fall into the following clusters, namely: cosmetic, healthcare and food industry (which is detailed in section 3). For usage in the above mentioned industries, *Aloe vera* is commercially cultivated in the United States, Mexico, India, China, Japan, Kenya, Bangladesh, South Africa and Australia [8-11]. Hence, the commercial value of *Aloe vera* based industries is increasing these days. The International Aloe Science Council (IASC) estimates that the sales of *Aloe vera* raw materials are $70-90 million currently, with an anticipated growth of 35% expected within next five years. In the mid-1990s the total sales value of products containing *Aloe vera* derivatives and ingredients was reported to be $1 billion; since then it has grown continuously and now it is estimated to be over $35 billion globally [12].

Nowadays, the active components present in *Aloe vera* has gained great attention in several biomaterials and nanotechnology-based medical applications. Biomaterials are viable materials intended to assist or replace desired systems in our body. Metals, ceramics, polymers, composites and few natural substances are common types of biomaterials which have been utilized for various medical applications. However, the overall efficiency of a biomaterial is greatly influenced by its physical, chemical, mechanical and biological properties [13]. But the advent of nanotechnology has appreciably altered the problems associated with biomaterials by improving their physicochemical and mechanical properties. Further, it has also opened doors for utilization of biomaterials in several nanostructures like nanoparticles, nanocomposites, nanofibers, nanocapsules, nanorods etc., [14]. Recently, awareness about the benefits of exploiting natural substances has paved a way for the incorporation of *Aloe vera* in those modernized systems. Accordingly, a reasonable number of research papers have been published about the use of *Aloe vera,* along with its applications in combination with both synthetic and natural materials for wound healing, drug delivery systems and tissue engineering applications. Researchers observed that the addition of *Aloe vera* has extensively improved the overall efficacy of the resultant product. So, in this review we have made an effort to summarize and discuss in detail the work reported on the usage of *Aloe vera* in modern biomaterials and nanoformulation systems. In the following subsections, we have provided a brief insight into the vital components present in *Aloe vera* and its typical applications.

2. Chemical constituents and its biological properties

World Health Organization (WHO) has reported that *Aloe vera* is the most biologically active flora among all the 420 *Aloe* species [15]. It has 75 potentially active constituents and the entire goodness of *Aloe vera* lies in its leaf, which can be divided into three parts: the thick protective outer layer; the thin yellowish middle layer; and the fleshy inner layer [16]. The outer layer is about 15-20 cells thick with saw-toothed small white spikes at the margin. The main function of the outer layer is to protect the inner portion from natural attacks, and recently it has been reported to have a high proportion of α-cellulose and also inferred to play a vital role in the synthesis of carbohydrates and proteins. The outer layer does not contain many nutrients, unlike the other two layers [17-19]. Immediately under the skin there lies a thin yellowish latex-like part which is called the bitter middle layer. It accommodates anthraquinones, aloe-emodin, aloetic-acid, anthranol, aloin A and B (collectively known as barbaloin), isobarbaloin, emodin, ester of cinnamic acid and glycoprotein. Aloin is generally prescribed for constipation and gastric problems since it is believed to interfere with the water reabsorption function of the colon which results in softer stools. But at higher doses it is observed to cause electrolyte imbalance, diarrhoea and abdominal pain due to adverse reactions of the components present in aloin [20, 21]. Furthermore, it is stated to cause irritations to normal cells when consumed orally as well as when used directly on the skin. On the other hand, the glycoproteins are reported to promote wound healing by boosting cell proliferation and aloe-emodin has purgative, antiviral, antibacterial and anticancer properties.

Almost 90% of *Aloe vera's* beneficial ingredients are accumulated in the white-opaque, fleshy, jelly-like innermost portion. The inner gel is made of water (99%) and the rest contains essential amino acids, glucomannans, minerals, lipids, vitamins, polysaccharides, major polypeptides, proteins and antioxidants [22-24]. The sugars (monosaccharides and polysaccharides) make up 25% of its essential ingredients; it comprise glucose, cellulose, mannose, aldopentose, pectic substances, acemannan, polymannose, acetylated glucomannan and mannan. These sugars are also called mucosaccharides since they are plant-derived. The sugars are reported to have excellent anti-inflammatory, anticancer, anti-allergic, antimicrobial and antitumor properties. Vital minerals such as calcium, chromium, copper, iron, selenium, magnesium, manganese, phosphorous, chlorine, potassium, sodium and zinc are highly essential for proper functioning of various enzymes involved in metabolism and maintaining good health. Few minerals have been employed as an effective antioxidant, antibacterial and antipuritic agent.

Furthermore, *Aloe vera* has been identified to contain sixteen distinct enzymes, namely amylase, carboxypeptidase, catalase, cyclo-oxygenase, lipase, oxidase, anthranol, barbaloin, alkaline phosphatase, phosphoenolpyruvate carboxylase, superoxide dismutase, chrysophanic acid, smodin, resistannol, bradykinase and cellulose. The above-mentioned enzymes are widely employed for antibacterial, antifungal, antiviral, anti-inflammatory and analgesic (bradykinase) purposes. In addition, a few enzymes are also observed to be involved in the breakdown of sugars and fats. More importantly, it embraces 20 of 22 essential amino acids required by the human body and seven of eight amino acids which our body cannot synthesise naturally. The amino acids present in *Aloe*

vera are reported to play a crucial role in reconstructing damaged tissues during the process of wound healing. In addition, lectin (protein) present in *Aloe vera* is reported to promote cell proliferation. Similarly, the plant-derived lipids and steroids such as arachidonic acid, γ-linolenic acid, campesterol, lupeol, campestrol, cholesterol, β-sitosterol, triglycerides, triterpenoid and lignins have been utilized as anti-inflammatory, antiseptic and analgesic agents. Vitamins B12, folic acid, choline, B (thiamine), B2 and B6 are utilized as an effective antioxidant and anticancer agents. A few vital vitamins present in the daily diet, such as vitamins A (beta-carotene), B1, C and E are also available in *Aloe vera*. On the other hand, salicylic acid (aspirin-like substance) and the hormones (auxins and gibberellins) present in *Aloe vera* possess anti-inflammatory and antibacterial properties [25-29]. The key constituents of *Aloe vera* and their corresponding biological properties are given in figure 1.

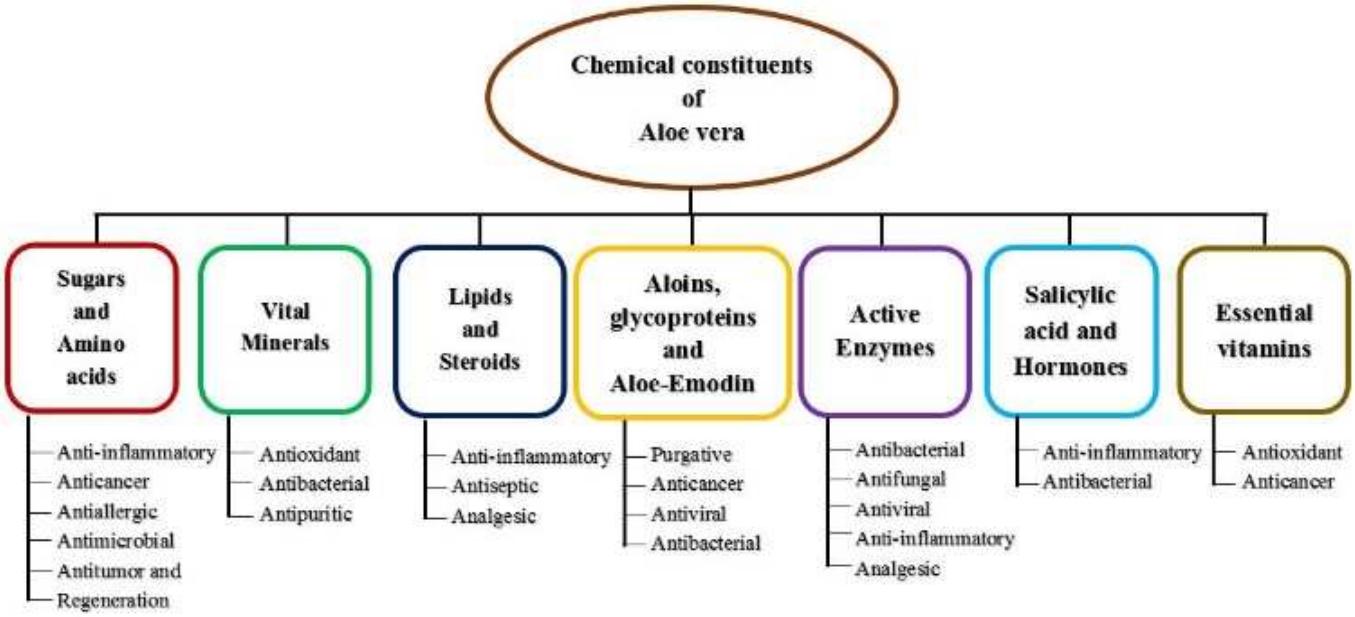

Figure 1: Chemical constituents of *Aloe vera* and its biological properties

3. *Aloe vera* and its typical applications

As mentioned in the introduction, the bioactive compounds of *Aloe vera* have been employed for various applications in cosmetic, healthcare and food industries. In cosmetics industries, *Aloe vera* is used as a base substance for skin moisturizers, hair gels, soaps, shampoos, sun-lotions, perfumes, shaving creams, facial gels, hand washes, hand and facial tissues [30, 31]. In the medical arena, the active compounds have found copious applications in treating burns, radiation dermatitis, wound dressings, allergies, arthritis, rheumatic fever, ulcers, diabetes (type 2), skin diseases, rashes, inflammation, splenopathy, constipation, asthma, jaundice, span menorrhea, abdominal tumors, dropsy carbuncles, sciatica, gastric problems, cancer prevention and dysentery [2, 10, 32, 33]. Meanwhile, it also serves as the principle ingredient in various ointments, bandages (Acemannan Hydrogelk, Carrasyn^{R}), tablets and gels [34]. Similarly, it also gained great significance in food industries which manufacture health drinks, beverages, bitter agents and functional foods [35].

Inspired by the presence of abundant active components, copious research has been carried out utilizing *Aloe vera* in the form of an extract, especially aloe gel for topical as well as oral administration. *Aloe vera* is highly utilized for topical covering of wounds and ample efforts were taken to study the healing mechanism induced by *Aloe vera* extract. Studies carried out on an animal model (guinea pig) revealed that biologically active components present in *Aloe vera* had the ability to improve oxygenation by increasing blood supply which in turn increased the speed of growth of new cells [36-39]. Also, it was reported to promote endothelial cell proliferation, the formation of new vascular tubes (angiogenesis) and encourage regeneration of tissues. Further, the fibroblast receptors present in *Aloe vera* were observed to increase fibroblast cell adhesion and subsequently led to the formation of extracellular matrix components such as collagen and hyaluronic acid, which have great potential to form new endothelial layers [40, 41]. Likewise, a few works disclosed the ability of *Aloe vera* to heal the effects of chemotherapy by encouraging the recovery of normal immune cells damaged during treatment. This creates appreciable chances to extend the life span of cancer patients [42-45]. Thomson *et al* witnessed the capability of emodin, a type of anthraquinone present in aloe sap, to inhibit the growth of malignant cancer cells [46]. Currently, the idea of nanotechnology and usage of biomaterials has upgraded its perspective and creates a platform for extensive usage.

4. Biomaterials and nanotechnology based applications of *Aloe vera*

Biomaterials have gained significant attention over the last 30-35 years as a possible material to treat and aid diseased parts. Until now they have found thousands of applications in the medical arena, ranging from imaging to repairing or replacing tissues. Though biomaterials have pronounced characteristics, a prerequisite still exists to design these materials in an effective manner with commendable mechanical, physicochemical and biological properties [47, 48]. Nanotechnology has emerged as a plausible approach to achieve these objectives. It has shown massive potential in its development in exploring new techniques as well as in expanding its application spectrum. The term nanotechnology describes the creation and exploitation of materials whose structural features are reported to lie in between atoms and bulk materials. A nanometre (nm) is approximately equivalent to the length of 10 hydrogen or 5 silicon atoms aligned in a line which means it is very minute and imperceptible. Nanoscale engineering has enabled researchers to influence macromolecular or even molecular scale properties of biomaterials which have improved their precision in both diagnostic and therapeutic fields. Further, nanophase materials have been produced to acquire enhanced surface and biological properties compared to their conventional counterparts with similar material chemistry [49, 50]. For medical applications, nanostructures in the form of nanocomposite, nanotubes, nanorods, nanospheres, nanoparticles and nanofibers have been extensively experimented for imaging, delivering growth factors, carrying genetic materials and drug agents [51, 52]. Accordingly, in recent days researchers have utilized *Aloe vera*, one of the most ancient medicinal plants, in combination with modern biodegradable biomaterials and proficient nanostructures for the purpose of wound healing, tissue regeneration and drug delivery applications respectively (figure 2).

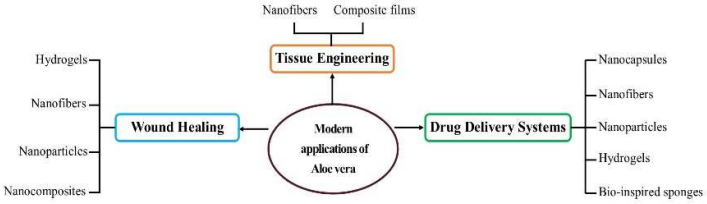

Figure 2: Nanotechnology and biomaterial based applications of *Aloe vera*

4.1 Wounds and burns Healing

Skin is the largest protective organ of the human body; it safeguards the internal organs by confining the incursion of microbes and other hazardous stuff. Some fatal human activities or exposure to extreme conditions may damage the skin by causing wounds, burns or ulcers with minimal to extreme loss of extracellular matrix either in the epidermal or the dermal region [53, 54]. The impairment which happens to the skin is collectively called an injury; as soon as skin encounters any sort of injury our body will start working on the restoration process which is generally termed healing. Nevertheless, the process of healing is complex and varies depending on the extent (epidermal, superficial partial-thickness, deep partial-thickness and full-thickness wound) and the type of damage (burns, lesions, acute and chronic). Though our body naturally starts the recovery process some medication in the form of gels, bandages or ointments will be generally be used to assist or hasten healing. The medication offers protection against the attacks of microbes and also enhances the healing process by releasing substances to promote haemostasis, proliferation and by reducing inflammation [55, 56].

The extract of *Aloe vera* has been extensively used since ancient times for its well-known anti-inflammatory, antiseptic and antimicrobial properties; in particular, the sugars (polysaccharides) present in *Aloe vera* are reported to act as an excellent wound healing agent. Hence, the extract has been preferred for both oral and topical applications [16, 57]. As the technology developed, the traditional way of using aloe extract for various applications also upgraded. *Aloe vera* coupled with biomaterials has gained interest as it can be easily tailored and transformed based on the requirements. Since most biomaterials, especially the biodegradable polymers are biocompatible in nature and they disappear once the healing process is over; meanwhile they also establish optimum conditions required for the recovery process. In this section, works available on the exploitation of *Aloe vera* extract in the form of hydrogels, nanoparticles, nanocomposites and nanofibers for wound healing applications is discussed. Further, a graphical representation of *Aloe vera* based wound healing materials is illustrated in figure 3.

4.1.1 *Aloe vera* in the form of hydrogels

Hydrogels are three-dimensional polymeric networks which are highly hydrophilic in nature and also have a peculiar ability to absorb as well as retain large amounts of water (swelling) when immersed in a liquid or biological fluids without dissolution. They can be made from both synthetic and natural polymeric substances. Hydrogels have several applications in wound healing, regeneration, and drug delivery systems because of their good biocompatibility, better surface properties and ability to load more drugs [58-60]. Various natural and synthetic polymer-based hydrogels loaded with drugs have been extensively used for a wide spectrum of wounds [61]. Pereira *et al* scrutinized the ability of sodium alginate (SA) -*Aloe vera* (AV) hydrogels to stimulate wound healing by employing both fresh and dried flakes of aloe gel available in the market. In both cases, the researcher used a

solvent-casting method to obtain different forms of alginate-aloe hydrogels.

Generally, alginate has a good reputation for the treatment of different degrees of wounds because of its excellent haemostatic nature, good elasticity and ability to maintain a moist environment which favours the healing process. Initially, the fresh Aloe vera gel obtained from healthy leaves and finely ground into a homogenous mixture was used. Then, the mixture was made into hydrogels by a cast/solvent evaporation method with 6% and 12% of AV, respectively. The formed hydrogel was cross-linked with $CaCl_2$ and then the samples were dried. The crude sodium alginate hydrogel was considered as the control against the SA-AV hydrogel. Various mechanical and physicochemical characterization studies show the addition of AV alters the thickness, moisture content and thermal properties of the hydrogel. Further, the Fourier transform infrared spectroscopy (FTIR) analysis confirms the establishment of chemical interactions between SA and AV, which is more apparent in hydrogel containing 12% aloe gel. Interestingly the addition of AV positively increases the strength of the hydrogel and the maximum force at break value was observed in the hydrogel with 12% AV. Nevertheless, 12% AV also decreased the flexibility of the hydrogel by making it more brittle while the hydrogel with 6% AV exhibited better elongation as well as a considerable maximum force at break value. Scanning electron microscope (SEM) images revealed an increase in surface roughness with the increase in AV content. Meanwhile, *in vitro* tests show the degradation rate was decreased with increasing additions of *Aloe vera* which ensures prolonged medication from the prepared hydrogel at the site of injury [62].

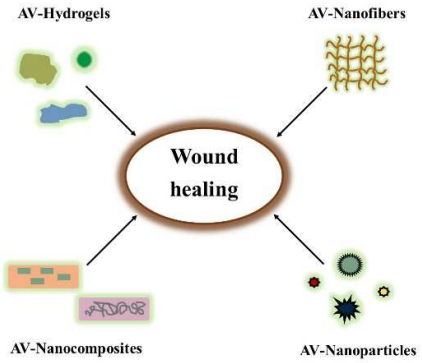

Figure 3: Modern forms of *Aloe vera* for wound healing

In their next work, the researchers used dried flakes of *Aloe vera* gel available in the market to form hydrogels. As with their previous research, they used a solvent-casting method to synthesize sodium alginate hydrogels with 5%, 15%, and 25% AV, respectively. In addition, they also cross-linked the hydrogels with $CaCl_2$ but this time the characterization studies were done by using both wet and dry hydrogel samples. The observations once again confirmed that the addition of *Aloe vera* significantly improved mechanical and physicochemical properties of both wet and dry cross-linked hydrogels when compared with non-cross-linked one. From this inference, it can be suggested that dry and wet hydrogels can be employed for both exuding and dry painful wounds respectively [63].

Hydrogels were also reported to have been generated from a mixture of *Aloe vera* and synthetic polymers. Park *et al* used *Aloe vera*, poly (vinyl alcohol) (PVA) and poly (N-vinylpyrrolidone) (PVP) mixture for the formation of a hydrogel by a two-step process of freeze-thaw and gamma-ray irradiation. They used fresh *Aloe vera* gel and the concentration of *Aloe vera* in the PVA-PVP-AV mixture was about 15%. Then, the mixture was exposed to different doses of 25, 35 and 50 kGy gamma radiation and the freeze-thaw was repeated up to 3 times to crosslink the PVA/PVP/AV solution physically to produce hydrogels. They observed that the swelling behaviour of the hydrogel increased with increase in *Aloe vera* content and decrease in radiation dose. In contrast, an increase in *Aloe vera* gel decreases the gel strength, whereas it was perceived to increase with radiation dose and number of freeze-thaw cycles. The *in vivo* studies conducted using rats clearly demonstrated the ability of PVA-PVP-AV hydrogel in improving the wound healing time. The results using a synthesized hydrogel were compared with groups which received normal wound dressings and commercially available urethane membranes respectively. They inferred that PVA-PVP-AV hydrogel was able to heal the wound completely within 15 days, even in the absence of pre-dressing. Inspired by the above results the researchers stated that *Aloe vera* based hydrogel can be considered as a plausible candidate for the application of wound healing [64].

In both synthetic and natural hydrogels, the addition of AV has been reported to influence the mechanical properties, water absorption ability, and drug release kinetics. However, after a certain concentration it was observed to produce some negative effects by making the hydrogel more brittle and hard. So, care should be taken while choosing the optimised concentration in favour of both physicochemical and would healing properties of the hydrogel. *Aloe vera* based hydrogels have also demonstrated dedicated properties such as sustained medication, maintaining a moist environment, absorbing wound debris etc., needed for the healing of painful dry wounds in moderate burn injuries.

4.1.2 *Aloe vera* in the form of nanofibers

Generally the products used for wound healing are in the form of gels, ointments, films and other woven materials commercially available. Although the above products yield a good outcome, they don't improve the skin regeneration process since they block gas exchange, waste excretion and

fails to deliver temporary support. But the usage of nanofibrous mats is reported to reduce these complications; in addition it provides nutrient infiltration and scaffolding aid. The introduction of an electrospinning technique has made the fabrication process simpler and also allows the assimilation of various substances (natural and synthetic) into a single system [65, 66].

Mary *et al* fabricated a potential wound healing nanofibrous scaffold by electrospinning of polycaprolactone (PCL) - *Aloe vera* mixture. The investigators used commercially available *Aloe vera* extract in powder form and fabricated four distinct fibrous mats with 0%, 5%, 10% and 15% *Aloe vera* along with PCL. Initially, PCL and AV powder was made into a homogenous mixture with the help of a concentrated chloroform-methanol solution. Then, the electrospinning process was carried out using an appropriate method which yields high porous scaffolds with fewer beads. The impact of the *Aloe vera* incorporation was diligently analysed through various physicochemical, mechanical and *in vitro* studies. The FTIR graph displayed the aromatic vibrations of active substances in *Aloe vera* which confirmed their presence in electrospun mats. Further, XPS, XRD, and TGA studies revealed changes in the crystalline structure and thermal stability induced by addition of *Aloe vera*. Similarly, *Aloe vera* addition, especially the sample containing 15% AV, produced a significant improvement in hydrophilic properties of PCL which was inferred through contact angle and wettability studies. Meanwhile, the mechanical and *in vitro* degradation studies show that strength and the solubility of samples are directly proportional to the concentration of AV.

More interestingly, the PCL containing 15% *Aloe vera* improved the attachment and proliferation of human dermal fibroblast cells which was clearly observed from the results of FESEM and MTS assay. Hence, they recommended that the proposed scaffold can be effectively employed for wound healing application [67]. In a different study, Uslu *et al* synthesized electrospun nanofibrous mats from a blend of polyvinyl hybrid polymers, *Aloe vera* and hydroxypropyl methylcellulose (HPMC). In this research, they used a series of polyvinyl polymers such as PVA, PVP and poly (ethylene glycol) (PEG). *Aloe vera* gel was added at different concentrations in the form of a solution (2 wt %) along with HPMC (2 g) to improve the water retention capacity of the fibrous scaffold. The physicochemical characterization shows the addition of *Aloe vera* positively alters the solution conductivity and viscosity. It results in the formation of fibrous mats without beads. FTIR studies confirm the presence of the PVA/PVP/PEG/AV structure by displaying characteristic stretching and DSC thermograms which clearly pictured the increase in melting point and the formation of an amorphous structure due to efficient cross-linking of hybrid polymers induced by *Aloe vera*. Finally, the SEM micrographs illustrate a decrease in fibre diameter with increasing AV content. Furthermore, the formation of a nanofibrous scaffold with fewer beads leads to an increase in porosity which will encourage oxygen penetration, maintain a moist environment and also prevent infiltration of microbes [68].

In a follow-up, the researcher used the same substances as the previous study (PVA/PVP/PEG/AV/HPMC) with the addition of poly (acrylic acid) (PAA). This time, they used *Aloe vera* solution in the following concentrations: 1%, 6%, and 10%, which resulted in fabrication of four distinct scaffolds including one control. As expected the characterization studies showed good results; additionally the fibrous mat containing 10% AV showed decreased fiber diameter and less bead formation than other samples. According to their observations, the distribution of fiber diameter size in the 10% AV system was between 60 and 280 nm, with an average diameter of 159 nm [69]. The researcher also suggested that the proposed system can be plausibly utilized to treat burn injuries.

AV incorporation has altered pore size, fiber diameter, mechanical strength and degradation of nanofibrous mesh based on its concentration. Moreover, its fibrous structure serves as a platform for gas exchange and waste materials elimination, and more importantly it avoids infiltration of microbes thereby exhibiting a captive scaffolding environment for the wounded cells to rehabilitate. These properties were observed to play a significant role in the *in vitro* proliferation of HDF cells. Hence, AV coupled nanofibers can be plausibly utilized for severe injuries like burn wounds and ulcers, especially in diabetic patients where prompt healing is required.

4.1.3 *Aloe vera* in the synthesis of nanoparticles and nanocomposites

Presently, manufacturing of materials using eco-friendly methods especially by consuming biological substances, microbes and plants have gained more attention rather than chemical and physical methods as they are very complex and hazardous to health. In accordance with the above trend, researchers started exploring several eco-friendly ways to synthesize various materials, including nanoparticles and nanocomposites. They revealed that plants have an immense ability to biosynthesize various substances in a simpler and more effective manner when compared to existing methods. Unlike chemical methods, they don't elicit serious side-effects; further the materials obtained by biological methods are bio-compatible in nature. *Aloe vera* has been experimented with as a reducing agent to green synthesize various nanoparticles and nanocomposites which can be effectively used against injuries [70, 71].

Silver nanoparticles (Ag NPs) are well-recognised for their effective antibacterial properties as well as a wide range of antimicrobial activities. Although the mechanism is highly complex, many researchers managed to determine that when Ag NPs encounter with specific receptors present on microbes

they release silver ions. As a consequence, this process causes de-energization of the cells, leakage of cellular content and disruption in DNA replication which eventually leads to lysis. The usage of Ag NPs synthesized by chemical methods was reported to elicit some adverse effects. So most of the research reported till now on utilizing AV as a reducing agent has mainly concentrated on the green synthesis of Ag NPs [72-74]. Zhang *et al* successfully produced AV conjugated Ag NPs by using *Aloe vera* pulp extract as a reducing agent. The research group used fresh leaves of AV to obtain the extract and for nanoparticles synthesis 5 mL of 10 mol/L $AgNO_3$ solution was added to 5 ml of extract. The crystalline structure of AV conjugated Ag NPs was confirmed by XRD analysis and the TEM images showed that nanoparticles were spherical in shape with a size of 25 nm. Meanwhile, the cytotoxicity and antibacterial properties of nanoparticles were analysed using human dermal fibroblast (HDF) cells and *E.coli* cells respectively. The results of MTT assay states that at lower concentrations (10-50 µmol/L) the nanoparticles didn't display significant cytotoxicity but at higher concentrations (100-500 µmol/L) cytotoxicity was observed. Similarly, the antibacterial activity of nanoparticles was observed to increase with increases in AV concentration; further, *Aloe vera* conjugated Ag NPs exhibited higher reactivity than other controls (*Aloe vera* extract and Ag NPs washed from AV solution) [75].

In another work, Yuvasree *et al* demonstrated the antimicrobial activity of green synthesized silver nanoparticles against *E.coli* and *Bacillus* species. In this work, gel (20 ml) obtained from the fresh leaves of *Aloe vera* plant was utilized to reduce silver nitrate solution (20 ml). The reduction of Ag ions was detected using UV-Vis spectrophotometry and the synthesis of Ag NPs was confirmed by XRD analysis. SEM studies were carried out to analyse the structure and shapes of nanoparticles. Finally, antimicrobial studies performed on *Pseudonomous aeruginosa* (Gram negative bacteria) and *Staphylococcus aureus* (Gram- positive bacteria) indicated the zones of inhibition which express the presence of antibacterial activity [76]. Likewise the antimicrobial and antifungal studies performed by Medda *et al* and Hashoosh *et al* using biosynthesized Ag-AV nanoparticles also supported enhanced activity [77, 78]. In a different study, Chandran *et al* synthesized triangular gold and spherical silver nanoparticles by using the reduction ability of AV extract. The extract obtained from the leaves of Aloe flora was added to chloroauric acid ($HAuCl_4$) and silver nitrate ($AgNO_3$) at different concentrations. The physicochemical characterization studies carried out using FTIR, XRD, TEM, UV-Vis, and AFM confirmed the presence of gold and silver nanoparticles. Additionally, they observed that the concentration of AV plays an important role in determining shapes and size of nanoparticles [79].

Similarly, the potential of AV extract in synthesizing nanocomposites through biological methods was demonstrated by Ayeshamariam *et al*. The researchers used a commercially available powder form of AV extract. The dried form of the nanocomposite was obtained from the solution containing 1g of In_2O_3, ZnO and AV powder. Positive changes in mechanical, electrical and crystal properties made by the addition of AV were witnessed through several characterization studies (XRD, SEM, TEM and UV-Vis). In addition they studied antibacterial and antifungal properties of the nanocomposite using a series of strains like *S. aureus* (MTCC-737), *S. pyogenes* (MTCC-1923), *P. aeruginosa* (MTCC-3542), *E. coli* (1576), *S. typhi* and *A. niger* (MTCC-1344), *A. flavus* (MTCC-1973), *A. fumigatous* (MTCC-2132), *Rhizopusindicus* and *Mucorindicus* (MTCC-918), respectively. As expected, a higher zone of inhibition was noted in nanocomposites containing In_2O_3, ZnO and AV [80]. AV was also reported to have been used in the form of films, membranes and composites coupled with natural polymers like chitosan and other synthetic materials which can be highly useful for several wound and burn healing applications [81-84].

These researches portray the advantages of modernized utilization of *Aloe vera* in the form of hydrogels, nanofibers, nanoparticles, and nanocomposites respectively. Each type of material has been observed to possess exceptional abilities to treat a broad range of wounds from fire burns to ulcers. In all the work, the addition of *Aloe vera* is thought to positively reform the properties of materials. Further, *in vitro* results were also reported to reproduce in native *in vivo* conditions which ardently express the potential of biomaterial-based *Aloe vera* products. Driven by the above outcomes, more investigations need to be followed on exploring synergetic and combinative materials by coupling various aloe-based nanostructures to improve its effectiveness in treating wounds.

4.2 Hard and soft tissue regeneration

Tissue regeneration is another ground-breaking and fascinating modern day application of *Aloe vera*. Basically, regeneration is a complex process which involves the restoration of partially or completely lost parts of a system. It mainly progresses with enlistment and differentiation of native stem cells assisted by supportive cells like macrophages, myofibroblasts, neutrophils and other immune cells. In the rebuilding process, the extracellular matrix (ECM) components such as collagen, fibrin, hyaluronic acid will be synthesized eventually, which in turn promotes revival. The science which deals with designing materials, exploring novel methods, finding effective cell combinations and other biochemical & physicochemical factors to improve or replace the natural remodelling process is termed tissue engineering [85, 86]. It mainly deals with devising a novel system which virtually offers a natural three-dimensional environment for better cell and tissue growth. Numerous techniques and approaches were brought to light as a result of ample research. Regarding tissue regeneration, the works reported on utilizing *Aloe vera* in modern biomaterial based nanosystems were mainly concentrated on nanofibers and composites. Meantime, researchers have illustrated its ability to regenerate skin,

bones and vascular tissues respectively. This is discussed in successive sub-sections since most of the works are reported on nanofiber an exclusive graphical representation of the same is given in figure 4.

4.2.1 *Aloe vera* coupled nanofibers for skin regeneration

The electrospinning based nanofibrous mat has gained much importance because of its admirable scaffolding ability to mimic a natural ECM. Moreover, the synthesizing process is also simple when compared to others. Through electrospinning we can easily obtain nanofibers in the range of 50-1000 nm; however solution properties like concentration, conductivity, viscosity and pH play a significant role in deciding those ranges. Meantime, synthetic and natural polymers or the combination of both can be meticulously formed into nanofibrous scaffolds. Although electrospun nanofibers have several applications, those involved in tissue engineering are of great interest to researchers. The affinity towards the fabrication of scaffolds based on biological substances is increasing nowadays since it is more biocompatible, non-toxic, low cost and it also produces essential nutrients for cellular regeneration [87, 88]. Suganya *et al* synthesized a nanofibrous composite using natural polymers such as AV, silk fibroin (SF) and collagen (CLG) by an electrospinning process, collectively for skin regeneration and wound healing applications. They fabricated four different nanofibrous scaffolds: poly (L-lactic acid)-co-poly (ε-caprolactone) (PLACL), PLACL-SF, PLACL-SF-AV and PLACL-CLG using PLACL as the principle element. The FTIR studies confirm the presence of appropriate structures by showing characteristic stretching, whereas the FESEM and SEM images revealed the fiber diameter was smaller in the PLACL-SF-AV scaffold than others. Contact angle studies demonstrated that PLACL-SF-AV exhibit high wettability among all four scaffolds. Meanwhile, the mechanical studies show that the PLACL-SF-AV scaffold exhibits high strain rates due to an increase in the elastic property of PLACL by the addition of AV. The characterization studies clearly showed that the PLACL-SF-AV scaffold has the capability to be used as a skin regeneration scaffold. Cellular compatibility studies were done using HDF cells supported the above declaration. FESEM and optical microscopy observations showed that HDF cells attach and proliferate better on a PLACL-SF-AV fibrous composite; further it was shown to expression components of ECM, such as collagen and F-actin proteins [89].

In a sequel, the researcher once again demonstrated the ability of AV in promoting skin regeneration by using synthetic polycaprolactone (PCL) polymer. Here, the researcher used a commercially available powder form of *Aloe vera* to fabricate four distinct systems such as PCL, PCL-5% AV, PCL-10% AV and PCL/CLG. The SEM micrographs once again showed that the PCL nanofibrous scaffold with 10% AV exhibited reduced fiber diameter due to an increase in conductivity of the solution. The mechanical and contact angle studies exposed higher tensile strength and improved hydrophilicity of PCL with 10% AV, respectively. As anticipated, the nanofibrous scaffolds with 10% AV showed higher fibroblast cell adhesion, proliferation and differentiation than other systems [90]. The above studies clearly demonstrate the capability of *Aloe vera* loaded nanofibers in promoting the growth of wounded cells by providing a scaffolding environment as well as releasing essential growth factors. In spite of using different types of synthetic substances to induce skin cell proliferation and deliver a native framework, AV nanofibers are the best choice as they deliver both required properties with higher biocompatibility. Since the fibers are biodegradable they will not damage the newly formed skin as recorded while using commercially available bandages.

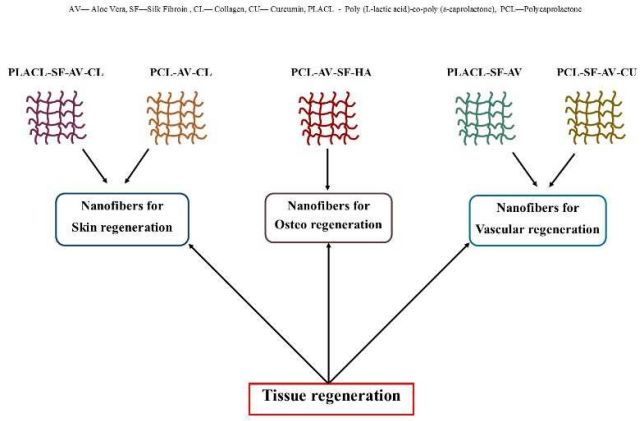

Figure 4: *Aloe vera* based nanofibers for tissue regeneration

4.2.2 *Aloe vera* inspired nanofibers for promoting osteo-regeneration

The polysaccharides present in *Aloe vera* have recently been reported to possess osteoinductive properties crucial for promoting osteogenesis. When given to rats, this significantly increased the proliferation and differentiation of bone marrow stromal cells, chiefly by improved alkaline phosphatase (ALP) activity and mineralization [91-94]. Driven by this unique ability, Suganyaa *et al* proposed AV based scaffolds for effective hard tissue regeneration. For that, they precipitated hydroxyapatite (HA) on fabricated PCL-SF-AV nanofibrous scaffolds using the calcium-phosphate dipping method to boost bone regeneration and pristine PCL was considered as controls. FTIR studies expressed characteristic stretching and SEM analysis demonstrated the fibrous structure of HA deposited PCL-SF-AV scaffold with a lower diameter. Moreover, it was also observed to have an increased strain rate and Young's modulus value which discloses suitable conditions for cell attachment and proliferation. The biological

properties were demonstrated using adipose-derived stem cells and the proliferation of the cells was analysed using MTS assay. With the use of osteoconductive HA and osteoinductive AV, the PCL-SF-AV-HA scaffold successfully guided the differentiation of pluripotent cells and it was validated using FESEM, confocal microscopy and MTS assay [95]. By coupling AV and SF, they successfully overcame the mechanical disadvantages associated with highly biocompatible HA, one of the fundamental mineral components of the human bone matrix. The improved cell adhesion, proliferation, and migration are inferred due to the combined bioactivity of AV, SF and HA present in a fabricated scaffold. Its mechanical property and integral surface morphology display a bony environment for significant cellular growth. Moreover, the osteoinductive property of AV and osteoconductive HA efficiently guided the cells for differentiation and mineral deposition. In addition, the presence of elevated levels of ALP on the PCL–AV–SF–HA scaffold confirms the successful differentiation of pluripotent cells. Hence, this bio-nanofibrous mesh can be possibly used as an implantable scaffold material for promoting hard tissue regeneration.

4.2.3 AV nanofibers for vascular regeneration

Besides skin and osteo-regeneration, Bhaarathy *et al* reported that *Aloe vera* also had the potential to enhance the proliferation and differentiation of cardiomyocytes. In this work, freshly isolated cardiac cells from 6 days old neonatal rats was cultured in DMEM cell culture medium and incubated at 37˚C humidified atmosphere containing 5% CO_2 for a few days. Then, the cells were seeded on electrospun PLACL, PLACL/SF, and PLACL/SF/AV fibrous scaffolds after performing a few sterilization procedures. Further, MTS assay, SEM and 5-chloromethylfluorescein diacetate (CMFDA) dye immune-fluorescent staining were used to scrutinise cell attachment, proliferation, and cardiac protein signatures respectively. The MTS assay disclosed healthier cardiac cell attachment and proliferation on the PCL-SF-AV scaffold than any other systems. The interactions among cells were reported to play a crucial role in proliferation and spreading. The images of cells dyed with CMFDA expressed the formation of well aligned intercellular junctions and interconnected monolayers of cardiomyocytes. More interestingly, cardiomyocytes were observed to arrange in a random manner and scatter throughout the nanofibrous mesh in the absence of SF and AV. The cardiac protein signatures were also clearly seen on scaffolds containing silk and *Aloe vera* extract. Similarly, the physico-chemical and mechanical characterization studies also demonstrated the ability of electrospun PLACL-SF-AV scaffold to host and boost the proliferation of cardiac muscle cells [96].

Recently, Karuppuswamy *et al* fabricated a biopolymer based highly porous electrospun scaffold which has great potential to mask the properties of the natural ECM. They used PCL as the principle element and it was coupled with natural polymers in different concentrations to obtain distinct electrospun systems such as PCL/*Aloe vera*, PCL/silk fibroin, PCL/*Aloe vera*/silk fibroin and PCL/*Aloe vera*/silk fibroin/curcumin respectively. Several characterization studies were employed to study several physicochemical and mechanical properties of nanofibers such as diameter, structure, pore size, stress-strain properties, and wettability. They observed diverse properties in all the above systems, yet PCL-AV-SF and PCL-AV-SF-CU nanofibers scaffolds displayed better results. FTIR and SEM monographs confirmed the presence of appropriate bonds and the nanofibrous structure of the scaffolds. The PCL-AV-SF-CU nanofibers exhibited a fibrous structure with minimal deformation rate and fascinating pore sizes whereas the PCL-AV-SF nanofibers showed better hydrophilicity and tensile strength. The pore size achieved in both PCL-AV-SF and PCL-AV-SF-CU nanofibrous scaffolds have greatly encouraged cell attachment, proliferation and differentiation into the ECM matrix. So it has great potential to act as an efficient scaffold system for both vascular and tissue regeneration [97]. Meanwhile, the above scaffolds also have potential features which could be utilized for regeneration and angiogenesis of vascular tissues especially after myocardial infarction.

4.2.4 *Aloe vera* loaded composites

Apart from electrospun nanofibrous scaffolds, few *Aloe vera* based composites examined have commendable regenerative properties. Jithendra *et al* synthesized a natural composite scaffold made of collagen, chitosan (CS) and different concentrations of *Aloe vera* gel (0.1%-0.5%) obtained from fresh leaves. Microstructure studies revealed that the porosity of the scaffold increases with the increase in AV content which allows better cell proliferation and infiltration of nutrients. The addition of AV was observed to decrease the tensile strength; however, the elasticity of the scaffold was directly proportional to AV content which may be due to increased number of pores. But the SEM micrograph showed that addition of AV above 0.2% significantly disturbed the structure of the scaffold. Hence, the composite containing 0.2% of AV alone was considered for further characterization. The TGA thermographs displayed the addition of AV alters the thermal stability and the water retention ability of scaffold containing AV was also significantly increased. Moreover, cytotoxicity studies were carried out using mouse fibroblast cells. The MTT assay showed that scaffold containing AV encouraged the growth of the fibroblast population. Meanwhile, SEM monographs confirmed the ability of AV in promoting fibroblast proliferation and migration [98].

The incorporation of *Aloe vera* is observed to improve the scaffolding properties of nanofibrous mats thereby making them more suitable for a wide variety of applications. Furthermore, a few *in vitro* studies demonstrated the inherent ability of AV in promoting adhesion, proliferation and migration of various stem cells, which has great potential to deliver re-forming effects. The utilization of AV for scaffold applications has been reported recently and the above results

demonstrate the requirement for conducting more research to disclose other hidden qualities.

4.3 Drug delivery systems

Drug delivery is another interesting domain which has made generous advances and rapid evolution in recent years. Drug delivery systems allow us to achieve controlled and sustained release of drugs, reduce side effects, maintaining desired drug concentrations in blood and producing site-specific delivery which ensures effective treatment and promising relief. Hydrogels, micelles, nanocomposites, nanoparticles, and nanofibers are some of the prime modern day drug delivery systems; these contain drugs and a carrying vehicle mostly made of biodegradable polymers [99-101]. It is widely used in cancer treatments and vascular regeneration (drug-eluting stents which contain metallic or polymer base coated with the drug in the form of a nanocomposite). Initially, synthetic drugs were extensively engaged, but in recent days the attention of scientists has switched towards the usage of natural biomolecules and drugs obtained from various medicinal plants. Aloes, sugars, minerals and vitamins present in *Aloe vera* are already reported to possess anticancer, antioxidant and tissue regenerative properties. It motivated researchers to employ *Aloe vera* in modern drug delivery systems such as nanocapsules, nanofibers, nanoparticle hydrogels and bio-inspired sponges (figure 5).

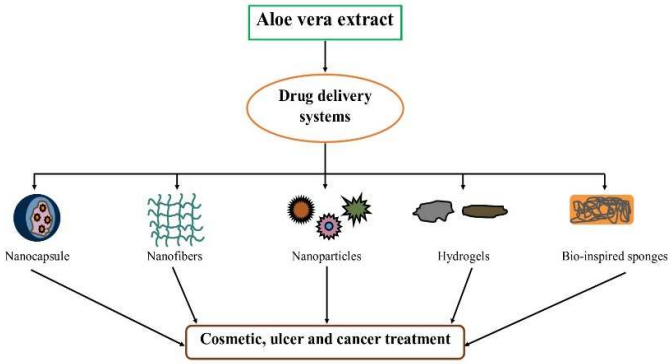

Figure 5: *Aloe vera* extract loaded modern drug delivery systems for clinical applications

4.3.1 *Aloe vera* extract loaded nanocapsules

Recently, Esmaeili *et al* synthesised nanocapsules made of triblock PEG and poly butylene adipate (PBA) containing *Aloe vera* extract. Nanocapsules are vesicular based systems where the drugs loaded into the capsules are confined to a nano-structured reservoir which is surrounded by a polymer membrane or coating. The core can accommodate active substances in the form of liquid, solid or molecular dispersion. Initially, the gel was obtained from the fresh leaves of *Aloe vera* and blend into an extract. Then, the nanocapsules (PEG–PBA–PEG) loaded with *Aloe vera* were prepared by emulsion and penetration to a solvent method. SEM and particle size analysis report (PSAR) confirms the nanostructure of formed capsules. They also studied the effects of polymer concentration, oil/polymer ratio, extract, and surfactant concentration. It clearly showed that in lower concentrations (polymer and *Aloe vera*), finer and smaller nanocapsules were obtained. Since AV extract is freshly utilized without the addition of any chemical agents these nanocapsules could be conceivably used for cosmetic purposes and treatment of ulcers and cancers [102, 103].

4.3.2 *Aloe vera* coupled nanofibers

Like tissue engineering, electrospun nanofibrous mats also have great hopes for drug delivery applications because they are easy to synthesize, offers a high loading of multiple drugs in a single system and sustained release of drugs over a long period. Currently, nanofibrous systems can be loaded with nanoparticles, nano micelles or nanocapsules which can provide combination therapy is gaining much attention. Sridhar *et al* scrutinized the medicinal applications of PCL nanofibers composite system containing natural extracts such as *Aloe vera*, curcumin (CU) and neem. They fabricated series of distinct nanofibrous mats such as PCL, PCL/CU, PCL/AV, PCL/Neem, PCL/CU/AV and PCL/CU/neem. The uniaxial testing machine was used to study the mechanical properties which showed the tensile strength and Young's modulus of the fibrous mats decreased with an increase in CU and neem. In contrast, the mechanical properties improved with the addition of AV when compared to the other two extracts. Similarly, the fiber diameter decreased with the addition of AV and SEM images which also confirmed that mats containing AV possess a better fibrous structure with smaller diameters. Conversely, PCL/CU fibers exhibit better drug encapsulation capacity and prolong degradation when compared to others. Further, the anticancer activities of different fibrous systems were demonstrated using human breast cancer (MCF7) and lung cancer (A459) cell lines. The MTT assay once again confirmed the effectiveness of natural constituents by showing that both PCL/CU and PCL/CU/AV appreciably reduced the growth of A459 and MCF7 cells when compared to PCL nanofibers containing commercial drug (1% cisplatin) [104].

In another study, Shukry *et al* fabricated PVA mats with smaller fiber diameter and increased the surface area with the help of AV. A commercially available AV powder was used without any further purification and nanofibers were fabricated from the solution containing PVA and 5% AV by an electrospinning method. FTIR studies expressed characteristic stretching; similarly, the differential scanning calorimetry (DSC) analysis displayed the formation of amorphous structures encouraged by aloin which confirms the presence of AV. The FESEM images confirmed the formation of a better fibrous structure with average size of 123 nm which is very much smaller than pristine PVA [105].

4.3.3 *Aloe vera* conjugated nanoparticles

Chauhan *et al* applied the reducing property of *Aloe vera* to synthesize 5-fluorouracil (5-FU) nanoparticles by a green method. The usage of nano-sized particles as a delivery vehicle not only makes them suitable for oral, pulmonary and transdermal administration but it also provides increased bioavailability, protection against biological activities and safe delivery of drugs to the targeted site. Further, the nano-range particles have the ability to invade cells which result in the greater accumulation of associated drugs exclusively at the desired destination [106, 107]. The drug 5-FU utilized in this research is one of the most effective anticancer agents extensively used against colorectal, head, pancreatic and breast carcinoma [108, 109]. *Aloe vera* gel extract obtained from the fresh leaves was mixed with 5-FU which ensures the formation of nanoparticles. UV and fluorescence spectra analysis showed the occurrence of chemical interactions and the formation of nanoparticles. On the other hand, studies using a TEM and a nanofox particle analyser reveal that the size of formed hexagonal nanoparticles decreases with an increase in AV concentration and it was calculated to have an average size of 35±5 nm approximately. The FTIR and XRD analysis were used to confirm the presence of associated chemicals and to study the changes in crystal properties. The sustained release of the drug over a period of time was observed through release kinetics studies. Meanwhile, the cytotoxicity of formed 5-FU nanoparticles against HT-29 and Caco-2 (human adenocarcinoma colorectal) cells was found to be time dependent. The drug loaded nanoparticles also exhibit better growth inhibition of both cancer cells; additionally the expression of various apoptotic factors studied by Western blot assay also demonstrated the extensive growth inhibition ability of 5-FU nanoparticles [110].

4.3.4 Bio-inspired beads, hydrogels and sponges

Besides having anticancer and antitumor properties, the gel present in *Aloe vera* is also reported to exhibit antiulcer activity. In ancient days, the gel was used as a preventive agent against gastric ulceration because of its ability to regulate gastric secretion and mucus stimulation along with its anti-inflammatory and healing effects [111, 112]. Inspired by this property, Singh *et al* designed an effective drug delivery system made of alginate and *Aloe vera* gel for the controlled release of the commonly used anti-ulcer agent ranitidine. By ionotropic gelation they synthesized both floating and non-floating AV and alginate beads using different cross-linking agents like calcium chloride, barium chloride, and aluminium chloride respectively. SEM and FTIR studies confirmed the formation of beads. In case of the floating type, the bead which contains Al^{3+} acquires better mechanical and swelling behaviour whereas the non-floating type bead containing Ca^{2+} observed to have better qualities. But, the floating beads displayed faster drug release than the non-floating beads [113]. In addition to nanofibers and nanocapsules, *Aloe vera* based hydrogels are also reported to have better swelling and drug release behaviour [62, 64].

Recently, Silva *et al* reported the ability of bio-inspired sponges made using *Aloe vera* to act as a promising drug delivery agent. They used *Aloe vera* gel obtained from fresh leaves and mixed them with low acyl gellan gum (GG) to obtain AVG matrices. Then the matrices were subjected to consecutive heating and cooling, and finally the sponges were formed by a freeze-drying method. In this work, bovine serum albumin (BSA) was utilized as a model drug which was incorporated into sponges composed of AVG and AV (without GG). Completely natural AV sponges attained better porosity and interconnectivity when compared to AVG. In contrast, AVG sponges showed better mechanical properties which seemed to mimic the properties of natural tissues. Similarly, AVG sponges displayed gradual degradation and better structural stability; however AV exhibits controlled release of the drug. From these results, they concluded that the interactions between AV sponges and drugs used were stronger than the interactions between AVG and drugs. It clearly shows that *Aloe vera* sponges have an immense capability to be used as an effective drug carrier. Meanwhile, they also demonstrated the wound healing property of sponges by conducting a cytotoxicity assay against the mouse fibroblast cell line (L929) [114]. Similarly, Gontijo *et al* disclosed an excellent activity of *Aloe vera* sponges against a series of bacterial strains as well as a reduced cytotoxicity. Further, it also highly encouraged the adhesion and proliferation of human gingival fibroblast cells. From the above studies, we can clearly infer that *Aloe vera* inspired sponges have extensive capability for use in wound healing and drug delivery applications respectively [115].

In both macro and nano drug delivery systems, the introduction of *Aloe vera* is reported to improve drug encapsulation as well as release kinetics. At the same time its medicinal properties were also reported to be retained significantly, which was proved by anticancer and antiulcer related studies. Hence, AV is a perfect choice to enrich both pharmacokinetic and therapeutic properties of the desired delivery system.

5. Conclusion

The notion of green or eco-friendly synthesis has created a cognizance among researchers about the benefits and usefulness of utilizing plant-based products for synthesizing novel materials and treating deadly diseases. Further, the usage of plant derivatives in biomaterial and nanostructure based applications is a growing field and most of the works summarized in this review are recent studies which evidently support the above statement. *Aloe vera* is well-known for its enriched nutrients and comprehensive medicinal values. It has been in use for a number of centuries but the evolution of new techniques has completely upgraded its traditional look. In addition, the unique properties of *Aloe vera* are of great

importance in the commercial field. As mentioned in the introduction, *Aloe vera*-based industries are expected to grow by more than 35% in the next few years mainly due to the application of modern technologies.

Until past decade, *Aloe vera* has been explored for oral and topical administration in the form of extract, pills or gels. Inspired by the advances made in nanotechnology and biomaterial fields, researchers started to employ various nano systems. This led to the utilization of *Aloe vera* in a rationalised form which it had never previously been used in. The modern day usage of *Aloe vera* has included its manufacture in the form of hydrogels, sponges, nanofibers, nanocomposites, nanoparticles and nanocapsules. In general, the nano-structure materials have better advantages since they are easy to administrate, provide resistance against biological attacks and, more importantly, will ensure effective results. The studies summarized in this review meticulously demonstrated the above-mentioned benefits of nano systems through several *in vitro* as well as *in vivo* characterization tests (listed in Table 1). In addition, a few biomaterial-based *Aloe vera* incorporated macro systems like hydrogels, composite films, and bio-inspired sponges also exhibited commendable properties. In the case of wound and burns healing, *Aloe vera*-incorporated systems demonstrated better cell adhesion, proliferation and differentiation of fibroblast cells, offered immense protection against microbial attacks and maintained suitable conditions to enhance the healing process, which is clearly reflected in animal studies too. Further, it also showed potential use for the regeneration of both soft and hard tissues like blood vessels, skin, and bones, respectively. Similarly, the *Aloe vera*-based drug delivery systems showed good outcomes in delivering drugs and inhibiting the growth of cancer cells. In figure 6, the current reported usages of *Aloe vera* are recapitulated for better understanding.

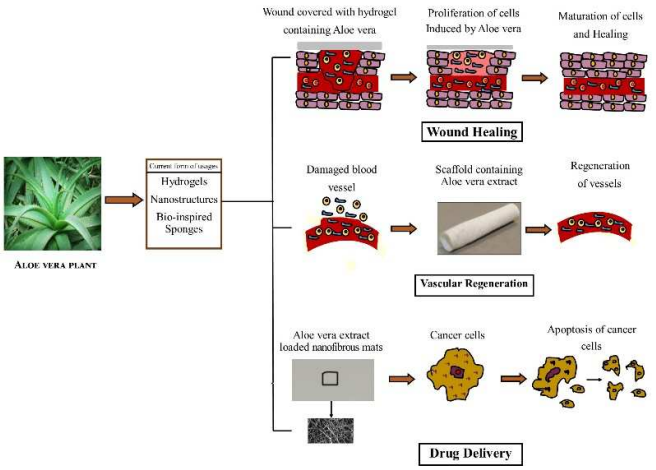

Figure 6: Current forms of *Aloe vera* usages and its mode of clinical applications

To summarise, the minimal amount of works published so far about the usage of *Aloe vera* in biomaterial and nano-based systems yield commendable results.

6. Future perspective

The field of nanobiotechnology is attracting numerous innovation in recent days because of its multifaceted abilities and crucial environmental benefits. Though various plant materials like Aloe vera extract have been explored for nanotechnology based biomedical applications, the research is still in its infant stage. Hence, detailed investigations need to be carried out, especially on the usage of Aloe vera as a potential drug delivery system in cancer treatment. On the other hand, Aloe vera has been predominantly used only in a few nanoformulations such as nanoparticles, nanofibers and nanocomposites. So, more work has to be done to explore the benefits of Aloe vera in other forms of nano structures like nano micelles, nanosponges, and nanocapsules etc. The plant extract also expressed excellent characteristics as a coating agent for various cardiovascular implants where properties like biocompatibility and re-endothelialization are greatly needed [116, 117, 118]. Similarly, it has been inferred that Aloe vera has the ability to successfully guide stem cells and progenitor cells to further differentiation which has great potential in the tissue engineering field. Although, the detailed competence has to be determined by experimenting with different lineages of stem cells. Meanwhile, the studies discussed have utilized only the crude form of Aloe vera; thus it is difficult to identify which particular component is responsible for the desired outcome. So, future research should be focussed towards unveiling the active constituents responsible for the particular application. Further, the research on other biomedical applications like coating agent for temporary blood contacting devices, etc., needs to be encouraged to explore its unplumbed capabilities. These efforts will help the industry players to recognise its immense potential and bring significant aloe products to the market.

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Graphical Abstract