Chapter

Curcumin-Alginate Mixed Nanocomposite: An Evolving Therapy for Wound Healing

Sulata Sahu and Bairagi C. Mallick

Abstract

A lot of advancements have taken place in the wound dressing materials and in wound healing process. Alginate based wound dressings materials are more preferable due to their biocompatibility and non-toxic unique biological characteristics. There's always a need to increase the efficacy of alginates by combining with other biopolymers like chitosan, collagen and cellulose etc. However, the recent trend towards the natural and herbal bio-compounds are more likely attracting to develop alginate based wound dressing materials with higher efficiency, antimicrobial and anti-inflammatory potency. Out of many natural compounds tested, curcumin has shown high potency and more effectively used for wound healing purpose. Due to curcumin's bio-medical properties it has been used as a vital ingredient combined with alginate and other biopolymers to prepare wound dressing materials. Based on the available literatures, this review chapter on alginate-curcumin nanocomposite will help the reader to develop better wound healing materials with evolutionary therapeutic applications.

Keywords: Alginate, curcumin, nanocomposite, wound healing dressing materials

1. Introduction

Despite the progress in wound dressing materials and also the level of expertise within the skilled discipline, the wound healing management still remains inconclusive [1]. The reason could be the price management of wounds is more and also the increasing population size and metropolitan lifestyle. These facts indicates towards the increasing demand for development of wound dressings that are effective, acceptable and cheap. In the year 2012, 184 million pound was spent on wound dressing merchandise in England [2]. Similarly, in the USA, annually approximately 20 billion dollar is spent on the management of chronic wounds [3, 4]. There are some barriers like educational, organisational, clinical and psychosocial for successful and effective treatment of wounds [5]. Biomaterials, biopolymers, synthetic polymers are the raw materials for preparation of wound dressing materials. Properties of biopolymers should be non-toxic, easily accessible, perishable, biocompatible and non-immunogenic like chitosan, alginate, fucoidan, mucopolysaccharide etc. [6, 7]. Due to the non-toxicity, biocompatibility, non-immunogenicity, affordability and high absorption capability specific and selective properties of polymers, alginates are best suitable used for dressing materials for wound dressing

purpose [8]. However, due to poor mechanical property of biopolymers they are incorporated with artificial polymers to boost their mechanical properties and tailored to change their degradation mechanism [1, 6, 7].

Alginate is a polysaccharide, generally used as bio-polymericmaterial for wound dressing [1]. It is a known and naturally collected biopolymer used in the management of wound dressings because of its selective characters like biocompatibility, nature of gelling and swelling, which creates moist and microenvironment at the damaged site enhancing the healing mechanism and declining the period of heling [1, 9]. The special properties of alginate convert it a model biopolymer with potential value, which might overcome the drawbacks related to other biopolymers used as wound dressing material [9, 10]. Alginate has already been incorporated within selective biomaterials for formulations of hydrogels, films, foams, gels, wafers, nanofibers, topical formulations, and several other novel systems for wound dressing [1, 9, 11]. Alginates are also utilised to prepare sponges as wound dressing products [1, 12]. The haemostatic property of alginate made appropriate for bleeding wounds also [13]. As alginate based hydrogel products are extensively used in tissue recreation and also acceptable in highly damaged wounds, these systems are most preferable in case of wound healing process [12, 14, 15].

2. Alginate

British Chemist E.C.C. Stanford in 1881 first described Alginate and available as the most common and abundant polysaccharide in the brown algae having 40% of the dry matter. It is composed of sodium, calcium, magnesium, strontium and barium ions in a gel form located in the intercellular matrix. It is mostly utilised for industrial purpose because of its capacity of retaining water, gelling, viscosifying and stabilising properties [16].

Alginate has been broadly investigated and employed for many biomedical implementations because of its biocompatibility, low toxicity, low cost, and mild gelation by adding of divalent cations such as Ca^{2+} [17, 18]. It is different from the other hydrocolloids like agar and carrageenan as it is collected from brown seaweed (Phaeophycean) exactly from outer layer cell wall because inner layer mostly made up of cellulose [19]. These alginate molecules allow both flexibility and mechanical strength to the algae [20, 21]. Apart from brown algae, it can also collected from different bacteria species such as *Azotobacter* and *Pseudomonas* [22]. Brown algal species like *Laminaria hyperborean*, *Macrocystis pyrifera*, *Laminaria digitata* and *Ascophyllumnodosum* are extensively used for commercial alginate preparation, while species like *Sargassum spp.*, *Laminaria japonica*, *Ecklonia maxima* and *Lessonia nigrescens*are utilised only if other brown seaweeds not accessible as these gave low and weak production of alginates [23, 24]. Although alginates can be produced both from algae and bacteria, mostly algae are used for commercial production [25].

3. Structure and composition

Alginates are unbranched polysaccharides that are made up of 1, 4 linked β-D-mannuronic acid (M) and its C-5 epimer, α-L-guluronic acid (G). It is composed of M sequences (M-blocks) and G sequences (G-blocks) distributed with MG sequences (MG-blocks) [25]. The D-mannuronate was thought to be the main component of alginate before Fischer and Dörfel discovered the α-l-guluronate residue [26]. Later, fractional precipitation with manganese and calcium salts revealed that alginates are also block copolymers with a different ratio of guluronate

to mannuronate depending on the natural source [27]. Alginate is now understood to be a group of linear copolymers made up of 1,4-linked β-D-mannuronate (M) and α-l-guluronate (G) residues. Consecutive G residues (GGGGGG), consecutive M residues (MMMMMM) and alternating M and G residues (GMGMGM) make up the blocks (**Figure 1**). The M and G contents of alginates extracted from various sources vary, as does the length of each block, and over 200 different alginates are currently manufactured [28]. The G-block content of L-hyperborean stems is 60%, compared to 14 to 31% for other commercially available alginates [29]. Only the G-blocks of alginate are thought to engage in the formation of hydrogels by intermolecular cross-linking with divalent cations (e.g., Ca^{2+}). The composition (i.e., M/G ratio), sequence, G-block length, and molecular weight of alginate and its resulting hydrogels are thus critical factors influencing their physical properties [30]. The length of the G-block and the molecular weight of alginate gels are usually increased to improve mechanical properties. Different alginate sources manufacture polymers with a variety of chemical structures, for example, bacterial alginate derived from Azotobacter has a high concentration of G-blocks and its gels are relatively stiff [31]. The stability of the gels, the rate of drug release from gels, and the phenotype and function of cells encapsulated in alginate gels are all influenced by their physical properties [18].

Commercially available sodium alginates have molecular weights ranging from 32,000 to 400,000 g/mol. For sodium alginate in 0.1 M NaCl solution at 25°C, the parameters of the Mark–Houwink relationship; [η] = KMv a) are K = 2 103 and a = 0.97, where [η] is intrinsic viscosity (mL/g) and Mv is viscosity-average molecular weight (g/mol) [32]. As the carboxylate groups in the alginate backbone become protonated and form hydrogen bonds, the viscosity of alginate solutions increases as the pH decreases, peaking around pH 3 to 3.5. The physical properties of the resulting gels can be improved by increasing the molecular weight of alginate. An alginate solution made from a high molecular weight polymer, on the other hand, becomes extremely viscous, making it difficult to work with [33]. The pre-gel solution viscosity and post-gelling stiffness can be regulated independently by manipulating the molecular weight and its distribution. By combining high and low molecular weight alginate polymers, the elastic modulus of gels can be greatly increased while the viscosity of the solution is minimally increased [18, 34].

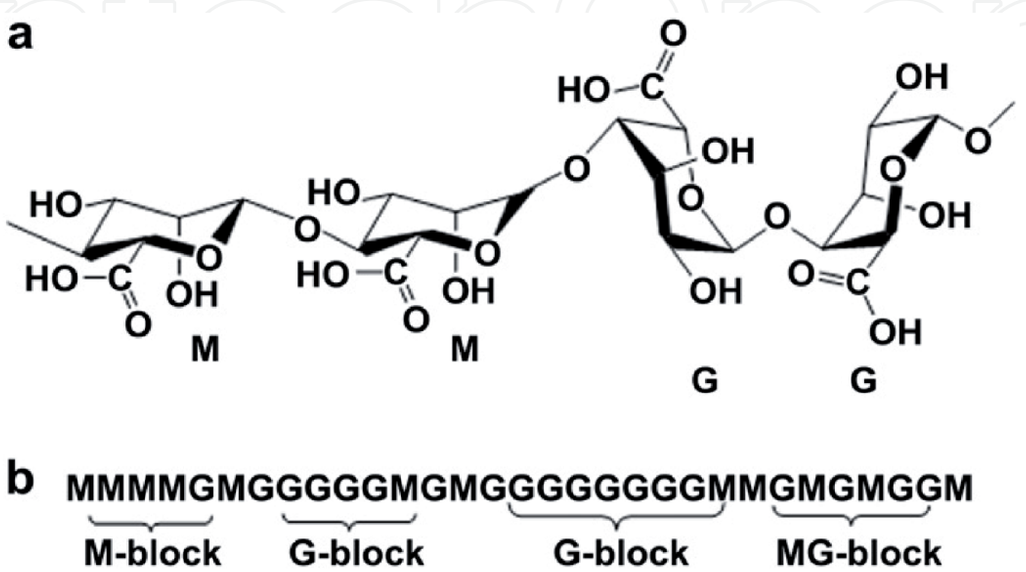

Figure 1.
Diagrammatic representation of alginates: (a) molecular chain, (b) M and G block distribution [25].

4. Biosynthesis

Several excellent research articles [22, 31] have analysed recent progress in bacterial alginates biosynthesis. The oxidation of a carbon source to acetyl-CoA, which enters the TCA cycle and is converted to fructose-6-phosphate through gluconeogenesis, is the first step in alginate biosynthesis. Fructose-6-phosphate is then transformed to GDP-mannuronic acid, which is a precursor to alginate synthesis, through a sequence of biosynthetic transformations. The biosynthetic process can be divided into four stages in general: (a) synthesis of the GDP-mannuronic acid precursor; (b) cytoplasmic membrane transfer and polymerisation of polymannuronic acid; (c) periplasmic transfer and modification; and (d) export through the outer membrane. Polymannuronic acid is acetylated at the O^{-2} and/or O^{-3} positions by multiple transacetylases at stage (c), resulting in post-polymerisation modification of alginates [35, 36]. A family of epimerase enzymes then performs epimerization to transform certain non-acetylated M residues to G residues [37–40]. Finally, transmembrane porin sallow alginate to exit the cell [25].

Alginate is generally available in sodium, potassium, or calcium forms in the market. Both alginate salts are widely used as biopolymers in medical, biomedical, medicinal, and cosmeceutical applications [1, 41–43]. In the presence of divalent and trivalent metal cations in the aqueous setting, sodium alginate can form ionotropic hydro-gelled matrices [44, 45]. Alginate is a biopolymeric excipient widely used in pharmaceutical and biomedical products such as capsules, hydrogels, gels, managed release systems, beads, bio-adhesives, pellets, patches, microparticles, and nanoparticles as an emulsifying agent, disintegrant, thickener, coating content, stabiliser, and so on [46–49]. Based on the cross-linkers used and cross-linking techniques used, alginates can entrap drug molecules and release them in a rate-controlled pattern. It's used in managed drug release systems and targeted drug delivery systems to ensure that drugs have the best bioavailability at their target sites [12]. Sodium alginate, calcium alginate, and alginate derivatives have also been used in the manufacture of wound dressings. Water absorption power, swelling and gelling capabilities, ability to be crosslinked, controllable porosity, biodegradability, and biocompatibility nonimmunogenic, haemostatic nature, bioactivity (support the proliferation process), bio-similarity to extracellular matrices, bio-adhesivity, ability to encapsulate drugs and control of drug releasing, cost-effective, etc. are all important properties that make these biopolymeric materials ideal for wound dressing formulations. Alginate has the ability to absorb up to 20 times its weight in body fluids and liquids, creating a hydrophilic gel. Alginate's excellent gelling properties made it suitable for wound dressing applications [12, 50].

5. Alginate nanoparticles

Nanoaggregates, nano-capsules, and nanospheres are nanoscale systems (10–1000 nm) that can contain enzymes, medicines, and other compounds by dissolving, encasing, or adding them to the matrix of the particle. Different methods used for prepare nanoparticles involves: (a) nanoaggregates, which are nanoscale colloidal structures in which the drug is mechanically distributed and can take on a variety of morphologies; (b) nano-capsules, which are vesicular systems in which the drug is confined to an oily or aqueous liquid centre enclosed by a polymeric membrane, (c) nanospheres, which are spherical particles with a gelled interior in which the entrapped component is physically distributed, or (d) nano-capsules with a structured interior, which are a hybrid of a nano-capsule and a nanosphere; they are made by first preparing a nanosphere and then forming an additional

shell on the nanosphere's interface [51–55]. As previously mentioned, there are two methods for producing alginate nanoparticles: (i) complexation, which occurs in an aqueous solution to form alginate nano-aggregates or on the interface of an oil droplet to form alginate nano-capsules; a crosslinker (e.g., calcium from calcium chloride) is used for complexation of alginate, and complexation may also occur by mixing alginate with an oppositely charged polyelectrolyte (*e.g.*, poly-L-lysine); and (ii) alginate in-oil emulsification, followed by external or internal alginate emulsion droplet gelation, resulting in alginate nanospheres [56]. We can summarise the methods used in synthesising alginate-based nanomaterials as-controlled jellification using Ca^{2+} ions, formation of polyionic complexes through ionotropic gelation via intermolecular interactions, spray drying followed by crosslinking, alginate nanoaggregates through self-assembly, fabrication of nanocomposite fibrous scaffolds and nanoparticles respectively by electrospinning and electro-spraying, fabrication of nanocomposite fibrous scaffolds by thermally-induced phase separation and formation of alginate nanoparticle using a microfluidics- aided polyelectrolyte Complexation [57].

6. Wound

By functioning as a physical/chemical barrier [9], skin the largest organ of body protects the internal organs and is responsible for protecting against infections and dehydration from environmental aggressions [58]. However, it is the human body's most often damaged organ. Skin (acuteand chronic) wound defence from pathogens when it is injured (diabetes mellitus, chronic venous, arterial insufficiency, immunological and other infections) is a very difficult problem for the recovery of the injured skin. Wound is described by the Wound Healing Society as the disturbance of normal anatomical structure and functions [59]. The prevalence and severity of wounds prompted researchers to focus on wound healing management studies, as well as the demand for wound dressings. Accidents, burns, surgical operations, and violent impact all cause breaks or lacerations in the skin's membrane layers, causing damage to underlying tissues or disruption of cellular integrity, resulting in wounds [60]. Physical, mechanical, thermal, biochemical, surgical, or metabolism-related problems can all result in wounds [61–64]. If left untreated, the wound can develop sepsis, necessitating amputation or even death [60].

Wounds are graded based on (a) the time and nature of the wound healing process, (b) the depth of the wound injury, and (c) the appearance of the wounds [12]. Acute and chronic wounds are the two types of wounds that are often encountered. An acute wound is a skin injury that happens unexpectedly rather than over time, and heals in 1–12 weeks, depending on the type of the wound. It should be noted that for optimal health and cost, the healing of an acute wound (which may occur in a variety of ways) is preferable for recovery [65]. Chronic wounds can be caused by a variety of factors, including venous insufficiency, arterial perfusion, diabetes, and so on. Chronic wounds do not heal in the expected time frame because they are more vulnerable to infections and are more difficult to treat [9, 66].

Chronic wounds are divided into four categories based on their aetiology: (a) decubitus ulcers (bedsores), (b) diabetic ulcers, (c) venous ulcers (leg ulcers), and (d) arterial insufficiency ulcers [67]. Wounds are also divided as (i) superficial wounds (injury of surface of epidermis only), (ii) partial-thickness wounds (injury on both epidermis and deep into dermis like blood vessels, sweat ducts etc.), and (iii) full-thickness wounds (injury on underlying the subcutaneous fatty layers along with the layers of epidermis and dermis), (iv) on the other hand, wounds may be categorised as necrotic, sloughy, granulating, epithelializing, contaminated,

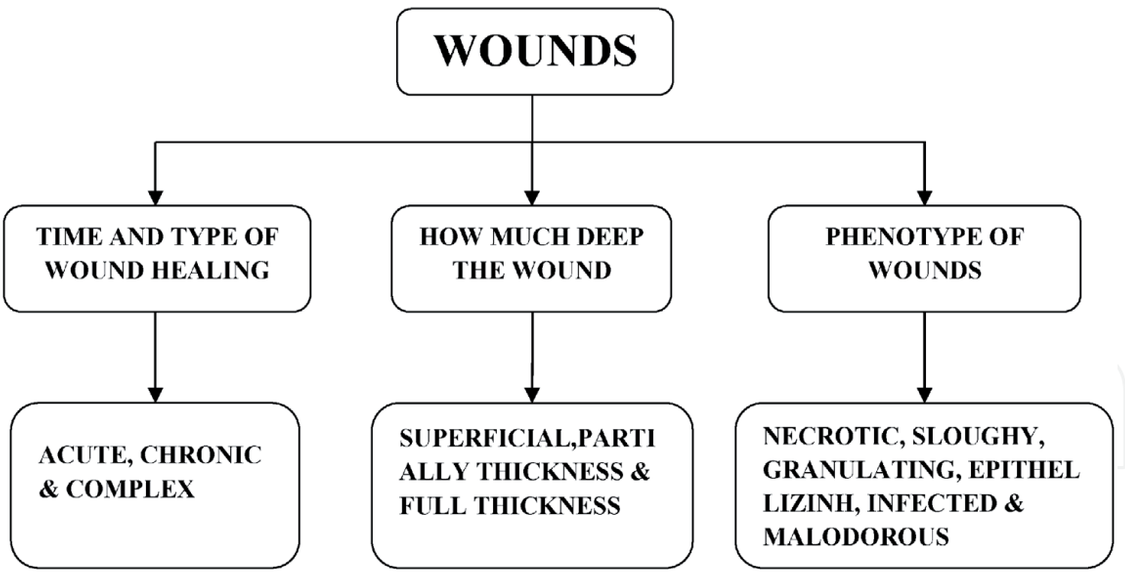

Figure 2.
Classification of wounds [12].

or malodorous depending on their appearance (**Figure 2**). Complex wounds, which are either acute or chronic wounds that are difficult to heal are another new type of wounds [68–70]. Burn injuries are a form of serious wound that is frequently painful and physically damaging, accompanied by pain and inflammation. Burn wounds may often result in prolonged sensory difficulties, serious illness, and mortality as a result of long hospitalisation and recovery [71, 72]. Medical Treatment forburn wounds is still difficult, and several studies are being conducted to develop better therapeutic aids. For successful care, current industrial wound dressing products and engineered skin replacements are being pushed towards a functionalized wound dressing strategy [72].

7. Wound dressing classification

Traditional, biomaterial-based, interactive, and bioactive dressings are the four types of wound dressings [73]. Traditional dressings, also called as passive wound dressings, are utilised to shield wounds from the environmental contact while also preventing bleeding [73, 74]. Traditional dressings include gauze and gauze-cotton composites, both of which have a high absorptive quality. These can, however, cause bleeding, having poor vapour permeability, and damage the freshly formed epithelium when removed. Exudates leaking from these dressings may also cause bacterial infections. Allografts, tissue derivatives, and xenografts are three types of biomaterial-based wound dressings [73]. Allografts can be defined as skin fragments collected from donors that may be fresh or freeze-dried, and their usages was restricted due to an immune response that causes the body to reject them. There's also the possibility of infection and disease transmission [75, 76]. They are costly and have a short shelf life. Tissue derivatives are made from collagen, but their use is restricted due to the possibility of infection over a long time. Artificial dressings, also called immersive wound dressings, are made up of gels, foams, films, sprays, composites, and other materials [73, 74]. Biopolymers and synthetic polymers are used to prepare them. Alginate, chitosan, gelatine, and other biopolymers are commonly used. Wound dressings may also be categorised as bioactive wound dressings, with alginates, collagens, hydro-fibres, and hydrocolloids being examples. Wound healing is aided by the addition of growth factors and antimicrobials agents.

A lot of biopolymers are now being frequently used to make the wound healing materials for different type of wounds [1, 73].

8. Wound healing process

Haemostasis, inflammation, migration, proliferation, and remodelling are the five stages of wound healing (**Figure 3**), [3, 68–80]. When an injury to the skin occurs, haemostasis and inflammation occur. Fibrinogen, a major component of the skin's connective tissue, aids in the coagulation of exudates and blood clotting in wounds to avoid bleeding [3, 73, 80, 81]. The inflammatory process occurs concurrently with the haemostasis phase, in which the phagocytic cells release proteases and reactive oxygen species, which clean the wound of debris and protect it from bacterial infection [3]. Blood monocytes transform into tissue macrophages at the wound site, releasing growth factors and cytokines that attract fibroblasts, endothelial cells, and keratinocytes to help repair damaged blood vessels. The epithelial cells migrate towards the wound site to replace dead cells during the migration process. The wound is fully covered by epithelium during the proliferation stage, and formation of granulating tissues starts. Tissue remodelling is the final step, in which fibroblasts fully cover the wound's surface as a new layer of skin. There is no evidence of wound in this process, which is also known as the maturation phase [1, 3, 78].

Damaged skin is vulnerable to microbial infection and is unable to protect the physiological functions of internal organs [82–84]. Wound dressing will hasten skin's physiological regeneration while also preventing infections and dehydration at the wound surface [85]. Furthermore, an ideal wound dressing should have good biocompatibility [86]. As a result, a variety of wound dressings in various types have recently appeared, the majority of which are made up of natural macromolecules such as chitosan, cellulose, alginate, and collagen [87–89]. Alginate is widely used in the pharmaceutical and biomedical fields as a natural biocompatible polysaccharide. Alginate has also been used as a wound dressing in the past. While alginate dressings can help with wound healing, they have poor haemostatic properties, particularly when it comes to massive haemorrhage [90]. Collagen which is the most abundant protein in animals, and it can be found in almost all soft and hard connective tissues. Collagen is also a vital constituent of the extracellular matrix (ECM), which organises itself around the cells in a logical manner.

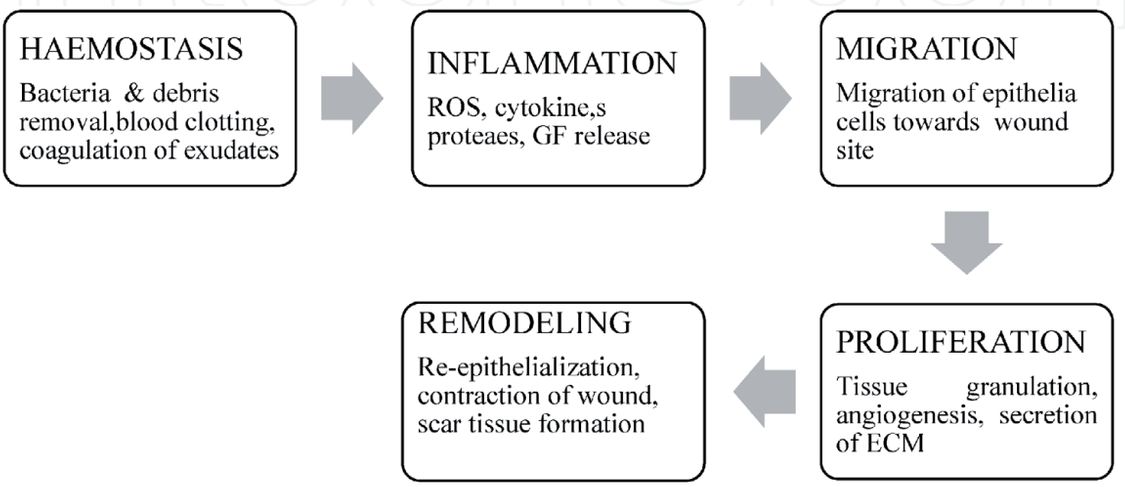

Figure 3.
Steps in wound healing processes [1].

Collagen has a high biocompatibility, a strong haemostatic activity, a higher water absorbing potential, and a low immunogenicity [91]. Collagen can also facilitate cell attachment and proliferation, affecting cellular activity and tissue function further. Collagen-based wound dressings were found to have a number of advantages in studies. The addition of collagen to alginate significantly improved the hydrogel's properties [92]. Meanwhile, the collagen–alginate composite had considerable water absorption and mechanical properties, allowing it to keep the wound surface moist as well as maintain local tissue and encourage cell adhesion and growth [93, 94]. On the other hand Collagen and alginate, on the other hand, display no antimicrobial activity. As a result, antimicrobial functionalization of collagen–alginate dressings is critical to promote wound healing and prevent secondary infection [95]. The abundance of cellulose in the biosphere, especially in herbal and bacterial sources, has made this natural polysaccharide more available. To make cellulose, D-glucose units are connected together by glycoside bonds of $\beta(1 \rightarrow 4)$to form the formula $(C_6H_{10}O_5)_n$, which has three hydroxyl groups for each unite. These functional groups are specifically targeted for cellulose modifications in order to enhance biomedical applications such as wound dressing manufacturing. For example, in the case of modified bacterial cellulose/keratin nanofibrous mats through a hydrogel of tragacanth natural gum, increased fibroblast cell attachment and proliferation were observed [96]. Due to its excellent biocompatibility, nontoxicity, antibacterial properties, and haemostasis, chitosan is also considered a highly favourable material, while gelatine has excellent film-forming and water absorbing properties [86, 97–99]. In addition to all as a natural and herbal medicine, curcumin was mixed into the chitosan and alginate sponge (CA sponge) as a multifunctional agent to prevent wound infection. Curcumin (CUR), a polyphenol derived from turmeric, is a well-known wound-healing agent that has been shown to have antimicrobial, antioxidant, and anti-inflammatory properties [100–102].

9. Curcumin

Curcumin is one of the most important curcuminoids found in *Curcuma longa*. Turmeric is the common name for it. Curcumin, also known as diferuloylmethane or 1,7-bis (4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione, is a polyphenolic phytoconstituent with a low molecular weight that occurs naturally [103, 104]. It is a member of the Zingiberaceae ginger family (chemically named diferuloyl methane). Turmeric has been used by the South Asians for treating diseases and skin problems since ancient times. In reality, it is a widely used spice and a staple in their diet [105, 106]. Curcumin is a powerful anti-inflammatory agent. It is also said to inhibit tumour growth to some degree. As a result, the scientific community has taken a keen interest in this material, and a significant number of experiments have been carried out with it for a variety of purposes. This is aided by the fact that curcumin is nontoxic when taken at a dose of 4 g/day for up to 120 days [107–109] (**Figure 4**).

Curcumin's pharmacological properties, including anti-inflammatory [111], antimicrobial [112], antiviral [113], anticancer [114], antioxidant [115], chemosensitizer [116], radiosensitizer [35], and wound healing activities [117, 118], indicate that it has potential in preclinical cell culture and animal studies. Topical usage of curcumin have been shown to enhance healing of wounds and protect tissues from oxidative damage by acting as an anti-inflammatory antioxidant (free radical scavenging activity), inducing detoxification enzymes, and providing defence against degenerative disease in patients [119, 120].

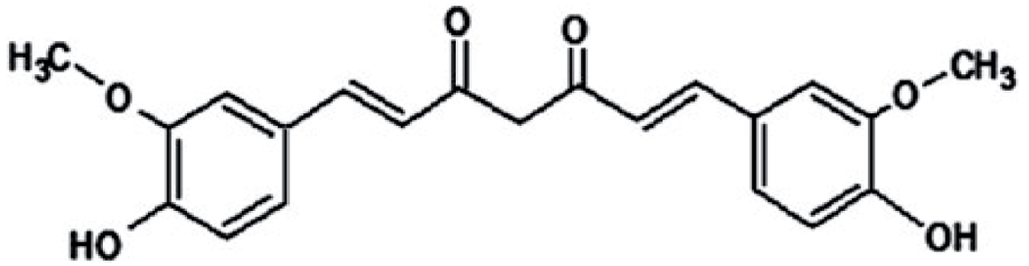

Figure 4.
Structure of curcumin (diferuloylmethane) [110].

10. Pharmacological activity of curcumin

Curcumin has been widely regarded as a "wonder drug of the future" due to its exceptional ability in preventing and treating many incurable illnesses, according to several clinical and preclinical studies performed on it over the past decades [121]. Curcumin has been studied for its anticancer properties for the past 50 years. According to some reports, Curcumin was shown to have chemotherapeutic impact on breast cancer [122], colon cancer [123], stomach cancer [124], liver cancer [125], and oral cancer [126]. It's effects on diseases including diabetes [127], Alzheimer [128], gastric ulcer [129], rheumatoid arthritis [130], psoriasis [131], and HIV [132] were studied in other studies, revealing its potential as a therapeutic agent. Curcumin's effects on the cardiovascular system, as well as pulmonary and metabolic disorders, have been studied further [133]. Curcumin's antimicrobial [134], antiviral [135], antioxidant [136], anti-inflammatory [137], and wound healing properties have also been widely recorded [117, 138].

Despite all of curcumin's potential usage in medicine, pharmacological studies have shown a number of disadvantages. Curcumin was discovered to have low absorption, poor solubility, and a low distribution property. As a result, curcumin is poorly absorbed in the body and cannot be used to treat diseases [139, 140]. It has a low bioavailability due to its rapid metabolism, elimination, poor tissue distribution, and low serum concentration [140, 141]. According to studies, curcumin bioavailability varies depending on the route of administration. In *in-vivo* study on mouse sample, it was discovered that when curcumin was administered intravenously, it was absorbed the most in the serum, while when curcumin was given orally, it was absorbed the least [142]. Researchers have been trying to increase the bioavailability of curcumin for the past three decades. They have devised a number of methods to improve the medicinal use of curcumin. Curcumin has been studied in various formulations to see whether they can solve the problem [143]. We have concentrated in this chapter on nanotechnology-based techniques that can aid in the delivery of curcumin and thus alleviate its disadvantages [110].

11. Curcumin as a nanoparticle

Nanoparticles (NPs) are now being researched and used in a variety of medical fields to allow for targeted drug delivery, lower active agent dosing, combination therapy, reduced side effects, and the use of more potent drugs that cannot be clinically used by traditional drug delivery. Because of its many unique characteristics, nanotechnology has become a major area of interest in response to the growing threat of microbial drug resistance. The ability to overcome barriers and gain access to biological molecules and more specifically, microorganisms is enabled by the

physical and chemical properties of NPs including their high surface-to-volume ratio and small size [144]. The mechanisms other than antibiotic arsenal, which has established resistance, this direct association with microbial cell membranes/walls and main proteins/enzymes can both inhibit pathogen growth and/or instigate cell death. Furthermore, the scale, shape, and chemical properties of NPs can be altered to promote these molecular interactions, thereby maximising their ultimate function [144, 145].

Curcumin encapsulation in a nanoparticle platform is a feasible and beneficial method of delivering it. Nanoparticles can pass through the skin barrier and intracellularly due to their small size and high surface-to-volume ratio [146], making them suitable for topical drug delivery. Since the potential maximum volume of substance is never in contact with skin at one time, toxicity is limited by the slow, continuous release of encapsulated contents. Nanoparticles allow the delivery of substances like curcumin that have physicochemical properties that prevent or delay their use in non-encapsulated form. Curcumin nano-formulations have been established for preclinical studies on cancer, inflammation, wound healing, and other conditions, with nano-versus non-encapsulated curcumin demonstrating improved therapeutic efficacy [146, 147]. However, there is minimal evidence in the infection landscape [148], with no *in-vivo* studies reported to date [149].

Nanomaterials have the ability to enhance and change the pharmacodynamic properties of drug molecules with solubility issues, such as curcumin. Curcumin's stability, solubility, and bioavailability can all be improved with nanoparticle-based drug delivery. Physical entrapment, adsorption, and chemical conjugation methods are used to bind drugs to the surface of nanoparticles [140, 143, 150]. Various forms of nanomaterials, such as liposomes, proteins, nano-emulsions, micelles, strong lipid nanoparticles, and polymeric nanoparticles, have been found to be promising carriers for the delivery of curcumin in previous studies. Polymeric nanoparticles are thought to be the most important of all nanoparticle-based delivery methods and are currently being studied for the curcumin delivery [110, 151–153].

12. Alginate-curcumin based systems for wound healing

Acute and chronic wound care is a pressing need, and alginate-based wound dressings provides many benefits over the conventional wound dressings. Alginate-based wound dressings come in a variety of shapes and sizes, including hydrogels, films, foams, nanofibers, membranes, and sponges. Alginate based dressings can absorb wound fluid, resulting in gels that keep the wound site physiologically wet and prevent bacterial infections. Efficacy of these wound dressings has been documented by several researchers [1]. To increase the efficacy of alginate dressing, curcumin was used as a potential antibacterial and ani-inflammatory biomaterial for rapid healing of wounds. In combination with alginate and other biopolymers curcumin increases the potency of wound healing of the wound dressing systems. Many alginate-curcumin systems have been used as drug delivery systems, wound dressing materials, tissue regeneration materials, and other applications in recent years. Curcumin's use in wound healing applications as wound dressing products has been well researched over the last few decades and published in numerous publications [154]. Other than alginate, chitosan was the mostly used biopolymers for preparation of wound care dressing materials. The focused on researches and experiments done with alginate and curcumin and related wound healing dressing systems and summarised in **Table 1**.

There are many attempts to improve the efficiency of wound healing through slow delivery of antioxidants including curcumin from collagen, which also serves as a supporting matrix for the regenerative tissue [167]. In the curcumin

Alginate-curcumin formulations	**Composition**	**Investigation level/stage**	**Result**	**Ref.**
Sponge	Chitosan, sodium alginate (CA) and curcumin	*in-vivo*	CA-Curcumin sponge can promote the formation of the collagen, thus accelerate the healing process.	[120]
Foam	Sodium alginate and curcumin	*in-vitro*	It can be removed easily from the wound site with wound healing effect.	[155]
Hydrogel	N,O carboxymethyl chitosan/oxidised alginate and nano-curcumin	*in-vivo*	It enhances the re-epithelialization, collagen deposition and accelerate the process of wound healing.	[156]
Polymeric bandage	Chitosan, Sodium alginate, oleic acid and Curcumin	*in-vivo*	It enhances wound healing.	[157]
Microfibre	sodium alginate, gelatine and Curcumin	*in-vivo*	The composite has the potential to wound healing platform.	[158]
Film	Bacterial cellulose, alginate, gelatine and curcumin	*in-vitro*	It has potency for wound care, periodontitis and oral cancer treatment.	[159]
Fabric scaffold	Curcumin and Gymnemasylvestre, graphene oxide, polyhydroxy butyrate-sodium alginate	*in-vivo*	Effective against diabetic wound as well as normal wound.	[160]
Film	Human Elastin-Like Polypeptide (HELP), alginate and curcumin	*in-vitro*	Effective for drug delivery, wound healing, and tissue regeneration.	[161]
Hydrogel	Curcumin, β-cyclodextrin Sodium alginate, Chitosan	*in-vitro*	It inhibits the Gram-negative (*E. coli*) and Gram-positive bacteria (*S. aureus*) growth to heal the wound.	[162]
Sponge	Curcumin, chitosan–alginate and β-cyclodextrin	*in-vivo*	It facilitate cutaneous wound healing.	[163]
Membrane	Alginate membrane, polycaprolactone (PCL) nanoparticles, Curcumin	*in-vivo*	It can accelerate wound healing without removal of the membrane.	[164]
Patch	Sodium alginate/PVA-Titanium dioxide (TiO_2) and curcumin	*in-vitro*	It shows antibacterial and antifungal activities and can be used for wound healing.	[165]
Curcumin Encapsulated particle	Pluronic F127 (PF127), calcium chloride ($CaCl_2$), sodium alginate, chitosan, curcumin	*in-vitro*	It has potency of good drug delivery and further research needed to test the efficacy for wound healing.	[166]

Table 1.
List of experiments on alginate-curcumin nanocomposite wound healing systems.

incorporated collagen matrix (CICM) group, biochemical parameters and histological analysis revealed increased wound healing, increased cell proliferation and effective free radical scavenging. As compared to standard collagen films, CICM films have a higher shrinkage temperature, implying greater hydrothermal stability. Curcumin was found to be bound to collagen without altering its triple helicity in spectroscopic tests. Curcumin absorbs a lot of light in the wavelength range of 300 to 500 nm. In methanol solution, it has a maximum absorption wavelength of 420 nm, which changes to 430 nm in dimethylformamide. As collagen solution is applied to curcumin, however, the maximum wavelength changes from 420to 429 nm. The change in the absorption shift stabilised and the amplitude of the peak increased with rising curcumin concentration, implying that curcumin is affected by the hydrophobic atmosphere. Further, lipid peroxidation method was used to determine the antioxidant performance of CICM [168]. The CICM's *in-vitro* antioxidant activity was tested by using 2,2-azobisisobutyronitrile antioxidant assay. According to antioxidant research, CICM is more effective at quenching free radicals. This concept supports the topical application of CICM as a viable and effective method for supporting dermal wound healing [167].

A nanocomposite sponge was made out of curcumin-chitosan-gelatine at various ratios of chitosan and gelatine [169], and the chemical structure and morphology were characterised using ATR- FTIR and FE-SEM. The water absorption ability, antibacterial activity, *in-vitro* drug release and *in-vivo* wound healing studies were also performed on these sponges using a rabbit excision wound healing model. The combine form of curcumin, chitosan, and gelatine has shown increase water absorption capacity, antibacterial function and wound closure potency. The cytotoxicity of curcumin sponge tested using the indirect MTT method on mouse fibroblast cells (L929) [170] indicates the controlled release of curcumin increased as the gelatine content of the prepared sponge increased. The drug in the sponge with a higher gelatine content is favoured to be released, instead of being dissolved by the sponge according to the partition ratio between sponge phase and water phase. The findings shows cell viability after 24 hours of incubation period with sponge-released medium. The results show that in the presence of medium containing sponge without curcumin and curcumin sponge, cell viability drops to around 90%. In the *in-vivo* analysis, wounds treated with curcumin-composite sponge closed faster than wounds treated with composite sponge without curcumin. According to the results of curcumin drug release, composite sponges with a higher gelatine content had a faster release activity up to 240 minutes. These composite sponges were also discovered to increase wound healing activity by enhancing collagen production *in-vivo*. These obtained results showed that combination of curcumin, chitosan and gelatine could improve the wound healing activity in comparison to chitosan, and gelatine without curcumin [169].

Hydrogels are most preferable system as their biodegradable and controlled drug delivery systems composed of curcumin loaded micelles are widely applied for cutaneous wound repairing [103]. Curcumin with strong antioxidant and anti-inflammatory properties and having high hydrophobicity was encapsulated in polymeric micelles (CurM) for high drug loading and encapsulation efficiency. To improve cutaneous wound healing, Cur-M loaded thermosensitive hydrogel (Cur-M-H) was prepared and applied as a wound dressing materials. At room temperature, Cur-M-H was a free-flowing solution that transformed into a non-flowing gel at body temperature. Cur-M-H system was found to have good tissue adhesiveness and the ability to release curcumin for a long time in vitro studies. It's *in-vivo* wound healing operation was also assessed using linear incision and full-thickness excision wound models. CureMeH-treated mice had a thicker epidermis and higher tensile strength in an incision model. In an excision model, the CureMeH treated group showed

improved wound closure. This group also had higher collagen content, stronger granulation, higher wound maturity, a drastic decrease in superoxide dismutase, and a small rise in catalase in both models. CureMeH may also improve cutaneous wound healing, according to histopathologic analysis. Thus the combination of curcumin bioactivity and thermosensitive hydrogel in the in-situ gel-forming composite, facilitates tissue reconstruction processes, implying that the CureMeH composite could be used as a wound dressing for cutaneous wound healing [103] .

According to past reports, materials commonly used to treat burn-wound infections are limited by their incomplete microbial coverage, toxicity, insufficient penetration and more resistance to antibiotics. Curcumin is a naturally occurring compound that has antimicrobial, anti-inflammatory and wound-healing properties. Working through a variety of pathways, is less likely than current antibiotics to select for resistant bacteria. But curcumin's weak aqueous solubility and rapid degradation profile make it difficult to use; however, nanoparticle encapsulation solves this problem and allows curcumin to be delivered to the skin for longer periods of time [149]. So, curcumin nanoparticles (Curc-NP) prepared by the modified sol–gel methods [171] is a major step forward in the treatment of contaminated burn wounds, as it reduces bacterial load while also improving wound healing. Curcumin nanoparticles (Curc-NP) inhibited methicillin-resistant *Staphylococcus aureus* (MRSA) and *Pseudomonas aeruginosa* growth *in-vitro* in a dose-dependent manner, and inhibited MRSA growth and improved wound healing in an *in-vivo* murine wound model. The sensitivity of murine PAM212 keratinocytes to curcumin determined using a semiquantitative FDA (fluorescein diacetate) metabolic assay showed no toxicity to the side tissues. These outcomes indicates, Curc-NPs may rise as a novel topical antimicrobial agent over the conventional antibiotics and wound healing adjuvant for the treatment of infected burn-wounds and other cutaneous injuries [149].

A novel collagen scaffold called nanohybrid-scaffold prepared by incorporating curcumin (CUR) in chitosan nanoparticles (CSNPs) to improve the stability and solubility of the scaffold followed by permeation of prepared CUR-CSNPs have shown better tissue regeneration application [172]. This novel nanohybrid collagen scaffold tested for morphology changes, biodegradability, biocompatibility, *in-vitro* drug release and *in-vivo* wound healing studies have shown high potency. *In-vitro*, the nanohybrid scaffold performed well in terms of water absorption, biocompatibility, and long-term drug availability. Whereas, *in in-vivo* wound closure analysis showed that wounds treated with nanohybrid scaffolds contracted substantially faster than wounds treated with control and placebo scaffolds. Thus the study indicate that in the nanohybrid scaffold community, full epithelialization with thick granulation tissue formation occurs, while there was no compact collagen deposition in the placebo scaffold group and the presence of inflammatory cells in the control group. These suggest that, combining CUR (anti-inflammatory and antioxidant), chitosan (sustain drug carrier, wound healing), and collagen (established wound healer as scaffold) is a promising strategy for addressing various pathological manifestations of diabetic wounds and improving wound healing capability [172].

Considering alginate as a vital ingredient and an unavoidable wound dressing system, a lot of steps have been taken place to develop a proper system having high efficiency for wound healing and low toxicity material. Hence, an ethereal, pliable and biodegradable sponge, composed of chitosan (CS) and sodium alginate (SA) in different ratio and curcumin was prepared and its sponginess, chemical composition and morphology characterised using ATR-FTIR and FE-SEM are similar as reported for other materials for wound dressing purpose [120]. The sponges of all kinds had biodegradable quality and the degree of crosslinking influences the

release of curcumin from the sponges. The sponges' water absorption capacity ranged from 10 to 43%. The wound healing test performed on Sprague–Dawley (SD) rats shown that the CA sponges have a continuous release activity for up to 20 days based on the effects of drug release of curcumin. This conclude that the CA sponge acts as an effective drug support for long-term release of curcumin up to 20 days at a time. The collagen bundles in the CA-curcumin sponge-treated wound were thicker than those in the gauze and CA sponge-treated wounds, and they were compact and well-aligned. The developed material, curcumin sponge can promote collagen production, which speeds up the healing process and has a positive impact on wound healing process [120].

Curcumin loaded to alginate foams with low cross-linking was developed based on the previously patented method for the treatment of infected wounds [155, 173]. Curcumin-loaded foam demonstrated a longer hydration time and the amount of curcumin released was adequate, for curcumin-mediated phototoxicity of viable *E. faecalis* cells *in-vitro*. *E. coli*, on the other hand, was less vulnerable to photokilling when curcumin-loaded foams were used, and this was affected by the curcumin solubilizers used in the foams. Only foams containing PEG-400 as the curcumin solubilizer with visible light radiation (29 J/cm^2) caused 81% inhibition of the viable *E. coli* cells to be inactivated. When the foams were exposed to the physiological solution, they quickly hydrated and stayed intact after the loaded curcumin was released, implying that they can be withdrawn from the wound site without causing tissue harm prior to irradiation, reducing light attenuation in photodynamic therapy (PDT) [155].

An injectable chitosan and alginate derivates based on hydrogel incorporating nano-curcumin was also prepared in view of a potential wound dressing with enhanced healing efficacy [156]. Nanocurcumin with a particle size of about 40 nm prepared by using methoxy poly(ethylene glycol)-b-poly(−caprolactone) copolymer (MPEG-PCL) as a carrier, followed by a simple nano-precipitation process and integrated into N,O carboxymethyl chitosan/oxidised alginate (CCS-OA) hydrogel shown slowly and continuously release of curcumin from the CCS-OA hydrogel to promote fibroblast proliferation, capillary development, and collagen output, both of which can have a major impact on the healing processes. The encapsulated nano-curcumin shown slowl released from the CCS-OA hydrogel in an *in-vitro* release analysis (with diffusion controllable release at first, followed by the corrosion manner) of hydrogel at terminal phase. According to the histopathology repots, the hydrogels injected into rat dorsal wounds as part of an *in-vivo* wound healing trial has shown significant improve in epidermis re-epithelialization generation and collagen deposition in wound tissue. The measured DNA, protein, and hydroxyproline content of wound tissue indicate that the nano-curcumin and CCS-OA hydrogel together significantly speed up the wound healing process. It was hypothesised that the nano-curcumin/CCS-OA hydrogel have a wide range of applications in wound healing [156].

On the other side a complete investigation of curcumin loaded oleic acid based polymeric bandage and its therapeutic potential in dermal wound healing in a rat model was carried out [157] to show that curcumin has high wound healing potency in various animal models, and a curcumin-loaded oleic acid-based polymeric (COP) bandage was developed to increase curcumin efficacy in the healing region. Due to its effective free radical scavenging properties, biochemical parameters and histological examination showed increased wound reduction and enhanced cell proliferation in COP bandage treated groups. Researchers believe this is due to increased intercellular curcumin retention and, as a result, an improved anti-inflammatory activity by quenching reactive oxygen species (ROS). Early implementation of fibroblasts and differentiation (increased amount of smooth muscle actin) resulted

in a comparative acceleration of wound healing. The COP bandage can effectively quench free radicals, resulting in decreased antioxidative enzyme activity. The mechanism is potent enough to reduce the inflammatory response mediated by the NFB pathway during wound healing, as evidenced from the mRNA and protein levels analysis. In light of this, it's possible that the curcumin-loaded polymeric bandage may have a new therapeutic use in clinical settings for cutaneous wound healing [157].

There are also studies which stated about characterisation and optimisation of different biodegradable and biocompatible formulations of curcumin encapsulated particles, in order to enhance the efficiency of curcumin wound healing effect [166]. The optimised curcumin particles ranged in size from 1286 nm to 1485 nm, with a 75% encapsulation performance. With a Polydispersity Index (PDI) of 0.4, the zeta potential showed values ranging from −7.20 to −7.96. The efficient fabrication and encapsulation of curcumin in the polymeric matrix, which had been fabricated in rod form, was ensured by physical characterisation using HR-TEM imaging. For curcumin particles, the release profile was biphasic, with an initial burst accompanied by a steady release pattern. *In-vitro* cytotoxicity assays and microscopic imaging verified the safety of the curcumin particle concentration used, which was less than 25 g/ml. Furthermore, the findings of a cellular uptake analysis confirmed that curcumin particles were internalised. Overall, the existing biocompatible and biodegradable curcumin encapsulation formulations have the potential to be used as a drug delivery vehicle for curcumin, according to this thesis. More evidence of this curcumin encapsulated particle's ability to improve wound healing is also required [166].

Incorporation of nanoforms of metal oxides into the wound care materials improves their antibacterial efficacy and thus used in wound healing process. This has open up a new window towards the use of metal oxide nanoparticles for therapeutic purpose [165]. Sodium alginate/PVA-titanium dioxide (TiO_2) based wound healing patches were synthesised. TiO_2 provides characters such as biocompatibility, no toxicity, antibacterial and antifungal etc. [165]. TiO_2 NPs and curcumin were incorporated into the polymeric patches and tested for antibacterial activity against *Bacillus subtilis*, *Klebsiella pneumoniae*, *Staphylococcus aureus*, and *Escherichia coli*, as well as antifungal activity against *Candida albicans* and *Aspergillus niger* [92]. This provides evidence that both TiO_2 nanoparticles and curcumin incorporated SA/PVA patches can be better used in wound healing [165].

Non-biodegradable, opaque and occlusive and low swelling capacity are the vital obstacles of few commercially available wound dressings materials used for clinical performance. Thus to overcome and improve such drawbacks, a novel biodegradable wound dressing material was prepared by using alginate membrane and polycaprolactone (PCL) nanoparticles loaded with curcumin [164]. Curcumin was employed as a model drug due to its important properties in wound healing, including antimicrobial, antifungal, and anti-inflammatory effects. Both, *in-vitro* and *in-vivo* trials were conducted to assess the possible use of this wound dressing material. The novel membrane had a wide range of functional properties that made it suitable for use as a synthetic skin substitute, including a high capacity for swelling and adherence to the skin, evidence of pores to control the loss of trans-epidermal water, clarity for wound monitoring, a high capacity for swelling, controlled drug release and effective adherence to the skin. The use of nanocarriers aids the drug's permeation through various skin layers, resolving curcumin's solubility issues. It also claimed that the clinical implementation of this method would cover large areas of mixed first- and second-degree wounds without the need for removal, reducing patient pain and the risk of changing the formation of the new epithelium tissues [164].

Recently biocompatible polymers are widely used in wound care systems especially for burn wounds as well as skin damages. Polymers such as polyvinyl alcohol and chitosan have been shown to be biocompatible with low toxicity have make them ideal for treating injuries with limited side effects [108]. Curcumin, a key component of turmeric, has anti-inflammatory and antimicrobial effects, but its bioavailability is extremely poor. Curcumin's bioavailability was increased exponentially after it was converted to its nano form, and allowing it to play an important role in wound healing. Considering the biopolymer and dynamic nature of curcumin, polymeric patches were prepared from Polyvinyl alcohol and chitosan with nano-curcumin for wound healing purpose. Slow vaporisation was used to successfully synthesise nano-curcumin, which was then integrated into polyvinyl alcohol and chitosan and obtained as a PVA/Chi/Cur patch using the gel casting process. Different characterisation methods were used to assess the patch: wwelling rate, evaporation rate, blood effect, cell biocompatibility, and antibacterial activity were all investigated. The patch was screened for antibacterial activity against common bacteria present on the wound site (*Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, and *Bacillus subtilis*). The study was completed by putting the patch wound healing efficiency to the test on Albino Westar rats for 16 days. The tests were successful and results of cell line experiments and the MTT-assay showed that the PVA/Chi/Cur patch improved cell proliferation. Its antibacterial activity against four major bacterial strains present in wound sites, as well as its water retention, makes it an ideal material for wound healing. Its superiority over commercial ointment was demonstrated in *in-vivo* trials. This procedure for epidermal wounds decreases the number of times the patch has to be replaced and speeds up wound healing [108].

The β-cyclodextrin (CD) is generally used as a good stabilising and solubilising agent for preparation of different pharmaceutical products. It also enhances the water solubility of curcumin by forming β-cyclodextrin (CD)–Cur complex [163]. To facilitate cutaneous wound healing, a composite prepared from curcumin (Cur), chitosan–alginate (CA) and β-cyclodextrin (CD) [163] by adding curcumin to the ring-shaped β-cyclodextrin (CD) to form a β-CD–Cur inclusion complex (CD-Cur) and tested in a skin model to shows higher skin permeability than free Cur [174–176]. These findings indicate that Cur-CD can be an useful component for cutaneous wound healing materials. Animal studies with cutaneous wounds in rats using CA-CD-Cur showed accelerated and better wound closure rates, good histopathological results, and lower SOD, lipid peroxidation, pI3K, and pAkt levels in comparison to other material. Thus, CA-CD-Cur can facilitate cutaneous wound dressing that facilitate faster wound healing process [163].

Another alginate based hydrogel system was developed using curcumin-β-cyclodextrin based inclusion complex for wound healing purpose [162]. The fabricated curcumin-β-cyclodextrin inclusion complex loaded sodium alginate/chitosan (CMx-loaded SA/CS) bilayer hydrogels was tested as a better wound healing materials. The improve materials with high $CaCl_2$ content has high tensile strength, percent elongation at split and Young's modulus. The release characteristics of CMx from all hydrogels exhibited a similar pattern of release. Furthermore, the CMx-loaded SA/CS bilayer hydrogels inhibited Gram-negative (*Escherichia coli*) as well as Gram-positive bacteria (*Staphylococcus aureus*). Finally, NCTC clone 929 and NHDF (normal human dermal fibroblast) cells were found to be non-toxic to all bilayer hydrogels. Therefore, these CMx loaded SA/CS bilayer hydrogels had the potency for wound healing and can be used as wound dressing materials [162].

As newer technologies are approaching for development of proper wound care management systems, elastin based biomimetics are one of the trending topic for current material development. This concept contributes for the preparation and

characterisation of series of cross-linked films based on the combination of an elastin-derived biomimetic polypeptide [Human Elastin-Like Polypeptide (HELP)] with alginate (ALG) to obtain a composite with enhanced properties [161]. There are a few examples of such elastin-like composites produced to date by combining alginate and HELP to tune the final properties of the resulting material, modulating the delivery of curcumin as a natural molecule used as an antioxidant compound. The existence of HELP in the composite was shown to be useful in controlling the release of the model compound curcumin, resulting in a high antioxidant activity of the material as well as maintaining and improving the final material's cytocompatibility. More research is required to assess the *in-vivo* behaviour of this composite material. However, the current findings showed that combining alginate with HELP to create customizable platforms for drug delivery, wound healing, and tissue regeneration is effective. Finally, HELP-based proteins can be easily customised by molecular fusion of exogenous domains to prepare dynamic biopolymers. These HELP fusion proteins may be used in the future to provide additional flexibility to final composite materials for therapeutic use [161].

Graphene oxide is one of the most preferable material which have characteristics like biocompatibility, greater surface area, high mechanical strength and also antimicrobial activity. *Gymnema sylvestre* is commonly known as "Gumar" plant product also having anti-inflammatory, antimicrobial properties [160]. Fabrication of a novel scaffold was done consisting of curcumin and *Gymnema sylvestre* incorporated graphene oxide polyhydroxy butyrate-sodium alginate (GO-PHB-SA-CUR and GS) composite as an extracellular matrix platform to improve wound healing in normal and diabetic wounds [160]. Curcumin and *Gymnema sylvestre* were integrated into the novel graphene oxide-polyhydroxybutyrate sodium alginate composite scaffold prepared by solution casting to enhance wound healing in regular and diabetic wounds for better tissue regeneration use. The particle size, surface charge (zeta potential), crystalline nature (XRD), and morphology (FE-SEM) content of the GO-PHB-SA-CUR and GS composite were all assessed. The presence of GO-PHB-SA improves wound closure and increases cell viability in both wounded and diabetic wound cells without causing cytotoxicity. The manufacturing of mesoporous composites improves fibroblast cell viability. The composite made from GO-PHB-SA-CUR and GS has been tested as a wound dressing material by clinical trials to validate its future use. *In-vitro* tests with normal and diabetic fibroblast cells indicated that the GO-PHB-SA-CUR and GS composite had strong biocompatibility in terms of increased wound cell migration. As a result the GO-PHB-SA-CUR and GS composite could help regular and diabetic wounds heal faster. According to the findings the GO-PHB-SA-CUR and GS composite scaffold appears to be a promising candidate for a new wound dressing material that is both reliable and affordable. More successful clinical trials of this material will help millions of diabetic patients with improve wound healing capacity and the quality of life they are going through [160].

Multifunctional biopolymer composites comprising mechanically disintegrated bacterial cellulose, alginate, gelatine and curcumin plasticized with glycerol (BCAGG-C) were also successfully made through a simple, naive, cost-supportive mechanical blending and casting method [159]. The composites had a well distributed structure, according to FE-SEM pictures. The water touch angles ranges from 50 to 70 degrees and its permeability value was 300–800 g/m^2/24 hrs, which was equivalent to commercially available dressing products. When the fil was immersion in phosphate buffer solution (PBS) and artificial saliva, no curcumin was released from the films and the fluid uptakes were in the range of 100–700%. Mechanical properties revealed that BCAGG-C films had sufficient strength and versatility to be used as wound dressings. The stretchable film provides adequate

stiffness and long-term deformation. The skin was tightly adhered by hydrated films. Under artificial saliva medium, the *in-vitro* muco-adhesion time was found to be in the range of 0.5–6 hrs using porcine mucosa as a model membrane. Despite being trapped within the biopolymer matrix composite, curcumin could possess useful biological activities. The curcumin-loaded films had successful antibacterial activity against *E. coli* and *S. aureus*. Human keratinocytes and gingival fibroblasts were not harmed by the films, but oral cancer cells displayed potent anticancer activity. As a result, these curcumin-loaded films can be used as leave-on skin applications. These inventive films can be further adapted to meet the needs of local topical patches for wound care, periodontitis, and also for mouth cancer [159].

Taking almost the similar components such as biocompatible biopolymers, sodium alginate and gelatine microfibers are prepared via extrusion-gelation into a physical crosslinking solution [158]. Curcumin, which is an ancient natural bioactive wound healing agent, was loaded into the fibbers. Biopolymers including sodium alginate and gelatine were used to make curcumin-loaded composite microfibers and blank microfibers. The different concentrations of sodium alginate and gelatine in the formulation batches were coded as A1G9-A10G0. The ATR-FTIR was used to describe the molecular transitions inside the composite microfibers, which was then confirmed using molecular dynamic analysis. The mechanical properties such as tensile strength and elongation-at-break (extensibility) were varying between 1.08 ± 0.01 to 3.53 ± 0.41 N/mm^2 and 3.89 ± 0.18% to 0.61 ± 0.03% respectively. The microfibers' formation and fabrication were verified by morphological examination. Physical evaluations, such as matrix degradation and entrapment performance, were also carried out to provide a comparative account of the various formulations. The water uptake ability of the blank and curcumin-loaded composite fibres is found to be 30.77 ± 2.17 to 100.00 ± 5.99 and 22.34 ± 1.11 to 56.34 ± 4.68, respectively. The cumulative release of composite microfibers was 85% in 72 hours, which demonstrating the composite fibres' long-term release capacity. The drug was released in an unusual (non-Fickian) pattern, implying the importance of degradation and diffusion. In an *in-vivo* full-thickness cutaneous wound model, the composite microfibers had higher degree of contraction (96.89 ± 3.76%) than the commercially available lead products such as Vicco turmeric cream. It can be concluded that natural, alginate–gelatine–curcumin composite has the potency to be explored as a cost-effective wound healing product [158].

13. Conclusions

Despite of rapid and extensive researches on curcumin as a natural ingredient with alginate for formulation of wound dressing materials for proper wound healing, till today, no such curcumin-alginate based commercial products are available in the market for pharmaceutical use. Recently, many patents have been filled and approved for preparing curcumin based biopolymers useful for wound healing materials, but in practical, the use of the same is in clinical stage. As stated in the text, curcumin has broad range of pharmacological activities, its antioxidant and anti-inflammatory properties, in particular, suggest that it may be very effective and useful in wound dressing [154]. As a best Indian herbal medicine over the years, curcumin topical formulations, including nano-architectures, have been developed and tested for enhancing curcumin's wound-healing activity. The key reason for choosing the topical nano-formulation of curcumin is that it provides better solubility, bioavailability and sustained release of curcumin in an active form, all of which are essential for delivering a consistent dose of the drug for a long period which further help in wound healing. Curcumin's perfect dose is critical for

a variety of reasons, but most importantly, its complex function in the inflammatory response in wound healing must be discussed before further clinical progress. As summarised in this chapter various topical formulations of curcumin are being developed with the aim of delivering curcumin to the wounded site in a sustained manner to enhance therapeutic outcomes. Nonetheless, the molecular mechanisms underlying its ability to control chronic inflammation and influence the genetic, cellular wound environment are expected to be studied in depth. While current research on various topical formulations of curcumin appears promising, the majority of published evidence is based on in vitro and *in-vivo* studies, and clinical trials are still required. Thus, in the near future, experiments on human clinical trials should provide answers to concerns about the safety of different topical formulations based on curcumin-alginate in biological systems, as well as their therapeutic wound-healing efficacy.

Author details

Sulata Sahu[1] and Bairagi C. Mallick[2*]

1 Department of Zoology, Ravenshaw University, Cuttack, Odisha, India

2 Department of Chemistry, Ravenshaw University, Cuttack, Odisha, India

*Address all correspondence to: bcmallick@ravenshawuniversity.ac.in

References

[1] Aderibigbe, B.A. and Buyana, B., Alginate in Wound Dressings. *Pharmaceutics.* 2018, 10(42), 2-19. doi:10.3390/pharmaceutics10020042

[2] Cullum, N., Buckley, H., Dumville, J., Hall, J., Lamb, K., Madden, M., Morley, R., O'Meara, S., Goncalves, P.R., Soares, M., Wounds research for patient benefit: a 5-year programme of research. *NIHR Journals Library.* 2016. doi:10.3310/pgfar04130

[3] Frykberg, R.G., and Banks, J., Challenges in the Treatment of Chronic Wounds. *Adv Wound Care (New Rochelle)*2015, 4, 560-582.doi: 10.1089/wound.2015.0635

[4] Schmidtchen, A., Pang, C. Ni, G.,Sonnergren, H., Car, J. Järbrink, K., Bajpai, R., The humanistic and economic burden of chronic wounds: A protocol for a systematic review. *Syst. Rev*. 2017,6(15),1-7. doi:10.1186/s13643-016-0400-8

[5] Flanagan, M. Barriers to the Implementation of Best Practice in Wound Care. *Wounds UK.* Available online: http://www.wounds-uk.com/pdf/content_9030.pdf

[6] Ulery, B. D., Nair, L. S., Laurencin, C.T., Biomedical applications of biodegradable polymers. *J. Polym. Sci. Pol. Phys*. 2011, 49(12), 832-864. doi:10.1002%2Fpolb.22259

[7] Yadav, P., Yadav, H., Shah, V.G., Shah, G., Dhaka, G., Biomedical biopolymers, their origin and evolution in biomedical sciences: A systematic review. *J. Clin. Diagn. Res*. 2015, 9(9), ZE21–ZE25 doi: 10.7860/JCDR/2015/13907.6565

[8] Sudarsan, S., Franklin, D.S., Guhanathan, S., Imbibed salts and pH-responsive behaviours of sodium-alginate based eco-friendly biopolymeric hydrogels:A solventless approach. *MMAIJ.* 2015, 11(1), 24-29.

[9] Varaprasad, K., Jayaramudu, T., Kanikireddy, V., Toro, C., Sadiku, ER., Alginate-based composite materials for wound dressing application: a mini review. *CarbohydrPolym.* 2020, 236:116025. doi: 10.1016/j.carbpol.2020.116025

[10] Sweeney, IR., Miraftab, M., Collyer, G., Absorbent alginate fibres modified with hydrolysed chitosan for wound care dressings—II. Pilot scale development. *CarbohydrPolym.* 2014,102, 920-927. doi: 10.1016/j.carbpol.2013.10.053

[11] Gupta, A., Kowalczuk, M., Heaselgrave, W., Britland, ST., Martin, C., Radecka, I., The production and application of hydrogels for wound management: a review. *Eur Polym J*. 2019,111,134-151.

[12] Kurakula, M., Rao, G. S. N. K., Kiran, V., Hasnain, M. S., and Nayak, A.K., Alginate-based hydrogel systems for drug releasing in wound healing. Alginates in Drug Delivery. *Elsevier Inc*. 2020, Book Chapter 13, 323-358

[13] Sood, A., Granick, MS., Tomaselli, NL., Wound dressings and comparative effectiveness data. *Adv Wound Care.* 2014,3(8),511-529. doi: 10.1089/wound.2012.0401

[14] Malafaya, PB., Silva, GA., Reis, RL. Natural-origin polymers as carriers and scaffolds for biomolecules and cell delivery in tissue engineering applications. *Adv Drug Deliv Rev.* 2007,59(4-5),207-233. doi: 10.1016/j.addr.2007.03.012.

[15] Dowling, MB., Chaturvedi, A., MacIntire, IC., Javvaji, V., Gustin, J., Raghvan, SR., Scalea, TM., Narayan, M.,Determination of efficacy of a novel

alginate dressing in a lethal arterial injury model in swine. *Injury.* 2016, 47(10), 2105-2109. doi: 10.1016/j.injury.2016.05.003.

[16] Matricardi, P., Meo, C. D., Coviello, T., Alhaique, F., Recent advances and perspectives on coated alginate microspheres for modified drug delivery. *Expert Opin Drug Deliv.* 2008,5(4),417-425. doi:10.1517/17425247.5.4.417

[17] Gombotz, WR., Wee, SF., Protein release from alginate matrices. *Adv Drug Delivery Rev.* 1998;31:267-85. doi: 10.1016/s0169-409x(97)00124-5.

[18] Lee, K. Y., Mooneya, D.J. Alginate: Properties and biomedical applications Progress in *Polymer Science.* 2012, 37(1), 106– 126. doi: 10.1016/j.progpolymsci.2011.06.003.

[19] Dhargalkar, V. K., Kavlekar, D., Seaweeds: A field manual. National Institute of Oceanography, Dona Paula, Goa. 2004, 1-42.

[20] Milani, J., Maleki, G., Hydrocolloids in food industry. Food industrial processes – Methods and equipment. *In Tech, Rijeka*, 2012, Book Chapter 2 17-21. (2012).

[21] Pereira, L. A review of the nutrient composition of selected edible seaweeds. Seaweed: Ecology, nutrient composition and medicinal uses. *Nova Science Publishers, New York*, 2011, Book Chapter 1, 15-47.

[22] Remminghorst, U., Rehm, B. H. A., Bacterial alginates: From biosynthesis to applications. *Biotechnology Letters*, 2006, 28(21), 1701-1712. doi: 10.1007/s10529-006-9156-x

[23] Draget, K. I. Alginates. Hand book of hydrocolloids,Woodhead Publishing Series in *Food Science, Technology and Nutrition*. 2009, Book Chapter 29, 807-82

[24] McHugh, D. J.: A guide to seaweed industry. FAO Fisheries and Aquaculture Department, Rome, 2003

[25] Pawar, S.N., Edgar, K. J.Alginate derivatization: A review of chemistry, properties and applications. *Biomaterials.* 2012, 33, 3279-3305 doi:10.1016/j.biomaterials.2012.01.00

[26] Fischer, FG, Dorfel, H., Die polyuronsauren der braunalgen-(kohlenhydrate der algen-I). *Z. Physiol. Chem.* 1955,302(4-6),186-203

[27] Haug, A., Fractionation of alginic acid. *Acta Chem Scand.* 1959;13,601-3

[28] Tonnesen, H. H., Karlsen, J., Alginate in drug delivery systems. *Drug Dev Ind Pharm.* 2002,28(60),621-30. doi: 10.1081/ddc-120003853

[29] Qin, Y. Alginate fibres: an overview of the production processes and applications in wound management. *Polym Int.* 2008,57(2),171-80. doi:10.1002/pi.2296

[30] George, M., Abraham, TE., Polyionic hydrocolloids for the intestinal delivery of protein drugs. *J Control Release.* 2006,114(1),1-14. doi: 10.1016/j.jconrel.2006.04.017.

[31] Hay, ID., Rehman, ZU., Ghafoor, A., Rehm, BHA., Bacterial biosynthesis of alginates. *J Chem TechnolBiotechnol.* 2010,85(6),752-759. doi:10.1002/jctb.2372

[32] Rinaudo, M. On the abnormal exponents a_η and a_D in Mark–Houwink type equations for wormlike chain polysaccharides. *Polym Bull.* 1992,27, 585-589. doi:10.1007/BF00300608

[33] LeRoux, MA., Guilak, F., Setton, LA., Compressive and shear properties of alginate gel: effects of sodium ions and alginate concentration. *J Biomed Mater Res.* 1999;47(1),46-53.

doi: 10.1002/(SICI)1097-4636 (199910)47:13.0.CO;2-N ·

[34] Kong, HJ., Lee, KY., Mooney, DJ., Decoupling the dependence of rheological/mechanical properties of hydrogels from solids concentration. *Polymer.* 2002,43(23),6239-6246. doi:10.1016/S0032-3861(02)00559-1

[35] Franklin, MJ., Douthit, SA., McClure, MA., Evidence that the algI/algJ gene cassette, required for O acetylation of *Pseudomonas aeruginosa* alginate, evolved by lateral gene transfer. *J Bacteriol.* 2004,186(14),4759-4773. doi: 10.1128/JB.186.14.4759-4773.2004.

[36] Franklin, MJ., Ohman, DE., Mutant analysis and cellular localization of the AlgI, AlgJ, and AlgF proteins required for O acetylation of alginate in *Pseudomonas aeruginosa*. *J Bacteriol.* 2002,184(11),3000-3007. doi: 10.1128/JB.184.11.3000-3007.2002

[37] Chitnis, CE., Ohman, DE., Cloning of *Pseudomonas aeruginosa* algG, which controls alginate structure. *J Bacteriol.* 1990,172(6),2894-2900. doi: 10.1128/jb.172.6.2894-2900.1990.

[38] Franklin, MJ., Chitnis, CE., Gacesa, P., Sonesson, A., White, DC., Ohman, DE., Pseudomonas aeruginosa AlgG is a polymer level alginate C5-mannuronan epimerase. *J Bacterio.l* 1994,176(7),1821-1830. doi: 10.1128/jb.176.7.1821-1830.1994.

[39] Franklin, MJ., Ohman, DE., Identification of algF in the alginate biosynthetic gene cluster of *Pseudomonas aeruginosa* which is required for alginate acetylation. J Bacteriol 1993;175(16):5057e65. doi: 10.1128/jb.175.16.5057-5065.1993

[40] Gimmestad, M., Sletta, H., Ertesvag, H., Bakkevig, K., Jain, S., Suh, SJ., The *Pseudomonas fluorescens* AlgG protein, but not its mannuronan C-5- epimerase activity, is needed for alginate polymer formation. *J Bacteriol* 2003,185(12),3515-3523. doi: 10.1128/jb.185.12.3515-3523.2003.

[41] Goh, CH., Heng, PWS., Chan, LW., Alginates as a useful natural polymer for microencapsulation and therapeutic applications. *CarbohydrPolym.* 2012;88(1),1-12. doi:10.1016/j.carbpol.2011.11.012.

[42] Hasnain, MS., Ahmad, SA., Chaudhary, N., Hoda, MN., Nayak, AK., Biodegradable polymer matrix nanocomposites for bone tissue engineering. *Elsevier Inc*; 2019, Book Chapter 1, 1-37.

[43] Smidsrod, O., Skjaok-Braek, G., Alginate as immobilization matrix for cells. *Biotechnol.*1990,8,71-8. doi:10.1016/0167-7799(90)90139-

[44] Nayak, AK., Ahmed, SA., Tabish, M., Hasnain, MS., Natural polysaccharides in tissue engineering application. Natural polysaccharides in drug delivery and biomedical applications. Academic Press, *Elsevier Inc*. 2019, Book Chapter 23, 531-548. doi:10.1016/B978-0-12-817055-7.00023-6

[45] Pal, D., Nayak, AK., Development, optimization and anti-diabetic activity of gliclazide loaded alginate-methyl cellulose mucoadhesive microcapsules. *AAPS Pharm Sci Tech*. 2011,12(4),1431-1441. doi: 10.1208/s12249-011-9709-8.

[46] Bera, H., Kandukuri, SG., Nayak, AK., Boddupalli, S., Alginate-sterculia gum gel-coated oil-entrapped alginate beads for gastroretentive risperidone delivery. *Carbohydr Polym*. 2015,120,74-84. doi: 10.1016/j.carbpol.2014.12.009.

[47] Hasnain, MS., Rishishwar, P., Rishishwar, S., Ali, S., Nayak, AK., Isolation and characterization of Linumusitatisimum polysaccharide to prepare mucoadhesive beads of

diclofenac sodium. *Int. J. Biol. Macromol.* 2018,116,162-72. doi: 10.1016/j.ijbiomac.2018.04.151.

[48] Pal, D., Saha, S., Nayak, AK., Hasnain, MS., Marine-derived polysaccharides: pharmaceutical applications. Natural polymers for pharmaceutical applications, vol. II: Marine and microbiologically derived polymers. Palm Bay, FL: *Apple. Academic Press.* 2019, 1-36. https://doi.org/10.1201/9780429328299

[49] Rath Adhikari, SN., Nayak, BS., Nayak, AK., Mohanty, B., Formulation and evaluation of buccal patches for delivery of atenolol. *AAPS Pharm. Sci. Tech.* 2010,11 (3),1034-1044. doi: 10.1208/s12249-010-9459-z

[50] Yadav, M., Ahmadi, Y., Alginates: source, chemistry, and properties.: Alginate: versatile polymer in biomedical applications and therapeutics. Palm Bay, FL: *Apple Academic Press*. 2019, 1-24.

[51] Brigger, I., Dubernet, C., Couvreur, P., Nanoparticles in cancer therapy and diagnosis. *Adv. Drug Deliv. Rev*. 2012, 64, 24-36. doi:10.1016/j.addr.2012.09.006

[52] Hamidi, M., Azadi, A., Rafiei, P., Hydrogel nanoparticles in drug delivery. *Adv Drug Deliv Rev*. 2008, 60(15), 1638-1649. doi:10.1016/j.addr.2008.08.00

[53] Lambert, G., Fattal, E., Couvreur, P., Nanoparticulate systems for the delivery of antisense oligonucleotides. *Adv. Drug Deliv. Rev*. 2001, 47(1), 99-112. doi: 10.1016/s0169-409x(00)00116-2.

[54] Lertsutthiwong, P., Rojsitthisak, P., Chitosan-alginate nanocapsules for encapsulation of turmeric oil. *Pharmazie.* 2011, 66(12), 911-915.

[55] Soppimath, KS., Aminabhavi, TM., Kulkarni, AR., Rudzinski, WE., Biodegradable polymeric nanoparticles as drug delivery devices. *J. Control Release.* 2001, 70(1-2), 1-20. doi: 10.1016/s0168-3659(00)00339-4.

[56] Severino, P., Silva, C.F., Andrade, L.N., Oliveira, D.L., Campos, J. and Souto, E.B., Alginate Nanoparticles for Drug Delivery and Targeting. *Current Pharmaceutical Design.* 2019, 25(11), 1312-1334. doi: 10.2174/1381612825666190425163424.

[57] Fernando, I.P.S., Lee, W.W., Han, E.J., Ahn, G., Alginate-based nanomaterials: fabrication techniques, properties, and applications. *Chemical Engineering Journal.* 2019,123823. doi:10.1016/j.cej.2019.123823.

[58] Hoque, J., and Haldar, J., Direct synthesis of dextran-based antibacterial hydrogels for extended release of biocides and eradication of topical biofilms. *ACS Applied Materials and Interfaces.* 2017, 9(19), 15975-15985. doi: 10.1021/acsami.7b03208.

[59] Lazarus, GS., Cooper, DM., Knighton, DR., Margolis, DJ., Percoraro, ER., Rodeheaver, G., Robson, MC., Definitions and guidelines for assessment of wounds and evaluation of healing. *Arch. Dermatol.* 1994,130(4), 489-93.

[60] Alam, P. Design considerations in the development of wound healing bionanomaterials. Nanostructures for novel therapy. *Elsevier Inc*. 2017, Book Chapter 13 343-73. doi:10.1016/B978-0-323-46142-9.00013-X

[61] Baranoski, S., Ayello, EA., Langemo, DK., Wound assessment. Wound care essentials: practice principles. Philadelphia, PA: *Lippincott Williams &Wilkins*. 2008, Book Chapter 6,79-90.

[62] Chaudhari, AA., Vig, K., Baganizi, DR., Sahu, R., Dixit, S., Dennis, V.,. Future prospects for scaffolding methods and biomaterials in skin tissue engineering: a review. *Int. J. Mol. Sci*.

2016, 17(12),1974. doi: 10.3390/ijms17121974.

[63] Dhivya, S., Padma, VV., Santhini, E., Wound dressingsa review. *Biomed.* 2015, 5(4), 22. doi: 10.7603/s40681-015-0022-9

[64] Parani, M., Lokhande, G., Singh, A., Gaharwar, A. K., Engineered nanomaterials for infection control and healing acute and chronic wounds. *ACS Applied Materials and Interfaces.* 2016, 8(16), 10049-10069. doi:10.1021/acsami.6b0029

[65] Stefanov, I., Pérez-Rafael, S., Hoyo, J., Cailloux, J., Santana Pérez, O. O., Hinojosa- Caballero, D., Tzanov, T., Multifunctional enzymatically generated hydrogels for chronic wound application. *Biomacromolecules.* 2017, 18(5), 1544-1555. doi:10.1021/acs.biomac.7b00111

[66] Eming, SA., Martin, P., Tomic-Canic, M., Wound repair and regeneration: mechanisms, signaling and translation. *Sci. Transl. Med.* 2014, 6(265). doi: 10.1126/scitranslmed.3009337

[67] Bolton, L., van Rijswijk, L., Wound dressings: meeting clinical and biological needs. Dermatol Nurs. 1991,3(3),146-161.

[68] Krasner, D., Sennedy, KL., Rolstad, BS., Roma, AW., The ABCs of wound care dressings. *Ostomy Wound Manage* 1993, 39(8), 68-72.

[69] Ferreira, MC., Tuma, Jr P., Carvalho, VF., Kamamoto, F., Complex wounds. *Clinics.* 2006, 61(6), 571-578. doi:10.1590/S1807-59322006000600014

[70] De Roche, R., Luscher, N. J., Debrunner, H. U., Fischer, R., Epidemiological data and costs of burn injuries in workers in Switzerland: an argument for immediate treatment in burn centres. *Burns.* 1994,20(1),58-60. doi: 10.1016/0305-4179(94)90108-2.

[71] Thomas, S., Assessment and management of wound exudates. *J Wound Care.* 1997,6 (7), 327-30.

[72] Sezer, A.D., Cevher, E., Biopolymers as wound healing materials: Challenges and new strategies. In Biomaterials Applications for Nanomedicine; Pignatello, R., Ed.; InTech: Rijeka, Croatia, 2011, Book Chapter 19,383-414.

[73] Zahedi, P., Rezaeian, I., Ranaei-Siadat, S.O., Jafari, S.H., Supaphol, P., A review on wound dressings with an emphasis on electrospun nanofibrous polymeric bandages. *Polym. Adv. Technol*. 2010, 21, 77-95. https://doi.org/10.1002/pat.1625

[74] Oro, F.B., Sikka, R.S., Wolters, B., Graver, R., Boyd, J.L., Nelson, B.,Swiontkowski, M.F., Autograft versus allograft: An economic cost comparison of anterior cruciate ligament reconstruction. *Arthroscopy*. 2011, 27(9), 1219-1225. doi: 10.1016/j.arthro.2011.04.008.

[75] Sheikh, Z., Hamdan, N., Ikeda, Y., Grynpas, M., Ganss, B., Glogauer, M., Natural graft tissues and synthetic biomaterials for periodontal and alveolar bone reconstructive applications: A review. *Biomater. Res.* 2017, 21, 9. 24. doi: 10.1186/s40824-017-0095-5.

[76] Guo, S.A., DiPietro, L.A., Factors affecting wound healing. *J. Dental Res.* 2010, 89(3), 219-229. doi: 10.1177/0022034509359125

[77] Sanchez, J. L., Pereperez, S. B., Bastida, J. L., Martinez, M. M., Cost-utility analysis applied to the treatment of burn patients in a specialized canter. *Arch. Surg.* 2007,142 (1), 50-7. doi: 10.1001/archsurg.142.1.50.

[78] Zuliani-Alvarez, L., Midwood, K.S., Fibrinogen-related proteins in tissue

repair: How a unique domain with a common structure controls diverse aspects of wound healing. Adv. *Wound Care*. 2015, 4(5), 273-285. doi: 10.1089/wound.2014.0599.

[79] Sun, B.K., Siprashvili, Z., Khavari, P.A., Advances in skin grafting and treatment of cutaneous wounds. *Science.* 2014, 346(6212), 941-945. doi: 10.1126/science.1253836.

[80] Aller, M.A., Arias, J.I., Arraez-Aybar, L.A., Gilsanz, C., Arias, J., Wound healing reaction: A switch from gestation to senescence. *World J. Exp. Med.* 2014, 4(2), 16-26. doi: 10.5493/wjem.v4.i2.16.

[81] Khor, E., Lim, LY., Implantable applications of chitin and chitosan. *Biomaterials*. 2003, 24(13), 2339-2349. https://doi.org/10.1016/S0142-9612(03)00026-7

[82] Loke, W. K., Lau, S. K., Yong, L. L., Khor, E., Sum, C. K., Wound dressing with sustained anti-microbial capability. *J Biomed Mater Res*. 2000, 53(1):8-17.doi: 10.1002/(sici)1097-4636(2000)53:1<8::aid-jbm2>3.0.co;2-3

[83] Ma, Y., Xin, L., Tan, H., Chitosan membrane dressings toughened by glycerol to load antibacterial drugs for wound healing. *Mat Sci Eng C Mater*. 2017 81:522-531. doi: 10.1016/j.msec.2017.08.052.

[84] Jayakumar, R., Prabaharan, M., Kumar, PTS., Nair, SV., Tamura, H. Biomaterials based on chitin and chitosan in wound dressing applications. *Biotechnol Adv*. 2011, 29(3),322-337. doi: 10.1016/j.biotechadv.2011.01.005.

[85] Xiea, H., Chena, X., Shena, X., Hea, Y., Chena, W., Luoa, Q., Geb, W., Yuana, W., Tanga, X., Houa, D., Jianga, D., Wanga, Q., Liua, Y., Liua, Q., Lia, K., The Preparation of chitosan-collagen-alginate composite dressing and itspromoting effects on wound healing. *Int J. Biol. Macromol*. 2018 107(Pta A):93-104 doi: 10.1016/j.ijbiomac.2017.08.142.

[86] Michalska-Sionkowska, M., Walczak, M., Sionkowska, A. Antimicrobial activity of collagen material with thymol addition for potential application as wound dressing. *Polym Test. 2017* 63:360-366. https://doi.org/10.1016/j.polymertesting.2017.08.03

[87] Pal, S., Nisi, R., Stoppa, M., Licciulli, A., Silver-functionalized bacterial cellulose as antibacterial membrane for wound-healing applications. *ACS Omega*. 2017, 2(7),3632-3639 https://doi.org/10.1021/acsomega.7b00442

[88] You, C., Li, Q., Wang, X. Wu, P., Ho AK.,Silver nanoparticle loaded collagen/chitosan scaffolds promote wound healing via regulating fibroblast migration and macrophage activation. *Sci Rep*. 2017, 7(1):10489 doi: 10.1038/s41598-017-10481-0.

[89] Dowling, MB., Chaturvedi, A., MacIntire, IC., Determination of efficacy of a novel alginate dressing in a lethal arterial injury model in swine. *Injury*. 201647(10),2105-2109. doi: 10.1016/j.injury.2016.05.003.

[90] Ye, J., Shi, X., Chen, X. Chitosan-modified, collagen- based biomimetic nanofibrous membranes as selective cell adhering wound dressings in the treatment of chemically burned corneas. *J Mater Chem B*, 2014 27:4226-4236 https://doi.org/10.1039/C3TB21845G

[91] Baniasadi, M., Minary-Jolandan, M., Alginate–collagen fibril composite hydrogel. *Materials (Basel).* 2015, 8(2),799-814 doi: 10.3390/ma8020799

[92] Lee, BR., Hwang, JW., Choi, YY., Wong, SF., Hwang, YH., Lee, DY., Lee, SH., In situ formation and

collagen–alginate composite encapsulation of pancreatic islet spheroids. Biomaterials 33(3):837-845. doi: 10.1016/j.biomaterials.2011.10.014.

[93] Lee, H-j., Ahn S-H., Kim GH., Three-dimensional collagen/ alginate hybrid scaffolds functionalized with a drug delivery system (DDS) for bone tissue regeneration. *Chem Mater*. 2011 24(5),881-891 https://doi.org/10.1021/cm200733s

[94] Zhang, H., Peng, M. , Cheng, T. , Zhao, P., Qiu, L. , Zhou, J. , Lu, G.,& Chen, J., Silver nanoparticles-doped collagen–alginate antimicrobial biocomposite as potential wound dressing. *J Mater Sci*. 2018 ,53,14944-14952 doi:10.1007/s10853-018-2710-9

[95] Azarniya, A., Tamjid, E., Eslahi, N., &Simchi, A., Modification of bacterial cellulose/keratin nanofibrous mats by a tragacanth gum-conjugated hydrogel for wound healing. *International Journal of Biological Macromolecules*. 2019, 134, 280-289. doi:10.1016/j.ijbiomac.2019.05.023

[96] Archana, D., Singh, B.K., Dutta, J., Dutta, P.K., Chitosan-PVP-nano silver oxidewound dressing: in vitro and in vivo evaluation. *Int. J. Biol. Macromol*. 2015, 73,49-57. doi: 10.1016/j.ijbiomac.2014.10.055

[97] Kumar, S., Dutta, ., Dutta, PK., Preparation and characterization of N-heterocyclic chitosan derivative based gels for biomedical applications, *Int.J. Biol. Macromol*. 2009, 45(4), 330-337. doi:10.1016/j.ijbiomac.2009.08.002

[98] Behera, SS., Das, U., Kumar, A., Bissoyi, A., Singh, A.K., Chitosan/TiO2compositemembrane improves proliferation and survival of L929 fibroblast cells:application in wound dressing and skin regeneration, *Int. J. Biol. Macromol.* 2017, 98329-340. doi: 10.1016/j.ijbiomac.2017.02.017.

[99] Akbik, D., Ghadiri, M., Chrzanowski, W., Rohanizadeh, R., Curcumin as a wound healing agent. *Life Sci.* 2014, 116(1), 1–7. doi: 10.1016/j.lfs.2014.08.016.

[100] Gupta, A., Briffa, S.M., Swingler, S., Gibson, H., Kannappan, V., Adamus, G., Kowalczuk, M., Martin, C., and Radecka, I., Synthesis of Silver Nanoparticles Using Curcumin-Cyclodextrins Loaded into Bacterial Cellulose-Based Hydrogels for Wound Dressing Applications. *Biomacromolecules.* 2020, 21(5), 1802–1811. doi: 10.1021/acs.biomac.9b01724.

[101] Gupta, A. Keddie, D. J. Kannappan, V. Gibson, H. Khalil, I.R. Kowalczuk, M. Martin, C. Shuai, X. Radecka, I., Production and characterisation of bacterial cellulose hydrogels loaded with curcumin encapsulated in cyclodextrins as wound dressings. *Eur. Polym. J.* 2019,118, 437–450. doi:10.1016/j.eurpolymj.2019.06.018

[102] Gong, CY., Wu, Q., Wang, Y., Zhang, DD., Luo, F, Zhao, X., Wei, Y., Qian, ZY., A biodegradable hydrogel system containing curcumin encapsulated in micelles for cutaneous wound healingBiomaterials. 2013 34(27), 6377-6387. doi: 10.1016/j.biomaterials.2013.05.005

[103] Singh, S., From exotic spice to modern drug? *Cell.* 2007;130(5),:765-8. doi: 10.1016/j.cell.2007.08.024.

[104] Madhumathi, K., Kumar, P.S., Abhilash, S., Sreeja, V., Tamura, H., Manzoor, K., Nair, S.V., Jayakumar, R., Development of novel chitin/nanosilver composite scaffolds for wound dressing applications. J. Mater. Sci. Mater. Med. 2010, 21(2), 807-813. doi: 10.1007/s10856-009-3877-z.

[105] Jayakumar, R., Nwe, N., Tokura, S., Tamura, H., Sulfated chitin and chitosan as novel biomaterials, *Int. J. Biol. Macromol. 2007,* 40(3), 175-181. doi: 10.1016/j.ijbiomac.2006.06.021.

[106] Madhumathi, K., Shalumon, K.T., Rani, V.D., Tamura, H., Furuike, T., Selvamurugan, N., Nair, S.V., Jayakumar, R., Wet chemical synthesis of chitosan hydrogel–hydroxyapatite composite membranes for tissue engineering applications. *Int. J. Biol. Macromol.2009,* 45(1) 12-15. doi: 10.1016/j.ijbiomac.2009.03.011.

[107] Niranjana, R., Kaushika, M., Prakasha, J., Venkataprasannaa, K.S., Christy, A., Pannerselvam, B., Venkatasubbu, G.D. Enhanced wound healing by PVA/Chitosan/Curcumin patches: In vitro and in vivo study Colloids and Surfaces B: *Biointerfaces*. 2019, 182, 110339. doi:10.1016/j.colsurfb.2019.06.068

[108] Rachmawati, H., Edityaningrum, CA., Mauludin, R., Molecular inclusion complex of curcumin-beta-cyclodextrin nanoparticle to enhance curcumin skin permeability from hydrophilic matrix gel. *AAPS PharmSciTech*. 2013,14(4), 1303-1312. doi: 10.1208/s12249-013-0023-5.

[109] Rai, M., Pandit, R., Paralikar, P., Nagaonkar, D., Rehman, F. Pharmaceutical Applications of Curcumin-Loaded Nanoparticles. Nanotechnology Applied To Pharmaceu ticalTechnology.*Springer International Publishing AG* 2017, Chapter 6, 139-154.

[110] Strasser, E-M., Wessner, B., Manhart, N., and Roth, E., The relationship between the anti-inflammatory effects of curcumin and cellular glutathione content in myelomonocytic cells. *Biochemical Pharmacology*. 2005 70(4) 552-559. doi: 10.1016/j.bcp.2005.05.030.

[111] Han, S., and Yang, Y., Antimicrobial activity of wool fabric treated with curcumin. *Dyes and Pigments*. 2005,64(2), 157-161. doi:10.1016/j.dyepig.2004.05.008.

[112] Vajragupta, O., Boonchoong, P., Morris, G.M., and Olson, A.J., Active site binding modes of curcumin in HIV-1 protease and integrase. *Bioorganic and Medicinal Chemistry Letters. 2005,*15(14), 3364-3368. doi: 10.1016/j.bmcl.2005.05.032.

[113] Aggarwal, B.B., Kumar, A., and Bharti, A.C., Anticancer potential of curcumin: preclinical and clinical studies. *Anticancer Research*. 2003, 23(1A), 363-398.

[114] Farombi, E.O., and Ekor, M., Curcumin attenuates gentamicin-induced renal oxidative damage in rats, *Food and Chemical Toxicology. 2006*, 44(9), 1443-1448. doi: 10.1016/j.fct.2006.05.005.

[115] Sreepriya, M. and Bali, G., Chemopreventive effects of embelin and curcumin against N-nitrosodiethylamine/phenobarbitalinduced hepato carcinogenesis in Wistar rats *Fitoterapia. 2005, 76(6),* 549-555. doi: 10.1016/j.fitote.2005.04.014.

[116] Panchatcharam, M., Miriyala, S., Gayathri, V.S. and Suguna, L., Curcumin improves wound healing by modulating collagen and decreasing reactive oxygen species. *Molecular and Cellular Biochemistry. 2006*, 290(1-2), 87-96. doi: 10.1007/s11010-006-9170-2.

[117] Phan, T.T., See, P., Lee, S.T. and Chan, S.Y., Protective effects of curcumin against oxidative damage on skin cells in vitro: its implication for wound healing. *Journal of Trauma.* 2001, 51(5), 927-931. doi: 10.1097/00005373-200111000-00017.

[118] Gopinath, D., Ahmed, M.R., Gomathi, K., Chitra, K., Sehgal, P.K. and Jayakumar, R., Dermal wound healing process with curcumin incorporated collagen films. *Biomaterials*. 2004, 25(10), 1911-1917. doi: 10.1016/s0142-9612(03)00625-2.

[119] Dai, M., Zheng, XL., Xu, X., Kong, XY., Li, XY., Guo, G., Luo, F., Zhao, X., QuanWei, Y., and Qian, Z., Chitosan-Alginate Sponge: Preparation and Application in Curcumin Delivery for Dermal Wound Healing in Rat. *Journal of Biomedicine and Biotechnology.* 2009 doi:10.1155/2009/595126.

[120] Epstein, J., Sanderson, I. R. and MacDonald, T. T., Curcumin as a therapeutic agent: The evidence from *in vitro*, animal and human studies. *British journal of nutrition.* 2010,103 (11), 1545-1557. doi: 10.1017/S0007114509993667.

[121] Carroll, C. E., Ellersieck, M. R. and Hyder, S. M., Curcumin inhibits mpa-induced secretion of vegf from t47-d human breast cancer cells. *Menopause.* 2008 15 (3), 570-574. doi: 10.1097/gme.0b013e31814fae5d.

[122] Shpitz, B., Giladi, N., Sagiv, E., Lev-Ari, S., Liberman, E., Kazanov, D. and Arber, N., Celecoxib and curcumin additively inhibit the growth of colorectal cancer in a rat model, *Digestion,* 2007, 74 (3-4), 140-144. doi: 10.1159/000098655.

[123] Ikezaki, S., Nishikawa, A., Furukawa, F., Kudo, K., Nakamura, H., Tamura, K. and Mori, H., Chemopreventive effects of curcumin on glandular stomach carcinogenesis induced by n-methyl-n'-nitro-n-nitrosoguanidine and sodium chloride in rats. *Anticancer research,* 2000,21 (5), 3407-3411.

[124] Chuang, S.-E., Cheng, A.-L., Lin, J.-K. and Kuo, M.-L., Inhibition by curcumin of diethylnitrosamine-induced hepatic hyperplasia, inflammation, cellular gene products and cell-cycle-related proteins in rats. *Food and Chemical Toxicology.* 2000, 38(11), 991-995. doi: 10.1016/s0278-6915(00)00101-0.

[125] Azuine, M. A., and Bhide, S. V., Protective single/combined treatment with betel leaf and turmeric against methyl (acetoxymethyl) nitrosamine-induced hamster oral carcinogenesis. *International journal of cancer.* 1992, 51 (3), 412-415. doi: 10.1002/ijc.2910510313.

[126] Usharani, P., Mateen, A., Naidu, M., Raju, Y. and Chandra, N., Effect of ncb-02, atorvastatin and placebo on endothelial function, oxidative stress and inflammatory markers in patients with type 2 diabetes mellitus. *Drugs in R & D.* 2008, 9 (4), 243-250. doi: 10.2165/00126839-200809040-00004.

[127] Pan, R., Qiu, S., Lu, D.-x. and Dong, J., Curcumin improves learning and memory ability and its neuroprotective mechanism in mice. *Chinese Medical Journal (English Edition).* 2008, 121 (9), 832-839.

[128] Prucksunand, C., Indrasukhsri, B., Leethochawalit, M. and Hungspreugs, K. Phase ii clinical trial on effect of the long turmeric (*Curcuma longa* linn) on healing of peptic ulcer. *Southeast Asian J Trop Med Public Health*, 2001,32(1), 208-215.

[129] Deodhar, S., Sethi, R. and Srimal, R., Preliminary study on antirheumatic activity of curcumin (diferuloyl methane. *Indian journal of medical research*. 2013 138 (1), 170-172.

[130] Heng, M., Song, M., Harker, J. and Heng, M., Drug-induced suppression of phosphorylase kinase activity correlates with resolution of psoriasis as assessed by clinical, histological and immunohistochemical parameters. *British Journal of Dermatology.* 2000, 143

(5), 937-949. doi: 10.1046/j.1365-2133.2000.03767.x.

[131] Balasubramanyam, K., Varier, R. A., Altaf, M., Swaminathan, V., Siddappa, N. B., Ranga, U. and Kundu, T. K., Curcumin, a novel p300/creb-binding protein-specific inhibitor of acetyltransferase, represses the acetylation of histone/nonhistone proteins and histone acetyltransferase-dependent chromatin transcription. *Journal of Biological Chemistry.* 2004 279 (49), 51163-51171. doi: 10.1074/jbc.M409024200.

[132] Aggarwal, B. B. and Harikumar, K. B., Potential therapeutic effects of curcumin, the anti-inflammatory agent, against neurodegenerative, cardiovascular, pulmonary, metabolic, autoimmune and neoplastic diseases, *The international journal of biochemistry & cell biology.* 2009, 41 (1), 40-59. doi: 10.1016/j.biocel.2008.06.010

[133] Basniwal, R. K., Buttar, H. S., Jain, V. and Jain, N., Curcumin nanoparticles: Preparation, characterization, and antimicrobial study. *Journal of agricultural and food chemistry.* 2011, 59 (5), 2056-2061. doi: 10.1021/jf104402t.

[134] Zandi, K., Ramedani, E., Mohammadi, K., Tajbakhsh, S., Deilami, I., Rastian, Z., Fouladvand, M., Yousefi, F. and Farshadpour, F., Evaluation of antiviral activities of curcumin derivatives against hsv-1 in vero cell line. *Natural product communications.* 2010, 5 (12), 1935-1938.

[135] Binion, D. G., Otterson, M. F. and Rafiee, P., Curcumin inhibits vegf-mediated angiogenesis in human intestinal microvascular endothelial cells through cox-2 and mapk inhibition, *Gut.* 2008,57 (11), 1509-1517. doi: 10.1136/gut.2008.152496.

[136] Liang, G., Zhou, H., Wang, Y., Gurley, E. C., Feng, B., Chen, L., Xiao, J., Yang, S. And Li, X., Inhibition of lps-induced production of inflammatory factors in the macrophages by mono-carbonyl analogues of curcumin. *Journal of cellular and molecular medicine.*2009, 13 (9b), 3370-3379. doi: 10.1111/j.1582-4934.2009.00711.x.

[137] Sidhu, G. S., Singh, A. K., Thaloor, D., Banaudha, K. K., Patnaik, G. K., Srimal, R. C. and Maheshwari, R. K., Enhancement of wound healing by curcumin in animals. *Wound Repair and Regeneration,* 1998,6 (2), 167-177. doi: 10.1046/j.1524-475x.1998.60211.x.

[138] Rai, M., Pandit, R., Gaikwad, S., Yadav, A., Gade,A., Potential applications of curcumin and curcumin nanoparticles: from traditional therapeutics to modern nanomedicine. Nanotechnol Rev. 2015, 4(2):161-172. doi:10.1515/ntrev-2015-0001

[139] Saikia, C., Sarmah, M., Das, MK., Ramteke, A., Maji, TK., Biodegradable polymeric nanocomposites: advances in biomedical applications. 2015 Chap. 8, https://doi.org/10.1201/b19314

[140] Tomren, MA., Masson, LM., Hjorth, TH., Studies on curcumin and curcuminoids XXXI. Symmetric and asymmetric curcuminoids: stability, activity and complexation with cyclodextrin. *Int J Pharm*. 2007 338 (1-2):27-34 doi: 10.1016/j.ijpharm.2007.01.013.

[141] Yang, KY., Lin, LC., Tseng, TY., Wang, SC., Tsai, TH., Oral bioavailability of curcumin in rat and the herbal analysis from *Curcuma longa* by LC-MS/MS. *J Chromatogr B Anal Technol Biomed Life Sci*. 2007 853 (1-2):183-189doi: 10.1016/j.jchromb.2007.03.010.

[142] Shutava, TG., Balkundi, SS., Vangala, P., Steffan, JJ., Biqelow, LR., Cardelli, JA., Patrick, O'Neal D., Lvov, YM., Layer-by-layercoatedgelatin nanoparticles as a vehicle for delivery of

natural polyphenols. *ACS Nano*. 2009 3(7):1877-1885. https://doi.org/10.1021/nn900451a

[143] Blecher, K., Nasir, A.,, Friedman A., The growing role of nanotechnology in combating infectious disease. *Virulence*.2011, 2(5),395-401. doi: 10.4161/viru.2.5.17035

[144] Kim, BYS., Rutka, JT., Wchan, WCW., Nanomedicine. *N Engl J Med*. 2010 363(25),2434-2443. doi: 10.1056/NEJMra0912273

[145] Flora, G., Gupta, D., Tiwari, A., Nanocurcumin: a promising therapeutic 610 advancement over native curcumin. *Crit Rev Ther Drug Carrier Syst*. 2013;30(4):331-68. doi: 10.1615/critrevtherdrugcarriersyst.2013007236

[146] Chereddy KK., Coco, R., Memvanga, PB., Ucakar, B., des Rieux, A., Vandermeulen, G., Combined effect of PLGA and curcumin on wound healing activity. *J Control Release*. 2013,171(2),208-15. doi: 10.1016/j.jconrel.2013.07.015.

[147] Bhawana, Basniwal, RK., Buttar, HS., Jain, VK., Jain, N., Curcumin nanoparticles: preparation, characterization, and antimicrobial study. *J Agric Food Chem*. 2011;59(5):2056-61. doi: 10.1021/jf104402t

[148] Krausz, AE., Adler, BL., Cabral, V., Navati, M., Doerner, J., Charafeddine, RA., Curcumin-encapsulated nanoparticles as innovative antimicrobial and wound healing agent. *Nanomedicine.* 2015, 11(1), 195-206. doi: 10.1016/j.nano.2014.09.004.

[149] Jiang, W., Kim, BYS., Rutka, JT., Chan, WCW., Nanoparticle-mediated cellular response is size-dependent. *Nat Nanotechnol*. 2008, 3(3),145-150. doi: 10.1038/nnano.2008.30

[150] Basnet, P., Hussain, H., Tho, I., Skalko-Basnet, N., Liposomal delivery system enhances anti-inflammatory properties of curcumin. *J Pharm Sci*. 2012, 101(2),598-609. doi: 10.1002/jps.22785.

[151] Chirio, D., Gallarate, M., Peira, E., Battaglia, L., Serpe, L., Trotta, M. Formulation of curcumin-loaded solid lipid nanoparticles produced by fatty acids coacervation technique. *J. Microencapsul*. 2011 28(6):537-548. doi: 10.3109/02652048.2011.590615

[152] Dhule, SS., Penfornis, P., Frazier, T., Walker, R., Feldman, J., Tan, G., He, J., Alb, A., John, V., Pochampally, R., Curcumin-loaded -cyclodextrin liposomal nanoparticles as delivery vehicles for osteosarcoma. *NanomedNanotechnolBiol Med.* 2012, 8(4), 440-451. doi: 10.1016/j.nano.2011.07.011

[153] Mohanty, C. and Sahoo, S.K., Curcumin and its topical formulations for wound healing applications. *DRUDIS*. 2017, 22(10), 1582-1592. doi: 10.1016/j.drudis.2017.07.001.

[154] Gopinath, D., Ahmed, M. R., Gomathi, K., Chitra, K., Sehgal, P. K., Jayakumar, R., Dermal wound healing processes with curcumin incorporated collagen films. *Biomaterials*. 2004, 25(10), 1911–1917. doi: 10.1016/s0142-9612(03)00625-2

[155] Gaserod, O., Andersen, PO., Myrvold, R., Gelled biopolymer based foam. FMC Corporation, United States patent application. 2005, publication no. US 2005/0137272 A1.

[156] Mohanty, C., Das, M., and. Sahoo, S.K., Sustained Wound Healing Activity of Curcumin Loaded Oleic Acid Based Polymeric Bandage in a Rat Model. *Mol. Pharmaceutics*. 2012, 9(10), 2801–2811. doi: 10.1021/mp300075u.

[157] Shahnia, M. Formulating curcumin in a biodegradable polymeric composite material: A step towards wound healing applications. 2017, Thesis.

[158] Abdul Khalil, H. P. S., Lai, T. K., Tye, Y. Y., Rizal, S., Chong, E. W. N., Yap, S. W., Hamzah, A. A. ,Nurul Fazita, M. R., Paridah, M.T., A review of extractions of seaweed hydrocolloids: Properties and applications. *eXPRESS Polymer Letters*. 2018, 12(4), 296-317 doi:10.3144/expresspolymlett.2018.27

[159] Sharma, A., Mittal, A., Puri, V. Kumar, P., Singh, I., Curcumin-loaded, alginate–gelatin composite fibers for wound healing applications. *3 Biotech*. 2020,10(11),464. doi: 10.1007/s13205-020-02453-5.

[160] Chiaoprakobkij, N., Suwanmajo, T., Sanchavanakit, N., and Phisalaphong, M. Curcumin-Loaded Bacterial Cellulose/Alginate/Gelatin as AMultifunctional Biopolymer Composite Film. *Molecules*. 2020, 25(17), 3800. doi:10.3390/molecules25173800

[161] Daisy, E.R.A.C., Rajendran, N.K., Houreld, N.N., Marraiki, N., Elgorban, A.M., Rajan, M., Curcumin and Gymnemasylvestre extract loaded grapheme oxidepolyhydroxybutyrate-sodium alginate composite for diabetic wound regeneration. *Reactive and Functional Polymers*. 2020, 154, 104671. doi:10.1016/j.reactfunctpolym.2020.104671

[162] Bergonzi, C., d'Ayala, G.G., Elviri, L., Laurienzo, P, Bandiera, A, Catanzano, O., Alginate/human elastin-like polypeptide composite films with antioxidant properties for potential wound healing application. *International Journal of Biological Macromolecules*. 2020, 164, 586-596. doi:10.1016/j.ijbiomac.2020.07.084

[163] Boztas, AO., Karakuzu, O., Galante, G., Ugar Z., Kocabas F., Synergistic interaction of paclitaxel and curcumin with cyclodextrin polymer complexation in human cancer cells. *Mol Pharm*. 2013,10(7),2676-2683. doi: 10.1021/mp400101k.

[164] Zhao, Y., Dai, C., Wang, Z., Chen, W., Liu, J., Zhuo, R., Yu, A. Huang, S., A novel curcumin-loaded composite dressing facilitates wound healing due to its natural antioxidant effect. *Drug Design, Development and Therapy*. 2019,13, 3269-3280. doi:10.2147/DDDT.S219224

[165] Monica, CGA., Raisa, AMF., Maria DPA., Development and Evaluation of Alginate Membranes with Curcumin-Loaded Nanoparticles for Potential Wound-Healing Applications. *Pharmaceutics*. 2019, 11, 389. doi: 10.3390/pharmaceutics11080389.

[166] Selvia, R.T.1, Prasannaa, A.P.S., Niranjan, R., Kaushik, M., Devasena, T., Kumar, J., Chelliahe, R., Ohe, D.H., Swaminathan, S., Venkatasubbub, G.D., Metal oxide curcumin incorporated polymer patches for wound healing. *Applied Surface Science*. 2018, 449,603-609. doi:10.1016/j.apsusc.2018.01.143

[167] Nostro, PL., Capuzzi, G., Romani, A., Mulinacci, N., Self-assembly and antioxidant properties of octanoyl-6-o-ascorbic acid. *Langmuir*. 2000,16(4),1744-1750. doi:10.1021/la990796j

[168] Nguyen, V.C., Nguyen, V.B., & Hsieh, M.F., Curcumin-Loaded Chitosan/Gelatin Composite Sponge for Wound Healing Application. *International Journal of Polymer Science*. 2013. doi:10.1155/2013/106570

[169] Madhumathi, K., Kumar, P. T. S., Abhilash, S. Development of novel chitin/nanosilver composite scaffolds for wound dressing applications. *Journal of Materials Science*. 2010, 21(2),807-813. doi: 10.1007/s10856-009-3877-z

[170] Friedman, AJ., Han, G., Navati, MS., Chacko, M., Gunther, L., Alfieri, A., Sustained release nitric oxide releasing nanoparticles: characterization of a novel delivery platform based on nitrite containing hydrogel/glass composites. *Nitric Oxide*. 2008,19(1),12-20. doi: 10.1016/j.niox.2008.04.003.

[171] Karri, VV., Kuppusamy, G., Talluri, SV., Mannemala, SS., Kollipara, R., Wadhwani, AD., Mulukutla, S., Raju, KR., Malayandi, R., Curcumin loaded chitosan nanoparticles impregnated into collagen-alginate scaffolds for diabetic wound healing. *Int J BiolMacromol*. 2016 93(Ptb):1519-1529. doi: 10.1016/j.ijbiomac.2016.05.038.

[172] Hegge, A.B., Andersen, T., Melvik, J.E., Bruzell, E., Kristensen, S., Tonnesen, H.H. Formulation and Bacterial Phototoxicity of Curcumin Loaded Alginate Foams for Wound Treatment Applications: Studies on Curcumin and Curcuminoides XLII. *Journal of Pharmaceutical Sciences*. 2011, 100(1), 174-185 doi: 10.1002/jps.22263.

[173] Li, X., Chen S., Zhang, B., Li, M., In situ injectable nano-composite hydrogel composed of curcumin, N,O-carboxymethyl chitosan and oxidized alginate for wound healing application. *Int. J. Pharm*. 2012,437(1-2), 110-119. doi: 10.1016/j.ijpharm.2012.08.001.

[174] Kaur, N., Garg, T., Goyal, AK., Rath, G., Formulation, optimization and evaluation of curcumin-beta-cyclodextrin-loaded sponge for effective drug delivery in thermal burns chemotherapy. *Drug Deliv.* 2016, 23 (7),2245-2254. doi: 10.3109/10717544.2014.963900.

[175] Rachmawati, H., Edityaningrum, CA., Mauludin, R., Molecular inclusion complex of curcumin-beta-cyclodextrin nanoparticle to enhance curcumin skin permeability from hydrophilic matrix gel. *AAPS PharmSciTech*. 2013,14(4),1303-1312. doi: 10.1208/s12249-013-0023-5.

[176] Kiti, K., Suwantong, O., Bilayer wound dressing based on sodium alginate incorporated with curcumin-β-cyclodextrin inclusion complex/chitosan hydrogel. *International Journal of Biological Macromolecules*. 2020, 164, 4113-4124. doi:10.1016/j.ijbiomac.2020.09.013