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CHITIN, CHITOSAN AND THEIR PHARMACOLOGICAL ACTIVITIES: A REVIEW

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ABSTRACT: Chitin is the second most important natural amino polysaccharide polymer after cellulose in the world. The main sources exploited are marine crustaceans, shrimp, and crab apart from that some other lobstera, insects, sulphur butter and fungi. Chitosan is the most important natural based common cationic polymer got from chitin has gotten developing consideration for the most part due to their bio-degradable, bio-compatible, bio-renewable and non-lethal properties. The deacetylated chitin derivative chitosan is a useful and interesting bioactive polymer; it has a large pharmaceutical application either. It has numerous reactive amino side groups, which offer possibilities of chemical modifications, formation of a large variety of beneficial derivatives. Chitosan has been found to be used as a support material for pharmaceutical application, gene delivery, cell culture, and tissue engineering. This review is based on the various pharmacological activity of chitosan such as wound healing, anti-hypertensive, anti-cancer, blood coagulant, anti-coagulant, anti-ulcer, anti-microbial, anti-viral, hypolipidemic and hypocholesterolemic *etc*.

INTRODUCTION: Chitin or poly (β-(1→4)-*N*-acetyl-D-glucosamine) is a natural polysaccharide of major importance. The name 'chitin' is derived from the Greek word 'chiton', meaning a coat of mail [1]. A french chemist Henri Braconnot firstly described the use of chitin in 1811 [2]. This bio-polymer is synthesized by living organisms and it is second most abundant natural polymers, after cellulose and categorized as a cellulose derivative, even it is not produced by the cellulose producing organismin [3]. Structurally it is similar to cellulose, but at the C2 position, it has an acetamide group ($NHCOCH_3$), which has a major role to change its properties and make it a versatile compound [4].

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Chitin, which occurs in nature as ordered macro-fibrils, is the major structural component which is present in the exoskeletons of the crustaceans, crabs and shrimps, as well as the cell walls of fungi. Crab shells and shrimp shells are mostly used for the commercial purpose [5]. Chitin synthase an enzyme which is found in nature catalyzed the biosynthesis of chitin. Industrially the extraction of chitin is done by acid treatment to dissolve the calcium carbonate followed by alkaline solution to dissolve proteins.

After that the additions of decolorizing agents to eliminate pigments thus obtain a colorless pure chitin, this step is called as a decolorization step [6]. The versatile properties of chitin such as, biocompatibility, biodegradablity, biorenewable, non-toxic, environmentally friendly and bio-functionality make it a promising candidate for further use, It is widely used in many applications such as chelating agent, water treatment additive, drug carrier, bio-degradable pressure-sensitive

adhesive tape, wound-healing agents, in membranes and has other advantages for numerous important applications. Because of these advantages, much attention is paid to this characteristic biomaterial [7].

However, now a day, chitin is not vastly employed by the pharmaceutical industry. Because of its weak solubility, it has limited applications. Chitin is insoluble in common organic solvents and diluted aqueous solvents because it is highly hydrophobic due to the highly expanded hydrogen-bonded semicrystalline structure of chitin [8].

Chitosan is a derivative of chitin. It is prepared by deacetylation and depolymerization of unadulterated chitin, based on infrared spectroscopy and X-beam diffraction information, local chitin can be found in of the three polymeric structures *α*-chitin, *β*-chitin, and, *Y*-chitin, contingent upon their source. In *α* -chitin molecules are orchestrated in an antiparallel mode while in *β*-chitin atoms are orchestrated in parallel mode, with solid intermolecular hydrogen bonding [9]. *α*-chitin is the most plenteous frame existing in crabs, lobsters, krill and shrimps shells, insects, contagious and yeast cells walls having a crystallinity higher than 80%. In, *β*-chitin present in squid pens and tubeworms. In *Y*-chitin molecules are orchestrated in both parallel and anti-parallel mode. *β*-chitin is more reactive and it is easily dissolved in some solvents due to the weak intermolecular interaction than the α-chitin.-chitin is different from *α*-family [10].

Chitosan is a spin-off of chitin found by Rouget in 1859 [11]. It is cationic natural amino basic poly-saccharide biopolymer made out of glucosamine and N-acetyl glucosamine. The primary favourable position of chitosan over chitin that it is promptly dissolvable in dil. CH_3COOH, while chitin gets broke down in lithium chloride and dimethyl-acetamide which are to a great degree toxic [12]. It is prepared by partial deacetylation and deploy-merization of chitin under basic conditions (conc. NaOH), or prepared in the existence of enzyme (chitin deacetylase).

Chitin and chitosan have numerous applications squander water treatment (evacuation of metal ions dyes, and as membranes in purification forms, sustenance industry (hostile to cholesterol and fat restricting [13] packaging material additive and nourishment added substance horticulture (seed and manure covering, controlled agrochemical [14] wound healing [15] as excipients for drug delivery and gene delivery. Chitin and chitosan are effectively handled into gels, membranes [16] nano fibers beads microparticles nanoparticles scaffolds and sponges [17].

Chitosan picked up interest of analysts as a result of its different properties as well as because of its extraordinary natural applications, for example, antimicrobial, hypocholesterolemic, anticancer, anti -inflammatory, antioxidant, angiotensin-I-converting enzyme (ACE) inhibition, barring poisons from the digestion tracts, diminishing overwhelming metal posoning in people, mucoadhesive haemostatic, pain relieving, radio-protective properties, averting tooth rot and tooth maladies and immunity improving activities [18].

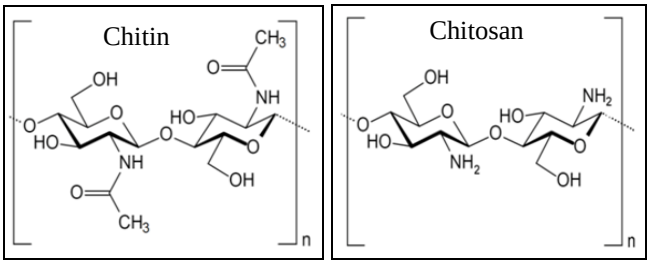

FIG. 1: CHEMICAL STRUCTURES

Chemical Properties of Chitosan:

- Linear polymine
- Reactive amino groups
- Reactive hydroxyl bunches accessible
- Chelates numerous transitional metal ions

Biological Properties of Chitosan: Following are the biological properties of chitosan:

- Biocompatible
- Natural polymer
- Biodegradable to typical body constituents
- Risk and non-poisonous.
- Binds to cells aggressively
- Regenerative impact on connective gum tissue.
- Accelerates the development of osteoblast in charge of bone development.
- Haemostatic
- Fungistatic
- Spermicidal
- Antitumor
- Anticholesteremic

- Speed up bone formation
- Central nervous system depressant
- Immunoadjuvant

Chitosan Contain Following Properties for Wound Healing:

- Bio adhesive
- Biodegradable
- Bacteriostatic activities
- Haemostatic action
- Biocompatibility
- Eventually will degrade into N-acetyl-b-D-glucosamine, which will eventually increase the level of hydroxyproline, hexosamine and total protein content
- It stimulates the migration of polymorpho nuclear and mononuclear cells
- Accelerates the reformation of connective tissue and angiogenesis.
- It arouses the level of natural hyalurouic acid synthesis at wound sites
- Accelerates wound re-epithelisation and rejuvenation of nerve within vascular dermis
- It also activates host defence to prevent infection
- It blocks nerve endings thus reducing pain
- Increases antioxidants and decreases MDA
- May have anti-inflammatory effect
- Soluble in aqueous medium
- Presence of multiple functional groups and non-toxicity
- Under acidic conditions, chitosan in its characteristic frame receives a positive charge which can pull in adversely charged plasma proteins which can prompt platelet attachment and enactment took after by thrombus formation and blood coagulation

Medicinal Uses of Chitosan's:

Wound Healant: Chitosan's properties enable it to quickly clump blood and have as of late picked up endorsement in the United States and Europe for use in bandages and other haemostatic agents [21]. Chitosan haemostatic items have been appeared in testing by the U.S. Marine Corps to rapidly stop bleeding, to diminish blood misfortune and result in 100% survival of generally deadly blood vessel wounds in swine [27, 28, 29]. Chitosan haemostatic items diminish blood misfortune in contrast with gauze dressings and increment patient survival. Chitosan haemostatic items have been sold to the U.S. Armed force and are as of now utilized by the U.K. military. Both the U.S. and U.K. have effectively utilized the bandages on the battlefields of Iraq and Afghanistan. Chitosan is anti-allergenic and has natural born antibacterial properties which additionally bolster its utilization in field gauzes. Chitosan's haemostatic properties additionally enable it to lessen torment by blocking nerve endings.

Chitosan salts produced using blending chitosan with an organic acids, (for example, succinic or lactic acid) [23]. The haemostatic agents works by an interaction between the cell film of erythrocytes (negative charge) and the protonated chitosan (positive charge) prompting contribution of platelets and fast thrombus formation [23]. The chitosan salts can be blended with different materials to make them more spongy, (for example, blending with alginate) or to change the rate of solvency and bioabsorbability of the chitosan salt [25]. The chitosan salts are biocompatible and bio-degradable making them valuable as absorbable haemostats.

The protonated chitosan is separated by lysozyme in the body to glucosamine and the conjugate base of the acid, (for example, lactate or succinate) is substances normally found in the body [24]. The chitosan salt may be placed on an absorbable backing. The absorbable sponsorship might be synthetic (for example produced using existing absorbable suture materials *e.g.* Tephaflex polymer) or normal (*e.g.* cellulose or gelled/ solidified honey) [25].

Notwithstanding salts, hydrogel-based chitosan bandages have been created to treat burn wounds. Burns are like other injuries, yet are tricky in light of the fact that they are associated with layer destabilization, vitality consumption, and hypoxia, all of which can cause serious tissue rot if not treated rapidly. Chitosan-gelation bandages using nanofibrin have been shown to be more durable than ointments, while still allowing gas exchange at the cell surface [26].

Blood Coagulating Agent / Hemostatic Agent: Chitosan when interacts with blood, the amino group of chitosan react with the acid group of the

blood cell and actuates the development of clots. The free amino groups of chitosan when react with the plasma protein it could cause thrombogenic/ hemolytic action.

Many author reported chitosn has thrombogenic action because it has the ability to activate both complement and blood coagulation systems. The biodegradability of chitin and chitosan was primarily attributed to their vulnerability to enzymatic hydrolysis by lysozyme, a non-specific proteolytic enzyme that exists in all human body tissues [30]. Lipase, an enzyme which exists in the salivation and in human gastric and pancreatic liquid can degrade chitosan. The products of the enzymatic degradation of chitosan were non-toxic. The mechanism of action of chitosan that it gets absorbed in the plasma protein followed by attachment and initiation of platelets that can prompt hemostatis and thrombosis [33, 34].

In a study researcher developed 2% chitosan scaffolds for wound healing. The *in-vivo* efficacy assessment was completed in Sprague dawley Rats. The chitosan scaffolds demonstrated 100% reduction in wound while standard medication betadine indicated 80% wound healing in rats and the examination revealed that 2% chitosans were found to have an incredible wound healing activity [31].

In another study researcher successfully developed a biodegradable sponge, made out of chitosan and sodium alginate. The sponge was exquisite and malleable [59]. The chemical structure and morphology of the sponge was portrayed by FTIR and SEM. The swelling capacity, *in-vitro* drug discharge, degradation behaviors' and an *in- vivo* animal test were utilized to affirm the applicability of this sponge as a wound dressing material [60].

As the chitosan content in the sponge diminished, the swelling ability diminished. All types of the sponges exhibited biodegradable properties [61]. A wide range of the sponges displayed bio-degradable properties. The arrival of curcumin from the sponges could be controlled by the cross linking degree. Curcumin could be discharged from the sponge in a stretched out period for up to 20 days. An *in-vivo* animal study utilizing SD rats demonstrated that sponge had better effect than cotton gauze, and including curcumin into the sponge improved the therapeutic healing effect [32, 35].

Antitumour Activity: Antitumour impact of chitosan demonstrated that the low molecular weight water-dissolvable chitosans and oligo chitosans such as n-succinyl chitosan, Carboxy methyl chitosan may be valuable in avoiding tumor development, somewhat through improving cytotoxic movement against tumors as an immuno-modulator [36]. Most anti-cancer chemotherapeutic agents have unsafe symptoms that are not great to drawing out the lives of malignancy patients [37]. In this manner, it is imperative to discover new hostile to growth specialists that are non-poisonous and biocompatible [38].

The antitumor mechanism of chitooligosaccharides was likely identified with their acceptance of lymphocyte factor, expanding White blood cell expansion to create the tumor inhibitory impacts [39]. Through examination of the splenic cell changes in cancerous mice, Suzuki *et al*., (1986) demonstrated that the antitumor component of chitooligo-saccharides is to improve acquired immunity by quickening Immune system (T-cell) separation to build cytotoxicity and keep up White blood cell movement [40].

N-Succinyl chitosan (NSCS) is notable as a medication transporter with low danger and a long flowing impact in the body [41]. As of late, n-succinyl chitosan turned into a principle part of micelles or nanoparticles utilized as conveyance frameworks in anticancer treatment. The anti-tumour impact of N-succinyl chitosan nanoparticles was explored on K562 cells [42]. The nanoparticles repressed the multiplication of K562 cells with an IC_{50} estimation of 14.26 g/ml. Cytomorphology concentrates, for example, transmission electron microscopy, fluorescence tests and DNA discontinuity examination uncovered attributes of apoptosis and putrefaction, showing that an antitumour impact was accomplished by both [43].

Paclitaxel a clinical water-insoluble anticancer tranquilize advancing microtubulin polymerization, is utilized against an assortment of malignancy sorts, particularly bosom and ovarian disease [44].

To upgrade its dissolvability, paclitaxel was accumulated with cyclodextrin, liposomes or diverse polymeric micelles that expanded the enhanced permeability and retention impact and

diminished the high poisonous quality of paclitaxel. Nanomicelles, framed from amphiphilically altered N-alkyl-O-glycol chitosan, having long alkyl chains as hydrophobic moieties and glycol gatherings as hydrophilic moieties, showed a low lethality and high biocompatibility. Paclitaxel was stacked into nanomicelles by means of a dialysis process. The upgraded level of alkyl chain substitution expanded the medication stacking limit, the medication stacking productivity and the long term soundness in watery arrangement [45].

Used as an Anticoagulant: Chitosan itself did not demonstrate any anticoagulant property but rather when auxiliary modicafication was done in the chitosan structure it indicated anticoagulant property. Some water solvent subordinates additionally act as an anticoagulant agent. Suphated subsidiary of chitosan showed dissolvability in water. Sulphated derivative have sulfate groups on one or both side, achieved by the substitution of hydroxyl gathering can be effortlessly broken up in water.

Described that chitosan when reacted with chloro-sulfonic acid in N, N-dimethylformamide under semi-heterogeneous conditions gave 87% of water-soluble sulfated chitosan with level of substitution both hydroxyl and amino groups revealed anticoagulant property. The position of sulfate substitution was at C-2, C-3 and C-6 position which was uncovered by 1H NMR. Sulphated derivative of chitosan gave 3 three parts with normal atomic weights of 7.1, 3.5 and 1.9×104 which revealed solid anticoagulant property same like heparin [46].

Anti-ulcer Effects and Repair of Arthritic Tissue: Chitosan is an alkaline polysaccharides having free amino groups which can neutralize the gastric acid thus make a protective layer in the stomach and could be effective in peptic ulcer [47]. The main mechanism of action to treat ulcer is the acid hydrolysis of chitosan, to glucosamine hydrochloride or its sulfate, phosphate and other salt preparation by salt conversion makes it promising agent in Ulcer [48]. Monosaccharides are also useful in the rheumatic arthritis and in bone hyperplasia [49]. Davyadova *et al*., described that *in-vitro* high molecular chitosan inhibit the anti-inflammatory cytokine the tumor necrosis factor alpha induced by endotoxin and in experimental animal by peroral high and low molecular chitosan increase the synthsis of anti-inflammatory cytokine, high molecular derivatives was to times faster than the low molecular and decrease the affected area inlarge intestine of inflammation while introducing by peroral and the action of chitosan and prednisolone, a hormone anti-inflammatory drug was similar [50]. Chitosan-alginate nano particles also indicated anti-inflammatory properties as they inhibited acnes-induced inflammatory cytokine synthesis in human monocytes and keratinocytes [51].

Hypolipidemic and Hypocholesterolemic Effect: Hyperlipidemia (HLP) is the primary hazard factor of cardiovascular infection (CVD) [52]. It was demonstrated that dietary fibers, for example, pectin, psyllium, and particularly chitosan, may play crucial roles in dropping down the plasma, liver triglycerol and cholesterol level [52, 53, 58, 60]. There are some proposed mechanisms for cholesterol reduction by chitosan. The viscous polysaccharide solution entrapment is believed to reduce the absorption of cholesterol and fat in the diet [55].

On the other hand, the amino gathering nearness in its structure decides the electrostatic force between chitosan and anion substances, *e.g*. unsaturated fats and bile acids. Interaction between the chitosan and anionic surface active materials (phospholipids, bile acids) mainly relies upon these three sorts of reactive functional groups: the amino gathering at C2 position and at essential and the optional hydroxyl bunches at C-3 and C-6 positions, respectively [61, 62]. Albeit extraordinary exertion has been made to discover a connection between's the physicochemical qualities of chitosan and its fat-restricting limit, just some noteworthy connections have been shown [57].

The hypolipidemic and hypocholesterolemic rate is also depend on degree of acetylation, molecular weight and particle size, the degree of deacetylation and the viscosity-average molecular weight of chitosan samples on their fat-binding, cholesterol and bile-salt-binding capacities *in-vitro* method. During the fat binding process, fat molecules are accumulated in the enormous chain of chitosan so long chain deposit more fat. The result also showed that chitosan and its oligosaccharides have greater affinity to bind with fat then the cellulose and it

increased with the increase of both degree of deacetylation and molecular weight [55, 56].

Antimicrobial Activity: The antimicrobial action of chitin, chitosan and their derivative against various groups of microorganisms, for example, microscopic organisms (gram negative, gram positive), yeast and parasites, are exceedingly susceptible and gotten impressive consideration in recent years. Specifically, water-solvent chitosan derivatives were assessed for their antimicrobial action [63, 65]. In particular, water-soluble chitosan derivatives were evaluated for their antimicrobial activity [64]. The derivative of chitin, chitosan play a major role to kill the bacteria, it is more promising than the native chitin because of the number of high polycationic amines which can interact the negatively charged residues of carbohydrates, lipids and proteins situated on the cell surface of bacteria, microscopic organisms, which therefore hinder the development of microorganisms [63, 65, 76].

Three main mechanisms have been recommended as the reason of the inhibition of microbial cells by chitosan. The first mechanism refers to the interaction between positively charge chitin/ chitosan molecule and adversely charged microbial cell surface. Due to the mediation of electrostatic force between protonated NH^{3+} groups and the negative residue, thus induce internal osmotic imbalances and consequently inhibit the growth of microorganisms [66]. Electrostatic power can cause the hydrolysis of the peptidoglycans in the microorganism wall which also provoke the spillage of intracellular electrolytes, for example, potassium ions and other low atomic weight proteinaceous constituents (*e.g.* proteins, nucleic acids, glucose and lactate dehydrogenase). Electron microscopy demonstrated that the site of action is the outer membrane of gram negative bacteria.

The second mechanism includes the binding of chitosan with DNA of microbes, which leads to the inhibition of the mRNA and protein synthesis by penetration into the cell nucleus [67, 68]. It is expected that chitosan able to penetrate the bacterial cell wall, composed of multilayers of cross-linked murein and reach the plasma membrane and then inhibit the protein synthesis. It is expected that chitosan ready to penetrate the bacterial cell divider, made out of multilayers of cross-linked murein and achieve the plasma layer and afterward restrain the protein synthesis. The third mechanism is the chelation mechanism in which chitosan may hinder microbial development by going about as a chelating agent rendering metals, basic supplements which adjust the normal rate of growth of organism.

Chitosan is additionally ready to interface with flocculate proteins, yet this activity is exceptionally pH-dependent. Bacteria which is susceptible by chitosan [69 - 75]. It is expressed that amine gathering of chitosan is capable to intake the cation of metal by chelation for such component a high pH is required where positive particles are limited to chitosan, since the amine bunches are unprotonated and the electron combine on the amine nitrogen is accessible for donation to metal particles gram-positive microorganisms (*e.g. L. monocytogenes, Bacillus megaterium, B. cereus, S. aureus, L. brevis, L. bulgaris, etc.*) than for gram-negative bacteria (*e.g. E. coli, Pseudomonas fluorescens, Salmonella typhymurium, Vibrio parahaemolyticus, etc.*) [77 - 79].

Anti-viral Activity of Chitosan: Chitosan can be used in the eye infection. Researchers have made chitosan microspheres with the antiviral drug acyclovir. Acyclovir which is an anti-viral drug which is used topically in eye infection showed a poor bioavailability [80].

Researcher found that chitosan can enhance the antiviral activity of acyclovir hence useful in ophthalmic preparations. Acyclovir incorporated chitosan microsphere were prepared by ionic gelation of chitosan with triphosphate anions and were characterized by DSC, FTIR, particle size, zeta potential and surface morphology.

Outcomes were quite fantastic the size of the particles were (2 to12 μm) and displayed spherical smooth morphology with Zeta potential (+36.1 to +43.6 mV). The encapsulation efficiency and loading capacity were 52% - 78% and 12% - 26% respectively [81]. Kinetic release profiles of acyclovir from microspheres seemed to fit best with Higuchi model with first order and the non- Fickian diffusion was superior phenomenon.

Thus the outcomes recommended that acyclovir loaded chitosan micro particle suspension seemed promising for effective management of opthalmic

viral infections. Enzymatic and chemical hydrolysis of chitosan with various degree of acetylation (25, 17 and 1.5%) was done. Purification and fractioning of the hydrolysis products were performed using dialysis, ultrafiltration and gel-penetrating chromatography the low molecular polysaccharides were produced and the molecular masses were 17 to 2 kDa of the obtained poly-saccharides [82]. Antiviral activity of these samples were seen against the tobacco mosaic virus (TMV) and found that these samples inhibited the formation of local necroses induced by the virus for 50 - 90%. The antiviral activity depend on the degree of polymerization, lower the degree of polymerization greater the activity of low level chitosan activity as an antiviral drug. Furthermore chemically hydrolysis chitosan found less effective than the enzymatically hydrolysis chitosan. It was revealed that the antiviral activity was depending on the degree of acetylation [83].

Anti-Hypertensive Activity: Impact of chitosan oligosaccharides on the ACE (angiotensin I converting enzyme restraint and antihypertension in SHR (Spontaneously hypertensive rodent) was inspected. The ACE inhibition activity was seen in all the chitosan oligosaccharides utilized as a part of this examination and chitosan trimer showed the most astounding inhibitory action contrasted in comparison to other chitosan oligosaccharides [84]. The outcomes recommended that chitosan trimer was a decent inhibitor of ACE in sub-atomic level. At the point when the single oral dosage (2.14 mg/kg, like measurements level of Captopril, known as solid ACE inhibitor) of chitosan trimer was given to 8 or 21 week matured SHR, the circulatory strain diminishment of both SHRs in 4 h was, separately.

In this way, it was proposed that chitosan trimer could be applicable natural material having properties to work as an ACE inhibitor identified with antihypertension. ACE I inhibitory activity of hetero-chitooligosaccharides (heteroCOSs) prepared from partially different deacetylated chitosans was investigated [85]. Partially deacetylated chitosans, 90, 75 and 50% deacetylated chitosan, were set up from crab chitin by N-deacetylation with 40% sodium hydroxide. Moreover, nine sorts of hetero-Chitosans with generally high atomic masses (5000-10 000 Da; 90-HMW chitosans, 75-HMW chitosans, and 50-HMW chitosans), medium sub-atomic masses (1000-5000 Da; 90-MMW chitosans, 75-MMW chitosans, and 50-MMW chitosans) and low sub-atomic masses (beneath 1000 Da; 90-LMW chitosans, 75-LMW chitosans and 50-LMW chitosans) were readied utilizing a ultrafiltration film bioreactor framework [86]. ACE inhibitor activity of heterochitosans was dependent on the degree of deacetylation of chitosans. 50-MMW chitosans that are chitosans hydrolyzed from 50% deacetylated chitosan, the generally most reduced level of deacetylation, showed the highest ACE inhibitor activity and the IC_{50} value was 1.22 (0.13 mg/mL). Also, the ACE inhibition pattern of the 50-MMW chitosans was researched by Line weaver -Burk plots, and the inhibition pattern was observed to be competitive [87].

CONCLUSION: This review concluded that chitosan has lots of medicinal properties and can play an important role in the pharmaceutical field. There are many activities have been reported of chitosan but still many works possible because of its versatile properties and tremendous resources. As one of the richest polysaccharide in nature, chitosan has created a lot of enthusiasm for its attractive biomaterial properties and wide applications. In the utilization of chitosan materials, hydro gel is a major and vital branch. In this review we have studied useful contribution of chitosan in pharmaceutical field such as an anti-cancer, anti-viral, anti-hypertensive, hypo-lipidemic, antimicrobial, *etc*.

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