RESEARCH ARTICLE

Curcumin Encapsulated Nanoscale Chitosan– A Potent Outcome

N. Annlin Bezy[1], K. Francy[2] and A. Lesly Fathima[3*]

[1]Research Scholar (Reg.No:20213042132006), Department of Physics, Holy Cross College (Autonomous), Nagercoil, (Affiliated to Manonmanium Sundararnar University, Tirunelveli), Tamil Nadu, India.
[2]Assistant Professor, Department of Chemistry, Holy Cross College (Autonomous), Nagercoil, (Affiliated to Manonmanium Sundararnar University, Tirunelveli), Tamil Nadu, India.
[3]Assistant Professor, Department of Physics, Holy Cross College (Autonomous), Nagercoil, (Affiliated to Manonmanium Sundararnar University, Tirunelveli), Tamil Nadu, India.

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***Address for Correspondence**
A. Lesly Fathima
Assistant Professor,
Department of Physics,
Holy Cross College (Autonomous),
Nagercoil, (Affiliated to Manonmanium Sundararnar University, Tirunelveli),
Tamil Nadu, India.
Email: leslysat@gmail.com

ABSTRACT

Cost effective drugs with high reliability is the most significant requirement in the field of biomedical engineering. The remedies to all human pathogens were occurring in nature, since the measures taking to seek the treatment is still in progress to provide better outcome. Here the review paper discusses the inbuild properties of biopolymer chitosan and golden spice curcumin, and how its nanosized formulation enhances the application in various fields. Chitosan is a biodegradable polymer obtained from sea food industry waste having enormous bioactivity. Same way the curcumin is an active compound being separate from natural turmeric. In separately, chitosan is being utilized as provision in agriculture, medicine in pharmaceuticals and in the water purification systems. Curcumin is absolutely used in medical industries. Thus, chitosan-based drug delivery of curcumin with confinement in nano range size can be used as a new therapeutic to human pathogens.

Keywords: chitosan, polymer, curcumin, pathogens, applications

INTRODUCTION

Nowadays biopolymers triggered great interest due to its usage as renewable sources for material engineering[1], [2]. By exploring techniques to preserve the polymer chain as much as possible, the biopolymers are sought as ideal precursors for high end functional material. Such biopolymers are synthesized by processing the exoskeletons of certain living organisms; they are greatly biodegradable and nontoxic unlike the synthetic polymers [3], [4]. Chitosan is such biopolymer of great industrial and biotechnological interest because of its abundant source, being compatible and reactive to enzymes in body, defining it as the active component delivery system [5]. Seafood waste is a potential source of raw material for chitin and chitosan extraction [6] with high benefits and can be used to produce the compounds [7]. However, it is a natural resource with high physical and chemical variability, the properties of chitin and chitosan have direct impact on their applications [8], [9]. Due to the difficulty in processing and reuse of waste form fishing industry, the significant percentage of biomass is discarded directly in the environment without undergoing any previous treatment [10]. Chitosan is a biomaterial which has the biological properties of biocompatibility, biodegradability and non-toxicity.This, chitosan is the only polycation in nature and its charge density depends on the degree of deacetylation and pH. Chitosan is soluble over a wide range of pH from acidic to basic and it depends on the degree of deacetylation and molecular weight. The chitosan with high molecular weight is only soluble in acidic aqueous solvents, even they have high degree of acetylation. This contraction in solubility has hindered chitosan application in many fields. Improved chitosan can be used as a therapeutic agent because it has antibacterial and antifungal characteristics, making it attention grabbing for applications in medicine, agriculture, food packing, cosmetics, water purification and textile industries [11]–[13].In the extraction process, features molecular weight, degree of deacetylation, degree of purity, viscosity and crystallinity [14]. Indeed, high molecular weight biopolymers attribute improved mechanical properties and glass transition temperature [15], [16]. Despite its high added significant applications, chitin remains a largely underutilized biomass waste; there is thus a dare need to develop a simpler method of extractions, and methods able to afford a broader range of products which are needed to implement the shell biorefinery theorized [17]. Such one method is seeking to reduce energy, chemical and solvent input for improved sustainability, while being safe. Therefore, many studies are pursed to improve the aqueous solubility of chitosan. The different pharmaceuticals approach to have the potential of solubility, formulation processing, and the overall delivery of hydrophobic drugs [18]. This review focuses on possibilities utilized for chitosan-based curcumin particles in various applications.

HISTORY

Natural Polymer – CHITOSAN

In 1811, the research on chitin isolation and characterisation began by the French chemist Henri Braconnot, in fungal species like mushroom which were subjected to an aqueous alkali treatment. Lassaigne in 1843 conducted research from exoskeletons of the species Bombyx mori (Silk worm), in which he demonstrated the presence of nitrogen in the structure of chitin. Late in 1859 chitosan was discovered by treating chitin with Potassium Hydroxide in high temperature. In 1878, Ledderhose suggested the presence of glycosamine and acetic acid in chitin but only in 1894, Glison confirmed the presence of glucosamine units. Still, in 1894, the German Felix Hoppe-Seyler named the compound as Chitosan and in 1950 the chemical structure of chitosan was formed [19]. The first production reports of Chitosanwereappearing in 1970 in United states and Japan. By 1986, Japan has fifteen industries actively working to produce chitin and chitosan commercially. In chitosan production Japan and the United States are outstanding and having great interest in the research of this natural polysaccharide in the variety of chitosan applications, being economically benefitable and sustainable[20]. Chitin is a natural polymer having high crystalline structure that is nitrogenous and white coloured. It is the second most abundant polysaccharide in nature next to cellulose having much bioactive ability. It is chemically composed of N-acetyl-2-amino-2-deoxy-D-glucose units joined by glycosidic bonds ($\beta 1 \rightarrow 4$) forming linear chain with some of the deacetylated monomers thus the chitin transforms to chitosan. It exchange ions while soluble with organic acids and diluted minerals[21], [22].

Golden Spice – CURCUMIN

Natural derivatives from the plant sources always have a significant and promising role in pharmaceutics in terms of therapeutic effects and biological activities. In such the golden spice – Turmeric has beneficial against the molecular, cellular, animal and human pathogens. Almost two centuries ago, Vogel and Pelletier reported the isolation of “yellow colouring matter” from the rhizomes of curcuma longa (turmeric) and named as curcumin. Curcumin is the mixture of resin and turmeric oil. Vogel in 1842, obtained the pure form of curcumin[23]. Later chemists in 1910 identified the chemical structure of curcumin as diferuloylmethane or 1,6- heptadiene-3,5—dione-1, 7-bis (4-hydroxy-3- methoxyphenyl) -(1E,6E)[24]. A chemist named Srinivasan a separated and quantified the components of curcumin by column chromatography [25], [26]. Such curcumin obtained from the root of turmeric is non-toxic, bioactive agent having antibacterial and anti-oxidant properties has been utilized in traditional medicine.

CHITOSAN A BIOPOLYMER – ORIGIN

Natural polymer chitosan is found in the exoskeletons of squid, fish scales, shrimp shell, and some of insects like silk worm, beetles, cockroaches and funguses. Among all the sources, the polymer from sea food is a rich resource obtained from the waste of sea food industry. Chitosan from shrimp shell waste has 30 – 40% weight as shell[27]. Shrimps and prawns are considered as important aquaculture products due to its health benefits and most wanted food among people. Shrimp shell contains a higher amount of chitin which is an expensive component used in cosmetics, foods and pharmaceuticals. Production of chitosan within the country can reduce the dependency on importing this valuable raw material[28].

EXTRACTION TECHNIQUES

Chitosan a basic biopolymer which is comprised of one of monomer of glucose. In general, two different methods are known for the synthesis of chitosan from chitin in degree of deacetylation variations. The one method is solid chitin heterogeneous deacetylation and the other is preswollen chitin in homogeneous deacetylation under vaccum in an aqueous medium. For both the cases, concentrated alkali solutions and long-time processing are required for thedeacetylation reaction which may vary depending on the heterogeneous or homogeneous conditions from 1 to nearly 80 hrs. In the preparation of chitosan from fishery waste materials which are hazard and toxic for environment is a simple practice. The typical production of chitosan from marine crustaceans generally consists of three basic steps: demineralization, deproteinization, and deacetylation. There is a possibility to produce both chitin and chitosan within the existing process. Therefore, researchers aimed at developing appropriate field support techniques for the huge commercial manufacture of chitin and chitosan from marine wastes.The quality and purity of chitin and chitosan were determined bysome subjective and objective methods. Subjective methods included sensory analysis, whiteness, pulverizing property etc., and the objective methods included biochemical parameters, moisture content, reabsorption property and solubility[29].

CURCUMIN - A NATURAL SOURCE

Curcumin originates from the Indian spice turmeric (curcumin longa) a type of ginger. It is a potent anti-inflammatory agent that can reduce inflammation and plays a key role in the treatment of AD (Anno Domini)[30], [31]. Still turmeric is used in cuisines as a spice.In ayurveda, turmeric is taken for medicines. In traditional, turmeric has been used as a medicine to treat wounds, colds and infections, and as a natural colouring agent in preparing foods. A turmeric root contains only 2-5% of curcumin. Turmeric by nature consist of several active constituents isolated from the rhizome, structurally related curcuminoids, including curcumin as the most important and main bioactive compound. Besides curcuminoids ingredients including yellow pigment curcumin (diferuloylmethane; 1,7-bis(4-hydroxy-3-methoxy-phenyl)hepta-1,6-diene-3,5-dione), demethoxycurcumin (DMCur), bismethoxycurcumin (BDMCur), and cyclocurcumin (CCur) are present in turmeric [32].

SEPERATION OF BIOACTIVE CURCUMIN

In 1815, the extraction and separation of active compound curcumin from the grounded turmeric was reported, but still the advanced and improved method is ongoing research[33]–[35]. The fresh turmeric was dried and grounded initially for Soxhlet extraction method. In Soxhlet apparatus the polar and non-polar solvents including acetone, ethanol, hexane, ethyl acetate, methanol etc can be preferred to extract. The extract is employed for column chromatography to separate the compound curcumin. Among the organic solvents employed ethanol is the highly preferred for curcumin extraction. The chlorinated solvent extraction being effective, is not used because of its non-acceptability in the food industry [36], [37]. Curcumin separation from turmeric constituents by column chromatography is done using silica gel to yield different fractions. The purification of the yielded curcumin can further be done by silica gel using chloroform/dichloromethane and ethanol/methanol mixtures as eluents [38]–[40]. High performance liquid chromatography (HPLC) technique is used for the detection and estimation of curcumin. The reverse phase C_{18} columns are used as stationary phase and different gradients of solvents containing acetonitrile/water or chloroform/methanol can be employed as the mobile phase [41], [42]. The presence of curcumin is confirmed by using absorption detectors in the wavelength range from 350 to 450 nmor in the UV region using a common detection wavelength in the range of 250 to 270 nm.

CHARACTERISTICS OF CHITOSAN

Chitosan is a cationic polysaccharide. It has drawn great attention in pharmaceuticals and medical applications, owning to its plenty availability and unique mucoadhesive[43]. The chitosan structure has amino group and it might be protonated providing solubility in dilute aqueous solutions[44]. The beneficial biological properties such as biocompatibility, biodegradability, non-toxicity and low immunogenicity[45]–[47]. The chitosan is insoluble in water, organic solvents, aqueous bases and it is soluble in acid such as acetic, nitric, hydrochloric, perchloric and phosphoric[48]. The haemostatic activity of chitosan is related to the positive charges. Due to its positive charges, chitosan interacts with the negative of cell membrane, helps to open the tight protein junction. Chitin polymorphism can be determined using X ray diffraction, where three crystalline structures α, β and γ are observed by unit size. The α-chitin is the most abundant form found in arthropod exoskeletons with anti-parallel polymeric chains, which favours the existence of numerous inter and intra hydrogen bonds. In β-chitin the disposition of chain is parallel and they are found in animals such as squids having flexibility and resistance. The γ-chitin show the combination of both chain positions [49], [50]. Functional properties of chitin and chitosan varies from product to product due to the season, quality of shell, species present, climate and by the whole processing method involved.

Physical properties

The chitin and chitosan are amorphous solids and almost insoluble in water. This is due to intermolecular hydrogen bonding, which forms between the neutral molecules of chitosan. Chitosan is a firm polymer due to hydrogen bonding in its molecular structure. Subsequently, it can be easily transformed into film with high mechanical strength. Chitosan is a weak polyelectrolyte, a poor anion exchanger. Therefore, it is likely to form films on negatively charged surfaces, and it also has the ability to chemically bind with fats, cholesterol, proteins and macromolecules [51], [52].

Chemical properties

Chitosan's cationic nature is due to the presence of amino and hydroxyl groups, which make it modifiable by including complexation, grafting, cross-linking and blending [53]. The aqueous solubility of chitosan depends upon the balance between electrostatic repulsion [54]. The degree of deacetylation plays a major role in molecular weight of chitosan. The lower deacetylation, higher the molecular weight, which results higher chemical stability and mechanical strength [55].Furthermore, the properties of chitosan not only depends on the degree of deacetylation, but also on the distribution of the acetyl groups along the chain, the solvent concentration and the type of solvent[56], [57].

Biological properties
Chitin derived biopolymer chitosan is non-toxic, biocompatible and biodegradable. They are amino polysaccharides having biological, physiological and pharmacological properties [58]. The prominent bioactivities include the promotion of wound healing, heamostatic activity, immune enhancement, mucoadhesion, eliciting biological responses and antimicrobial activity. Chitosan is also a promising supporting polymer for gene delivery, cell culture and tissue engineering. Chitin and chitosan as dietary fibre's exhibithypolipidemic activity, as confirmed by the reduced cholesterol and triglyceride levels in bloodplasma and lier of rats [59]. Chitosan was highly effective than chitin[60];thus, chitosan's derivatives are important for medical field[61].

BIOACTIVE PROPERTIES OF CURCUMIN
Curcumin is a chemotherapeutic agent with antioxidant, anti-inflammatory, anti-proliferative, anti-cancer and anti-microbial effects. However, the potential of curcumin mentioned is limited by its hydrophobicity and poor availability[62]. Being curcumin as a strong anti-bacterial drug, it is valid to prevent the growth of several bacteria's including staphylococcus aureus and pseudomonas aeruginosa also it is a good candidate for treating inflammatory diseases[63]. Curcumin also possesses anti-amyloidogenic, anti-oxidative and metal chelating properties[64] having the potential neuroprotective effects [65], [66]. The combination of low solubility and poor availability negatively effects its biological efficiency [67]. Improving the poor biopharmaceutical properties of curcumin and to improve its aqueous solubility is the size confinement, that needed using nanotechnology [68]–[70]. The anticancer and radio protective effects of curcumin have been demonstrated on many types of tissues including skin, brain, colon, gastrointestinal, liver, lungs, pancreas, mammary glands, prostate, breast, blood and bone marrow [71]–[74]. In nature, curcumin is not only has the potential to prevent radiation damage with its antioxidant properties, but also initiate DNA repair processes in radiation damaged cells [75].

CURCUMIN – CHITOSAN ENCAPSULATION
Chitosan is a positively charged polymer with tendency to interact with negatively charged cell surface or enzymes in body[76]. These beneficial properties made chitosan to one of most popular biopolymers for the development of bioactive compounds delivery systems in a wide range of applications [77]. Due to the real fact that, the surface of all physiological membranes including intestine having negative surface charge can be easily interact with positively charged chitosan, thus proven to enhance the properties and making them very attractive[78], [79]. Curcumin as a natural photosensitizer is active against cancer cells. Chitosan's destabilization in excessive heat, light and alkaline conditionsand poor water solubility had led to decrease its bioavailability[80], [81]. Thus, to make bioavailable for a long time and to increase its bioactivity, chitosan-carboxymethyl cellulose particle encapsulated with curcumin was considered. Encapsulation includes the immobilization of a particular compound in a material that makes coating or got dispersed. Curcumin a traditional drug having high anti-oxidant, antibacterial activity will promote for tissue engineering like tissue regeneration by tissue remodelling, new tissue formation, granulation and collagen deposition. The photosensitive property of curcumin also makes it to be a suitable carrier enabling penetration to skin effectively. Some of mediated drug delivery systems having wound healing benefits are polymer – curcumin nanoparticles[82], [83],polymer – curcumin nano emulsion gel [84], [85], self-assembled nanogels [86], and hydrogels[87], [88]. Still research is under process to develop the scaffolds in the form of sponges, films and nanofibers[89]–[91]. Encapsulation can improve the disadvantages and difficulties in low aqueous solubility and protect a molecule from degradation or loss of functionality due to the effects of photons, oxygen, pH and moisture.

ACTIVITIES OF CURCUMIN-CHITOSAN IN NANO SCALE
Nano sized resources have improved or unpredicted properties than bulk materials. The organic and inorganic particles size can be varied by numerous preparation routes like top-down, bottom-up, crosslinking, microbial methods. Nanoparticles by any of routes have been investigated intensely to put in applications in the field of electronics, textiles, medicine, agriculture. In medical area, the nanosized formulation shields the loaded drug from degradation by pH and increases its half-life. Curcuminas a natural therapeutic agent consists of two symmetric o-

methoxy phenolic groups attached to α and β-unsaturated β-diketone which have potential photochemical properties. In vitro and in vivo analysis results that nanocurcumin loaded with a nano carrier having more health-span-promoting features than traditional or native curcumin. The water solubility and bioavailability of curcumin compound can be improved through nanoencapsulation with lipids, polymeric nanoparticles, nanogels, dendrimers and conjugating to some metal oxide nanoparticles[92]. Nanoencapsulation compound act as a high potential carrier of bioactive substances due to their subcellular size, allowing relatively higher intracellular intake, improved stability and protection of reliable substances against degradation [93]–[95]. Particle size plays a main role drug delivery of all human pathogens. As by reviewing many reports, the nanosized particles has relatively better intercellular bonding comparing to micron sized particles [96]. In chitosan nanoparticles the variety hydrophilic and hydrophobic drugs can be included during the synthesis process as nanoparticle. The loading efficiency of the drug may depend on its physicochemical features and the adopted synthesis methods of micro and nano particle systems [97], [98]. Solubility of curcumin can be improved by developing nano formulation using chitosan as biodegradable and biocompatible polymer, having the ability to encapsulate curcumin and improve its therapeutic effect [99]. Curcumin nanoparticles exhibit superior drug delivery, enhanced transdermal permeation and superior cell viability [100]. Covalent linkage of curcumin and chitosan to produce chitosan -curcumin polymer has (1) improved curcumin stability for more than 1 month at above freezing and ambient temperatures, (2) solubility improvement in aqueous medium, (3) improved bioavailability, (4) controlled release of conjugated curcumin, (5) curcumin's anti-oxidant can be retrieved through ester hydrolysis[74], [101]. When nano formulation is considered, the biopolymers are the best choice for better treatments. Ionic gelation, solvent evaporation, complex coacervation, emulsion cross linking, spray drying, solvent displacement is the most popularly considered method for the preparation of polymer-based nanoparticles [102]. Among the mentioned methods, ionic gelation and complex coacervation are alike and ideal for improved biostability of drugs [103]. However, curcumin's bioactivities are hindered due its lower solubility, lower cellular uptake and bioavailability, but the progress in nanotechnology has disabled all the hinderances, thus polymeric nanoparticles can be used to encapsulate curcumin. By these, the curcumin's limitations can overcome and get improved bioavailability, target disease cells, prevent from degradation or metabolism, thus increases its therapeutic potential [104].

APPLICATIONS OF NANO CHITOSAN-CURCUMIN COMPOUND

In current scenario new technological approaches are needed to improve human lives and the environment. Researchers broadly investigated the chitosan nanoparticles for numerous applications in medicine, water treatment, agriculture and pharmaceutics. Its broad spectrum of properties such as cationic biopolymer, capable of forming gels, pH range, enzymatic interaction chitosan material reveals great industrial interest [105]. Chitin and chitosan-based nanomaterials are used as a carriers of cosmetic manufacturing ingredients such as chitin nano fibrils face masks capable of releasing active compounds at different doses with time, thus can be used as anti-bacterial, anti-inflammatory, sunscreen, anti-aging cosmetics [106]. Chitosan alone is not suitable for blood interacting drugs, inspite of its biocompatibility. Due this blood coagulating property, chitosan is a desirable material for haemostatic agent. This haemostatic activity of chitosan with the mechanism of action as a coagulant is used for developing medical bandages which control bleeding during surgery. The haemostatic mechanism induced from chitosan is independent of traditional blood coagulation cascade[107]–[110]. Chitosan in target to antimicrobial action of bacteria, it easily gets bind and inhibits the transport of nutrients to cells [20], [111], [112].Molecular weight and viscosity of chitosan have to be low; hence high surface charge and smaller particle size can be achieved while confining to nano scale, thus penetration of drugs to skin will be effective[113].Microwave method of low molecular weight chitosan-curcumin nanoparticles hold effective in skin manifestation treatment, through the curcumin reaction with skin [114]. Chitosan also considered for fat binder, wound healing, hypocholesterolaemia effect treatments [115].

Medicine and Pharmaceutics

Chitosan nanoparticles allows encapsulation and chain grafting of the drugs and active constituents. Remarkable features such as reducing the damage of non-targeted tissue or cells and preventing enzymatic degradation of drugs

[116] makes their use in drug delivery, cancer treatment and biological imaging and diagnosis [117]. Curcumin loaded chitosan nanoparticles reduces the progression of staphylococcus aureus and pseudomonas aeruginosa bacterial infection in skin. Curcumin alone or chitosan – TPP will not inhibit bacterial infection. The antimicrobial action of curcumin loaded chitosan nanoparticles significantly high [63]. Skin repair treatment can effectively be achieved by curcumin and chitosan nanoparticles. In wound healing, existing fibrous mats are difficult to fix into wound; also, not able fit the shape of irregular wounds. The availing soft hydrogels fix to the irregular wound; still its poor permeability affects the supply of nutrients like oxygen during skin repair [118], [119].

Agriculture

In agriculture chitosan nanoparticles is a necessary compound helps to increasethe sustainable and agro friendly agrochemicals like fertilizers and pesticides. Similar as in medical field, chitosan nanoparticles act as a nano carrier to enhance the stability and to create controlled release [120], [121]. Through these effects, agrochemicals can be feed in low quantity, hence contamination risk to the environment and other toxic effects to non-targeted organisms and species were decreased[122], [123]. In food packing the polymer-based antioxidant compound enhances the food freshness. The chitosan film can be improved by incorporating curcumin an antioxidantagent as a source of phenolic compounds [124]. The non-thermal technology is used to prevent food from microbial contamination, extend shelf life and ensure food safety. The light absorption properties of curcumin results to get a decreased light transmittance of composite film with good transparency [125].

Water Treatment

The lack of a cost effective, sustainable, effective absorbent to replace the activated carbon has improved the bio-based alternatives [126]. Chitosan with functional amino and hydroxyl group and curcumin in nano size helps for the removal of a wide range of pollutants like heavy metals, dyes, impurities and pesticides [127]. These nanoparticles exhibit higher capacity than conventionally used macro and micro sized purification sponge sorbents due to their higher surface area [128].

CONCLUSION

Curcumin loaded chitosan nanoparticles with potential drug delivery systems and applied as an approach to activate anti-bacterial systems. The higher cytotoxicity effect of curcumin loaded chitosan nano range particles may be due to their higher cellular uptake as compared to curcumin separately. Curcumin loaded nano formulations, therefore a promising compound in cancer therapy [129]. Chitosan is simply obtained from shrimp shell waste by a simple treatment and some reactions. Chitosan derivatives are relatively inexpensive for taking in haemostatic agents being fibrinogen-based treatments are expensive and infectious. The applicability of chitosan curcumin nanoparticles in pharmaceuticals and medicine can be efficient by the controlled release of drugs and stability in unaffected cells. The incorporation of curcumin chitosan nanosized compound is an enriching feed to stimulate immunity and boost the diet formulations.

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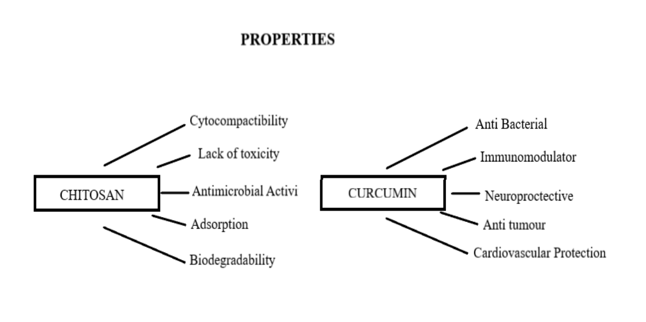

Graphical Abstract

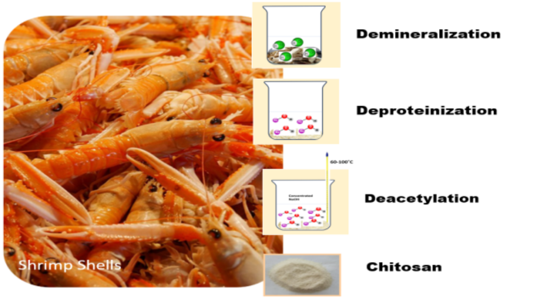

Figure 1 Extraction process of chitosan from shrimp shells

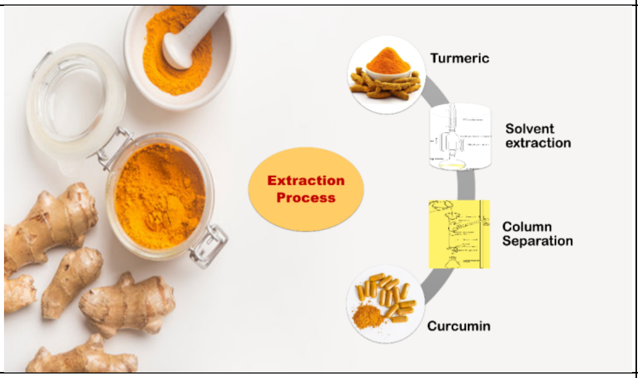

Figure 2 Extraction process of curcumin from turmeric

Figure 3 Applications of chitosan-curcumin matrix