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Curcumin And Chitosan Loaded Nano Scaffold For Targeting Chronic Wounds Through Tissue Engineering In Regenerative Medicine

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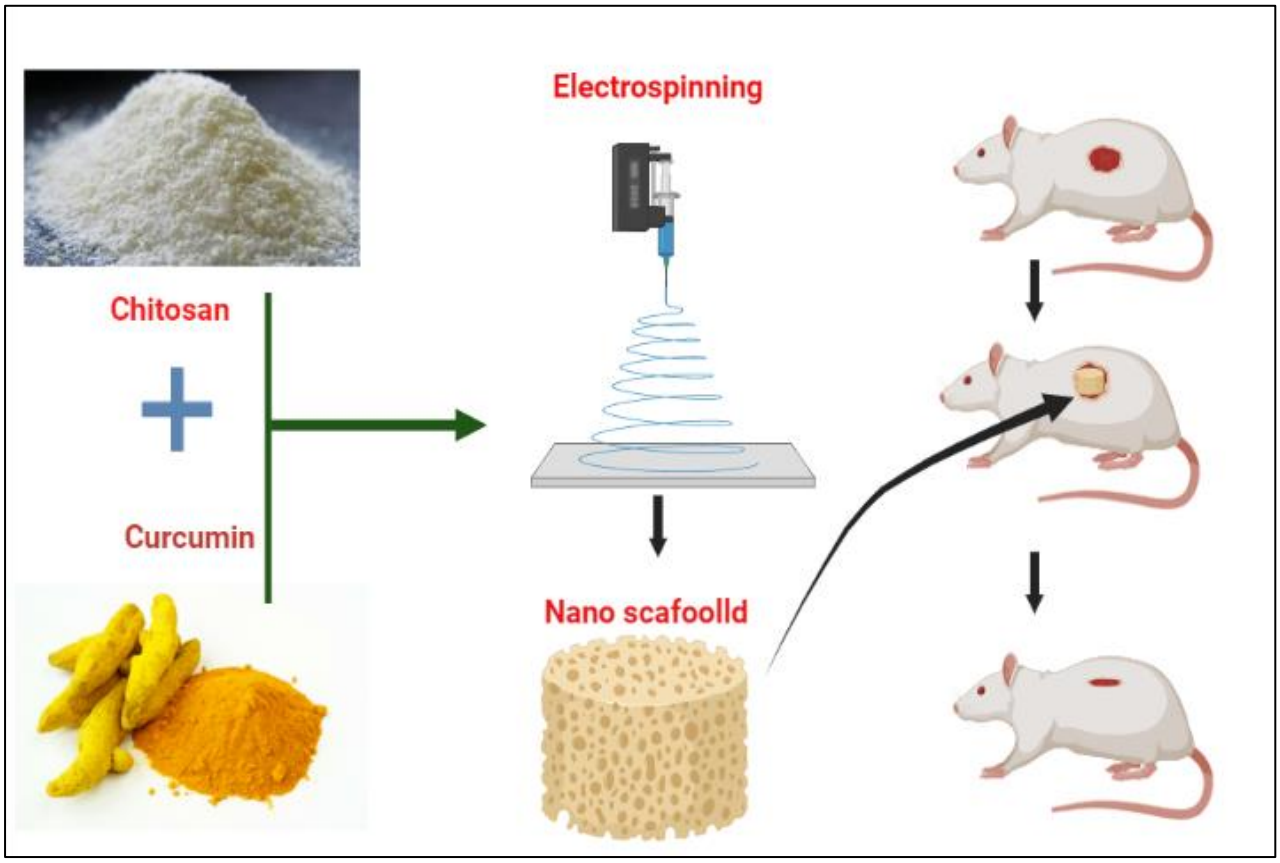
ABSTRACT:

Regenerative medicine will increasingly rely on tissue engineering as a therapeutic tool. Scaffolds are an essential component of tissue engineering. The invention and enhancement of scaffolding that may be utilized to heal or regenerate a tissue or organ tissue focus on functional biomaterials research. Scaffolds made of natural polymers have lately acquired favour since they have been created more efficiently. Open deep cuts and wounds can take a long to heal and lead to infection and scars. A simple biomimetic electrospun nanofibrous antimicrobial scaffold with antioxidants was designed to address this issue. Using the electrospinning process, a chitosan-Curcumin composite nanofibrous scaffold will be created. Curcumin-chitosan NFS has been shown to have a well-regulated amount of Curcumin and Chitosan in granulation tissues, indicating it as a possible wound healing and regenerative agent. Curcumin has been proven to have anti-infective, anti-inflammatory, antioxidant, anti-mutagenic, anti-carcinogenic and anticoagulant properties. Curcumin has also been found to have wound-healing effects. It works on several phases of the natural wound healing process to speed up healing. Using Chitosan, alkaline deacetylation of chitin may reduce scarring. These scaffolds' chemical and biological properties continue to improve as new biomedical uses are discovered. Because of their many biological features, such as biodegradable, biocompatible, and bioactive, they have provided a blueprint for tissue engineering in chronic wound healing. This study concentrates on the intrinsic features of Curcumin and

Chitosan and their use in chronic wound healing through tissue engineering as a viable option for regenerative medicine.

KEYWORDS: Curcumin, Chitosan, Regenerative Medicine, Nano Scaffold, tissue engineering, chronic wound.



GRAPHICAL ABSTRACT

INTRODUCTION:

Since the beginning, turmeric has been used as a nutritious spice and colourant in Indian and Chinese cuisines [1]. Since ancient times, Indian and Chinese herbalists have relied on the plant's rhizome (root) for its therapeutic properties[1,2]. Curcumin is now widely used in Indian traditional medicine to treat cough, biliary problems, sinusitis, diabetic ulcers, rheumatism, and hepatic disorders. Curcumin paste combined with lime has long been used as a home medicine for inflammation and wound healing[3]. As one of the three curcuminoids in turmeric, Curcumin has been found to make up anywhere from 2 to 5% of such spice and 77% of a solitary extract [4]. Curcumin has recently received substantial research for its potential use as a wound-healing agent [5], anti-cancer agent[6] and anti-ageing agent[7]. Recent biomaterials research has focused on developing new drug delivery methods and bioactive chemicals for regenerative medicine [8].

In the last few years, tissue engineering advancements have made all of this feasible, allowing for the regeneration of almost all human tissues and organs. Tissue engineering is a critical therapeutic method for both current and future medicine. As a result, tissue engineering aims to repair, regenerate, preserve, or increase function is faulty or lost tissue due to various medical situations. This may be accomplished by inventing biological replacements or reconstructing structural scaffolds

that stimulate tissue regeneration. Tissue engineering refers to cell replacements, tissue inducers, and isolated cells placed on or in a matrix for tissue repair and regeneration[9]. There are three types of strategies: (1) cells placed on or in different matrices or substrates to act as a vehicle or scaffold for tissue regeneration (2) chemical tissue inducers (such as growth hormones), and (3) isolated cell transplants or cell replacements in the body [10]. Hence, the focus on tissue engineering relates to the use of structures to heal injured tissue or tissues with structural abnormalities and reinforce and, in some instances, organize regenerative tissue that will work as a scaffolding to repair or regenerate the injured cells [11]. This study made an effort to make an antioxidant-loaded composite wound healing material with Chitosan to help the granulation tissues build a skeleton to help them heal faster. When new tissues start to form, the electrospun fibrous scaffold will break down with them. This would protect the new tissues from rupturing because the scaffold would break down as the tissues grew. Curcumin, a natural antioxidant, has been used to keep wounds from getting worse.

HEALING OF A WOUND:

The skin serves as a natural defence against the elements and performs several other essential functions. Following a skin injury, the body initiates a multi-step, variable series of events that partially heal and restore such skin's membrane integrity. This process is triggered by both acute and chronic skin damage. Achieving tissue integrity and homeostasis is the primary objective in wound healing[12]. Hemostasis, inflammation, proliferation, and remodelling are all stages in the natural healing process. Injury triggers hemostasis, which results in platelet aggregation and the production of blood clots[13]. The blood clot acts as an alternative extracellular matrix to aid cell motility [14]. A phagocytic neutrophil and a macrophage migrate to the wound site during the inflammatory phase[13].

Phagocytes produce cytokines to promote fibroblast migration and proliferation when the inflammatory phase ends. The proliferative phase involves wound re-epithelialization, which begins within hours following injury. New blood vessels (angiogenesis or neovascularisation) are formed during this phase, re-establishing perfusion to support the new tissues[15]. Additionally, extracellular matrix proteins, like collagen and granulation tissue, are synthesized, and deposition occurs [13]. Cell ingrowth is supported by the extracellular matrix produced by fibroblasts, which are made up of collagen as its essential component. Fibroblasts play an important part in wound healing. The last step is the remodelling of collagen and creating scar tissue—the length of each wound healing phase and the fact that it shows how the process is intertwined[14].

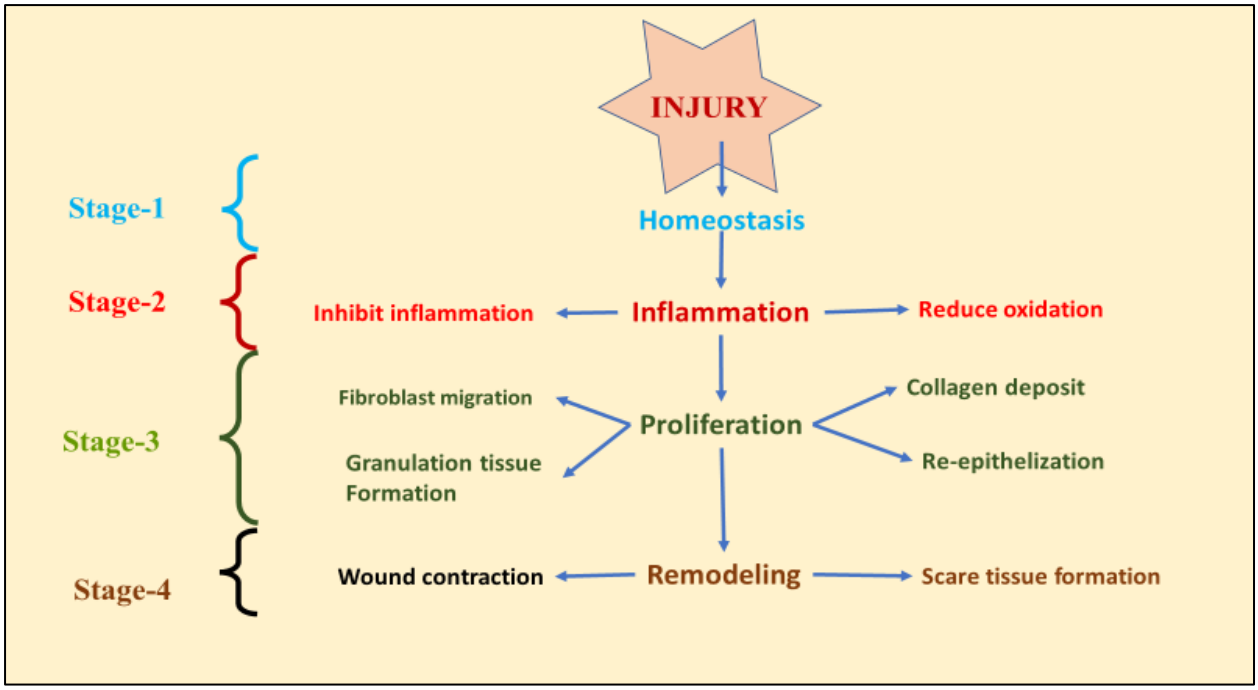


Figure 1 various Stage involved in the wound healing process

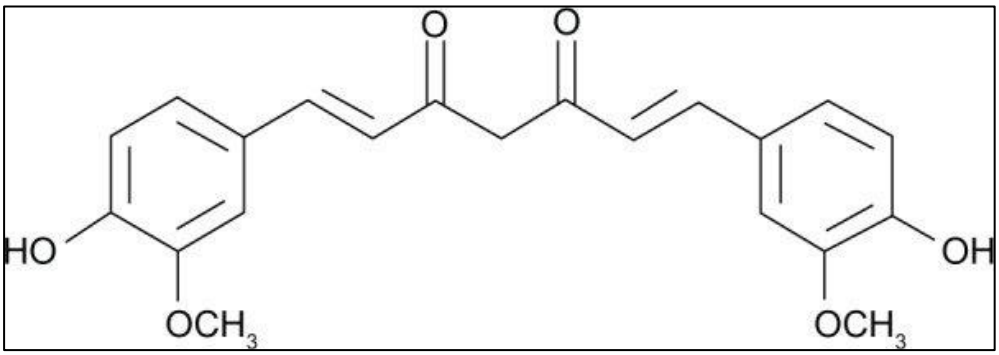
MECHANISMS BY WHICH CURCUMIN AFFECTS THE STAGES OF HEALING A WOUND

MECHANISM OF CURCUMIN ON INFLAMMATORY STAGE:

Controlling inflammation is important because tissue damage results in an almost immediate commencement of acute inflammation, which may aid healing. For optimal skin regeneration, the wound healing process begins with inflammation, which may be regarded as the initial phase of this process[16]. Inflammatory illnesses such as rheumatoid arthritis may damage tissue if inflammatory responses are not adequately regulated[17]. Interleukin-1 (IL-1) and Tumour necrosis factor-alpha (TNF-α) are two critical cytokines generated by macrophages and monocytes and play essential roles in regulating inflammatory reactions, and Curcumin has been demonstrated to suppress their production. Curcumin's ability to decrease stimulation of the transcriptional activation factor NF(κ)B (nuclear factor kappa light-chain-enhancer of activated B cells), which regulates multiple genes associated with inflammation, is also significant. Several pathways are involved in NF-(κ)B activation that curcumin effects, including those activated by kinases such as AKT, PI3K, and IKK. NF-(κ)B was previously oxidant sensitive, underlining the link between inflammation and oxidation in wound healing[18]. Using a curcumin-loaded chitosan-based polymeric fibre (COP), the fibre was applied to the back of injured rats and discovered several kinases in the PI3K/AKT/NF-(κ)B pathway downregulated[19]. When the bandage was put on, P13K and PAKT kinase expression was lowered, which resulted in less NF-(κ)B gene activity and less inflammation. There was also an enhancement in the I-(κ)B-(α) protein, which is involved in inhibiting the NF-(κ)B pathway.

Consequently, Curcumin decreases wound inflammation by activating the NF-(κ) B pathway[19].In contrast to results, an in-vivo investigation found that rats treated with Curcumin had higher levels of inflammatory cell infiltration into burn wounds than rats in the control group[20]. There was no indication of which inflammatory cells were examined in the study; thus, additional research is required to prove Curcumin's wound-healing properties. The gamma radiation-exposed mice's

excision wounds produced more nitric oxide (NO) when added curcumin[21]. Increased NO production has aided wounded patients' wound healing[22]. In contrast to earlier studies that show Curcumin improves wound healing by lowering the inflammatory response, this study found that an increase in NO was partially responsible for wound healing with curcumin treatment. Even though this research found that curcumin therapy promoted wound healing by increasing the body's natural inflammatory response, the overwhelming majority of studies found that Curcumin lowers inflammation. Proliferation and remodelling of injured skin might occur more quickly if the skin's inflammatory response is reduced. The wound healing process is slowed down by Prolonged chronic unregulated inflammation, which causes the last stages of healing to be delayed.



Structure of Curcumin

Curcumin inhibits oxidation: A significant characteristic of inflammation

Aerobic respiration produces reactive oxygen species (ROS), which are essential in various biochemical and physiological processes such as intracellular communication, apoptosis, differentiation, cell formation, and immunology[23,24]. Defending the body against microorganisms requires ROS, which plays a role in healing wounds. Wound healing is hindered by oxidative stress, a significant element in the process[25]. Due to oxidative stress, long-term exposure to high amounts of ROS may be harmful to human cells [26,27]. One way to measure the level of oxidative stress in a system is to look for ROS like superoxide (O2) and hydrogen peroxide (H_2O_2) [23]. When ROS are released into the environment, they may cause oxidative damage to the cells, leading to the breakdown of DNA and the inhibition of enzyme activity, all of which limit optimal wound healing. Wound healing activity is thought to be exacerbated by ROS, the primary source of inflammation. Enzymes like catalase and glutathione peroxidation protect human cells against harmful reactive oxygen species[24]. For this reason, free radicals must be appropriately scavenged since they target and destroy proteins in tissue. Wound healing may be dramatically improved by topically applying antioxidants with free radical scavenging capacity[28].

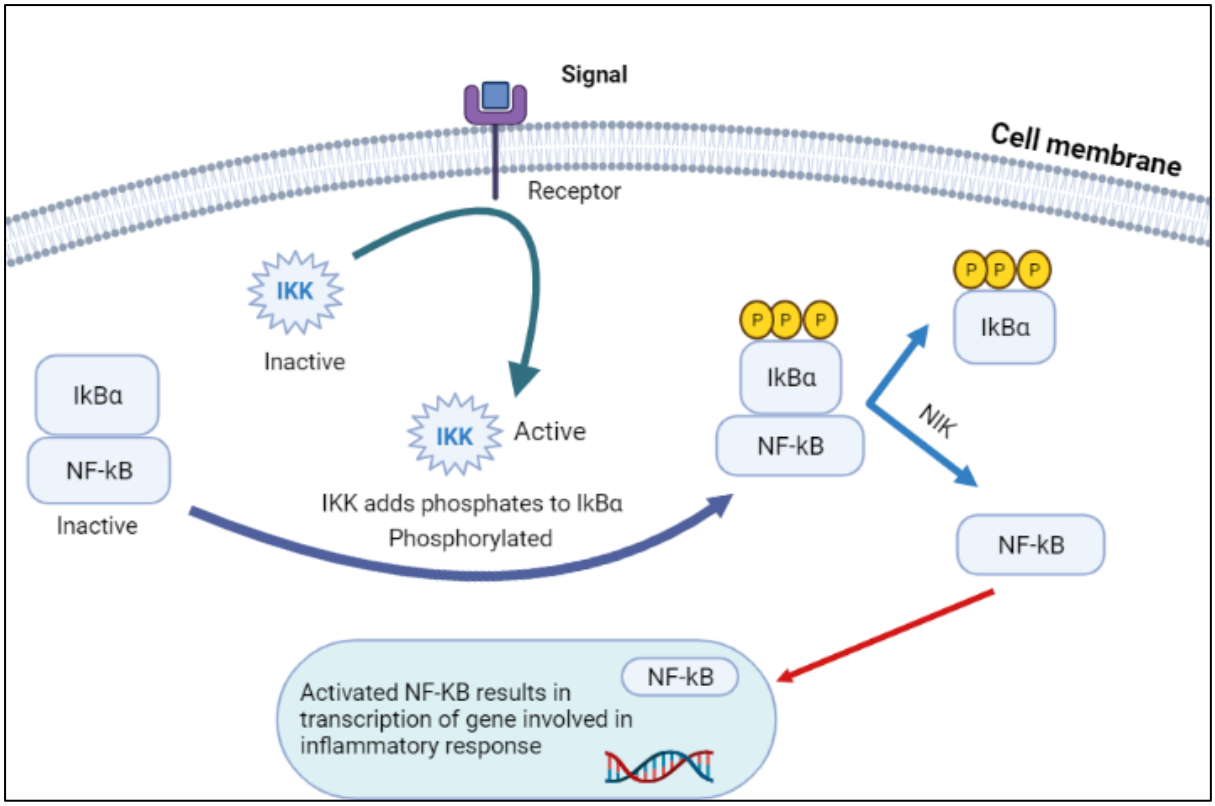


Figure 2 Curcumin blocks NF-[κ]B's ability to trigger inflammation & Curcumin inhibits NF-[κ]B in three ways: 1, 2, and 3.

CURCUMIN'S EFFECTS ON WOUND HEALING IN THE PROLIFERATIVE STAGE:

In wound healing, the proliferative phase entails the creation of fibroblast proliferation, granulation tissue epithelialization, collagen deposition (the production of the extracellular protein matrix), and death of undesirable cells[29]. As mentioned above, various studies have examined Curcumin's effect on these processes while comparing the time necessary for wound healing in curcumin-treated animals to controls.

The impact of Curcumin on fibroblast proliferation:

Fibroblast penetration into the wound site is crucial for the formation/remodelling of granulation tissue, collagen synthesis, and [29,30]. Chronic wounds that did not heal within the specified time frame had decreased fibroblast proliferation and migration inside the wound site [31,32]. Thus, the presence of fibroblasts in the wound environment is undoubtedly the most critical factor in ensuring rapid and aesthetic wound closure. By producing granulation tissue, fibroblasts naturally evolve into myofibroblasts [33]. Various researches have already shown fibroblast infiltration into injury sites after curcumin therapy. Myofibroblasts were found deposited in the stages of wound healing treated with a curcumin-loaded chitosan-based polymeric (COP) fibre as early as four days after wound excision [34]. Myofibroblasts were found in various wounds, including diabetic wounds [35,36.]

On the other hand, Curcumin did not affect the fibroblasts' migration kinematics to the wound location in an in-vitro wound healing model (by scratching a line through the cell layer) (scratch line). This perplexing discovery was ascribed to the difficulty of adequately duplicating the complex wound

healing process in vitro. The migration of fibroblasts is controlled by various characteristics that cannot be mimicked entirely in vitro. These include interactions between cells and between cells and their environment and homeostatic mechanisms[37]. It is worth noting that curcumin-treated groups exhibit decreased fibroblast infiltration due to Curcumin's cytotoxicity. Curcumin may cause fibroblast mortality in vitro wound models (25 M). At this dosage, cell death reached a maximum of 60% 48 hours after treatment. At high quantities, Curcumin oxidizes and creates reactive oxygen species (ROS). This is the fundamental mechanism behind the observed apoptosis of fibroblasts in the curcumin-treated group. Curcumin did not affect fibroblast shape at lower doses, and no apoptosis was seen in curcumin-treated cells [38].

CURCUMIN'S ROLE IN THE GENERATION OF GRANULATION TISSUE:

Four days after a skin injury, a new stroma (also known as granulation tissue) forms. Fibroblasts infiltrate the tissue, which helps to produce the extracellular matrix, and tiny capillaries develop [29]. As epithelial cells move and repair the wound space, granulation tissue provides a base from which they may do so [35]. Compared to gauze-treated wounds, excised wounds in treated groups with Chitosan–alginate sponges containing Curcumin revealed improved granulation tissue alignment (control group). In rats treated with CICM (curcumin-containing collagen matrix), an increase in the wound's hydroxyproline content was seen compared to the control[39]. Collagen production is the primary source of the protein marker hydroxyproline. Myofibroblasts may be found in abundance if hydroxyproline levels are high in a wound setting. Although fibroblasts undergo differentiation into myofibroblasts throughout granulation tissue development, the existence of myofibroblasts is a strong predictor of granulation tissue synthesis. It has also been shown that wounds treated with curcumin-loaded polymeric Curcumin (COP) had more well-organized and well-formed tissue ten days after therapy and less well-formed or granulation tissue that was not produced until four days following therapy. Assuming that granulation tissue production starts four days after an injury, the delay is predicted. Topical Curcumin also improved the organization of granulation tissue and increased the number of myofibroblasts in diabetic rats' wounds. Curcumin-treated diabetics also saw an increase in neovascularisation or the creation of tiny capillaries.

Way curcumin affects collagen production:

The extracellular matrix must be reorganized and remodelled for wounds to heal fully. A variety of polysaccharides and proteins, including collagen and granulation tissue, make up the extracellular matrix. In the skin's extracellular matrix, collagen accounts for 70% to 80% of the skin's total protein content [40]. In the end, scar tissue is formed, which is primarily made of collagenous fibres [41]. For this reason, wound healing would be enhanced if enough collagen production and deposition occurred at the wound site. In a rat model, wounds treated with a CLCA sponge contained much more collagen than wounds treated with gauze. The resulting collagen is more compact and well-aligned in the curcumin-treated group, and the collagen bundles seem thicker[42]. Curcumin has been shown to improve the injured tissue's tensile strength and shrinkage temperature. In comparison to the control group, increasing the collagen content in COP bandages resulted in a higher aldehyde concentration in wounds in a rat model. COP bandage wounds were shown to have a strongly cross-linked collagen bed because of a high quantity of aldehyde in the collagen [34,43]. Curcumin-treated wounds in rats resulted in an increase in the amount of collagen in the body and a more rapid maturation of collagen fibres [44]. These freshly generated collagen fibres also had an effective aldehyde content, indicating

their strongly cross-linked character. Curcumin topically administered to diabetic mice, rats, and guinea pigs resulting in a much more impressive production of compact and well-aligned collagen fibres at the wound surface [35,36]. Compared to oral treatment on the wounds of gamma-radiation-exposed mice, curcumin therapy resulted in the highest level of collagen formation eight days after treatment began [21]. Three days after a wound forms, fibroblasts begin to migrate into the wound site, and by the seventh day, they have changed into myofibroblasts. Finally, myofibroblasts constrict the wound such that Collagen deposition is not required anymore.

APOPTOSIS WITH CURCUMIN'S IMPACTS:

Inflammatory cells are removed from the wound site by several different apoptotic processes. This helps the wound grow and progress into the proliferative phase [35,36,45]. Apoptosis may be triggered by Curcumin's ability to create reactive oxygen species (ROS), but the exact mechanism of action is uncertain and depends on the cell type [38]. Researchers have discovered that the early stages of wound healing are marked by an increase in the number of dead cells, which they attribute to Curcumin's role as an apoptotic agent [34]. It was shown that Curcumin could expedite wound healing by increasing apoptosis rates in the proliferative phase while causing minor inflammation compared to control therapies that did not. Curcumin-treated wounds had no apoptotic cells 11 days after wounding, while the control group had higher levels of apoptosis. Wound healing was still in its infancy for those who received curcumin treatment, but wound proliferation was well on for those who received no treatment[34,35].

Inflammatory response to Curcumin in wounds:

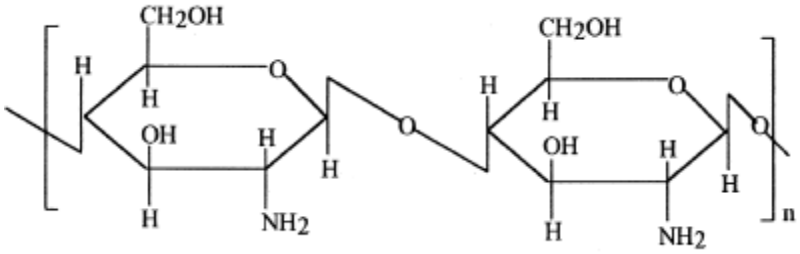
Cells, cytokines, and extracellular matrix proteins interact in various ways are involved in wound contraction during the last phases of healing [14]. When fibroblasts become myofibroblasts approximately two weeks after wounding, the wound starts to constrict [46]. Increasing the -smooth muscle actin expression in the myofibroblasts, granulation tissue promotes wound contraction and healing [47]. platelet-derived growth factors (PDGFs) and Transforming growth factor (TGF) are also needed to stimulate wound contraction when collagen bundle cross-linking occurs [48,49]. Several trials studies show that Curcumin accelerates wound healing by enhancing the contraction rate. Planimetric measurements of the wound site in a rat model revealed that curcumin administration significantly increased the percentage of wound shrinking by 20% compared to the control group [50]. Twelve days after injury, wounds in rats treated with curcumin-loaded sponge were 90% smaller than those treated with gauze. An eight-day post-wound interval is required to assess wound contraction between Curcumin and controls since negligible contraction occurs before this period [34]. There were similar findings when oral curcumin treatment was administered to mice six to 12 days after irradiation[21]. Cytokine TGF- β is essential for wound healing, chemotaxis and collagen deposition [51]. Fibroblasts are one of the cells that release this chemical. Fibroblasts in curcumin-treated wounds were more numerous and positive for TGF-β staining than those in untreated wounds[36]. Curcumin has also been demonstrated to increase the expression of TGF- β in the granulation tissues of diabetic wounds, as shown in this study. There was just a modest expression of TGF- β in wounds that had been untreated [35].

TABLE.1 Topical curcumin therapy's potential effectiveness on wound healing at different stages

Wound Healing process phases	The impact of topical curcumin treatment on wound healing
Inflammation	➢ T1:5 reduces the synthesis of IL-1 cytokines and TNF-α by cramping the activation of the NF-(κ)B transcription factor, lowering inflammation. ➢ Anti-ROS scavenging effect (Curcumin at a lower dosage) ➢ Lowering or Increasing the synthesis of antioxidant enzymes ➢ Increasing or decreasing ROS generation (at higher doses of Curcumin)
Proliferation	➢ Improving granulation tissue development, fibroblast migration, re-epithelialization and t1:6 collagen deposition in general ➢ In the early phases of wound healing, they are apoptotic, enabling unwanted inflammatory cells to be eliminated from the wound site.
Remodelling	➢ Enhancing wound contraction by increasing TGF- production t1:7, which leads to enhanced fibroblast proliferation

TISSUE REPAIR AS WELL AS REGENERATIVE MEDICINE USING CHITOSAN

Biomaterials for tissue remodelling are used as bone fillers orthopaedic implants; in regenerative wound treatment, adhesives for tissue healing and scaffolds for tissue creation are used; The latter is employed for cartilage, skin, nerve tissues, and bone repair and regeneration, which have been the focus of more regenerative medicine research. This involves using Chitosan as a scaffolding material or as an alternative or extracellular matrix (ECMD) to aid in the repair of wounded tissue [52.]



Structure of chitosan

Chitosan's popularity in tissue repair and regeneration stems from its ease of processing and manufacturing in various forms, including fibres, hydrogels, sponges and films. It is feasible to regenerate primary tissue cells and perhaps even stem cells due to the properties listed above; its chemical composition is comparable to that of several polysaccharides and ECM ingredients, enabling

it to be chemically changed to adapt structurally and functionally to the host tissue. This allows the geometry of the biomaterial tissue or receiving tissue contact to be mimicked. Regenerative medicine is one of the possible uses of this technology [53-56.]

TISSUE ENGINEERING USING CHITOSAN

In developing epithelial and soft tissue engineering, scaffolds having porous architectures are critical. The manufacturing of Chitosan in a porous form allows the seeding of cells. Cell migration, multiplication, and the exchange of nutrients are all possible because of the porous structure. Angiogenesis is necessary for the survival and function of regenerated soft tissues may be facilitated by chitosan scaffolds' controlled porosity. Chitosan scaffolds are cytocompatible in vitro and biocompatible in-vivo. Chitosan-specific reactions are uncommon when chitosan scaffolds are implanted because they rarely elicit more than a little in vivo foreign body reaction [57]. Chitosan should be coupled with biomaterials having tissue-specific binding sequences, such as fibronectin or collagen, to create scaffolds with higher cell affinity. Specific biomaterials based on chitin do not offer a hospitable surface for particular tissue types of cell adherence. Chitosan is also combined with other biomaterials to generate scaffolds suited for guiding desired cell behaviours and mechanically strengthening tissues such as the skeleton [59,60]. The physical adsorption of bioactive substances into the scaffolds may add biological activity that aids tissue regeneration [58]. When it comes to gene transfection, trimethylated Chitosan is effective[61]. There is research that chitin-based substances promote neuronal development in specific tissues. Chitin-based scaffolds have been supplemented with substrates and bioactive compounds to improve their affinity for nerve cells [62]. A chitosan tube that has been immobilized with laminin peptides may stimulate the sprouting of proximal nerves and the regeneration of axon bridges. In 2004 discovered a way to promote the growth and attachment of nerve cells in the peripheral nervous system by using chitosan fibres [63]. Autologous grafts have been used for decades as the standard treatment for any peripheral nerve injury, but numerous and severe complications have plagued them. Various biomaterials have been used to solve this issue, but functional recovery is still lacking. It was shown that cross-linking the polymer chitosan with the acidic solution of 1-azido propyl trimethyl ammonium bromide yielded scaffolds that could be used to develop the N1E-115 cells originating from the neuroblastoma C-1300 mouse tumour. Because of their capacity to synthesize and distribute nerve growth factors, the resulting hybrid membranes have shown good cytocompatibility when grown in the presence of cyclic AMP (cAMP) or dimethylsulfoxide (DMSO). This is important for repairing peripheral nerve lesions, which necessitates the production and delivery of nerve growth factors locally. Because of their porosity structure, chemical changes, and strong affinity for biological systems, in vivo investigations imply that these chitosan-based membranes offer promising outcomes in peripheral nerve engineering[64]. Chitin-based materials now have a more comprehensive range of applications for soft tissue regeneration because of these improvements. Similar to this, it was shown that chitosan-hyaluronic hybrid polymers might create good conditions for cellular adhesion, proliferation, and the creation of the extracellular membrane (ECM) and facilitate the biological effects of implanted cells in the regeneration of ligaments. Collagen has been cross-linked with Chitosan to form a tubular scaffold that imitates blood vessels' morphological and mechanical qualities and increases long-term patency rates. Cell adhesion, proliferation, and ECM synthesis were all improved with this biocompatible scaffold [65,66]. Chitosan/collagen composite scaffolds have been used in adipose tissue regeneration and vascular applications. Experimentally, the cytocompatibility and biocompatibility of scaffolds were shown when the adipocytes were sown [67]. After injuries or burns, skin healing and regeneration may also

benefit from chitosan usage. No cytotoxicity against L-929 cells was observed 24 hours following the development of the membranes containing Chito-cross-linked silica particles (SiO2). Because of its good cell adhesion and proliferation of culture, the microporous membrane may be suitable for skin tissue engineering[68]. Melanocyte, corneal, and cutaneous keratinocyte phenotypes have been successfully maintained and induced using chitin-based materials[69,70]. In salivary glands, Chitosan enhances the mesenchyme-derived growth factor morphogenetic efficiency significantly. Chitosan has been shown to increase epithelium morphogenetic factors' impacts, including fibroblast growth factors 10 (FGF10), 7 (FGF7), and HGF (hepatocyte growth factor). Because Chitosan may attach to collagen through polyanionic–polycationic interactions and hydrogen bonding, it was used to construct novel tissue adhesives [67]. Adhesions in the abdominal wall may be prevented using hydrogel and mesh Chitosan cross-linked with other biomaterials Using thermosensitive hydroxybutyl Chitosan (HBC), a novel derivative of Chitosan whose key feature is an intelligent reaction to changing temperature; researchers were able to avoid postoperative abdominal adhesions in rats. HBC was shown to have anti-adhesive properties and be user-friendly throughout the surgical procedure. Three meshes were tested: Dynamesh-IPoM, polypropylene, and a polypropylene/chitosan combination. According to the lowest incidence of inflammatory response in connective tissue, this mesh was demonstrated to be least irritating to recipients and surrounding tissues, assuring implant acceptability and the least amount of adhesion to interior organs, as well as a lower chance of complications [71]. Lastly, they found that a modified chitosan-gelatin film efficiently reduces peritoneal adhesions generated by ischemia, wound, and infection but not in foreign body-induced adhesions [73]. Preventing postoperative adhesions may thus be a benefit [72]. Chitosan is also being investigated for its possible use in the repair and regeneration of the abdominal wall in ventral hernias due to its success in reducing and preventing postoperative intraperitoneal adhesions. Silk fibroin and chitosan mix scaffolds were tested in guinea pigs to see whether they might be used to heal ventral hernias. A non-biodegradable polypropylene mesh with a biodegradable human acellular dermal matrix was used to evaluate this hybrid scaffold's performance. Although mesh and matrix scaffolds demonstrated tissue remodelling in all three dimensions and flawless integration with neighbouring native tissues, the silk fibroin and chitosan mix scaffolds were intact. Their mechanical strength seemed equivalent to that of the original abdominal wall. The mechanical strength of the tissue was raised as a consequence of these characteristics, as the scaffold encouraged the deposition of a new extracellular matrix (ECM), uniform vascularisation, and cell infiltration. In this way, the abdominal wall may be reconstructed and regenerated using this scaffold [74]. Because of its use in the treatment of ventral hernias, it may also be employed in inguinal hernias and other types of herniation. Omphalocele and gastroschisis are two examples of congenital malformations that may benefit from this treatment; however, there are currently no models to support its usage in people for these sorts of issues.

As a result of the increasing need for intestinal lengthening and replacement surgeries after major bowel resections, intestinal tissue engineering has emerged as an emerging topic. Rejection rates, organ supply, and the size of the donor graft are all factors that make intestinal transplantation a complicated procedure. Researchers were able to assess the biocompatibility of Chitosan by growing rabbit colonic circular smooth muscle cells on chitosan-coated plates. The cells' spindle-like shape and smooth muscle phenotype markers were intact. A 1:1 mix of Chitosan and collagen was used to construct tubular scaffolds. A fibrin-based hydrogel implanted with circular muscle cells from rabbits produced 3D circular muscle structures. Potassium chloride (KCl) and Acetylcholine (Ach) caused the

muscle constructions to contract, whereas vasoactive intestinal peptide (VIP) caused them to relax (VIP). Results show that Chitosan may be ideal for intestinal tissue engineering because of its biomaterial properties [75,76]. It is reasonable to conclude that Chitosan has promise in soft tissue engineering applications, whether utilized for wound closure or to generate specialized tissue grafts. Despite this, there is still much to be discovered about their characteristics and how scaffolds are formed. They should carry many bioactive elements and release them in a predetermined sequence for the next generation of scaffolds. Therefore, the most challenging choice is adjusting the loading capacity, drug release kinetics, and substrate degradation rate separately [67].

THE NANO-SCAFFOLDING:

Biomaterials scaffolding is characterized as three-dimensional permeable solid biomaterials (3D) developed for functionalities like Biomaterials, and extracellular matrix deposits (ECMD) may promote interactions between cells, biomaterials, and extracellular matrix deposits (ECMD) to facilitate cell survival and proliferation. Scaffolding constructed of natural or synthetic materials is widely used in modern healthcare as a scaffold to interact with biological systems and accomplish desired medicinal effects, allowing choices to overcome the limitations and restrictions given by the use of autograft and allograft tissues[77]. The scaffold should be broken down at a pace similar to the target tissue to facilitate cell proliferation and differentiation. A scaffold used in tissue engineering must fulfil specific needs or features to execute the activities as mentioned earlier. Tissue engineering & regenerative medicine could benefit from the usage of biocompatible polymers. They might be biodegradable, non-biodegradable, or a mixture of the three.

The first biodegradable materials utilized in human therapeutic settings were natural polymers. Natural and synthetic biodegradable polymers are most often utilized as biomaterials because of their chemical adaptability and the ability to degrade into tiny molecule fragments that may be excreted or reabsorbed by the human body [78,79]. There are several different types of naturally occurring polymers, including proteins (silk, collagen and fibrinogen), polysaccharides (cellulose and amylose), and polynucleotides (DNA/RNA) [80.] Because of their bioactive qualities, these natural materials are more likely to interact biologically with cells and function better in the body. Polymer materials for use as biomaterials in biomedical applications have been chosen based on characteristics such as shape and structure, chemical composition, solubility, molecular weight, surface energy, hydrophobicity/hydrophilicity, water absorption, breakdown capacity, and erosion mechanism, among others. Polymers, for example, have been widely used in medical devices and scaffolds for tissue engineering [81,82]. Many researchers are interested in polymer scaffolds because their distinguishing characteristics include a high surface-volume ratio, excellent porosity on the surface with minimal particle size, and the ability to regulate biodegradation. Their biocompatibility characteristics encompass a broad spectrum of surface chemical and physical properties crucial in tissue engineering and organ replacement applications. [83].

WOUND HEALING USING ELECTROSPUN CURCUMIN LOADED CHITOSAN NANO-SCAFFOLDS:

Localized drug delivery applications have been achieved using electrospun materials, including Chitosan (Chitosan). Chitosan-based scaffolds play a crucial part in wound healing. Therefore, choosing Chitosan is critical to obtaining nanofibrous scaffolds that match wound healing materials' characteristics. Curcumin-chitosan facilitates wound healing with its unique features. The antimicrobial and hemostatic properties of curcumin-chitosan are only two examples[84]. Nanofibrous

scaffolds for wound healing might be made using chitosan particles with biocompatibility cross-linked with Curcumin. Recent research on curcumin-chitosan's biological and physical features suggests it might be used in medication delivery systems and wound healing applications [85]. Electrospinning biopolymers with a synthetic polymer may be used to fine-tune the porous membranes' mechanical, degradation, and morphological properties to meet the specific demands of each patient. For wound healing to be accelerated and post-surgical infections to be reduced, electrospun fibres have been used to release two or more different medications at the right time and the right amount. A prolonged release of Curcumin from electrospun fibres has been discovered to be beneficial in overcoming post-surgical problems, such as infection.

SUMMARY & CONCLUSION:

According to the results of this study, Curcumin has been proven to have substantial regulating wound therapeutic properties. The review discusses Curcumin's impact on the various stages of wound healing that it influences. Studies have shown that it lowers wound healing time by affecting the inflammatory phase, proliferative stage, and remodelling stages of wound healing using Curcumin. Due to Curcumin's poor solubility, quick metabolism, and light sensitivity, its bioavailability is restricted. Nanofibrous scaffolds may be used to avoid these side effects and maximize the usage of Curcumin to its full potential. The field of regenerative medicine is dealing with a new set of obstacles. To stimulate the healing of damaged tissue in vivo, Bioactive chemicals for injured tissue are now readily available due to technological advancements. Regenerative and wound-healing properties are required, and low morbidity and good biocompatibility. Chitosan polymers have been demonstrated to be scaffolds for tissue regeneration, but they are also regarded as suitable polymers for producing bioactive chemicals. Because of the synergy between their byproducts and Curcumin, this is conceivable. Translational questions about the function of bioactive polymers and related effects on regenerative medicine should be confirmed in more investigations. An electrospun, biomimetic biocompatible curcumin-chitosan Nannofibrous scaffold should be created for persistent wounds. It supplied a large surface area microporous skeletal structure with its nanofibrous scaffold to avoid microbial infiltration for fast cell proliferation and granulation. Due to its unique properties, Curcumin was able to reduce the appearance of scars. The patient is protected from the pain of wound tissue rupture by disintegrating the curcumin-chitosan Nanofibrous scaffold during cell development.

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CONFLICT OF INTEREST:

The authors declare that there is no conflict of interest

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