INTRODUCTION

Diabetes mellitus often referred to simply as diabetes is a syndrome of disordered metabolism, usually due to a combination of hereditary and environmental causes, resulting in abnormally high blood sugar levels (hyperglycemia). Long-term manifestations of diabetes include retinopathy, neuropathy, nephropathy, angiopathy, atherosclerosis, periodontitis, and other diabetic complications, such as impaired wound healing. [(1)]
Wound is a physical bodily injury characterized by disruption of the normal continuity of body structures. Wounding may cause injury to superficial cutaneous structures and to the structures underlying the skin.

Open wounds have lost the barrier that protects tissues from bacterial invasion and allow for the escape of vital fluids. Wound healing and tissue repair are complex processes that involve a dynamic series of events including clotting, inflammation, granulation tissue formation, epithelization, collagen synthesis, and tissue remodeling.[(2)]There are many factors which may negatively affect wound healing. Among these diabetes mellitus is characterized by enhanced glycaemia and micro- and macro angiopathy.

Diabetic wounds are complex microcosms of multiple pathophysiologic processes. The wounds are predominantly characterized by poly microbial infection, peripheral neuropathy, structural deformity, altered immune function or increased susceptibility to infection, decreased wound nitric oxide (NO) production, and often hypoxia/ischemia.[(3)]Diabetic wounds present a major problem for modern health care. Healing in patients with diabetes mellitus is characterized by reduced tensile strength of wounds when compared with controls, suggesting either defective matrix production or deposition.

Formation of super-bugs has become a main problem due to frequent use of the antibiotics. Generally, due to genetic transformation of microbial strains had created resistance against the present antibiotics. In order to have complete removal of pathogenic strains during wound healing process, there is a need to have an alternate strategy. [(4)]Since most of the antibiotics seem to be less sensitive to many organisms, researchers started finding a new potential antimicrobial agent. [(5)]

There is a need to bring researchers together to develop alternative new therapies to improve diabetic wound healing. [(6)]Most studies concerning wound healing focus on accelerating wound and soft tissue healing, obtaining normal wound breaking strength and preventing keloidand scar formation. Some researchers concluded that some physical methods, including therapeutic ultrasound and laser treatments, accelerate and facilitate wound healing and increase scar quality. [(7-10)]

Phototherapy has been shown to positively affect wound healing in diabetic patients.[(11)]

In recent years, low-intensity laser therapy has gained considerable recognition and importance among treatment modalities for various medical problems including wound repair processes, musculo-skeletal complications, and pain control.[(12-14)] Clinical studies have shown low energy lasers to be effective as analgesics and to accelerate thehealing of injured tissue.[(15)]Although the beneficial effects of laser photo stimulation are now

generally accepted, the mechanisms by which laser light facilitates wound healing and tissue repair yet to be clearly understood.[16, 17]

The bio modulatory effects of low level laser therapy (LLLT) have been reported since the beginning of laser development for biological applications. Many studies have focused on the effects of laser photo modulation on a broad range of pathological conditions such as wound healing, reduction of edema, and the relief of pain from various etiologies. [18]

Wound healing is a complex biologic and biochemical process that starts right after an injury. Several studies had been performed aiming to clarify the different mechanisms that interfere with it. LLLT effects have been investigated not only at experimental basis, but also in clinical trials [19]. This has been motivated by the necessity of enhancements on the healing process of post-surgical wounds, burns, implants and flap surgeries, leading to a shorter length of stay in a health care facility, which results in a lower risk of nosocomial infections. [20]

It could be shown that LLLT at adequate parameters may promote alterations in cellular metabolism leading, for instance, to an increased proliferation of fibroblasts, faster formation of granulation tissue, promotion of collagen synthesis, angiogenesis and earlier epithelization. [21]

The effect of laser light on target tissue is dependent on the optical, chemical, and mechanical properties of the tissue as well as the characteristics of the incident laser beam.[22]

When a photon hits an object, it may be reflected, transmitted, scattered, or absorbed and the optical properties of a substance are characterized by coefficients for each of these events .When the photon is reflected or transmitted it retains its energy, and when it is absorbed the energy is delivered to the atoms of the absorbing object (photo acceptor or chromophore). This energy may in turn change to heat oscillations (atom/material becomes hot), excite other atoms or molecules (electrons change their energy levels), ionize an atom or molecule (deliver an electron), or break chemical bonds (build new compounds). [23] At low intensities, the photochemical conversion of the energy absorbed by the photo acceptor is predominant. [24] The effects of photo therapy are photochemical rather than thermal, [25] and the amount of heat generated is insignificant and minimal [26], typically in the range of 0.1 to 0.5◦C. [27, 28]

Therefore, tissue healing highlighted as one of the main effects of LLLT, [29] is characterized by three main factors. First, there is an increment of ATP production, as laser is considered to raise the production of ATP,[30] leading to a boost in mitotic activity and to an increase in protein synthesis by mitochondria, resulting in greater tissue regeneration in the repair process. Second, there is a stimulus to microcirculation, which increases the delivery of nutritional elements associated with increased speed of mitosis, facilitating cell multiplication.[29] Finally, new vessels are formed from preexisting vessels.[29,31]

Low Intensity Laser Therapy speeds up the recovery process of wound healing by delivering light energy (photons) to the cells. The cells use this energy in the natural healing process and known as photo bio stimulation. Low intensity laser is painless and has been use for over 20 years with no known side effects. [32]Low level laser therapy is

gaining acceptance in clinical applications. For example, it is used as therapeutic modality for the repair of diabetic foot ulcer when conventional therapies are not effective. [33, 34]

Tissue repair is a dynamic interactive process which involves different parameters like mediators, cells and extra-cellular matrix. Several reports on the use of laser therapy were submitted describing that the healing process is positively affected when the correct parameters of laser are used. Low level lasers have been introduced as one of the treatment modalities for non-healing wounds and several indications have been introduced for its use in wound healing processes, particularly in indolent wound resistant to conventional treatments. Low-energy photo-stimulation at certain wave lengths can enhance tissue repair by releasing growth factors from fibroblasts and can facilitate the healing process of diabetic wounds. [33] The molecular and cellular mechanisms of LLLT are as follow:

1) Target cells are blood leukocytes, fibroblasts, keratinocytes, endotheliocytes, etc.

2) Primary acceptors of radiation are porphyrins, which may cause radicals for secondary free radical reactions

3) The initiation of the secondary free radical reactions due to lipid peroxidation of cell lead to increase in ion permeability, including Ca^{2+}. The increase in intracellular Ca^{2+} concentration cause phagocytosis to increase production of reactive oxygen species (ROS)

4) ROS in the cytoplasm of some cells induces a free-radical activation of synthesis of proteins; the most significant is the de novo synthesis of inducible Nitric oxide (NO) synthase (iNOS), super oxide dismutase, and various cytokines. NO has many functions in wound healing. [35]

Therapeutic ultrasound has been widely used over the past 50 years to treat many musculoskeletal complaints, including tendon injuries, pressure sores, venous ulcers, poor wound healing, lateral epicondylitis, herpeszoster, muscle damage, Dupuytren's contractures, and others. Since the 1960s, the effects and benefits of ultrasound on wound healing have been investigated by various studies. [36-39] Because many studies have produced conflicting findings, the clinical use of ultrasound for wound healing is still under investigation. [40, 41] Although some investigators saw no acceleration in the repair of wounds with ultrasound treatment, [41-43] positive results and treatment effects have been reported in studies of ultrasound treatment on tendon injuries, lateral epicondylitis, and wound healing. [36-38, 44, 45]

Ultrasound at lower intensities (0.3-1W/cm) has been shown to enhance collagen synthesis and tensile strength, angiogenesis and cellular recruitment [46] and may be a promising approach to wound healing, although little robust evidence is available. [47]

Noncontact low-frequency ultrasound therapy is a newer modality used to promote healing in chronic wounds by cleansing and maintenance debridement to remove yellow slough, fibrin, tissue exudates, and bacteria. Ultrasound initiates 2 processes that release energy to the tissues capable of inducing cellular change: surface cavitation (creation and dissipation of tiny bubbles in the tissues) and acoustic micro streaming (movement of fluids along acoustic boundaries, such as cell membranes). [48]These processes are associated with a number of biophysical effects that are non-thermal and relevant to wound

healing, including alterations in cellular protein synthesis and release, blood flow, and vascular permeability, angiogenesis, and collagen content and alignment. [46]

Nanotechnology is the discipline of manipulating matter at the nanoscale (1-100 nm) yielding nanoparticles or materials that often possess novel biological, physical or chemical properties, [49] and has been identified as a technology that can be useful in resolving many problems.

Dressings for wound healing function to protect the wound, exude extra body fluids from the wound area, decontaminate the exogenous microorganism, improve the appearance and sometimes accelerate the healing process. For these functions, a wound dressing material should provide a physical barrier to a wound, but be permeable to moisture and oxygen. Electrospun nanofiber mat is a good wound dressing candidate because of its unique properties: the highly porous mat structure and well interconnected pores are particularly important for exuding fluid from the wound; the small pores and very high specific surface area not only inhibit the exogenous microorganism invasions, but also assist the control of fluid drainage; in addition, the electrospinning process provides a simple way to add drugs into the nanofibers for any possible medical treatment and antibacterial purposes.

A study on using electrospun polyurethane (PU) mat as wound dressing material revealed that the mat effectively exuded fluid from the wound, without fluid accumulation under the mat, and no wound desiccation occurred neither. [50] The mat also showed a controlled water loss from evaporation, excellent oxygen permeability, and high fluid drainage ability, besides inhibiting the invasion of exogenous microorganism. Histological test indicated that the rate of epithelialization was increased and the dermis became well organized when the wounds were covered with the electrospun nanofiber mat. Silk nanofiber mats were electrospun with epidermal growth factor to promote wound healing process, [51] and it has been found the functionalized mat increased the wound closure by 90%.

An open wound healing test using an electrospun collagen nanofiber mat showed that the early stage healing using collagen nanofiber mat was faster than that of using normal cotton gauze [52]. In the first week, the wound surface in the cotton group was covered by fibrous tissue debris, below which dense infiltration of polymorph nuclear leukocytes and the proliferation of fibroblasts were formed. By comparison, the surface tissue debris in the collagen nanofiber group disappeared, and prominent proliferation of young capillaries and fibroblasts was found. Later stage healing processes were similar for both groups. PLGA/collagen nanofiber mats also showed an effective wound healing behavior with an active response to human fibroblasts in the early stage. [53]

In vivo wound healing of diabetic ulcers was investigated using electrospun block copolymer (PCL-PEG) and PCL. When the nanofibers were chemically modified with a recombinant human epidermal growth factor (rhEGF), the expression of keratinocyte specific genes and EGF-receptor were enhanced. [54] Systematic *in vivo* wound healing evaluations have been carried on PVA, PCL, polyacrylonitrile (PAN), poly (vinylidene fluoride-co-hexafluoropropene) (PVdF-HFP), PAN/PEU blend, and wool protein coated PVA and PCL nanofibers. [55, 56] The results showed that wound healing performance was mainly influenced by the porosity, air permeability and surface wettability of the nanofiber mats. A mat with good hydrophilicity and high porosity facilitated the healing at the early

stage. However, the fiber diameter and antibacterial activity had a limited effect on the healing efficiency.

Post-surgery tissue adhesion is a widely recognized problem for abdominal surgeries. It not only renders future operations more difficult but also causes other problems such as small bowel obstruction, female infertility, and chronic debilitating pain. An electrospun nanofiber mat containing antibiotic agents has been used as a barrier to prevent the post-surgery abdominal adhesions. It was found that the nanofiber mat eliminated post-surgery abdominal adhesion significantly, thus improving the healing process. [57]

To decontaminate the bacteria invasion, biocides, such as silver [58, 59] and iodine complex [61] have been added to the electrospun nanofibers. It was reported that polyvinyl pyrrolidone (PVP)-iodine complex (PVP-iodine) gradually released active iodine. Because of the broad-spectrum microbicidal activity of iodine, electrospun PVP-iodine nanofibers had external antibacterial, antimycotic and antiviral applications. Ag ions were incorporated into electrospun nanofibers via adding AgNO3 into the polymer solution for electrospinning.

To maintain a long term antibacterial activity and control the release of Ag ions, the Ag was embedded in the form of elementary state by a post-electrospinning treatment. Ag nanoparticles can also be directly incorporated into electrospun nanofibers via the electrospinning process. An Ag/PVA nanofiber mat exhibited excellent antimicrobial ability and good stability in moisture environment, as well as a quick and continuous release with good effectiveness. [60]

Besides adding antibacterial additives, antimicrobial nanofibers can also be prepared by directly using antimicrobial polymers. For instance, polyurethanes containing quaternary ammonium groups were electrospun into nanofiber nonwovens, and the nanofibers showed very strong antimicrobial activities against Staphylococcus aureus and Escherichia coli. [61]

Cellulose acetate (CA), a derivative of cellulose, can be easily obtained from natural resources and recycled in environment by biodegradation. It can be easily fabricated into films, membranes and fibers. [62]

Cellulose acetate (CA), the acetate ester of cellulose, has been widely investigated for a wide variety of potential applications in the form of electrospun nanofiber mats because of its advantageous properties, such as good biocompatibility, biodegradability, regenerative properties, high affinity with other substances, high modulus, and adequate flexural and tensile strength. [63, 64] Cellulose acetate has been applied in affinity membranes; antimicrobial membranes, three-dimensional structures resembling urinary bladder matrices, filament-forming matrices for biomedical nanocomposites, biosensor strips, water treatment films, and biomedical separation because of its good hydrolytic stability and relatively low cost. [21]

Besides itself nanofibers, polymers can also be used as template or host to load nanoparticles or functional molecules. The produced composite nanofibers exhibit various electronic, optical, magnetic, and biological properties. [65, 66]

LITERATURE REVIEW

Wound Healing Using Laser

Osman A H et al (2013), [67] evaluated the effect of Low Level Laser Therapy (LLLT) using diode laser 808 nm on wound healing in 40 diabetic male albino rats. Gross examination showed faster wound closure in the laser exposed groups with minimal scar tissue formation in comparison with non-laser treated group. The histopathological examination show that earlier granulation tissue formation and re-epithelization and revealed moderate inflammatory reaction in the laser group versus severe suppurative inflammatory reaction with keloid formation in the control non-treated group so this indicate that low level laser therapy using diode laser 808 nm can be applied as an efficient method to accelerate wound healing in diabetic.

Nasirian N et al (2012), [68] investigated the effect of red light laser 630 nm on cutaneous surgical wound in hamster. The intervention group was radiated with red-light laser 630 nm. After 2, 5, 10 and 14 days, skin biopsy were obtained and number of blood vessels, fibroblast and collagen production were compared with the control group. Results revealed significant increased in number of vessels and fibroblasts as well as collagen production in laser radiating groups. This indicates that laser therapy (630 nm) can accelerate wound healing in comparison with control group**.**

Kajagar B M et al (2012), [69] studied the efficacy of Low Level Laser Therapy (LLLT) in diabetic ulcer healing dynamics. Patients were randomized into two groups of 34 each. Patients in study group received LLLT with conventional therapy and those in control group were treated with conventional therapy alone. Healing or percentage reduction in ulcer area over a period of 15 days after commencement of treatment was recorded. Percentage ulcer area reduction was 40.24±6.30 mm^2 in group treated with laser and 11.87±4.28 mm^2in control group. Low Level Laser Therapy is beneficial as an adjunct to conventional therapy in the treatment of diabetic foot ulcers.

Kaskos H H et al (2011), [70] studied the histological and biochemical response of intra-oral soft tissue in rat to low level laser light. Each rat received a laser dose of 0.75 J/cm^2 in each session daily for 11days. Laser therapy showed enhancement of neovasculazation at days 5and 9 postoperatively .While collagen arrangement showed significant changes at the 5^{th},9^{th} and 11^{th} postoperative days.The results indicated that low level laser therapy at a dose of 0.75 J/cm^2 enhanced wound healing.

Hussein A J et al (2011), [71] used a low level laser to accelerate and facilitate wound healing and reduce scar formation and wound contraction of an open wound in male rabbits. A wound was made on the gluteal region; six hours later, the wound was treated with gallium aluminum and an arsenide diode laser with a power output of 10 mW at a wavelength of 890 nm in pulsed mode, with a frequency of 20 KHz for 5 minutes over a 7 -day period. They found that low level laser therapy give better regeneration and faster restoration of structural and functional integrity as compared to the control group.

Alipanah Y et al (2011), [72] determined the efficacy of Low Level Laser Therapy (LLLT) on wound healing in rabbits. A low level pulsed GaAlAs laser (wavelength: 685 nm, power: 45 mW, radiant exposure: 3 J/cm^2 , frequency: 10 Hz, duty factor: 80%; application time: 1 min) was used on the left side. The right side was not lasered as a control. Tissue specimens from each site on days 3, 7, and 14 after surgery were examined microscopically. Less inflammation was observed on days 3 and 7 in the treatment group . The inflammation rate on both sides was the same on day 14. They concluded that, LLLT with optimal parameters can accelerate full thickness wound healing.

Mokmeli S et al (2010), [73] studied the effect of local and intravenous LLLT for the healing of diabetic foot ulcer. The wounds irradiation are performed by the combination therapy of 650 nm and 860 nm laser, with the total energy density of 3.6 J/cm² plus intravenous laser therapy (IVL) with 2.5 mW, 650 nm for 30 minutes. They definitely can express that, all the Patients received some degrees of healing, during their laser receiving treatments. The combined local and intravenous LLLT promote the tissue repair process of diabetic foot ulcer.

Bayat M et al (2008), [74] investigated the effects of Low-Level Laser Therapy (LLLT) on mast cell number in the inflammation, proliferation, and remodeling phases of the wound healing process of experimental burns. Sixty rats subjected to third-degree burns were divided into four groups: two laser-treated, one control, and one nitrofurazone-treated group. In the two laser-treated groups, burned areas received LLLT with a helium-neon laser at energy densities of 38.2 J/cm2 and 76.4 J/cm^2, respectively. The effects on mast cell number and degranulation were assessed. Five rats with no burns were used for baseline studies. LLLT on the experimental third-degree burns significantly increased the total number of mast cells during the inflammation phase of wound healing; also, topical application of 0.2% nitrofurazone ointment on the same burns significantly increased the total number of mast cells during the proliferation phase of burn healing.

Al-Waiban F H et al (2007), [3] studied the effects of wound healing acceleration in diabetic rats and compared it using different laser wavelengths and incident doses. They used 532,633,810, and 980 nm diode lasers. Incident doses of 5, 10, 20, and 30 J/cm^2 and treatment schedule of 3 times/week were used in the experiments. There weresignificant differences in the mean slope value of wound healing on diabetic rats between controlgroups and treatment groups in 532, 633, 810, and 980 nm lasers this indicated that the wound healing on controlrats with diabetes was slower than on control rats without diabetes. LLLT at appropriate treatment parameters can enhance the wound healing on diabetic rats. The optimum wavelength was 633 nm, and the optimumincident dose was 10 J/cm^2 in our study.

Garavello I et al (2004), [75] studied the influence of He-Ne laser radiation on the formation of new blood vessels in the bone marrow compartment of a regenerating area of the mid-cortical diaphysis of the tibiae of young adult rats. Incident energy density dosages of 31.5 and 94.5 Jcm-^{2} during the period of the tibia wound healing. Low-level energy treatment accelerated the deposition of bone matrix and histological characteristics compatible with an active recovery of the injured tissue. He-Ne laser therapy significantly increased the number of blood vessels after 7 days irradiation at an energy density of 94.5 Jcm-2, but significantly decreased the number of vessels in the 14-day irradiated tibiae.

These effects were attributed to laser treatment, since no significant increase in blood vessel number was detected between 8 and 15 non-irradiated control tibiae.

Demir H et al (2004), [76] investigated the effects of electrical stimulation (ES) and laser treatment on wound healing in rats. They concluded that ES and laser treatment both have beneficial effects during the inflammatory, proliferation, and maturation phases of a wound. Both ES and laser treatment can be used successfully in decubitis ulcers and chronic wounds, in combination with conventional therapies such as daily care and debridement of wounds; however, ES has more beneficial effects during the inflammatory phase in some parameters than laser treatment.

Wound Healing Using Ultrasound

Mahran H G (2014), [77] investigated the effect of ultrasound power density on wound-healing process in rat. They used ultrasound of power density of 0.5 W/cm^2 and 1 W/cm^2 for treatment of excisional dorsal wound in comparison sham control. After 14 days of treatment, wound area reduction were more pronounced in group treated with pulsed ultrasound of power density of 0.5 W/cm^2 and to a lesser extent in group treated with pulsed ultrasound of power density 1 W/cm^2 in comparison to control group. This indicated that ultrasound at 0.5 W/cm^2 and 1 W/cm^2 caused positive changes in the healing process with ultrasound at 0.5 W/cm 2 being more effective.

Sadraie S H et al (2010), [78] investigated the effect of US as a fracture-healing adjunct on the de-nervated tibial fractures in rabbit model. Twenty four male Dutch rabbits were randomly divided into four groups including two control and two ultrasound-treated (US-treated) groups. Ipsilateral sciatic nerve was cut two centimeter above the right knee. After three days, the rabbits of US-treated groups received the therapeutic dose (100 mW/cm²) of ultrasound for 15 minutes per day until the 6th and 8thweek and the control groups did not receive any treatment. Biomechanical, histomorphic and immunohisto-chemical evaluations had no significant difference between control and US-treated groups after 6 and 8 weeks post operation. These finding suggest that ultrasound therapy with features which applied in this study had no significant effect on de-nervated tibial fracture repair in rabbits.

Kavros SJ et al (2008), [79] evaluated the clinical role of noncontact, low-frequency ultrasound therapy in the treatment of chronic lower-extremity wounds. One hundred sixty-three patients who received noncontact, low-frequency ultrasound Therapy plus standard of care (treatment group) and 47 patients who received the standard of care alone (control group). In the treatment group, noncontact, low-frequency ultrasound Therapy was administered to wounds 3 times per week for 90 days or until healed. A significantly greater percentage of wounds treated with noncontact, low-frequency ultrasound therapy and standard of care healed as compared with those treated with the standard of care alone. They found that the rate of healing and complete closure of chronic wounds in patients improved significantly when noncontact, low-frequency ultrasound therapy was combined with standard wound care.

Demir H et al (2004), [80] evaluated the effects of low-intensity US and Low-Level Laser Therapy (LLLT) on tendon healing in rats; the left Achilles tendons were used as treatment and the right Achilles tendons as controls. They applied the treatment protocols including low-intensity US treatment in Group I, Sham US in Group II , LLLT in GroupIII,

Sham L in Group IV, US and LLLT in Group V, and Sham US and Sham L in Group VI (SUS and SL Group). The US treatment was applied with a power of 0.5 W/cm^{2}m, a frequency of 1 MHz,continuously, 5 minutes daily. A low-level Ga–As laser was applied with a 904 nm wavelength, 6 mW average power,1J/ cm^{2}dosage, 16 Hz frequency, for 1 minute duration,continuously. In the control groups, the similar procedures as in the corresponding treatment groups were appliedwith no current (Sham method). Although US, L, and combined US and Ltreatments increased tendon healing biochemically andbiomechanically more than the control groups, no statistically significant difference was found between them. Also, they did not find significantly more cumulative positive effects of combined treatment. As a result, both of these physical modalities can be used successfully in the treatment of tendon healing.

Rubin C et al (2001), [81] illustrated that low-intensity ultrasound exposure results in stronger and stiffer callus formation and in acceleration of the endochondral ossification process using animal studies. Extensive clinical evidence demonstrates that ultrasound represents a safe, noninvasive method of accelerating the healing of fresh fractures of the tibia, the distal aspect of the radius, the scaphoid, and the metatarsals. Clinical studies indicate that ultrasound reduces the confounding effect of smoking and patient age on the fracture-healing process. Ultrasound requires a brief, twenty-minute, daily at-home treatment regimen and has no known contraindications. The effectiveness of low-intensity ultrasound has also been demonstrated in the clinical treatment of delayed unions and non-unions.

Nussbaum E L et al (1994), [40] studied on patients with spinal cord injury, they compared the effect on wound healing of nursing care alone with the effect on wound healing of nursing care combined with either laser treatment or a regimen of ultrasound and ultraviolet-C (US/WC). Patients received standard wound care consisting of wound cleaning twice daily, application of moist dressings, and continuous relief of pressure until the wounds were healed. The laser protocol consisted of three treatments weekly using a cluster probe with an 820-nm laser diode and 30 super luminous diodes (10 each at 660, 880, and 950 nm), an energy density of 4 ~/cd, and a pulse repetition rate of 5,000 pulses per second. The US/WC regimen consisted of five treatments weekly, alternating the treatment modality daily. The pulsed US was applied at a frequency of 3 MHz and a spatial average-temporal average intensity of 0.2 ~lcd (1:4 pulse ratio) for 5 minutes per 5 cd of wound area. Ultrasound ultraviolet-C may decrease healing time and may allow faster return to rehabilitation program.

Wound Healing Using Nanofibers Dressing

Kataria K et al (2014): [82] investigated that antibiotic ciprofloxacin loaded hydrophilic biodegradable polyvinyl alcohol (PVA) and sodium alginate (NaAlg) electrospun composite nanofiber based transdermal patch was developed for local delivery of antibiotic drug. The antibiotic drug ciprofloxacinwas loaded in it by active loading. The in vivo studies were carried on male rabbits by using the drug loaded and unloaded composite nanofibers transdermal patch and marketed one. It is observed that, in vitro activity provides a sustained and controlled release pattern of the drug from transdermal patch. The in vivo studies demonstrate that, wound healing takes place in less time as compared drug unloaded patch. Hydroxyproline produced

in wound bed with time shows that it content is maximum in case drug loaded PAV-NaAlg patch.

Lee S J et al (2014), [83] utilized an electrospinning (ELSP) technique to design a novel wound dressing. Chitosan (CTS) nanofibers containing various ratios of silver nanoparticles (AgNPs). AgNPs were generated directly in the CTS solution by using a chemical reduction method. These nanofibers were subsequently tested to evaluate their antibacterial activity against gram-negative *Pseudomonas aeruginosa* (*P. aeruginosa*) and gram-positive *Methicillin-resistant Staphylococcus aureus* (MRSA). This antibacterial testing suggests that CTS/Ag NPs nanofibers may be effective in topical antibacterial treatment in wound care.

Wu J et al (2014), [84] developed a novel method to synthesize and impregnate silver nanoparticles on to bacterial cellulose nanofibres (AgNP-BC). Uniform spherical silver nanoparticles (10–30 nm) were generated and self-assembled on the surface of BC nanofibers, forming a stable and evenly distributed Ag nanoparticles coated BC nanofiber. Such hybrid nanostructure prevented Ag nanoparticles from dropping off BC network and thus minimized the toxicity of nanoparticles. Regardless the slow Ag+ release, Ag NP-BC still exhibited significant antibacterial activities with more than 99% reductions in *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa*. Moreover, AgNP-BC allowed attachment and growth of epidermal cells with no cytotoxicity emerged. The results demonstrated that AgNP-BC could reduce inflammation and promote wound healing.

Dubsky M et al (2012), [85] examined the effect of Electrospun gelatin and poly-e-caprolactone (PCL) nanofibers on wound healing using a full thickness wound model in rats and compared with a standard control treatment with gauze. Significantly faster wound closure was found with gelatin after 5 and 10 days of treatment, but no enhancement with PCL nanofibers was observed. Histological analysis revealed enhanced epithelialisation, increased depth of granulation tissue and increased density of myofibroblasts in the wound area with gelatin nanofibers. The results show that gelatin nanofibers produced by needleless technology accelerate wound healing and may be suitable as a scaffold for cell transfer and skin regeneration

Leung V et al (2011), [86] explored recent efforts in developing a new class of active textiles for wound care. The wound care sector is one of the most advanced in the medical industry, with a massive global demand from patients suffering from wounds, burns, and diseases such as diabetes. Ensuring satisfactory wound healing is often difficult due to the dynamic nature of the skin, requiring fulfilment of multiple objectives at different stages of the healing process. They demonstrated that by controlling how wound dressing release therapeutic agents, its mechanical responses to the wound and in aqueous environment, a wound dressing that can interact with different wounds can be developed.

Ma Z et al (2011), [87] made an exploration of inorganic SiO_2 nanofibers as reusable wound cover. SiO_2nanofibers were fabricated with the sol–gel technique and the electrospinning method. Silver nanoparticles (Ag NPs) are grafted on fiber surface through post treatment to endow this material with antibacterial effect. They demonstrated that, the SiO_2 nanofibers are very soft and flexible. They can be conveniently patterned into nonwoven film (the required shape of wound cover). The Ag NPs grafted SiO_2 nanofibers can efficiently inhibit the proliferation of

Escherichia coli with a long-term antibacterial effect. More importantly, this inorganic antibacterial wound cover can be renewed through calcinations without lost of its flexibility and antibacterial effect. Consequently, the Ag NPs grafted SiO_2nanofibers inthis investigation are very suitable to be applied as reusable wound cover

Miao J et al (2011), [88] generated biocompatible fibers by electrospinning from homogeneous solutions of cellulose, cellulose-chitosan, and cellulose-poly (methylmethacrylate) (PMMA) and1-ethyl-3-methylimidazolium acetate ([EMIM][OAc]) at room temperature ionic liquid. Electron microscopic analysis shows that these fibers have submicron-scale diameter. The fibers were chemically treated to generate aldehyde groups for the covalent immobilization of Lst. The resulting Lst-functionalized cellulose fibers were processed to obtain bandage preparations that showed activity against *S. Aureus* in vitro skin model with low toxicity toward keratinocytes, suggesting good biocompatibility for these materials as antimicrobial matrices in wound healing applications.

Choi J S et al (2008): [54] Biodegradable polymers were electrospun and recombinant human epidermal growth factor (EGF) was immobilized on the electrospun nanofibers for the purpose of treating diabetic ulcers. Amine-terminated block copolymers composed of poly(e-caprolactone) [PCL] and poly(ethyleneglycol) [PEG] and PCL were electrospun to biocompatible nanofibers with functional amine groups on the surface via PEG linkers. EGF was chemically conjugated to the surface of the nanofibers. The conjugation amount of EGF on the nanofibers was quantitated by X-ray photoelectron scattering. Human primary keratinocytes were cultivated on EGF-conjugated nanofibers in order to investigate the effect of EGF nanofibers on the differentiation of keratinocytes. Wound healing effects of the EGF nanofibers were confirmed in diabetic animals with dorsal wounds. The expression of keratinocyte-specific genes significantly increased with application of EGF-conjugated nanofibers. The EGF-nanofibers exerted superior in vivo wound healing activities compared to control groups or EGF solutions. Furthermore, immunohistochemical-staining results showed that EGF-receptor (EGFR) was highly expressed in the EGF nanofiber group. This study showed that EGF-conjugated nanofiber could potentially be employed as a novel wound healing material by increasing proliferation and phenotypic expression of keratinocytes.

Wound Healing Using Silver

Mathivanan V et al (2012), [89] studied the impact of silver nanoparticles on the wounded skin of fresh water fish, Anabastestudineus. Five fishes were taken and released into to experimental trough with 5 litter of water to which 10 and 20% concentration of the silver nanoparticle solution was taken. The wounded test fish Anabustestudineus was allowed to rear in the 2 experimental trough. From the present investigation, it was found that the wounded fish Anabas testudineus showed wound healing after 12 days only when it was kept in 10% solution of silver nanoparticles. Whereas, the wounded test fish kept in 20% solution of silver nanoparticles showed the wound healing within 8 days.

Ghosh S et al (2010), [90] prepared stable silver nanoparticles by the chemical process; these particles are incorporated in cotton fabrics. These cotton fabrics with silver nanoparticles are sterile and can be useful to prevent or to minimize infection with pathogenic bacteria such as *Staphylococcus aureus* and *Escherichia coli*. The antimicrobial

activity of Ag nanoparticles was investigated against *Escherichia coli* (MTCC-2940) Gram-negative bacterium, and *Staphylococcus aureus* (MTCC-74) Gram-positive bacterium. They found that, the growth-inhibitory effects on *S. aurous* were mild where as the growth-inhibitory effects on *E.coli* more potent and also perform dose dependent potency test of silver nanoparticles, when doses are increase so antimicrobial activity of Ag particles are increase. The bacteriostatic activity of Ag nanoparticles was evaluated by the help of SEM after 24 h incubation of bacterial strain inoculated cotton fabrics and calculated percent reduction of bacteria. They therefore hypothesized that silver nanoparticles could improve the healing of burn wounds initially on the basis of the known antimicrobial property of silver.

Atiyeh B S et al (2007), [91] examined all available evidence about effects, often contradictory, of silver onwound infection control and on wound healing trying to determine the practical therapeutic balance between antimicrobial activity and cellular toxicity. The ultimate goal remains the choice of a product with a superior profile of infection control over host cell cytotoxicity.

Tian J et al (2007), [92] investigated the role of silver nanoparticles in wound-healing in an animal model and they found that rapid healing and improved cosmetic appearance occur in a dose-dependent manner. Through quantitative PCR, immunohisto-chemistry, and proteomic studies, they found that silver nanoparticles exert positive effects through their antimicrobial properties, reduction in wound inflammation, and modulation of fibrogenic cytokines. These results have given insight into the actions of silver and have provided a novel therapeutic direction for wound treatment in clinical practice.

BASIC CONSIDERATIONS

I. Wound healing

A wound can be described as a defect or a break in the skin, resulting from physical or thermal damage or as a result of the presence of an underlying medical or physiological condition. Wound healing involves a complex series of interactions between different cell types, cytokine mediators, and the extracellular matrix. The phases of normal wound healing include hemostasis, inflammation, proliferation, and remodeling. Each phase of wound healing is distinct, although the wound healing process is continuous, with each phase overlapping the next. [93]

II. The process of wound healing

All tissues in the body are capable of healing by one of two mechanisms: regeneration or repair. Regeneration is the replacement of damaged tissues by identical cells and is more limited than repair. In humans, complete regeneration occurs in a limited number of cells for example, epithelial, liver and nerve cells. The main healing mechanism is repair where damaged tissue is replaced by connective tissue which then forms a scar. Wound healing can be defined as the physiology by which the body replaces and restores function to damaged tissues. [94]

In simple terms the process of wound healing can be divided into four dynamic phases: vascular response, inflammatory response, proliferation and maturation as in figure (1). There is considerable overlap between these phases, and the time needed by an individual to progress to the next phase of healing depends on various factors. [95, 96]

II.1. The Four Phases of Wound Healing

Tissue injury initiates a response that first clears the wound of devitalized tissue and foreign material, setting the stage for subsequent tissue healing and regeneration. The initial vascular response involves a brief and transient period of vasoconstriction and hemostasis. A 5-10 minute period of intense vasoconstriction is followed by active vasodilation accompanied by an increase in capillary permeability.

Platelets aggregated within a fibrin clot secrete a variety of growth factors and cytokines that set the stage for an orderly series of events leading to tissue repair. The second phase of wound healing, the inflammatory phase, presents itself as erythema, swelling, and warmth, and is often associated with pain. The inflammatory response increases vascular permeability, resulting in migration of neutrophils and monocytes into the surrounding tissue.

The neutrophils engulf debris and microorganisms, providing the first line of defense against infection. Neutrophil migration ceases after the first few days post-injury if the wound is not contaminated. If this acute inflammatory phase persists, due to wound hypoxia, infection, nutritional deficiencies, medication use, or other factors related to the patient's immune response, it can interfere with the late inflammatory phase.3. In the late inflammatory phase, monocytes converted in the tissue to macrophages, which digest and kill bacterial pathogens, scavenge tissue debris and destroy remaining neutrophils.

Macrophages begin the transition from wound inflammation to wound repair by secreting a variety of chemotactic and growth factors that stimulate cell migration, proliferation, and formation of the tissue matrix.

The subsequent proliferative phase is dominated by the formation of granulation tissue and epithelialization. Its duration is dependent on the size of the wound. Chemotactic and growth factors released from platelets and macrophages stimulate the migration and activation of wound fibroblasts that produce a variety of substances essential to wound repair, including glycosaminoglycans (mainly hyaluronic acid, chondroitin-4-sulfate, dermatan sulfate, and heparan sulfate) and collagen. [97] These form an amorphous, gel-like connective tissue matrix necessary for cell migration.

New capillary growth must accompany the advancing fibroblasts into the wound to provide metabolic needs. Collagen synthesis and cross-linkage is responsible for vascular integrity and strength of new capillary beds. Improper cross-linkage of collagen fibers has been responsible for nonspecific post-operative bleeding in patients with normal coagulation parameters. [98] Early in the proliferation phase fibroblast activity is limited to cellular replication and migration.

Around the third day after wounding the growing mass of fibroblast cells begin to synthesize and secrete measurable amounts of collagen. Collagen levels rise continually for approximately three weeks. The amount of collagen secreted during this period determines the tensile strength of the wound and all this steps is illustrated in figure (2).

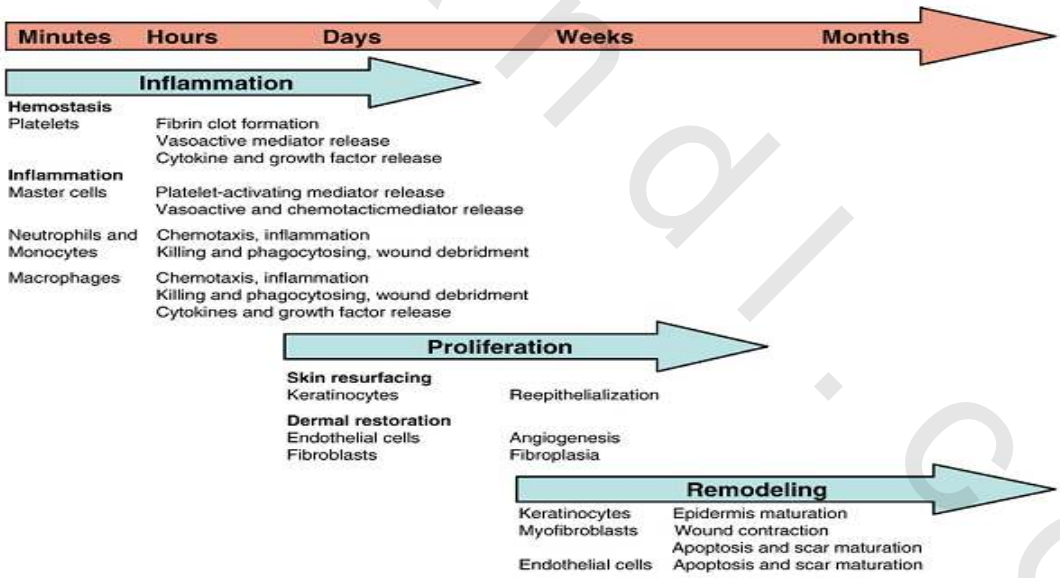

Fig.1: show stages of normal wound healing

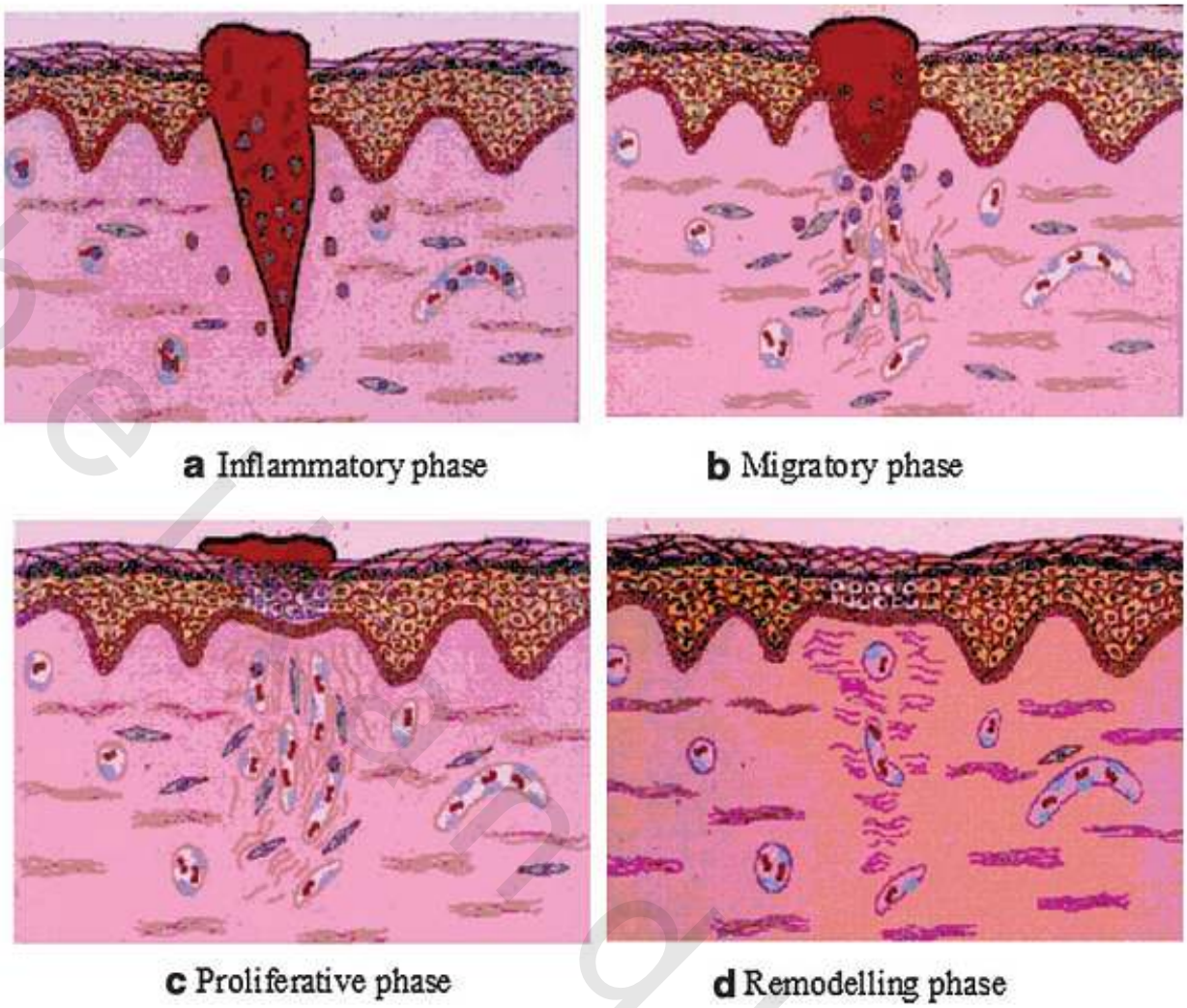

Fig. 2: **Schematic representation of the phases of wound healing (a) infiltration of neutrophils into the wound area (b) invasion of wound area by epithelial cells (c) epithelium completely covers the wound (d) many of the capillaries and fibroblasts, formed at early stages have all disappeared .**

III. Abnormal wound healing

Because successful wound healing requires adequate blood and nutrients to be supplied to the site of damage, the overall health and nutritional status of the patient influences the outcome of the damaged tissue. Some wound care experts advocate a holistic approach for wound patients that consider coexisting physical and psychological factors, including nutritional status and disease states such as diabetes, cancer, and arthritis lead to abnormal wound healing.

III.1. Diabetes mellitus

Diabetes mellitus (DM), long considered a disease of minor significance to world health, is now taking its place as one of the main threats to human health in the 21st

century. [99] It is the most common non-communicable disease worldwide and the fourth to fifth leading cause of death in developed countries. [100]

Diabetes mellitus (DM) is a serious problem of public health worldwide and it tends to increase in numbers, mainly in the developed countries. One of the most serious and debilitating complications of diabetes is the development of chronic non-healing foot ulcerations. Diabetic foot ulceration (DFU) is estimated to occur in 15% of diabetic patients; of-ten requires prolonged hospitalizations for its management and is the major cause of disease-associated amputations in the western world. [101-103]

Wound healing is an innate host response for restoration of tissue integrity. It is a complex process encompassing a number of coordinated steps, including homeostasis/coagulation, inflammation, and migration-proliferation and remodeling. [104] After a skin break is produced, leakage of blood from blood vessels occurs and a fibrin clot is formed, plugging the defect. This provides an immediate, provisional repair and initiates a cascade of events that culminate to wound closure. In this process, the aggregated platelets release cytokines and growth factors that recruit neutrophils and monocytes. Fibroblasts, epithelial cells and endothelial cells (EC) also migrate to the wound site to form a contractile granulation tissue that brings the wound margins closer.

Meanwhile, a fresh surface epithelium covers the wound surface and the granulation tissue differentiates progressively approaching the structural and functional characteristics of the mature dermis, finally repairing the lost tissue. This cascade implies the orderly initiation and arrest of many complex biological phenomena including cell proliferation, cell migration, cell differentiation and extracellular matrix (ECM) deposition.[105] The coordinated actions of cell and matrix signals orchestrate these processes.

The pathophysiologic relationship between diabetes and impaired healing is complex. In contrast to acute wounds that progress through the phases of wound healing linearly in healthy individuals, chronic wounds in diabetic patients become stalled in different phases and progression does not occur in synchrony due to diabetes associated neuropathy, micro angiopathy and impaired immune function. [104, 106]

The term “chronic wound” is generally accepted, but yet no simple definition has been agreed upon. A mechanistic definition such as “those not following normal wound healing trajectory” have been proposed but the most common definition have been “ulcers (wounds) older than 3 months of age”. Indeed, some ulcers have been present for years. One to two percent of the population in the developed countries will experience a chronic wound in their lifetime. [107]

It is expected that the number of chronic wounds will increase worldwide due to the increase of lifestyle diseases, such as diabetes, obesity, and cardiovascular diseases. Chronic wounds cause a significant burden to healthcare systems as well as morbidity and mortality to mankind.

IV. Wound Treatment

Ideally the wounds are treated according to their origin, i.e., pressure ulcers are treated with off-loading and ambulation, venous ulcers with compression therapy, and diabetic ulcers with off-loading and management of ischemia. However, the lack of

recognition of underlying predisposing factors leads to insufficient treatment and delays or even prevents healing. This includes restoration of the patient's health status in general if at all possible. This will need to new types of therapy.

IV.1. Physical Therapy

Novel approaches to managing and treating chronic wounds are continually being proposed, encompassing chemical, biological or physical treatments, or even combinations of these different approaches. [108] Physical therapy modalities are widely applied to wound healing enhancement, such as electrical, ultrasonic, and low-level laser stimulations. [109]

IV.1.1 Laser

Laser light is a very concentrated beam of light of a single wavelength (monochromatic), with all light waves aimed in a single direction (collimated) and all in phase with each other (coherence).

IV1.1.a Pulsing

There are principally two types of pulsing in laser phototherapy – chopped (switched) or super pulsed. A chopped beam is a continuous beam that is electronically (or mechanically) switched between on and off. During the moments when it is on it has typically the same output power as in continuous mode, but as it is not on all the time, the average output power is less than when it is continuous.

The average power is a function of the continuous wave power and the duty cycle (the ratio of the "on" time of the beam to the total emission ("on" + "off") time, usually expressed as a percentage). Typical laser types are most of the gas lasers (such as the He-Ne laser) and all semiconductors (diode) lasers.

In order to generate laser light, the current density in the Gas semiconductor crystal had to be extremely high. As a consequence of the high electric current the output power of this semiconductor laser is very high. Typical peak power is in the order of many watts. However, when an electric current is conducted through a material heat is generated, and with the necessary high current in this laser the crystal will burn up immediately unless the time of current conduction is extremely short, i.e., super-pulsed Gas lasers cannot work continuously.

The maximal pulse time for this laser is in the order of 100 to 200 nanoseconds and, after each such pulse, a long cooling time is needed, usually about a thousand times longer than said pulse time.

This form of pulsing is called super pulsing and, although the peak power is very high, the average output of super-pulsed lasers is comparatively low. Typical the Gas laser produces its maximum emission at 904 nm. [110]

IV1.1.b Emission And Absorption Of Light

A laser produces coherent light through a process termed "stimulated emission." The word **"LASER"** is an acronym for "**L**ight **A**mplification by **S**timulated **E**mission

of **R**adiation." A brief discussion of the interaction of light with atoms is necessary before stimulated emission can be described.

IV1.1.c Energy Levels In Atoms

An atom is the smallest particle of an element that retains the characteristics of the element. An atom consists of a positive nucleus surrounded by a "cloud" of negative electrons. All neutral atoms of a given element have the same number of positive charges (protons) in the nucleus and negative charges (electrons) in the cloud. The energy content of atoms of a particular type may vary, however, depending on the energies contained by the electrons within the cloud.

Each type of atom can contain only certain amounts of energy. When an atom contains the lowest amount of energy that is available to it, the atom is said to be in its **"atomic ground state."** If the atom contains additional energy over and above its ground state, it is said to be in an **"excited atomic state."**

Figure 3 is a simplified energy-level diagram of an atom that has three energy levels. This atom can contain three distinct amounts of energy and no others. If the atom has an energy content of E_1, it is in the atomic ground state and is incapable of releasing energy. If it contains energy content E_2 or E_3, it is in an excited state and can release its excess energy, thereby dropping to a lower energy state. Real atoms may have hundreds or even thousands of possible distinct energy states. The three-level mode is utilized here for purposes of clarity.

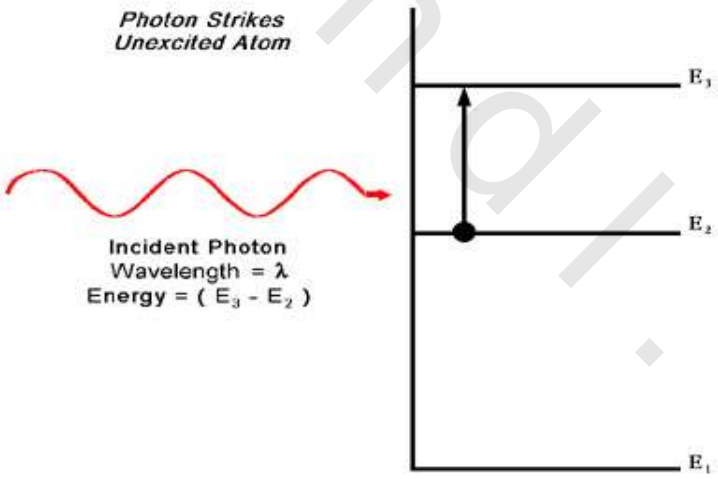

Fig. 3: Absorption of light

IV1.1.d Spontaneous Emission of Light

An atom in an excited state is unstable and will release spontaneously its excess energy and return to the ground state. This energy release may occur in a single transition or in a series of transitions that involve intermediate energy levels. For example, an atom in state E_3 of Figure 4 could reach the ground state by means of a single transition from E_3 to E_1, or by two transitions, first from E_3 to E_2 and then from E_2 to E_1. In any downward atomic transition, an amount of energy equal to the difference in energy content of the two levels must be released by the atom.

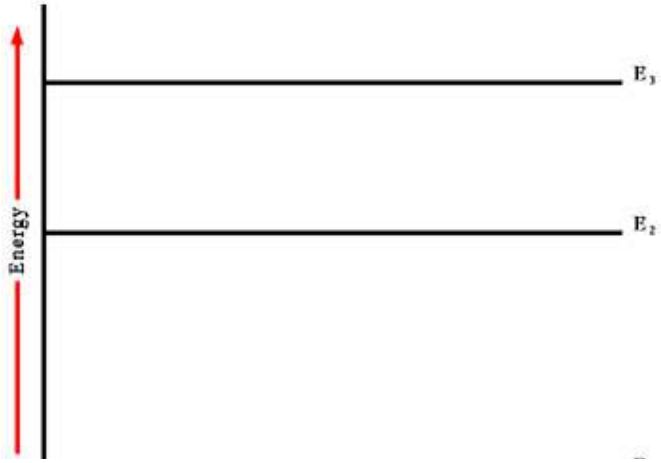

Fig. 4: Atomic energy-level diagram

In many cases, this excess energy appears as a photon of light. A **photon** is a quantum of light having a characteristic wavelength and energy content; in fact, the wavelength of the photon is determined by its energy. A photon of longer wavelength (such as that for red light) possesses less energy than one of shorter wavelength (such as that for blue light), as illustrated in Figure 5.

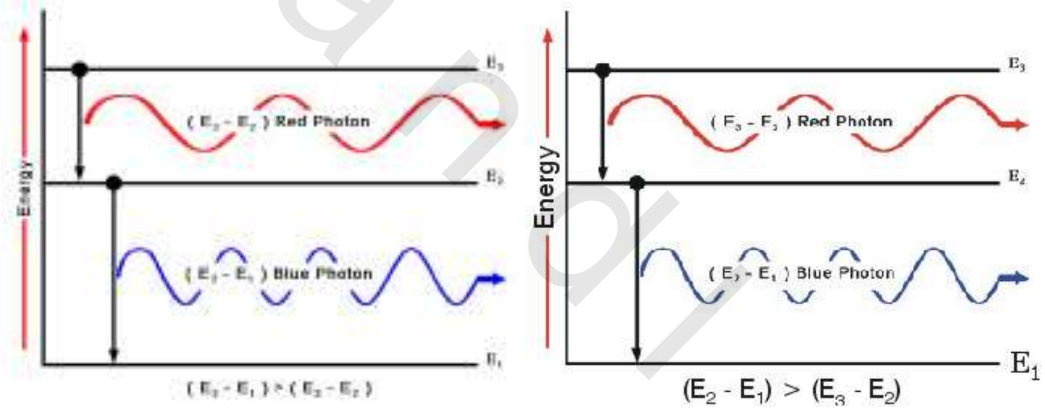

Fig. 5: Spontaneous emission

In ordinary light sources, individual atoms release photons at random. Neither the direction nor the phase of the resulting photons is controlled in any way, and many wavelengths usually are present. This process is referred to as "spontaneous emission" because the atoms emit light spontaneously, quite independent of any external influence. The light produced is neither monochromatic, directional, nor coherent.

IV1.1.e Stimulated Emission of Light

The coherent light of the laser is produced by a "stimulated-emission" process (Figure 6). In this case, the excited atom is stimulated by an outside influence to emit its energy (photon) in a particular way.

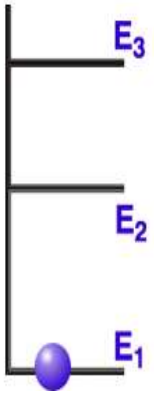

Fig.6 : Stimulated emission

The stimulating agent is a photon whose energy $(E_3–E_2)$ is exactly equal to the energy difference between the present energy state of the atom, E_3 and some lower energy state, E_2. This photon stimulates the atom to make a downward transition and emit, in phase, a photon identical to the stimulating photon. The emitted photon has the same energy, same wavelength, and same direction of travel as the stimulating photon; and the two are exactly in phase. Thus, stimulated emission produces light that is monochromatic, directional, and coherent. This light appears as the output beam of the laser. Figure 6 illustrates another process that occurs within a laser. Here, a photon strikes an atom in energy state E_2 and is absorbed by that atom. The photon ceases to exist; and its energy appears as increased energy in the atom, which moves to the E_3 energy level. The process of absorption removes energy from the laser beam and reduces laser output.

IV1.1.f Population Inversion

In order for a laser to produce an output, more light must be produced by stimulated emission than is lost through absorption. For this process to occur, more atoms must be in energy level E_3 than in level E_2, which does not occur under normal circumstances. In any large collection of atoms in matter at any temperature T, most of the atoms will be in the ground state at a particular instant, and the population of each higher energy state will be lower than that of any of the lower energy states. This is called a "normal population distribution."

Under "normal" circumstances, each energy level contains many more atoms than the energy level just above it, and so on up the energy lever ladder. For example, at room temperature, if there are N_o atoms in the ground state of Neon (He-Ne laser) there are only $10^{-33}N_o$ atoms in the first excited state, even fewer in the second excited state and so forth. The population of the ascending energy levels decreases exponentially.[111,112] Thus, in any large collection of atoms in matter at any temperature T, most of the atoms will be in the ground state at a particular instant, and the population of each higher energy state will be

lower than that of any of the lower energy states. This is called a "normal population distribution.

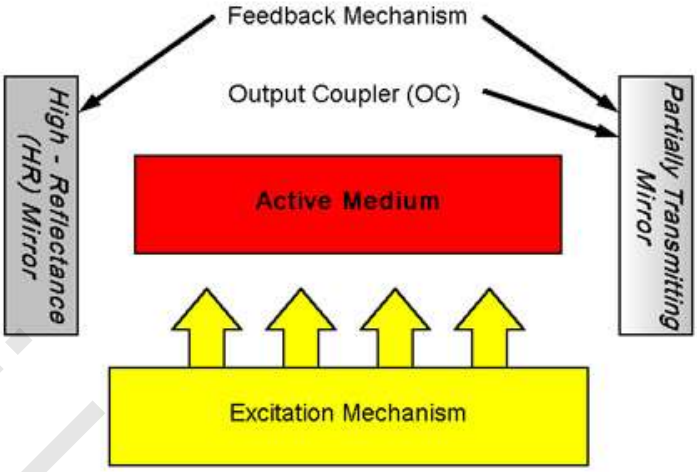

Fig.7 : Elements of a laser

Exists whenever more atoms are in an excited atomic state than in some lower energy state. The lower state may be the ground state, but in most cases it is an excited state of lower energy. Lasers can produce coherent light by stimulated emission only if a population inversion is present. And a population inversion can be achieved only through external excitation of the atoms.Four functional elements are necessary in lasers to produce coherent light by stimulated emission of radiation. Figure 7 illustrates these four functional elements. [113]

Since their inception in 1960, lasers have found many applications in medicine, including surgery, dental disease, pain management, and rheumatoid arthritis. [113] Interest in the efficacy of lasers as a noninvasive tool for wound healing has also developed. These lasers include helium-neon, gallium-arsenide, gallium-aluminum-arsenide (GaAlAs), Nd:YAG, carbon dioxide, ruby, and argon dye lasers. [114, 115]

IV1.1.g Medical application of laser

The use of low level lasers has gained popularity in the medical sciences over the past 30 years. [116] Lasers in dentistry often take advantage of a high power laser that can burn or disintegrate tissues. [117, 118] Mester et al. [119] was the first to report the beneficial effect of the low-energy laser (ruby laser) on wound healing. In contrast to other applications of the laser, which usually depend on photo thermal effects, the therapeutic benefit of a low level laser depends on photochemical and photo biological effects. Furthermore they do not lead to an increase of temperature in the exposed tissue . [116,120] Low level lasers work in the milli watt (mW) range with wavelengths in the red or near infrared spectrum range (400—900 nm) . [121] In addition, low level lasers do not cut or ablate tissue; in fact the basic principle of low level laser therapy (LLLT) is based on the biostimulation or biomodulation effects that are induced by the laser [122, 123]. Laser irradiation administered at a specific wave length has been shown to alter cellular behavior . [124] In vivo and in

vitro data suggest that LLLT can facilitate the motility of fibroblasts and keratinocyte cells, angiogenesis, growth factor release, and collagen synthesis. [122,125-129] After surgery, the healing process of wounds establishes tissue integrity quickly and effectively in most patients. Any delay or halt in wound healing is an important factor in overall recovery for both the clinician and the patient. Wound healing and tissue repair processes occur through a complex series of events that include clotting, inflammation, granulation, tissue formation, epithelialization, collagen synthesis, and tissue remodeling. [130] The use of LLLT for wound healing remains a controversial topic. Some clinical studies have shown that LLLT can accelerate the healing of injured tissues.[130-132]

There are perhaps three main areas of medicine and veterinary practice where LLT has a major role to play (Figure 8). These are (i) wound healing, tissue repair and prevention of tissue death; (ii) relief of inflammation in chronic diseases and injuries with its associated pain and edema; (iii) relief of neurogenic pain and some neurological problems. The proposed pathways to explain the mechanismsof LLLT should ideally be applicable to all these conditions.

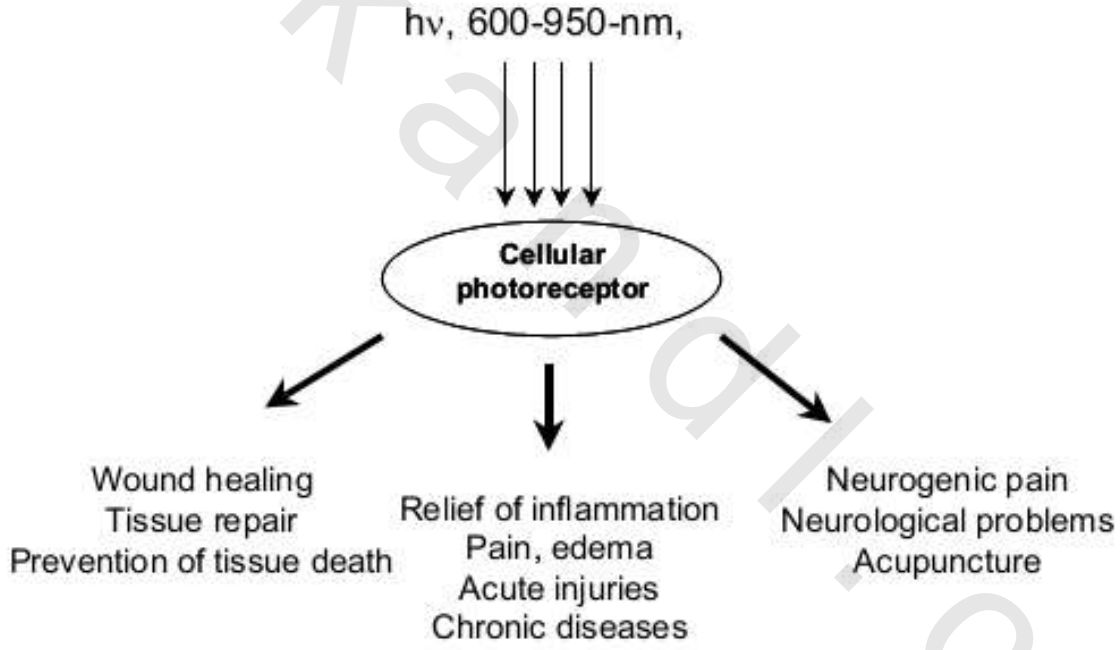

Fig. 8 : Schematic representation of the main areas of application of LLLT

IV1.1.h Low Level Laser Therapy In Wound Healing

Periodontal wound healing is necessary when periodontitis and gingivitis, or trauma , have affected the composition and integrity of the periodontal structures. LLLT (laser periodontal therapy) has also been shown to cause vasodilation, with increased local blood flow. This vasoactive effect is of relevance to the treatment of joint inflammation .LLLT causes the relaxation of smooth muscle associated with endothelium. This vasodilation brings in oxygen and also allows for greater traffic of immune cells into tissue. These two effects contribute to accelerate healing. [133, 134] Several in vitro studies have shown that

LLLT at certain wavelengths may stimulate fibroblast proliferation when certain combinations of exposure parameters and power densities are used. [135-142]

The range of radiation doses at which stimulation of fibroblast proliferation has been observed is wide (0.45 -60 J/cm^2).Of note high dose LPT suppresses both fibroblast proliferation and autocrine production of basic fibroblast growth factor.[143] LLLT effects on macrophages include increased ability to act as phagocytes, and greater secretion of basic fibroblast growth factor. Macrophages resorb fibrin as part of the demolition phase of wound healing more quickly with LLLT, because of their enhanced phagocytic activity during the initial phases of the repair response(for example,6 hours after trauma).

More rapid demolition of the wound establishes conditions necessary for the proliferative phase of the healing response to begin. Wound healing consists of several distinct phases, all of which can be affected at the cellular level by LLLT. The initial, pro-inflammatory and vasoactive phases of inflammation include clotting of any cut blood vessels and deposition of a platelet plug, after which the site is infiltrated by neutrophils and macrophages.[144] The second phase of wound healing involves proliferation, with the formation of granulation tissue as a result of new blood vessel growth. Direct evidence for enhanced collagen gene expression both in skin fibroblast cultures in vitro, as well as in animal models of wound healing in vivo, has been presented. [145]

A final aspect of the effect of LLLT on cells relates to the effects of laser light on the cytoskeleton. Several studies have suggested that LLLT can modulate cell behavior by causing rearrangements of the cytoskeleton.[146,147] Faster wound closure is of great importance in compromised patients, such as diabetics ,and patients undergoing treatment for malignancies. Because LLLT can enhance the release of growth factors from fibroblasts, and can stimulate cell proliferation, it is able to improve wound healing in such compromised patients. Histological studies have demonstrated that laser irradiation improves wound epithelialization, cellular content, granulation tissue formation, and collagen deposition in laser-treated wounds, compared to untreated sites. [148, 149] These findings have been confirmed in oral mucosal wound healing in clinical studies in humans.[150]

IV1.1.i Proposed mechanism of action of Laser

There has been an increased interest in the use of low-intensity red and near infrared laser radiation to accelerate wound healing and tissue regeneration. Photobiological responses are the result of photochemical and/or photophysical changes produced by absorption of non-ionizing electromagnetic radiation. [151]

Lasers have been evaluated as a non-invasive treatment for wound healing. Several different lasers have been identi-fied as producing a beneficial biological effect, including the argon, helium–neon (He Ne), gallium–aluminum–arsenide (GaAlAs), gallium–arsenide (GaAs) and neodymium: yttrium–aluminum–garnet (Nd:YAG) lasers. [152]

This effect, called “photostimulation” or “biostimulation”, producesnon-destructive effects on tissues at the cellular level. All of these effects may enhance wound healing. Furthermore, a decrease in time required for experimental and clinical wound healing is reported in several reviews and studies. [152-159] Laser stimulation does not appear to alter

the inflammatory effect of monocytes and endothelial cells in vitro; such cells that are also important for good wound healing. [160]

Photostimulation results in increased cellular activity during wound healing. [161] The chemical and metabolic changes that occur within the cells during laser biostimu-lation are poorly understood. [162] Some effects of photo-stimulation that may influence wound healing have been reported in vitro, including fibroblast proliferation, collagen synthesis, macrophage stimulation, and a greater rate of extracellular matrix production. [163, 25]

A basic feature of the low level laser is that an interaction between photons and cells takes place. Absorption of the photon energy into molecules increases their kinetic energy. It modulates cell behavior, creating either stimulation or inhibition. A number of hypotheses have been proposed to explain the photobiological effects of low intensity light on cells. [25,162-166] These have been divided into primary or light induced, reactions, and secondary, dark, or non-light induced reactions.

Of the primary reactions, it is thought that the absorption of light by mitochondrial enzymes may enhance molecular vibration and cause local heating. It has been suggested that stimulation or inhibition may also result from the absorption of light by mitochondrial flavins and cytochromes, causing transfer of electrons.

Other suggestions are the induction by light of singlet oxygen by porphyrins, and the direct activation by the radiation of calcium channels in the cell membrane, causing cell proliferation. Possible 'dark' reactions may be the alteration of the intracellular pH, leading to activation of ATP, and an increase in intracellular calcium. High levels of intracellular calcium are known to stimulate biological processes as in figure (9). Red monochromatic light, as used in phototherapy has been shown to cause either stimulation or inhibition depending on the dose applied. [25]

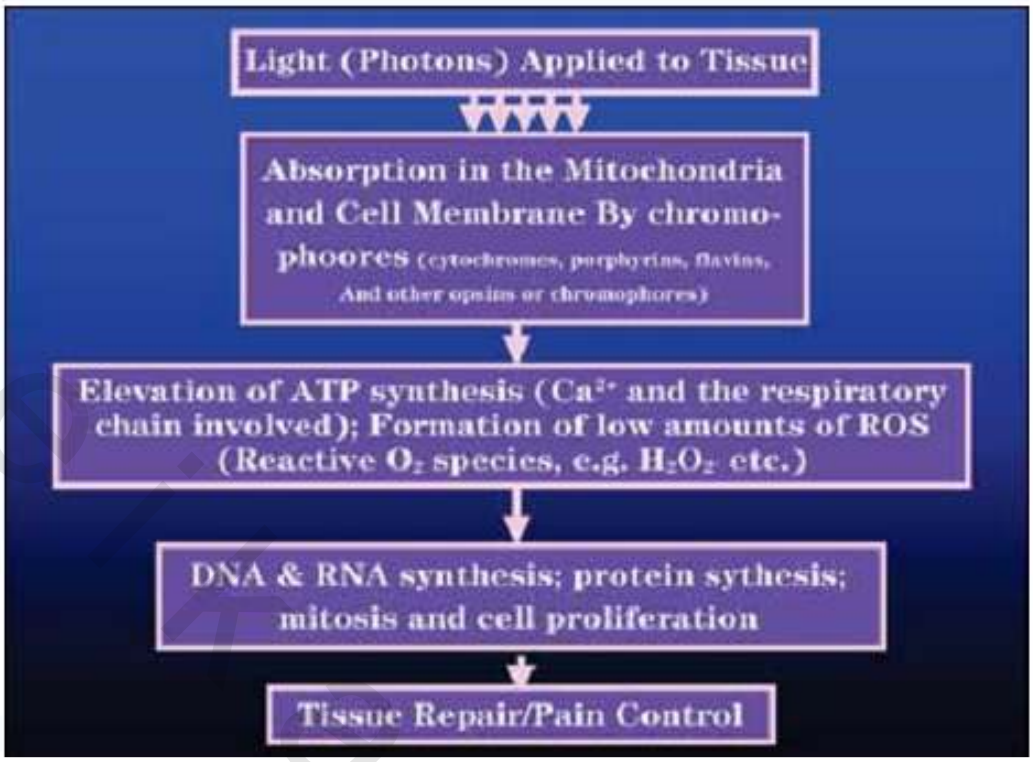

Fig. 9: **Schematic showing how light is absorbed by cells and the cascade of events resulting from light absorption. ATP is produced in this process and used to synthesize needed proteins, enzymes, and other tissue components.**

IV.2 Ultrasound

The ability of ultrasound to interact with tissue to produce biological changes has been known for a long time.

It is convenient to divide therapeutic ultrasound into two classes, applications that use 'low' intensity (0.125-3 W cm^2) and those using 'high' intensities (15 Wcm^2). The intention of the lower intensity treatments is to stimulate normal physiological responses to injury, or to accelerate some processes such as the transport of drugs across the skin. The purpose of the high intensity treatments is rather to selectively destroy tissue in a controlled fashion. An alternative classification scheme would be in terms of applications for which the sound is directly coupled to the tissue via a coupling medium, and those for which the ultrasound transducer is coupled to a wave guide terminated with a tool specifically designed for the task required. [(167)]

IV.2.1 Physiotherapy

Ultrasound was originally introduced into physiotherapy as an alternative diathermy technique, to compete with hot pack, microwave and radiofrequency heating. Its main use has been in the treatment of soft tissue injuries, but it has also been applied to bone and joint conditions and to accelerate wound healing.

Most physiotherapy units offer spatial average intensities up to 3 W cm2 and offer one or more transducers operating at discrete frequencies in the range 0.75-5 M Hz. The choice of transducer depends on the depth of the target to be treated, deeper targets requiring lower frequencies because of the frequency dependence of ultrasonic attenuation.

Devices offer either discrete intensity settings or continuously variable controls. The output may be continuous or pulsed. Pulsed exposures are often chosen when thermal effects are to kept to a minimum. Commonly available pulsing regimes are 2:2 and 2:8 ms. [(167)] Therapy transducers are usually made of low loss lead zirconate titanate (PZT4). They are mounted in a light-weight, hand-held waterproof housing, and are air-backed. For physiotherapy applications, the sound is usually coupled directly into the patient through a thin layer of coupling medium (e.g. aqueous gel or mineral oil), al-though for awkward geometries the limb to be treated may immersed in a small water bath.

IV.2.2 Biomedical Applications of Ultrasound

Ultrasound, a form of mechanical energy that is transmit-ted through and into biological tissues as an acoustic pressure wave at frequencies above the limit of human hearing, is used widely in medicine as a therapeutic, operative, and diagnostic tool. [(168)] Therapeutic ultrasound, and some operative ultrasound, use intensities as high as 1 to 3 W/cm^2 and can cause considerable heating in living tissues. To take full advantage of this energy absorption, physical therapists often use such levels of ultrasound acutely to decrease joint stiffness, to reduce pain and muscle spasms, and to improve muscle mobility.

The use of ultrasound as a surgical instrument involves even higher levels of intensity (5 to 300 W/cm^2), and sharp bursts of energy are used to fragment calculi, to initiate the healing of non-unions, to ablate diseased tissues such as cataracts, and even to remove methylmethacrylate cement during revision of prosthetic joints. At the opposite end of the ultrasound-intensity spectrum, much lower magnitudes of 1 to 50 mW/cm^2 are used to drive diagnostic devices that noninvasively image vital organs, fetal development, peripheral blood flow, and metabolic bone diseases such as osteoporosis [(169)] and, coincidentally, to evaluate fracture callus during healing. [(170)]

The intensity level used for imaging, which is five orders of magnitude below that used for surgery, is regarded as non-thermal and nondestructive. Nevertheless, low-intensity ultrasound is still a mechanical force, and it therefore holds the potential to influence bone mass and morphology through bone tissue's strong sensitivity to physical stimuli.

IV.2 .2.a Bone injuries

Repair of bone injuries follows the same inflammatory, proliferative and remodeling phases seen for soft tissue repair. Experimental studies using fractures in rat fibulae have found that ultrasound treatment during the inflammatory and early proliferative phases of repair enhanced healing, but that exposure during late proliferative phase proved disadvantageous, leading to a delay in boney union. For bone healing, it appears that while low intensities (0.03 – 0.5 W cm^2 spatial averages, temporal average intensity) can produce beneficial effects, too high intensity (B0.5Wcm^2 spatial average, temporal average intensity) can be deleterious.

IV.2.2.b Soft tissue injuries

It has been demonstrated both in the laboratory, and in clinical trials that ultrasound can stimulate tissue repair and wound healing if correctly applied. [171] It appears that exposure to ultrasound during the initial 'inflammatory' phase of tissue repair can lead to an acceleration of this phase, although ultrasound is not in itself an anti-inflammatory agent. The second phase of healing is the 'proliferative' stage. This is the stage at which cells mi- grate to the site of injury and start to divide, granulation tissue is formed, and fibroblasts begin to synthesize collagen. Ultrasound has been shown to enhance collagen synthesis by fibroblasts. The final phase of tissue repair is one of 'remodeling'. There is also evidence that scar tissue treated with ultrasound may be stronger and more elastic that 'normal' scar tissue.

Ultrasound has found a place in management of chronic wounds. The wound healing actions include collagen synthesis, angiogenesis, fibroblast stimulation, reduction of inflammation and cellular proliferation. In chronic wounds it has been found to facilitate transition to the stage of granulation from the stage of inflammation. A typical effect of ultrasound is cavitation i.e. formation of holes/gas bubbles in liquid medium. With respect to chronic wounds it causes holes in bacterial cell membrane leading to increased uptake of antiseptics and antibiotics, thus facilitating their action. [172] Low frequency ultrasound at 40 kHz at low intensity coupled with saline mist has been found as a novel alternative to surgical debridement. [173] Multiple studies have demonstrated the beneficial effect of ultrasound in treatment of chronic wounds. [173-175]

V. Nanotechnology

Nanotechnology literally means any technology on a nanoscale that has applications in the real world. Nanotechnology encompasses the production and application of physical, chemical, and biological systems at scales ranging from individual atoms or molecules to submicron dimensions, as well as the integration of the resulting nanostructures into larger systems.

Nanotechnology or Nanoscaled Technology is generally considered to be at a size 100 nm (a nanometer is one billionth of a meter, 10^{-9}m). Nanoscale science (or nanoscience) studies the phenomena, properties, and responses of materials at atomic, molecular, and macromolecular scales, and in general at sizes between 1 and 100 nm. In this scale, and especially below 5 nm, the properties of matter differ significantly (i.e., quantum-scale effects play an important role) from that at a larger particulate scale. Nanotechnology is then the design, the manipulation, the building, the production and application, by controlling the shape and size, the properties-responses and functionality of structures, and devices and systems of the order or less than 100 nm.

Nanotechnology is considered an emerging technology due to the possibility to advance well-established products and to create new products with totally new characteristics and functions with enormous potential in a wide range of applications. In addition to various industrial uses, great innovations are foreseen in information and communication technology, in biology and biotechnology, in medicine and medical technology, in metrology, etc. Significant applications of nanosciences and nanoengineering lie in the fields of pharmaceutics, cosmetics, processed food, chemical

engineering, high-performance materials, electronics, precision mechanics, optics, energy production, and environmental sciences. (176)

Nanotechnology can help in solving serious humanity problems such as energy adequacy, climate change or fatal diseases: "Nanotechnology" Alcatel-Lucent is an area which has highly promising prospects for turning fundamental research into successful innovations. Not only to boost the competitiveness of our industry but also to create new products that will make positive changes in the lives of our citizens, be it in medicine, environment, electronics or any other field. Nanosciences and nanotechnologies open up new avenues of research and lead to new, useful, and sometimes unexpected applications. Novel materials and new-engineered surfaces allow making products that perform better. New medical treatments are emerging for fatal diseases, such as brain tumours and Alzheimer's disease. (177)

VI. Nanomaterials

Nanomaterials with unique properties such as: nanoparticles carbon nanotubes, fullerenes, quantum dots, quantum wires, nanofibers, and nanocomposites allow completely new applications to be found.

Nanomaterials are corner stones of nanoscience and nanotechnology. Nanostructure science and technology is a broad and interdisciplinary area of research and development activity that has been growing explosively worldwide in the past few years. It has the potential for revolutionizing the ways in which materials and productsare created and the range and nature of functionalities that can be accessed. It is already having a significant commercial impact, which will assuredly increase in the future.

Once within the body, the larger surface area of nanomaterials per unit of mass makes them more chemically reactive than their normal-scale counterparts, and therefore more likely to interact with biological molecules. This is particularly likely where the size and shape or other characteristics of a nanomaterial mimic biologically active components of the body's systems, such as immune molecules, DNA-binding proteins, or cell components. Cell studies indicate that some nanomaterials may interact with cell DNA, cause inflammation and oxidative damage, and impair cell function.(178) Engineered modifications to nanomaterials, such as surface coatings, can alter a material's solubility, chemical activity, toxicity, and other properties, providing an opportunity to reduce the risks associated with a material early in its design. (179)

Nanoscale materials are defined as a set of substances where at least one dimension is less than approximately 100 nanometers. A nanometer is one millionth of a millimeter approximately 100,000 times smaller than the diameter of a human hair. Nanomaterials are of interest because at this scale unique optical, magnetic, electrical, and other properties emerge. These emergent properties have the potential for great impacts in electronics, medicine, and other fields.

VI.1 Where are nanomaterials found?

Some nanomaterials occur naturally, but of particular interest are engineered nanomaterials (EN), which are designed for, and already being used in many commercial products and processes. They can be found in such things as sunscreens, cosmetics,

sporting goods, stain-resistant clothing, tires, electronics, as well as many other everyday items, and are used in medicine for purposes of diagnosis, imaging and drug delivery. Engineered nanomaterials are resources designed at the molecular (nanometre) level to take advantage of their small sizeand novel properties which are generally not seen in their conventional, bulk counterparts.

The two main reasons why materials at the nano scale can have different properties are increased relative surface area and new quantum effects. Nanomaterials have a much greater surface area to volume ratio than their conventional forms, which can lead to greater chemicalreactivity and affect their strength. Also at the nanoscale, quantum effects can become much more important in determining the materials properties and characteristics, leading to novel optical, electrical and magnetic behaviors.

Nanomaterials are already in commercial use, with some having been available for several years or decades. The range of commercial products available today is very broad, including stain-resistant and wrinkle-free textiles, cosmetics, sunscreens, electronics, paints and varnishes. Nanocoatings and nanocomposites are finding uses in diverse consumer products, such as windows, sports equipment, bicycles and automobiles. There are novel UV-blocking coatings on glass bottles which protect beverages from damage by sunlight, and longer-lasting tennis balls using butyl-rubber/nano-clay composites. Nanoscale titanium dioxide, for instance, is finding applications in cosmetics, sun-block creams and self-cleaning windows, and nanoscale silica is being used as filler in a range of products, including cosmetics and dental fillings.

VI.2 Nanofibers

VI.2.1 Techniques of Electrospinning for Nano Fibers:-

Unlike conventional methods of fiber formation like dry-spinning or wet-spinning, electrospinning makes use of electrostatic forces to stretch the solution or melts as it solidifies. Similar to the conventional methods, drawing solution to form the fibers will continue as long as there is enough solution to feed the electrospinning jet. Thereby, the collected fiber mat would be distribution of continuous nanofibers. [180]

For a typical electrospinning setup as shown in Figure (10), there are basically three components to fulfill the process: a syringe with a metal spinneret of small diameters, a high voltage supplier, and a rotating collector. In the electrospinning process, a high voltage in the range of 10-100 kV is used to create an electrically charged jet of polymer solution or melt out of the spinneret. A cone-shaped of the polymer solution droplet directed to the counter electrode is formed under the high voltage. [181, 182] As the voltage increasing, the droplet on the spinneret is slowly stretched, and if the voltage is increased keeping continue, a jet is formed from the deformed droplet, which moves towards the counter electrode and becomes narrower in the process. Before reaching the collector, the solution jet which is loaded with electrostatic charges undergoes stretching. With evaporation of solvents, the jet eventually solidified on the collector in the form of nanofibers.

Electrospinning is a widely used technique for the production of nanofibers from various natural or synthetic polymers, but also from metal, ceramic and glass material with a broad range of applications, such as filtration, textiles, energy, acoustics, as well as

medicine. [183, 184] There have been various processing techniques used to produce nanofibers (e.g., drawing out [185], molecular self assembly [186] or thermally induced phase separation [187]), but the electrospinning technique [187, 188] is the only method capable of producing continuous polymeric nanofibers that provides numerous opportunities to manipulate and control surface area, fiber diameter, the porosity of the nanofibrous layer (fiber density) as well as base weight (fiber weight per area). [189]

The promising modifications of electrospinning technique are e.g., co-axial electrospinning that enables the encapsulation of drugs or bioactive components in core shell nanofibers [180] or electrohydrodynamic printing. [190] Regarding the nanofiber formation in the electrospin-ning process, the polymer jets can be ejected either at the needle tip (needle or capillary spinners) or from liquid surfaces on a rotating spinning roller or wire (needleless technology). In contrast to needle electrospinning, which create single nanosized fibers at a time and thus is limited by low process efficiency, needleless technology is very flexible and enables the creation of nanofibers with diameters ranging from tens of nanometers to tens of micrometers with high production capacity on an industrial scale. [191]

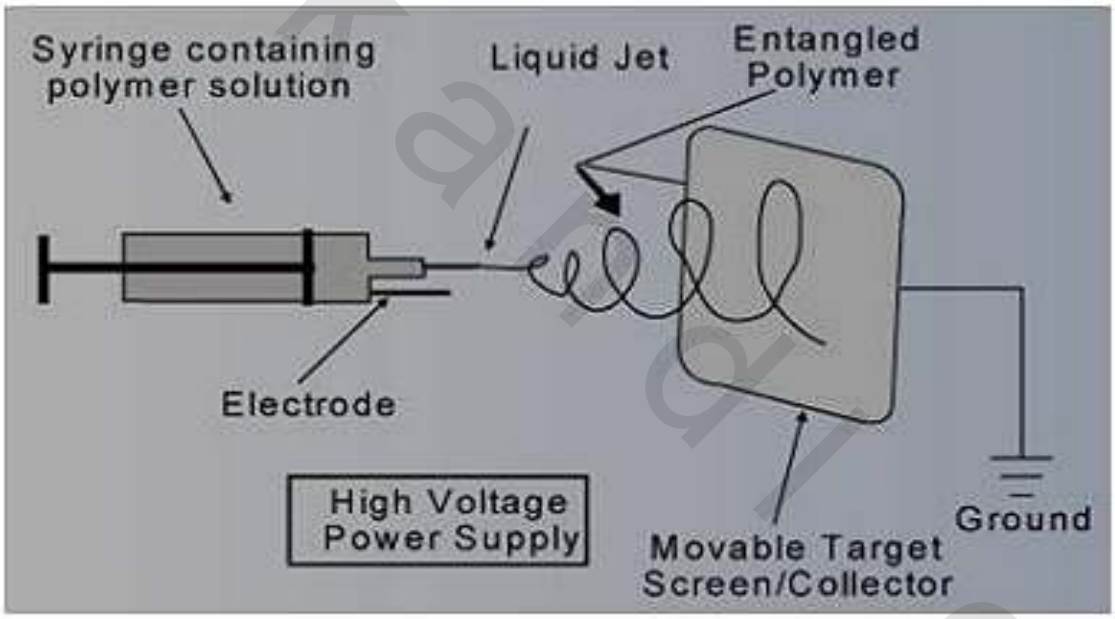

Fig. 10 : schematic diagram of the electrospinning setup

VI.2.2 Polymer- Solvents Used For Nano Fibers:-

The polymer is usually dissolved in suitable solvent and spun from solution. Nanofibers in the range of 10-to 2000 nm diameter can be achieved by choosing the appropriate polymer solvent system such as Nylon 6 and nylon 66- Formic Acid, Polyacrylonitrile- Dimethyl formaldehyde, PET-Trifluoroacetic acid/Dimethyl chloride, PVA-Water, Polystyrene- DMF/Toluene, Nylon-6-co-polyamide-Formic acid, Polybenzimidazole-Dimethyl acetamide, Polyramide- Sulfuric acid, Polyimides-Phenol.[192]

VI.2.3 Properties of Nano Fibers

Nanofibers exhibit special properties mainly due to extremely high surface to weight ratio compared to conventional nonwovens.how much smaller nanofibers are compared to a human hair, which is 50-150 μm and the size of a pollen particle compared to nanofibers. The elastic modulus of polymeric nanofibers of less than 350 nm is found to be 1.0±0.2 Gpa. Low density, large surface area to mass, high pore volume, and tight pore size make the nanofiber nonwoven appropriate for a wide range of filtration applications. [193]

VI.2.4 Applications of Nano Fibers

The attractive feature of electrospun nanofibers for biomedical applications consists in their highly porous structure resembling the structure of extracellular matrix, which has been shown to support the adhesion, proliferation and differentiation of various cells and which can be also used as therapeutic agent delivery systems. [194] Additionally, characters of nanofibrous membranes have been also proved as suitable material for wound dressing[195, 196]. High porosity with essential small pores enables the good permeability for oxygen and water and the adsorption of liquids, and concomitantly protects the wound from bacterial penetration and dehydration as in figure (11). [195, 197]

High surface area and porosity of the nanofibers promote migration of keratinocytes on the wound surface and may have role in accelerating of the healing process. Nanofibers composed of natural polymers, such as chitosan a chitosan–gelatin blend, chitosan coated poly(vinyl alcohol), collagen, or synthetic polymers or their blends, such as PCL, polyvinyl alcohol (PVA), polyacrylonitrile (PAN), heparin-coated aligned poly-lactic acid (PLA) gelatine/polyuretan, poly(L-lacticacid)-co-poly(epsilon-caprolactone) [197] or polyethersulfone have been specifically engineered as dressings for wound healing or as tissue engineered scaffolds for skin substitutes.

In addition to physical protection of the wound site, nanofibrous materials have also been developed for the local delivery of therapeutic agents, such as antibiotics [198] or growth factors [54], and they can be enriched with silver nanoparticles as an antibacterial agent. [199] As a new approach for skin tissue engineering, an attempt to form dermal-like or bilayer skin tissue from fibroblast/fiber layered constructs or keratinocyte/fibroblast/fiber layered 3D constructs has been made using poly-e-caprolactone/ collagen nanofibers. Beneficial effects on wound healing were also found using nanofiber membranes com-posed from poly (3-hydroxybutyrate-co-3-hydroxyvalerate) nanofiber matrices co-cultured with hair follicular epithelial and dermal cells.

Some major application of Nano fibers given below

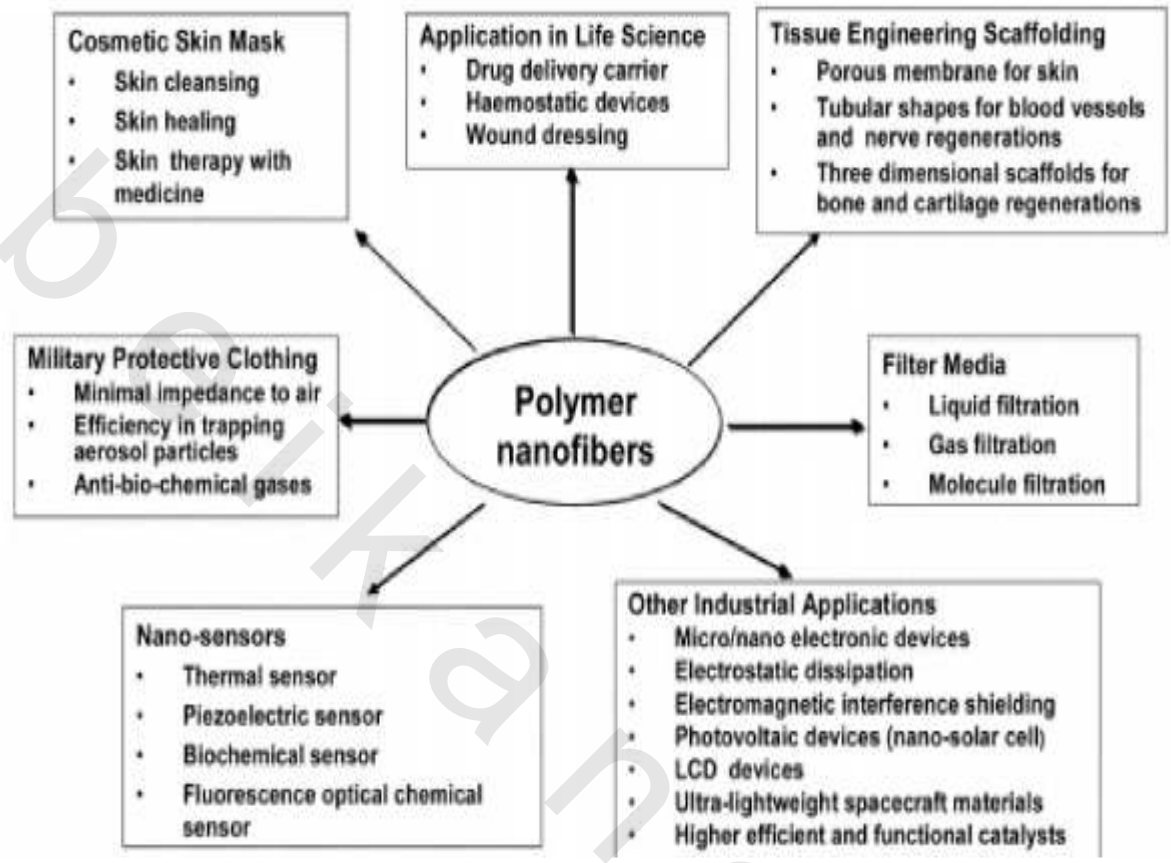

Fig. 11 : potential application of nanofibers

1- Nano Fibers in Tissue Engineering:-

Developing scaffolds that mimic the architecture of tissue at the nanoscale is one of the major challenges in the field of tissue engineering. The development of nanofibers has greatly enhanced the scope for fabricating scaffolds that can potentially meet this challenge. Currently, there are three techniques available for the synthesis of nanofibers: electrospinning, self-assembly, and phase separation. Of these techniques, electrospinning is the most widely studied technique and has also demonstrated the most promising results in terms of tissue engineering applications. The availability of a wide range of natural and synthetic biomaterials has broadened the scope for development of nanofibrous scaffolds, especially using the electrospinning technique.

The three dimensional synthetic biodegradable scaffolds designed using nanofibers serve as an excellent framework for cell adhesion, proliferation, and differentiation.

Therefore, nanofibers, irrespective of their method of synthesis, have been used as scaffolds for musculoskeletal tissue engineering (including bone, cartilage, ligament, and skeletal muscle), skin tissue engineering such as (Cosmetic Skin Masks, Skin Cleansing, Skin Healing, Skin Therapy), vascular tissue engineering, neural tissue engineering, and as carriers for the controlled delivery of drugs, proteins, and DNA. nanometer scale. The high

surface area to volume ratio of the nanofibers combined with their microporous structure favors cell adhesion, proliferation, migration, and differentiation, all of which are highly desired properties for tissue engineering applications. Therefore, current research in this area is driven towards the fabrication, characterization, and applications of nanofibrous systems as scaffolds for tissue engineering. Due to their potential, the nanofiber-based systems are also being pursued for a variety of other biological and non-biological applications.

2- Nano Fibers in Air and liquid filters:-

Today mostly air filter required for automobile fume, Dust cake Filtration. Maintenance Decisions are largely made based on Economic factors and trained personnel provide oversight on Maintenance intervals and filter selection. The use of Nano fiber filter media has provided extended service Life in a variety of on-road and off-Road Applications. In mining Applications, Nanofiber filters have provided four Times the Filter Life. In on-Road applications, Nanofiber Filters are available with twice the filter Life of Conventional Cellulose Filters. the application of nanofibers is enormous and one of the break through domains in future will be to use them as filter media in clean air applications in hospitals and research laboratory where maintain to aseptic environment.

This idea is based on the fact the filtration efficiency of nylon-6 nanofibrous membranes, which is better than the commercialized high-efficiency particulate air filter (HEPA). One of the drawbacks is that they observed high pressure drop across the membrane. However, this study suggests that they can be potentially employed as HEPA filter with high efficiency in clean air applications such as in hospitals (and other applications) wherein the contaminated air (bacteria and other pathogens) in a room can be filtered before entering into other rooms due to centralized air conditioning systems.

Nanofibers have significant applications in the area of filtration since their surface area is substantially greater and have smaller micropores than melt blown (MB) webs. High porous structure with high surface area makes them ideally suited for many filtration applications. Nanofibers are ideally suited for filtering submicron particles from air or water. Electrospun fibers have diameters three or more times smaller than that of MB fibers.

This leads to a corresponding increase in surface area and decrease in basis weight. The fiber surface area per mass of nanofiber material compared to MB fibers. Nanofiber combined with other nonwoven products have potential uses in a wide range of filtration applications such as aerosol filters, facemasks, and protective clothing. At present, military fabrics under development designed for chemical and biological protection have been enhanced by laminating a layer of nanofiber between the body side layer and the carbon fibers. e-Spin Technologies, Inc has produced a prototype of activated carbon nanofiber web. PAN- based nanofibers were electrospun. Then these webs were stabilized, carbonized, and activated. These activated PAN nanofibers gave excellent results for both aerosol and chemical filtration

Electrospun nanofiber webs are used for very specialized filtration applications. Donaldson is making and marketing filter media that incorporate electrospun nylon fibers for gas turbines, compressor and generators NanoFibers in Medicals:-Nanofibers are also used in medical applications, which include, drug and gene delivery, artificial blood

vessels, artificial organs, and medical facemasks. For example, carbon fiber hollow nano tubes, smaller than blood cells, have potential to carry drugs in to blood cells. Nanofibers and webs are capable of delivering medicines directly to internal tissues. Anti-adhesion materials made of cellulose are already available from companies. Researchers have spun a fiber from a compound naturally present in blood.

This nanofiber can be used as varieties of medical applications such as bandages or sutures that ultimately dissolve in to body. This nano fiber minimizes infection rate, blood lose and is also absorbed by the body to meet these varied requirements a layered composite structure is used. The bulk of the filter is generally made of one or multiple MB layers designed from coarse to fine filaments. This is then combined with a nanofiber web. The MB layer provides fluid resistance while the outer Nano fiber layer improves sm oothness for health, wear and comfort.

Nanofibers greatly enhance filtration efficiency (FE). Scientists at the U.S. Army Natick Soldier Center studied the effectiveness of nanofibers on filter substrates for aerosol filtration. They compared filtration and filter media deformation with and without a nanofiber coating of elastic MB and found that the coating of nanofiber on the substrate substantially increases FE. With most of the nanofiber filter media, a substrate fabric such as SB or MB fabric is used to provide mechanical strength, stabilization, pleating, while nanofiber web component is used to increase filtration performance.

3- Nano Fibers in Industry composite construction:-

Nanofibers were applied to 0.6 ounces per square yard (osy) nylon SB material and to 1.0 osy nylon SB then two such layers were laminated together Three different types of nanofiber composite fibers designed by altering the thickness and weight of base cloth. The performance and the durability of the composite structure depend on the finished fabric architecture. The final nanofiber fabric architecture is as two types of constructions are; First the nanofiber/SB layer between outer shell layer fabric and chemical filtration layer. Second Nanofiber /SB layer is impregnated over the shell fabric and free floats against chemical filtration layer.

Polymeric nanofiber composites can provide enhanced protection against chemical agent micro droplets, biological aerosols, radioactive ducts, etc. some significantly use of nano fibers at Industrial applications as electronic, optical instruments are Micro/nano electronic devices, Electrostatic dissipation, Electromagnetic interference shielding, Photovoltaic devices (nano-solar cell), LCD devices, Higher-efficiency catalyst carriers etc.

4- Nano Fibers in Wound dressings:-

On traditional time wound care and dressing by some plants fibers in which contained cellulose polymers, now advanced wound care dressings operate in moist environments, require less frequent changing and help reduce the pain of dressing changes and lessen scarring. Acute wounds, including those caused by burns, surgical or traumatic wounds Chronic wounds, such as ulcers, not proceeding through the normal stages of healing Permeability of gases and liquids High absorption capacity of liquids (exudate) High filtration efficiency for bacteria resulting in decreased infections Possibility to add drugs – haemostatic or antimicrobial dressing .

Swelling and gel forming capability to keep moist environs Anti adhesive effect to the derma painless removal of the dressing without destroying newly formed tissue .Contribution of Nanofibers In Advanced Wound Care Relevant polymers produced with technology include, Polyvinyl alcohol, Chitosan, Carboxymethyl celulose, Gelatine, Collagen, Hyaluronic acid, Polyurethane and others. Polymer nanofibers can also be used for the treatment of wounds or burns of a human skin, as well as designed for haemostatic devices with some unique characteristics which can let wounds heal by encouraging the formation of normal skin growth and eliminate the formation of scar tissue which would occur in a traditional treatment as in figure (12).

Wound dressing usually have pore sizes ranging from 500 nm to 1 mm, small enough to protect the wound from bacterial penetration via aerosol particle capturing mechanisms. Nano Fibers in Surface modifications:-Generally, surface modify by hydrophobic membranes can be modified to hydrophilic membranes by using various methods such as Plasma induced surface grafting (PISG) treatment, Chemical oxidation, Organic chemical surface functionalization and Radiation induced surface grafting method.

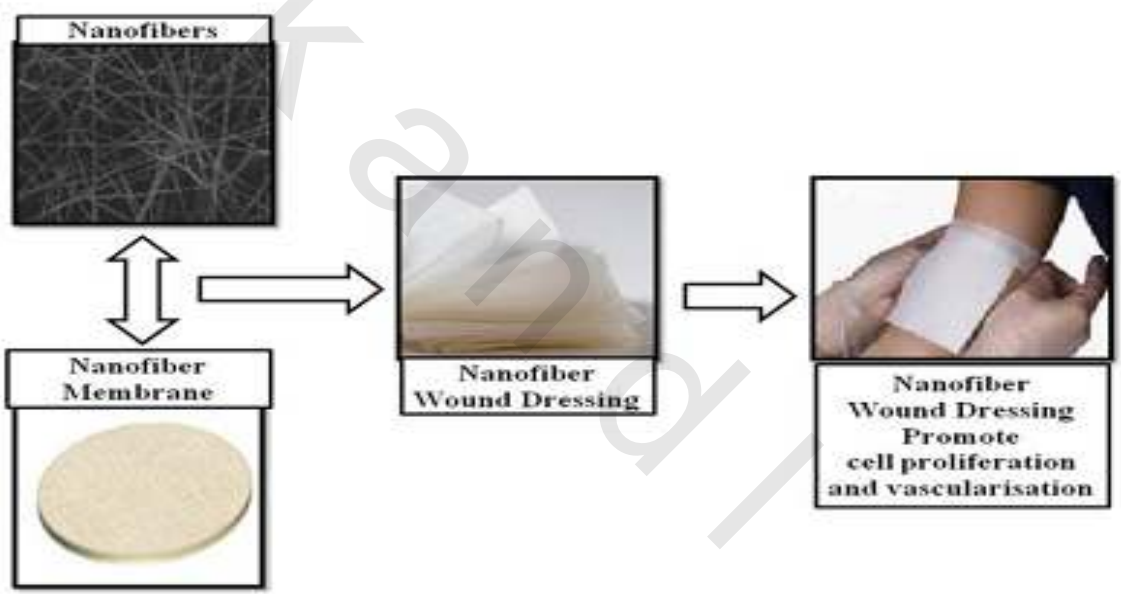

Fig. 12: Nanofibers can be used for the treatment of wounds or burns of a human skin

5- Nano Fibers in Sound absorptive materials:-

Traditional sound absorption materials include paper, cotton, cork, foams, fibers, membranes, perforated panels and so on. Among these acoustical materials, fibers are the most commonly used due to their good noise reduction performance. Researches on the fibrous sound absorption materials involve natural fibers, metal fibers, inorganic fibers and synthetic fibers. These traditional acoustical fibrous materials have good noise reduction abilities in the high frequency range, but exhibit little sound absorption properties in the low and medium frequency range (250-2000 Hz) in which human sensitivity to noise is high. The nanofibrous materials are promising alternatives in the noise reduction field. However, there are few reports about nanofibrous membranes for acoustical application.

Herein, PAN nanofibrous membranes were prepared by electrospinning and the sound absorption behavior of the nanofibrous membranes and their composites with traditional acoustical materials (perforated panel, foam and fiber) were evaluated. The results demonstrate that the nanofibrous membrane has a promising acoustical damping performance, especially in the low and medium frequency range

6- Nano Fiber in textile's

More Textiles materials like as clothes is generating at the industries level, where in nanotechnology products are commercially applied to protect humans through harmfully effects and their environment. The nanomaterials are embedded into textile products to impart antimicrobial properties, decrease luster, and protect against UV rays. When compared to conventional materials, nanomaterials offer several advantages such as needing lesser amounts of nanomaterials and enhancing product'sperformance. To cite a few: metal oxide nanoparticles to decrease luster or provide UV protection. Alkoxysilane-modified TiO_2 nanoparticles to absorb UV radiation and Ag, TiO_2, and ZnO nanoparticles to provide antimicrobial and UV protection properties and monazite as thermal protection blankets for reentry space craft

7- Silver Containing Dressings

Microorganisms in wounds retard or prevent healing. Prevention and treatment of wound colonisation or infection can be achieved by using silver-based dressings, which have been used as an antimicrobial agent for centuries. They are effective against a broad range of bacteria (including methicillin and vancomycin-resistant strains), yeast, fungi and viruses. [200]

VII. Polymer/Inorganic Hybrids

The additions of inorganic components to the polymer system allow the fabrication of nanofibers with special functionalities. A Patent [201] described an approach of the preparation of hybrid nanofiber by addition of nanoparticles into the polymers. In this innovation, the dispersion of the solid nanoparticles is easily carried out and the porous structure was also conducted after the dissolution of salts. Since elemental silver and silver salts have been used for decades for anti- bacterial agents in curative and preventive health care, antibacterial nanofiber containing Ag was prepared by electrospinning. [202, 203] Initially, electro-spinning was carried out from Cellulose Acetate (CA) or PAN solution with $AgNO_3$. The nanofiber was further reduced to silver nanoparticles by a photo-reduction technique using UV irradiation. Silver nanoparticles in cellulose acetate fibers were stabilized by interaction with carbonyl oxygen groups on cellulose acetate and showed very strong anti- bacterial activity.

Nanofibers containing other notable-metal nanoparticles were also prepared via electrospinning, such as poly (acrylonitrile-co-acrylic acid) (PAN-co-PAA)/Pd (by reduction with hydrazine after electrospinning), poly (vinyl pyrrolidone) (PVP)/Au, and so on. Except the notable-metal nanoparticles, some other functional metal oxide nanoparticles were also introduced into the polymer nanofiber, such as the electrospun fibers containing magnetic nanoparticles have been reported. The present magnetic nanofiber was responsive to magnetic field provided by a small laboratory magnet, and the field-responsive behavior extended its application. Yang et al. demonstrated a novel

method to fabricate aligned fibrous arrays through electrospinning of composite magnetic nanofiber. [204]

To direct the deposition of the nanofiber, the researchers added two magnets to the apparatus of conventional electrospinning setup. The resultant nano-fibrous arrays can be transferred onto to any substrate from any angles with full retention of their structures. Because of the low quantity of magnetic nanoparticles used (0.5%), the morphology of the fibers were not affected. If appropriate parameters were chosen, the addition of some additives or special particles would be helpful to control the fiber morphology or functionalize the fiber.

Nanofibers electrospun from composites of ceramics and biopolymers were demonstrated recently. Hydroxylapatite (HA) is a kind of widely used bioceramics which is a major component of the bone. The HA can be used as a subsidiary in the bone generation, and HA implants exhibit high medical strength and good biocompatibility. The composite nanofiber was fabricated by electrospinning of PLA and HA [205].

SEM analysis showed that the incorporation of HA did not change the overall morphology, and resulted in the formation of smooth nanofibers with high pore volume and inter connective pores. The nanofibrous PLA/HA composites scaffold combine the advantages of mechanical strength of HA and the nanometer scale of electrospinning, and hold great promise as a temporary substrate for osteoblast culture in guide generation of bone tissue.

The combine of electrospinning and sol-gel processes has also been used for the production of inorganic compounds nanofiber. The composite nanofiber of polymer and inorganic is often used as precursor fibers. Further treatment such as pyrolysis can convert these fibers into inorganic nanofibers.