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CHITOSAN & ITS DERIVATIVES: A REVIEW IN RECENT INNOVATIONS

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ABSTRACT: Chitosan a natural polymer available and easy to produce in countless parts of the world; is a material that can significantly improve the standard of living in developing countries where the industry is often surpassing the need to protect the environment and/or where the environment protection is strongly dependent on limited financial resources available to those in charge of environmental protection. Its physicochemical properties such as its poor solubility in water or in organic solvents limit its utilization for a specific application. A smart way is to impart new properties to chitosan is its chemical modification of chain, generally by grafting of functional groups without disturbing the initial skeleton in order to keep the original properties intact. In this way the modified chitosan offers huge relevance in terms of its modified derivatives. The present review is dedicated to the advancements in the chitosan based derivatives and their special attention in food industry as the packaging material is also addressed.

INTRODUCTION: Over the last few decades, the global environmental problem has attracted significant awareness of the research community and policymakers for the development of polymeric materials which are degradable in a natural environment. The production of biodegradable polymers which are decomposed by microorganisms and photodegradable polymers that are decomposed by sunlight is a priority among researchers. An ideal biodegradable polymeric material is one which after being disposed of can be recycled many times before promptly being decomposed by microorganisms or sunlight providing carbon dioxide and water. Chitosan is such a type of polymer which is degradable in natural environment.

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Chitosan is a polycationic naturally occurring bio-degradable, non-toxic, non-allergenic biopolysaccharide derived from chitin which is found in abundance in nature[1-2]. It contains more than 5000 glucosamine units and is obtained commercially from shrimp and crab shell containing chitin which is an *N*- acetyl glucosamine polymer. The *N*- acetyl glucosamine gets converted in to glucosamine units by alkaline de-acetylation with NaOH (with 40-50% conc.)[3-5].Chitosan is considered as most promising materials for future applications on account of its excellent biodegradability, biocompatibility, non-toxicity, antimicrobial activity, and its economic advantages[6]. The chemical structure of chitin is made up of linear monomeric units of 2-acetamido-2-deoxy- D-glucopyranose attached through β-(1-4) linkages[7].

Sources and extraction of chitosan from raw materials:

Chitin, the main source of chitosan is widely distributed both in the animal and the plant

kingdom. Henry Braconnot (1780–1855) was the first who isolated chitin from mushrooms in 1811 about two centuries ago. It was the first polysaccharide which was identified by man preceeding by cellulose about 30 years[8]. The main sources of chitin are Fungi, Algae, Echiruda, Annelida (Segmented worms), Mollusca, Cnidaria (jellyfish), Aschelminthes (roundworm), Entoprocta, Bryozoa (Moss or lace animals, Phoronida (Horse shoe worms), Brachiopoda (Lamp shells), Arthropoda and Ponogophora. Chitin; also the major component of arthropods tendons, exoskeletons and the linings of their digestive, excretory and respiratory systems and insect's external structure as well as of some fungi.

It is also found in the iridophores (reflective material) of both eyes and epidermis of cephalopods and arthropods of phylum Mollusca and the epidermal cuticle of the vertebrates. Epidermal cuticle of Paralipophrystrigloides is also chitinous in nature[9-11].

Chitin occurs in three polymorphic solid state forms designated as α, β, and γ chitin which differ in their degree of hydration, size of unit cell, and number of chitin chains per unit cell[12]. Chains of chitin may be arranged in a tightly compacted crystalline structure of antiparallel sheets and extensive intermolecular hydrogen bonding (α-chitin), in a more mobile allomorph of parallel sheets (β-chitin), or a combination of both (γ-chitin) (**Fig. 1**). α-Chitin is most abundant and is found in shellfish exoskeletons and fungal cell walls. β-Chitin is mainly found in squid pens and diatoms while γ-chitin may be predominantly found in squid and cuttlefish stomach lining[13-15].

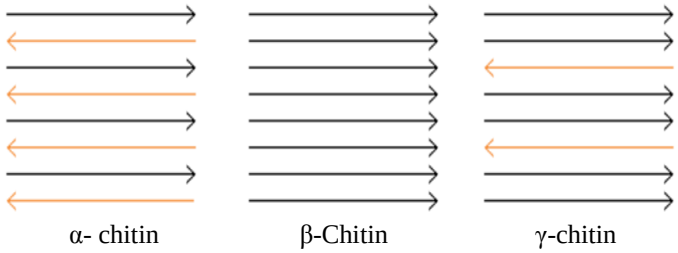

FIG.1 SHOWING α, β AND γ-CHITIN

Chitosan is commercially interesting compounds because of its high nitrogen content (as compared to synthetically substituted cellulose) which makes chitosan a very useful chelating agent[16].The elemental composition of chitosan[17] is described in **Table 1**.

TABLE. 1 ELEMENTAL COMPOSITION OF CHITOSAN

SR. NO	ELEMENTS	% IN CHITOSAN
1.	Carbon	44.11
2.	Nitrogen	7.97
3.	Hydrogen	6.84

Both chitin and chitosan have unusual multifunctional properties, including high tensile strength, bioactivity, biodegradability, biocompatibility, nontoxicity and non-antigenicity which made them possible to be used in many applications[18-19].

Furthermore, the chemical modifications of the three reactive functional groups of chitosan had increased the applications of chitosan in different fields. Chitosan has three reactive groups, which is primary (C-6) and secondary (C-3) hydroxyl groups (**Fig. 2**) on each repeat unit and the amino (C-2) group on each deacetylated unit. The presence of these reactive functional groups which may readily subject to chemical modifications to alter physico-mechanical properties of chitosan formulates it wonderful material for different purposed applications[20].

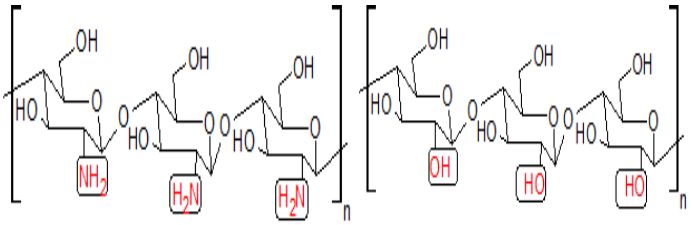

FIG.2 SHOWING STRUCTURES OF (a) CHITOSAN AND (b) CELLULOSE

Chitosan, the deacetylation of chitin to form a soluble amine salts; is not a single chemical entity; it varies in composition depending on the source and method of preparation and also on physiological conditions.

It is manufactured commercially by a chemical method; for example the isolation of chitin from shellfish waste consists of three steps: deproteinization (Extraction and/or removal of protein), demineralization, followed by the decolourization/de-pigmentation. The order of the

first two steps is generally considered irrelevant if protein or pigment recovery is not an objective. Several procedures for the preparation of chitin and chitosan from different shellfish wastes have been developed over the years, some of which form the basis of the chemical processes used for the industrial production of chitin and derivatives.

Firstly the sources such as crab or shrimp shells are washed and grinded in to powdered form and then it is deproteinized by treatment with an aqueous 3-5% solution of sodium hydroxide. After that it is neutralized and demineralized at a room temperature by treating it with aqueous 3-5% of hydrochloric solution to form a white or slightly pink precipitate of chitin. After that chitin is deacetylated by treatment with an aqueous 40-45% solution of sodium hydroxide and the precipitate is then washed with water (**Fig. 3**). The insoluble part is removed by dissolving in an aqueous 2% acetic acids solution. The supernatant solution is then neutralized with an aqueous sodium hydroxide solution to obtain a purified chitosan[21-22].

Enzymatic methods are an alternative to the chemical method for chitin and chitosan production. In addition, the protein often remains high and reaction times are significantly increased compared to chemical methods. Enzymatic methods are limited in industrial production of chitosan, due to higher cost of enzymes. Several commercially available enzymes such as alcalase, chymotrypsin, and papain are also used for the production of chitosan[23].

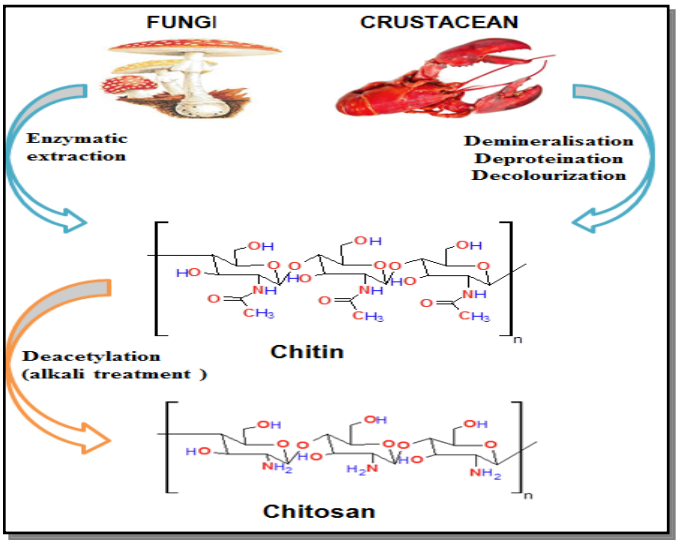

FIG.3 PROCESSING OF CHITOSAN FROM RAW MATERIALS

Properties of Chitosan:

Chitosan has attracted increasing attention in the past decade due to its unique properties including nontoxicity, biocompatibility, and biodegradation[27-31] including many others discussed in the pending text. One; among the notable and much exploited is; its antimicrobial commotion inhibiting the growth of a wide variety of fungi, yeasts and bacteria making it beneficial for use in the field of biomedicine.

It can also bind toxic metal ions, beneficial for use in air cleaning and water purification applications. These properties arise as a result of protonation of NH_2 groups on the chitosan backbone[24-26]. Structurally, chitosan is a linear-chain copolymer composed of D-glucosamine and N-acetyl-D-glucosamine being obtained by the partial deacetylation of chitin.

The structure of chitosan is very much similar to that of cellulose and is the second most abundant natural polymer after cellulose[32-33]. The solubility, biodegradability and reactivity of chitosan and adsorption of substrates depend on the extent of protonated amino groups in the chain of polymer. Chitosan is incapable of being dissolved in water, organic solvents and aqueous bases however get dissolved after stirring in acetic, nitric, hydrochloric, perchloric and phosphoric acids[34]. The amino group of chitosan is not protonated in alkaline or neutral medium and therefore it is insoluble in water; while in acidic pH it gets the resultant soluble protonated polysaccharide.

Chitosan forms water-soluble salts with inorganic and organic acids including glyoxylate, pyruvate, tartarate, malate, malonate, citrate, acetate, lactate, glycolate, and ascorbate[21, 35]. Inherent chitosan becomes soluble in organic acids when the pH of the solution is less than 6.5. The water-soluble salts of chitosan may well be formed by neutralization with acids such as lactic acid, hydrochloric acid, acetic acid, or formic acid.

There are various other factors which may affect the physicochemical properties of chitosan **(fig. 4)** enabling the researchers to formulate different grades of chitosan which differ primarily in molecular weight, crystallinity and degree of

deacetylation. During its processing from raw material, different conditions such as type and concentration of reagents, time and temperature employed can affect the physical characteristics of chitosan product. Its molecular weight also depends on solubility, viscosity, elasticity and tears strength.

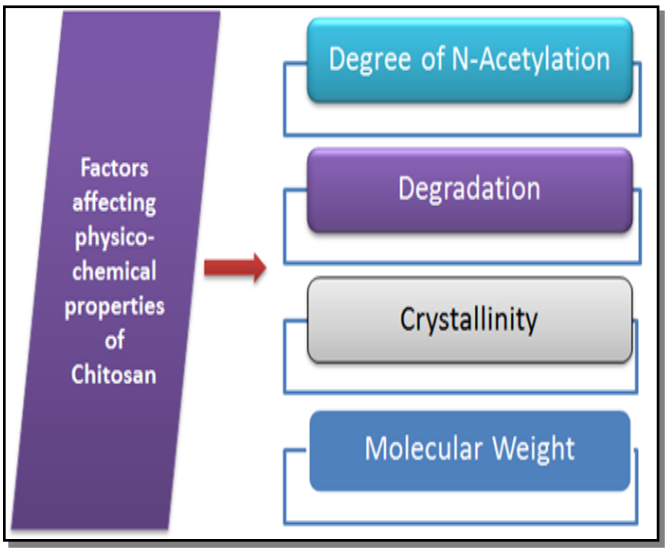

FIG.4 FACTORS AFFECTING PHYSICO-CHEMICAL PROPERTIES OF CHITOSAN

Chitosan is a pseudo plastic material and is an excellent viscosity-enhancing agent in acidic environments. The viscosity of chitosan solution is affected by the molecular weight, degree of deacetylation, pH, ionic strength, concentration, and the temperature. Generally, there is a decrease in the viscosity of the solution on the increase in temperature and increases with an increase in chitosan concentration. The effect of the pH on the viscosity depends on particular type of acid used[37].

The characteristics of chitosan required for a particular application are dependent upon the degree of acetylation (DA) and its molecular weight[36]. The degree of deacetylation of molecular chain of chitin; however, an extrinsic property; hence increased by increasing the temperature or strength of the alkaline solution. The viscosity of chitosan also influences the biological properties such as wound-healing properties as well as biodegradation by lysozyme.

As the Chitosan is hydrophilic in nature, therefore it has the ability to form gels at acidic pH. This type of gels can be used as a slow-release drug-delivery system. The solubility of Chitosan can be decreased by cross-linking it with covalent bonds using glutaraldehyde. The swelling property of the chitosan decreases with an increase in the concentration of cross-linking agent[21, 35].

The various chemical and biological properties of chitosan (**Fig.5**) are as follows:

⇒ Natural, linear polyamine with reactive amino and hydroxyl groups[38-39].
⇒ Chelates with transitional metal ions[40-41].
⇒ Biocompatible and biodegradable to normal body constituents[42].
⇒ Non-toxic and safe to use[43].
⇒ Binds to microbial and mammalian cells[44].
⇒ Haemostatic, fungistatic and spermicidal agent[45].
⇒ Antitumor and anti-inflamatory agent[46].
⇒ Accelerate bone regeneration[47].
⇒ Immunoadjuvant and drug delivery agent[48-49].

FIG.5 SHOWING VARIOUS PROPERTIES OF CHITOSAN

DERIVATIVES OF CHITOSAN:

The use of chitosan has been postulated in numerous areas of biopharmaceutical research such as mucoadhesion, permeation enhancement, vaccine technology, gene therapy and wound healing. Recent applications of chitosan are in ophthalmic, nasal, sublingual, buccal, periodontal, gastrointestinal, colon-specific, vaginal, transdermal drug delivery and mucosal-vaccine and gene carrier. It can also be used in the

pharmaceutical industry in direct tablet compression, as tablet disintegrant, for the production of controlled release solid dosage form or for the improvement of drug dissolution Chitosan derivatives were developed to improve not only biological activities but also water-soluble property, because the water-insoluble property was a major limiting factor for industrial application in spite of its unique biological aspects.

The improvement of structural properties of chitosan for a particular application can be easily brought about by chemical modification. Fortunately, chitosan is amenable to chemical modifications due to having of hydroxyl, acetamido and amine functional groups. For that reason, chemical modifications would not change the fundamental skeleton of chitosan and would keep the original physicochemical and biochemical properties while bringing new or improved properties[50].The various derivatives of chitosan (**Fig.6**) developed by different researchers during the recent years are briefly described as:

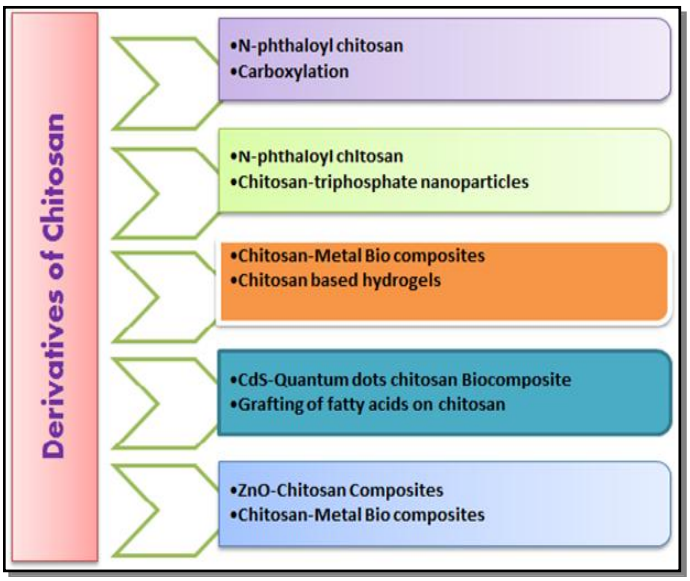

FIG.6 SCHEMATIC ILLUSTRATION OF DERIVATIVES OF CHITOSAN

Quaternarized water-soluble derivatives of chitosan:

Chitosan and its derivatives; having solubilities in pH values of lower than 6.0 are not desired for their use in cosmetics, medicine and food relevance[51]. In order to improve its solubility at neutral pH, firstly it is derivatized with substituents containing quaternary amino group, caboxymethylation and then sulfonation by adding strongly hydrophilic substituent[52-53]. The simplest derivative of chitosan is the trimethyl ammonium salt. The treatment of chitosan in N-methyl-2 pyrrolidone containing sodium iodide and methyl iodide with chloride ion in presence of sodium hydroxide resulting into the trimethyl ammonium salt of chitosan having high degree of substitution[54]. The anionic changes of iodide with chloride ions are necessary for stabilization resulting in water soluble product at neutral pH[55].

Chitosan chains with graphene oxide (GO) nanosheets:

Graphene, a member of the family of carbon nanoscaled materials arranged in a honeycomb two-dimensional lattice is a single-atom-thick nano structured sheet; used as material in a diverse range of applications due to its intrinsic unique mechanical and electronic properties. Graphene exhibits unusual electronic conductivity, high specific surface area, high mechanical, thermal and chemical stabilities properties making it a suitable material for electrochemical catalysis and biosensing. To expand and optimize the use of graphene in the different applications in bio-technology, it is necessary to functionalize graphene with biomaterials such as chitosan and other polysaccharides.

Recently Han and Yan (2014) have prepared supramolecular hydrogels of chitosan and GO by the non-covalent interactions between them where GO nanosheets work as 2D cross-linkers. At high GO concentration, hydrogel can be obtained at room temperature, while at low GO concentration, supramolecular hydrogel formed only at high temperature of 95 °C. These new kinds of hydrogels have potential applications in both biomaterials and environmental science as a smart soft material[56].

Caboxyalkylation:

In the process of caboxyalkylation, there is introduction of an acidic group on backbone of the base polymer. Such derivatives of chitosan are amphoteric in characteristic due to the occurrence of the amino group. By using carboxyaldehyde in a reductive amination sequence which results in N-caboxyalkylation[58], however, sequential substitutions giving rise to the formation of bis-

carboxymethyl derivatives by using glyoxalic acid[59].

Water solubility for these derivatives is attained at pH values above or below the isoelectric point (pI, sometimes abbreviated to **IEP**, is the pH at which a particular molecule or surface carries no net electrical charge).In order to increase the water solubility of chitosan, Toh et al. grafted succinic acid onto chitosan reporting a higher solubility in water at pH 7.3 which is revealed through measuring of the cloud point (when 20 mol% of primary amine were converted into carboxylic acid)[57].

The grafting of carboxylic acids on the chitosan chains not only improved the transfection efficiency (involves opening transient pores or "holes" in the cell membrane, to allow the uptake of material) but directed to the formation of a weaker complex with DNA hence reducing the unexpected morphologies and abnormalities in target cells might be occurring because of a change in cell properties caused by introduction of DNA[43].

N-phthaloyl chitosan:

Since the N-phthaloylation of chitosan is a very important reaction for the design of innovative materials, as this reaction requires no organic solvents; a great contribute to the advancement of green chemistry. A highly chemo-selective N-phthaloyl chitosan was successfully prepared in aqueous acetic acid reaction media for the first time by Ifuku et al. (2011). Changes in the concentrations of aqueous acetic acid from 0-10% did not affect the structural regularity of the products.

It should be emphasized that the irregular structure of the chitosan intermediate and acidic conditions caused by partial hydrolysis of phthalic anhydride allowed for a homogeneous reaction in pure water. It was also assumed that an N-acylation method is an eco-friendly aqueous media which would be applicable to any other cyclic acid anhydrides[60]. The implication of such derivatives in the form of membranes; the controlled permeability could be optimized by adjusting the substituting value of the chitosan, representing a significant potential application for these materials in agrochemicals[61].

Chitosan Esters:

Chitosan succinate and chitosan phthalate both the esters of chitosan have been successfully used as potential matrices for the colon-specific oral delivery of sodium diclofenac (a prescription medication which has been licensed to treat several conditions related to pain, inflammation, swelling, and stiffness).

During the conversion from an amine to a succinate in the polymer matrix, the significant solubility profile changes were observed[62]. The implants of hydrophobic, biocompatible and biodegradable aliphatic polyester chains, and more particularly poly (e-caprolactone) chains, were investigated for the preparation of biocompatible and biodegradable chitosan based amphipathic grafted copolymers for formation of the nanoparticles[63-66]. These modified polymers are insoluble under acidic conditions and act as sustained release for the encapsulated agent under basic conditions as well as for colon-targeted system[67-68].

Chitosan-triphosphate nanoparticles:

Ionotropic gelation methods are the most common to achieve a pharmaceutical product with desired characteristics. Super-paramagnetic iron oxide nanoparticles (SPIONPs) were encapsulated by Sanjaia, et al. at various concentrations within chitosan-triphosphate (SPIONPs-CS) using the ionotropic gelation method. Ionotropic gelation is based on the ability of polyelectrolytes counter ions to cross link to form hydrogels. Naturally occurring polysaccharides such as chitosan which have relevant use as biopolymers has been increased in the novel area such as hydrogel sustained release formulation, thus providing an eco-friendly pharmaceutical product development process.

The dispersion ability of CS nanoparticles get enhanced by encapsulation of SPIONPs in aqueous solution, with all particles being lower than 130 nm in size and having high positive surface charge. The SPIONPs-CS nanoparticles exhibited super-paramagnetic properties at room temperature. These SPIONPs-CS nanoparticles can be applied as tissue-specific MRI contrast agents. This system has advantages over other MR agents in that preparation is simple, and can be undertaken under mild conditions. Furthermore, SPIONPs CS

nanoparticles showed low cytotoxicity against skin fibroblast cells at proper concentrations, and excellent stability for over prolonged periods. These SPIONPs-CS nanoparticles have the potential to be utilized as a MR contrast agents in tissue environments in the human body[69].

Grafting of fatty acids on chitosan:

The strong functionality of chitosan i.e. two hydroxyl groups and the one primary amine which can donate a free pair of electrons, make chitosan soluble in diluted aqueous acetic acid solvents and allow the formation of coordination bonds, offering a considerable opportunity of chemical modification. The modification of chitosan chains (hydrophilic in nature) with hydrophobic compounds such as carboxylic acids including fatty acids can results in the products with an amphiphilic nature. Such amphilic chitosan derivatives are able to self- assemble and form nano particles (micelles) under appropriate conditions.

Grafting of fatty acids such as, saturated stearic acid[70-73] and unsaturated lineoic acid[74-75] are two examples successfully grafted onto chitosan oligomers. With this purpose, the carboxylic acid of oleic acid was first converted into acid chloride by Zhang et al.[76]. Using a similar strategy, Jiang et al. grafted stearic, palmitic, or octanoic anhydride onto chitosan[77].

CdS Quantum dots chitosan Biocomposite:

Quantum dots (QDs) are the semiconductor nanoparticles in the size range of 2-6nm are being studied extensively. Their biological applications are not only because of their size dependent properties but also because of their dimensional similarities with biological macromolecules such as chitosan. Li et al. have synthesised derivatives of CdS Quantum dots with improved aqueous solubility and stability of chitosan.

The thermal decomposition of chitosan also gets influenced by these CdS Quantum dots. In the presence of these quantum dots thermal decomposition of chitosan was shifted to 50°C. An efficient procedure for the preparation of CdS QDs chitosan biocomposite is achieved by mixing chitosan with $Cd(Ac)_2$ and subsequently dissolving in one percent HAc aquous solution followed by treatment with CdS and thus smooth, flat, yellow CdS QDs chitosan composite films were obtained[78]. A novel bio functionalized CdS quantum dots conjugates were synthesized in aqueous media using chitosan and N-acylated chitosan as ligands via a single-step colloidal process[79].

ZnO-Chitosan Composites:

Existing commercial sorbents including, activated carbon, zeolites, activated alumina, and silica gels play important roles in adsorptive separation and purification. Recently Shafiq, et al. synthesised the chitosan composites containing different concentrations of ZnO using sol-cast transformation method. Chemical interactions between the chitosan and ZnO in the composites that became more evident at higher concentrations of filler. The composites exhibited significantly lower degradation rate and higher thermal stability than that of chitosan. These composites exhibited biocidal activity to gram positive and gram negative bacteria[80].

N-benzyl derivatives of Chitosan:

Chelatant amino polymers like chitosan have a low efficiency in metal uptake in the acidic pH range (due to the protonation of the amino groups). More-over, the amino polymers, like chitosan, are soluble in acidic media and therefore cannot be used as sorbents in these conditions. However, their activity is as the strong cation exchanger can be improved by derivatizing chitosan with N-benzyl sulfonate for the removal of metal ions as sorbents in acidic medium.

These sulfonated derivatives leads to the adsorption of heavy metals(Cd^{2+}, Zn^{2+}, Ni^{2+}, Pb^{2+}, Cu^{2+}, Fe^{3+}, and $Cr^{3+)}$. Chitosan was reacted with 2-formylbenzene sodium sulfonate and 4- formyl benzene sodium disulfonate in the presence of sodium cyano borohydride to yield N-benzyl derivatives[81].

Weltrowski et al. reacted Chitosan with 8-formyl benzene sodium sulfonate and 4-formyl-1,3-benzene sodium disulfonate in the presence of $NaCNBH_3$ to yield N-benzyl mono- and disulfonate derivatives of chitosan. The disulfonate compounds

showed better sorption capacities than for monosulfonate compounds. This phenomenon is attributed to the amphoteric character of the monosulfonate derivatives. The sorption capacity of monosulphonated compounds were improved by protecting the amino group by benzyl oxycarbonyl.

The protection of amino group of disulphonated derivative by the same group (benzyl oxycarbonyl) also improves its efficiency for heavy metal sorption. The synthesized sulfonate derivatives of chitosan are especially adapted to the sorption of heavy metals from the acidic industrial effluents[82].

Aromatic aldehydes were reacted with Chitosan by reductive amination involving formation of the corresponding imines, followed by reduction with sodium borohydride to produce the N-(benzyl) chitosan derivatives. Rabea et al. evaluated the antibacterial activity in vitro against the crown gall disease Agrobacterium tumefaciens and the soft mold disease Erwiniacarotovora by the nutrient agar dilution method.

They also obtained a higher activity of chitosan and its derivatives with N-(o-ethylbenzyl) chitosan with a MIC of 500 mg/L against E. carotovora, while N-(o,p-diethoxybenzyl) chitosan was the most active one against A. tumefaciens. Most of these derivatives exhibited high inhibition percentage (>90%) of spore germination[83].

Quercetin - Loaded Lecithin / Chitosan Nanoparticles:

Quercetin has been successfully encapsulated in lecithin/chitosan nanoparticles using the self-assembly technique by Marthyna P. Souza et al. (2014).

Their study showed that Quercetin-Nanoparticle is stable to temperature of 5 to 70 °C and pH variations in values ranging between 3.3 and 5.0. NP's stored at 4°C showed resistance to aggregation for 90 days and stability to retention of quercetin concentration for 40 days. Quercetin-Np can be used as an ingredient of functional foods or as an alternative in the defence against free radicals damaging foods in hydrophilic environments. The features presented by these types of nanoparticles make them attractive not only for the food industry, but can also be useful for cosmetic and pharmaceutical industries[84].

Chitosan/CNT nanobiocomposite:

Chitosan biopolymers have a great potential in biomedical applications, due to their biocompatibility and biodegradability. However, the low physical properties of chitosan limit its applications. The development of high performance chitosan biopolymers involves the incorporation of fillers that display significant mechanical reinforcement[85]. Polymer nanocomposite has been reinforced by nano-sized particles with a high surface area to volume ratio, including nanoparticles, nanoplatelets, nanofibers and carbon nanotubes.

Nowadays, carbon nanotubes are considered as potential fillers, as they improve the properties of biopolymers[86]. To optimize the use of CNT for biological applications it is necessary to functionalise CNT with biomaterials such as bio-molecules or biopolymers. Based on such reports, the researchers assessed the effect of CNT fillers in the chitosan matrix, and evidenced the appropriate properties of CNT/chitosan nano-biocomposite with a high potential for biomedical applications[87].

Acid functionalized single walled carbon nanotubes were covalently grafted to chitosan by first reacting with oxidized carbon nanotubes with thionyl chloride to form acyl-chlorinated carbon nanotubes which are subsequently dispersed in chitosan and covalently grated to form composite material, CNT–chitosan. The incorporation of CNTs in chitosan has been shown to improve the thermal properties of the CNT–chitosan[88]. Azeez et al. (2013) have prepared cryomilled multiwall carbon nanotube (MWCNT) reinforced chitosan nanocomposites having improved conductivity by solution casting method.

The cryomilled CNTs were chemically oxidized by both acidic and basic methods, where basic oxidation lead to the generation of high graphitic structure. The conductivity of the nanocomposites was improved by cryomilling and it was further improved by chemical oxidation. Base oxidized cryomilled CNT/chitosan nanocomposite showed large improvement in conductivity compared to all

other nanocomposite having 1 wt. % CNT content. Thermal stability and tensile properties of the CNT/chitosan nanocomposite also have been improved significantly by the incorporation of acid and base oxidized cryomilled CNTs[89].

Multi-walled carbon nanotubes (MWCNTs) were used as doping material by Carolin Lau et al. for three-dimensional chitosan scaffolds to develop a highly conducting, porous, and biocompatible composite material. When MWCNTs were used as a filler to introduce conductive pathways throughout the chitosan skeleton, the solubilizing hydrophilic and hydrophobic properties of chitosan established stable polymer/MWCNT solutions that yielded a homogeneous distribution of nanotubes throughout the final composite matrix[90].

Chitosan-Metal Bio composites:

Chitosan composites are the novel material that exhibits good sorption behaviour toward various toxic pollutants in aqueous solution. These composites have a speedy adsorption rate and soaring efficiency to remove various pollutants and are easy to recover and reuse. These features highlight the suitability of composites for the treatment of water polluted with metal and organic materials.Since ancient times, metallic elements such as gold and silver have been used extensively as fillers for synthetic or natural matrix[91].

Magnetic Chitosan Composites (MCCs) are among these series to do perform such innovative job together with the antimicrobial and antibacterial activities. Researchers have developed a biosensor based on the gold nano particles (Au)–Cs sol–gel composites to detect various types of a specific electrode. The Au provided a conductive pathway for electron transfer and improved electrochemical reactions at a lower potential[92-93].

At the same time, Au permits direct electron transfer between immobilized enzyme and targeted electrode and allowed electrochemical sensing to be performed without the need for electron transfer mediation[94]. The advantage of Ag/Cs composites over Au/Cs composite is the antibiotic or antimicrobial properties of Ag particles[95-96]. Ag has been reported to induce generation of intracellular reactive oxygen species in bacterial cells[97]. The Ag ion enters the bacterial cells, makes pores on the cell walls, releasing the cytoplasmic content to the medium and consequently, leads to cell death without affecting the intracellular and extracellular proteins and nucleic acids of the bacteria[98-100].

Corn Cob Filled Chitosan Biocomposite Films:

The researchers are much interested in the utilization of agricultural wastes such as corn cob[123], palm kennel shell[124], coconut shell[125-126] and chitosan[127] to produce biocomposites that reduces cost as well as enhance the properties and biodegradability of biocomposites. Corn (Zeya mays) is a biomass resource that is cultivated around the world which during its processing yields corn cob, natural filler in polymer can give rise to economic advantages.

Yeng and his co-workers in 2013 synthesised a chitosan biocomposite film by using corn cob as filler. The incorporation of corn cob in chitosan biocomposite films was found with improved the modulus of elasticity, but tensile strength and elongation at break decreased. Its treatment with acetic acid enhanced the mechanical properties of biocomposite this films. The treated Chitosan-Corn Cob biocomposite films have higher tensile strength and elongation at break compared to untreated. The treated biocomposite films exhibited better thermal stability than untreated biocomposite films[101].

Bentonite/Chitosan Beads:

Bentonite is a common group of clay minerals, which is a hydrous aluminium silicate, and it has been reported as an economical material for adsorption of fluoride from water. Chitosan has been cited as an excellent material for defluoridation from water. However, raw chitosan used in the form of flakes or powder is unstable and the adsorption capacity reported is minimum, thus, it is necessary to modify chitosan physically or chemically in order to improve its practical uses.

Recently Zhang et al. has synthesized a new adsorbent namely bentonite/chitosan beads for its defluoridation efficiency. Bentonite was activated and the beads were prepared by using the inverse suspension polymerization method. The adsorption of fluoride onto the adsorbent followed Freundlich

isotherm model and pseudo-second order kinetic model. The fluoride loaded adsorbent could be regenerated using sodium hydroxide. Bentonite/chitosan beads are of low-cost, effective and reusable adsorbent for adsorption of fluoride[102].

Plasticized chitosan with hierarchical structure:

Chitosan shows a degradation temperature lower than its melting point, which prevents its development in several applications. One way to overcome this issue is the plasticization of the polysaccharides. Different plasticizers such glycerol, sorbitol, sucrose and polyethylene glycol were tested with chitosan as the plasticizing agent. Plasticized chitosan with hierarchical structure, including multiple length scale structural units, was prepared by a "melt"-based method, that is, thermo-mechanical mixing, as opposed to the usual casting-evaporation procedure.

Chitosan was successfully plasticized by thermo-mechanical mixing in the presence of concentrated lactic acid and glycerol using a batch mixer. Concentrated lactic acid was used as protonation agent as well as plasticizer. The thermo-mechanically plasticized chitosan obtained was actually a composite material in which the amorphous phase was reinforced by nanofibrils, nanofibril clusters, and microfibers.

With an increase in plasticizer content the crystallinity of the plasticized chitosan decreased from 63.7% for the original chitosan powder to 43.0% and then further to almost a completely amorphous phase for the sample plasticized with extra water. Thermo-mechanical plasticization can be a promising way to plasticize chitosan on an industrial scale[103]. These materials may also be promising for tissue engineering applications to elaborate 2D or 3D scaffolds, considering the antibacterial activity of chitosan.

Chitosan based hydrogels:

Hydrogel (also called aquagel) is a network of polymer chains that are hydrophilic, sometimes found as a colloidal gel in which water is the dispersion medium. Hydrogels are highly absorbent (they can contain over 99.9% water) natural or synthetic polymers. Hydrogels also possess a degree of flexibility very similar to natural tissue, due to their significant water content.

Hydrogels based on covalently cross-linked chitosan can be divided into three types with respect to their structure: chitosan cross-linked with itself (**Fig. 7a**), hybrid polymer networks (HPN) (**Fig. 7b**) and semi- or full-interpenetrating polymer networks (IPN) (**Fig. 7c**). The simplest structure presented here is chitosan cross-linked with it. As represented in (**Fig. 7a)**, crosslinking involves two structural units that may or may not belong to the same chitosan polymeric chain[104].

The final structure of such a hydrogel could be considered as a cross-linked gel network dissolved in a second entangled network formed by chitosan chains of restricted mobility[105]. In hydrogels formed by a HPN, the crosslinking reaction occurs between a structural unit of a chitosan chain and a structural unit of a polymeric chain of another type (**Fig. 7b**), even if crosslinking of two structural units of the same type and/or belonging to the same polymeric chain cannot be excluded.

Finally, semi- or full- IPNs contain a non-reacting polymer added to the chitosan solution before crosslinking. This leads to the formation of a cross-linked chitosan network in which the non-reacting polymer is entrapped (semi-IPN). It is also possible to further crosslink this additional polymer in order to have two entangled cross-linked networks forming a full-IPN, whose microstructure and properties can be quite different from its corresponding semi-IPN[106].

Semi and full interpenetrating polymer network (IPN) type hydrogels were prepared by free radical in situ polymerization of methacrylic acid in presence of chitosan using N, N methylene-bis-acrylamide (MBA) and glutaraldehyde (for full IPN) as cross-linker. Several semi and full IPN type hydrogels were prepared by varying initiator and cross-linker concentration and also monomer to chitosan mass ratio.

These hydrogels were characterized and used for removal of methyl violet and congo red dye from water. Isotherms and kinetics of dye adsorption were also evaluated JayabrataMaity, et al.[107].

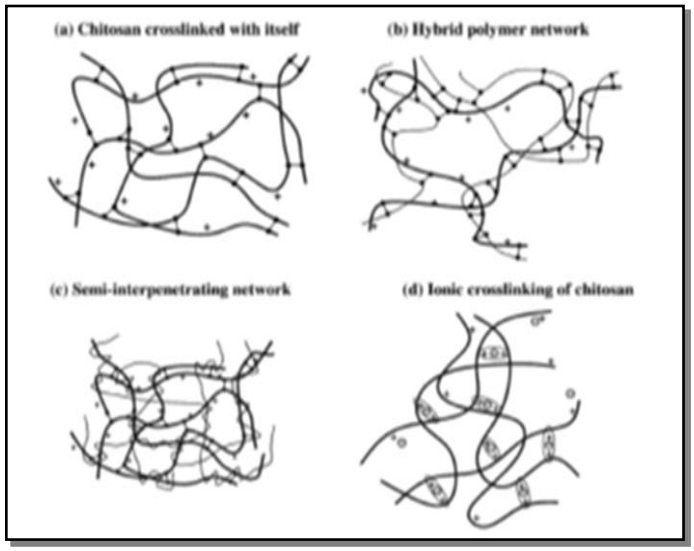

FIG.7. STRUCTURE OF CHITOSAN HYDROGELS FORMED BY (a) CHITOSAN CROSS-LINKED WITH IT SELF; (b) HYBRID POLYMER NETWORK; (c) SEMI-INTERPENETRATING NETWORK; (d) IONIC CROSSLINKING

Recently Abdel kaderDilmi and et al. prepared a hydrogel which consists of hydroxy ethyl methacrylate and chitosan, and investigated its swelling kinetics and ibuprofen release. In their work, it was found that swelling capacity decreased when the chitosan concentration was increased, most probably because of changes in the hydrogel porosity. This, in turn, caused an increase in the cross-linking density and the hydrophobicity of chitosan, thus reducing the hydrophilicity of the hydrogel. Furthermore, the swelling process followed second-order kinetics, while ibuprofen diffusion into the hydrogel showed Fickian behaviour in their study[108].

The novel hydrogels (termed HCD hydrogels) were synthesized based on human-like collagen (HLC) and chitosan (CS) cross-linked with dialdehyde starch (DAS). The biological stability and biocompatibility of HCD hydrogels were determined through in vitro and in vivo tests. The mechanism of hydrogel formation showed that covalent bonds formed via acetalization and Schiff base reactions.

HCD hydrogels afford both enhanced biological stability and excellent biocompatibility, making them potentially promising for skin patch scaffolds, wrinkle treatments, and tissue cavity fillers[109]. A standard technique was used by Sowmya Ramesh, et al. which involves the cross-linking of chitosan and hyaluronic acid at 2:1 (w/w). In this modified technique, cells were initially added to 33 % of hyaluronic acid dialdehyde and the gelation process was completed with the remaining 67 %. This minimised the cell loss and improved the encapsulation of the cells.

After 20 days, the modified technique showed better seeding density, with matrix synthesis (per scaffold) of 11µg as compared to 1.1µg in the current technique. The modified technique was superior for matrix synthesis and maintenance of phenotype[110]. Another approach to improve the properties of chitosan hydrogels is via the preparation of chitosan composites. Porous hydrogels of N-carboxymethyl chitosan/polyvinyl alcohol were prepared by Lee et al.[111]. Hydroxy-propyl chitosan was combined with sodium alginate for the formation of biodegradable hydrogels[112-113].

Wrapping applications for food stuffs:

Increasing consumer demand for microbiologically safer foods, greater convenience, smaller packages, and longer product shelf life is forcing the industry to develop new food-processing, cooking, handling, and packaging strategies.

During the last few decades, there is an increase in interest to develop and use bio-polymer based active or edible films for food packaging applications which are not only of natural origin but can also enhance food safety, quality during storage i.e. length of time it is stored and be pretty helpful to reduce the use of chemical preservatives, where the packaging material is a means of providing the correct environmental conditions for food during and/or distributed to the consumer.

A good package has to perform the following functions like it must keep the product clean and provide a barrier against dirt and other contaminants. It should prevent losses. Its design should provide protection and convenience in handling, during transport, distribution and marketing. In particular, the size, shape and weight of the packages must be considered. It should also provide protection to the food against physical and chemical damage (e.g. water and water vapour, oxidation, light) and insects and rodents. It must

provide identification and instruction so that the food is used correctly and have sales appeal.

The increased attention for chitosan applications in the food industry is being readily considered due to its several distinctive biological activities and functional properties. As chitosan belongs to very interesting family of β-(1-4) linked polysaccharides; this kind of glycosidic linkage leads to relatively extended and rigid structures in the solid, particularly in the dry state and as a consequence, this biopolymer similar to cellulose possess a good film forming capability[114].

The positively charged groups on chitosan interact with opposite charged groups of the solvent yielding three-dimensional networks[115]. The chemical structure of CS has been exploited for its innovative features in biotechnology and medicinal field. The presence of free amino group within molecule makes it highly interesting for immobilization of bioactive substances. This is where the modification of Chitosan in the form of its derivatives become highly attractive for assorted applications.

Chitosan can be used against a broad spectrum of target organisms like bacteria, fungi, viruses or algae. Microbial growth on the surface of food is a major cause of food spoilage and food-borne illness. Chitosan possesses unique properties that make it an ideal ingredient for development of antimicrobial edible film.

Antimicrobial character of chitosan is due to its positively charged amino group which interacts with negatively charged microbial cell membrane leads to the leakage of proteinaceous and other intracellular constituents of the microorganisms making it an extraordinary material for food packaging substance. Chitosan and its derivatives have significant potential in the food industry in view of contaminations associated with food products and the increasing concerns in relation with the negative environmental impact of conventional packaging materials such as plastics.

The biopolymer-based edible films for food packaging are generally characterized by several parameters, including mechanical properties (elongation, tensile strength and breaking force), thickness, water vapour and oxygen permeability, as well as moisture content and colour evaluations. Chitosan films are tough, long-lasting, flexible and very difficult to tear. They also possess moderate water vapour permeability values and could be used to increase the storage life of fresh foodstuffs with higher water activity values[116-117] and also exhibit an excellent barrier to oxygen permeation[118]. Chitosan also offers real potential for applications in the food industry due to its particular properties like physico-chemical, biodegradability and its biocompatibility with the human tissues, antifungal and antimicrobial activities. Due to these properties, chitosan and its derivatives based films have attracted more attention in food preservation and food packaging technology[119].

Chitosan shows particular interest over synthetic polymers, because it is Generally Recognized as Safe (GRAS) by Food and Drug Administration (FDA). This is mainly due to high antimicrobial activity of chitosan against pathogenic and spoilage micro-organisms, including fungi and both Gram-positive and Gram-negative bacteria[120]. Designing and manufacturing of packaging materials (**Fig.8**) is a multistep process and involves careful and numerous considerations to successfully engineer the final package with all the required properties.

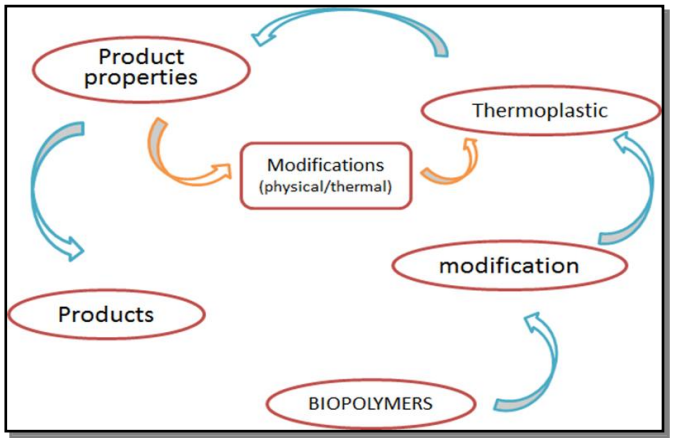

FIG.8. A MULTISTEP APPROACH REQUIRE FOR DESIGNING AND MANUFACTURING OF BIO BASED PACKAGES AND PACKAGING MATERIALS.

The properties need to be considered in relation to food distribution are manifold and may include gas and water vapour permeability, mechanical properties, sealing capability, thermoforming properties, resistance (towards water, grease, acid, UV light, etc.), machinability (on the packaging

line), transparency, anti-fogging capacity, printability, availability and, of course, costs.[121]

Abundant researches have clearly demonstrated that chitosan can be used as an effective preservative or coating material for improvement of quality and shelf life of various foods. Chitosan had been approved as a food additive in Korea and Japan since 1995 and 1983, respectively. In the United States, upon receiving the US FDA approval for GRAS status, chitosan as a food additive and its applications in food systems will certainly be in more demand in the near future, however much research is still needed to evaluate feasibility of using various chitosan and its oligomers products prepared from simplified production processes for specific food usage.

TABLE. 2 FOOD APPLICATIONS OF CHITOSAN AND THEIR DERIVATIVES IN FOOD INDUSTRY[117].

Area of application	Examples
antimicrobial agent	Bactericidal
	Fungicidal
	Measure of mould contamination in agricultural
	Commodities
Edible film industry	Controlled moisture transfer between food and surrounding environment
	Controlled release of antimicrobial substances
	Controlled release of antioxidants
	Controlled release of nutrients, flavours and drugs
	Reduction of oxygen partial pressure
	Controlled rate of respiration
	Temperature control
	Controlled enzymatic browning in fruits
	Reverse osmosis membranes
Additive	Clarification and deacidification of fruits and beverages
	Natural flavour extender
	Texture controlling agent
	Emulsifying agent
	Food mimetic
	Thickening and stabilizing agent
	Colour stabilization
Nutritional quality	Dietary fibre
	Hypocholesterolemic effect
	Livestock and fish feed additive
	Reduction of lipid absorption
	Production of single cell protein
	Antigastritis agent
	Infant feed ingredient
Recovery of solid materials from food processing wastes	Affinity flocculation
	Fractionation of agar

CONCLUSION: Chitosan and its derivatives exhibit a variety of physicochemical and biological properties resulting in numerous worldwide applications in areas ranging from pharmaceutical, biomedical, dentistry, food industry, waste water treatment, agrochemical, environmental and industrial uses.

Their derivatization is contributed towards the expansion of its applications also decreasing toxicity. Because of its antimicrobial properties, chitosan is especially a promising material for food packaging. Antimicrobial activity of chitosan is related to its cationic nature, and has been successfully explored to extend shelf life of a variety of foods. Chitosan has three reactive functional groups, the amino (C-2) group and the primary (C-6) and the secondary (C-3) hydroxyl groups on each monomeric unit on each deacetylated unit.

These reactive functional groups are readily subject to chemical modifications to change its physico-mechanical properties. The incorporation of other natural antimicrobials or antioxidative agents in chitosan films can also improve its antimicrobial activities due to which the shelf life of food can be increased. Natural plant extracts could act as both an antimicrobial agent and as an odour/flavour enhancer. As the conventional food packaging leads to serious environmental issues due to their non-degradability; improperly disposed plastic material is a significant source of environmental pollution.

Though there are many papers focused on chitosan and its derivatives, there are still extensive reviewing studies of recent advancements in the chitosan based derivatives needed to be compiled. Examination of better ways to incorporate these derivate products into Everyday Life Management strategies remains to be pursued.

Interesting theoretical and applied findings are assembled in recent years, whereas more are needed to examine the mechanisms governing the mode of action of these derivatives when applied at large scales. In the case of antimicrobial mode of action to work as the food covering material or packaging material, future work should aim at clarifying the molecular details of the underlying mechanisms and their relevance to the

antimicrobial activity of chitosan. Moreover, further investigations in this area, in particular with regard to microorganism resistance mechanisms against this compound, are reasonable justified and moreover warranted. It is clear that the future will bring a lot of new developments in the area with special focus on the use of biopolymer as matrices in the development of natural and biologically derived antimicrobial agents for increasing efficiency and specificity in food industry.

As one looks to the future, chitosan based derivatives used in food packaging are likely to evolve considerably. Further our current understanding of fundamental properties of chitosan may enable future advances in antimicrobial food packaging.

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