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FUNCTIONALIZATION OF POLYSACCHARIDES-VERSATILE STRATEGIES AND THEIR APPLICATIONS

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ABSTRACT: Polysaccharides are composed of monosaccharide's linked by glycosidic bonds. These are abundantly available and are obtained from renewable resources. Polysaccharides provide an array of primary structures and conformations used in the pharmaceutical industry. Natural polysaccharides properties can be substantially modulated by chemical, physical, and enzymatic modifications and have received increased attention to expanding the landscape of application of polysaccharides in diverse sectors. Modifying the natural polysaccharides properties and structures gives functionally improved polysaccharides with excellent bioavailability, biocompatibility, structural stability, and versatile chemical. By modifying the physicochemical properties of polysaccharides, systems like micelles, hydrogels, liposomes, niosomes and vesicles are produced. The modified polysaccharides have a remarkable application in gene delivery, targeted cancer therapy, delivery of the drug, wound dressings, tissue engineering, nanocarriers, biosensors, pharmaceutical formulations, agricultural applications, and food industry. This article covers different types of polysaccharides and distinct methodologies applied during the new modified synthesis of polysaccharides and also the study of their properties after modification. This review also highlights the application of these modified polysaccharides in various pharmaceutical, biomedical and allied fields.

INTRODUCTION: Polysaccharides are ideal resources obtained naturally used in supplements and pharmaceuticals, which received increasing consideration in the last many years. These polysaccharides have essential in pharmaceutical sciences. Due to this, there is a growing interest in their synthesis, modification, characterization, and application [1].

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Natural polysaccharides are reported to possess fewer side effects; however, due to their inherent physicochemical properties, their bioactivities are difficult to equate with synthetic drugs. Hence, the structures and properties of these polysaccharides have been modified to obtain functionally improved polysaccharides.

The properties of natural polysaccharides are improved via chemical, physical and enzymatic modification. Such advances in modifications provide polymer variability, help to optimize its utilization in product application, and produce new product applications. These modified polysaccharides are widely used in gene therapy,

drug delivery, biosensors, nanocarriers, agricultural application, and food sector applications. **Table 1** indicates the major polysaccharides used in several industries.

TABLE 1: POLYSACCHARIDES USED IN DIVERSE SECTORS

Polysaccharides	Structure	Applications
Cellulose		Drug delivery system in the pharmaceutical industry in food industry in paper and textile industry as excipient in pharmaceuticals
Dextran		Cryoprotectant viscosity enhancer hydrogels
Carrageenan		Stabilizing and suspending agents in food products in the paint industry
Alginates		Welding rods textile and printing industry fertilizer and chemical industry wound dressing
Chitosan		Biomedical industry bioadhesive tissue engineering gene delivery drug carrier
Hyaluronic Acid		Cosmetic industry surgery and wound healing dermatology ophthalmic delivery
Starch		Controlled release formulations biofuel paper and textile industry excipient in the pharmaceutical industry
Pectin		Biomedical field wastewater treatment food and dairy industry wound healing

Modifications of polysaccharides are explored to enhance drug solubility, physicochemical properties of polysaccharides, and their stability. Synthetic polymers show toxicity and immunogenicity problems; hence natural polysaccharides are explored as substitutes for synthetic polymers in developing new drug-delivery systems. Polysaccharides have the ability for targeted delivery and controlled release that improves the therapeutic index of drugs. The application of polysaccharide derivatives to increase mucoadhesion and active targeting the drug to the action site was reported for various carrier systems- nano and microparticulate systems, hollow particles, coated liposomes, and polymer-drug conjugates. Various biomedical applications of functionalized polysaccharides include tissue engineering, regenerative medicine, and cancer theranostics. Modified polysaccharides are used for diagnosis as biosensors. A biosensor is a self-sufficient unified device that helps detect different analytes like fungi, bacteria, pollutants, food, and drug additives. These are used not only for biomedical purposes but also for identifying biomarkers in biomedical screening. They assimilate functionalized proteins, organelles, or whole living cells additionally nucleic acids. These cells are fixed on a physicochemical transducer surface alongside its corresponding binding partner, which can translate specific interactions of immobilized bio entities into measurable and relative electrical signals [2].

1. Functionalization Strategies of Poly-saccharides / Major Method for Modification of Polysaccharides: Molecular modification involves native structural modification through biological, physical and chemical that produces many types structural derivatives. Molecular modification usually modifies polysaccharide's molecular weight, structural dimensions, and the substituent group types, numbers, and positions that improve bioactivities such as antitumor, anticoagulant, antioxidant, and theranostics. **Fig. 1** indicates the major chemical, physical and biological methods used to modify native polysaccharides for diverse applications.

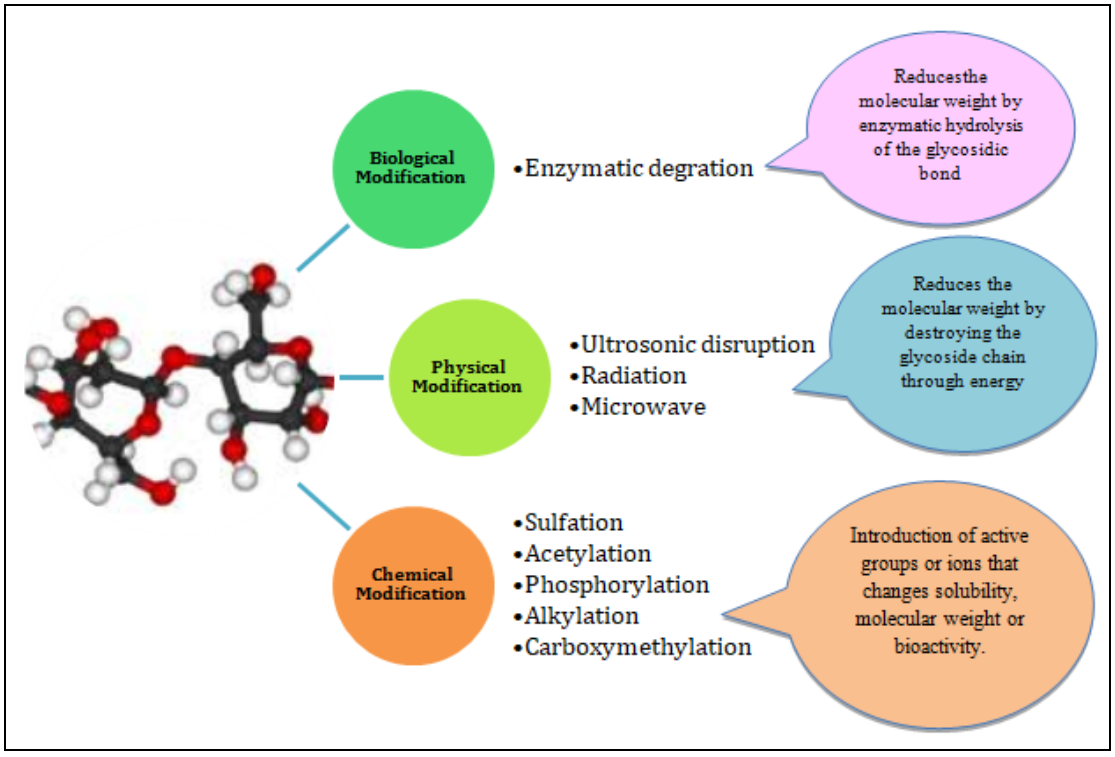

FIG. 1: FUNCTIONALIZATION STRATEGIES OF POLYSACCHARIDES

1.1 Biological Modification: The polysaccharides are modified biologically that is greatly related to the mediated degradation by the enzymes. It contains deterioration of polysaccharides by the catalytic effect of enzymes. In comparison with other physical and chemical modification methods, the advantages of biological modification include high efficiency, high specificity, and lower side

effects [3]. The main aim of enzymatic degradation is to reduce the polysaccharides, thus degrading their mass and viscosity. The application of biological modification is currently limited to the degradation of a few polysaccharides. The polysaccharides which are variable to biological modification include cellulose, chitin, starch and pectin. Due to several uses of modified starch in pharmaceutical products, its modification is discussed here [41].

Starch: Starch is made of amylose (α-1, 4 linked glucan) and amylopectin (α-1, 4 linked glucans; α-1, 6 linked branches). Starch is modified by utilising enzymes such as amylase and glucotransferase to generate glucose and fructose syrups, maltodextrin, or modified starches. The starch is enzymatically treated in the granular state with a fungal α-amylase and glucoamylase at 35 °C for 16 h to obtain enzyme-hydrolyzed-hydroxypropyl (HP) starch. This Enzyme-hydrolysed-HP starch exhibits remarkably various useful properties than unmodified hydroxypropyl starch that is prepared from native (untreated) starch. Modified starch has high bioavailability, and pH stability similar to branched amylopectin or resistant starch (RS).

Thus, starches are modified to overcome limitations like retrogradation, loss of viscosity on processing, and gelatinized starch structure is stabilized as occurred during the native starch temperature storage conditions. These modified starches are used in the pharmaceutical industry as tablet diluents, disintegrants, binders, additives, thickening agents, and quality enhancers in the food industry [5]. **Fig. 2** depicts the enzymatic modification of starch.

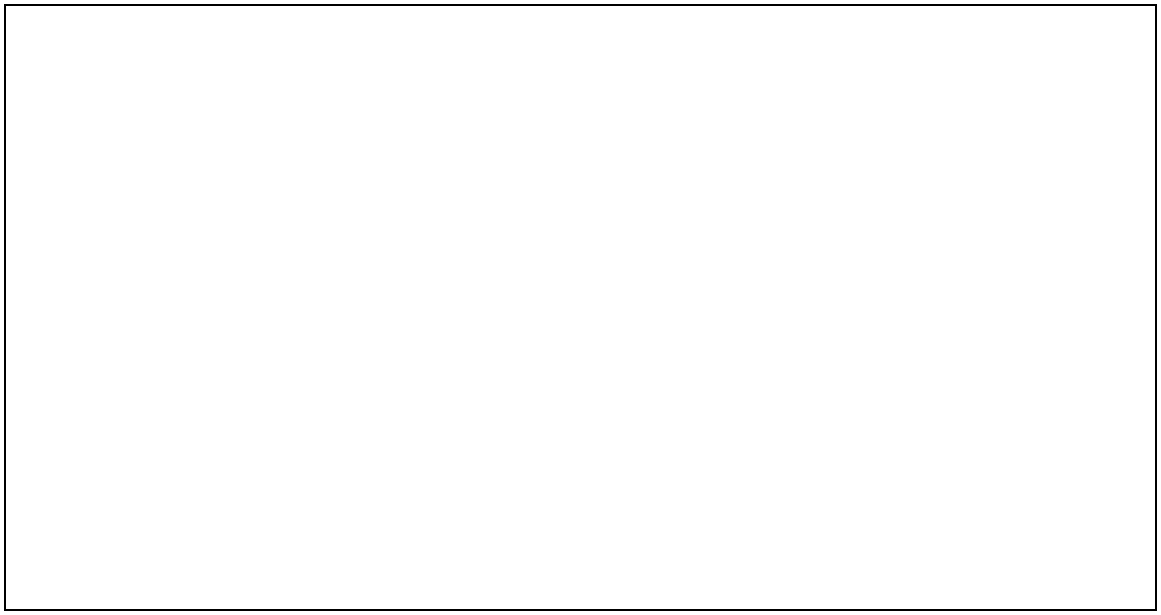

FIG. 2: ENZYMATIC MODIFICATION OF STARCH

1.2 Physical Modification: The physical modification mechanism includes the conversion of the original larger molecular weight polysaccharide chain into lower molecular weight fragments. This modification guarantees the conservation of the polysaccharide structure and causes conformational changes. The physical modification is carried out using ultrasonic disruption, radiation-caused reaction, and microwave exposure. Sonication involves breaking polymer chains on the center, which is the weakest point in the structure. Molecules with long-chain length and high molecular mass are broken first at the center, then at shorter chains, and lastly at sider chains. Additionally, linear polymer chains are more effectively sonolysed than the branched ones. Thus, the polymer's initial mass plays a significant role in the polymer's overall degradation rate. As polymers are broken down, a factor is reached wherein the chains become so short, that further degradation isn't always viable, and a decreased molecular weight restriction is attained. Sonication is an efficient technique for polysaccharide modification and nano molecule processing.

The polysaccharides modified by the physical process include pectin, carrageenan, guar gum, and

starch. Physical modification of pectin and carrageenan is widely observed hence discussed below. **Fig. 3** indicates the effects of physical modification on polysaccharides.

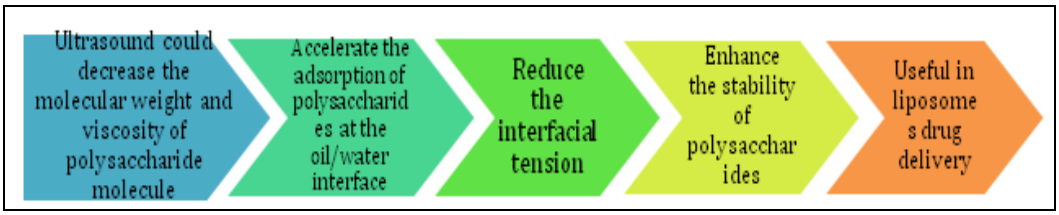

FIG. 3: EFFECTS OF PHYSICAL MODIFICATION

Pectin: Pectin is a polymer of alternate units of α-1,2 L-rhamnose and α-1,4 linked D-galacturonic acid with neutral sugars, including galactose and arabinose. Pectin is modified by various physical (sonication), chemical, and enzymatic modification methods. The Sonication process of citrus pectin is notified, observed, and analyzed that the pectin's average molecular weight decreases from 464 kDa to 296 kDa after 30 mins of the treatment. The degree of methylation is slightly decreased, after which the neutral sugar side chain gets degraded. The modified pectin is used for anti-cancer activity as it shows higher potency than untreated pectin. Thus, modification of pectin reduces its turbidity, viscosity, and molecular weight. The Sonication method is used to produce micro and nano- sized pectin derivatives utilized as drug carriers and in the pharmaceutical industry [6].

Carrageenan: Carrageenan exists in several varieties- κ-kappa with a single sulphate group, i - iota with two sulphate groups and ג-lambda with three sulphate groups. Carrageenan is degraded by sonication; with increased intensity, the time of sonication increases the degradation rate of carrageenan. The degradation rate reduces with reduced pH and concentration. The degradation rate is higher in K-carrageenan than ג-carrageenan; asan, additional sulphate groups, is present in ג-carrageenan that reducing the vulnerability in the sonication method. As the sonication temperature increases the molecular weight of carrageenan decreases. The molecular weight of k-carrageenan is 545 kDa which on sonication at 300C gives low molecular weight fragments of 329 kDa, 301 kDa at 400C and 285 kDa at 500C. The Sonication method provides an efficient carrageenan oligomer processing method. It forms thermoreversible gels along with metallic ions or potassium ions that can produce gels with proteins.

Thus, utilized in fresh cheese and chocolate milk. The carrageenan oligomers are antiviral, antitumor, plant growth promoter, anticoagulant, antioxidants hydrogels for burns dressings. Other applications encompass toothpaste, processed meats, infant formula, cosmetics, and dermatological preparations [7]. **Fig. 4** indicates a decrease in molecular weight of carrageenan after sonication at various temperature conditions.

FIG. 4: SONICATION OF CARRAGEENAN

1.3 Chemical Modification: Chemical modification is a familiar method that modifies polysaccharide structure by introducing substituent groups in the structures. This modification helps to reinforce the polysaccharide bioactivities, including antioxidant, antithrombotic and antitumor activity

[8]. It deals with selective derivatization and degradation of polysaccharides for structure elucidation. Chemical modification strategies consist of sulfation, alkylation, carboxymethylation, phosphorylation, and acetylation [1].

1.3.1 Sulfation: The synthesis of sulfated polysaccharides is carried out by substituting carboxyl, hydroxyl or amino-terminal groups with sulfate groups, which improves their bioactivities. Sulfation of Polysaccharides are done by using methods such as SO3-pyridine method, ionic liquids-CSA-pyridine, oleum-dimethylformamide (DMF) method, chlorosulfonic acid (CSA)-pyridine method and amino sulfonic acid (ASA)-pyridine methods, of which the extensively used methods are CSA-pyridine method and the ASA-pyridine methods [9, 10]. **Fig. 5** indicates sulphation of polysaccharides.

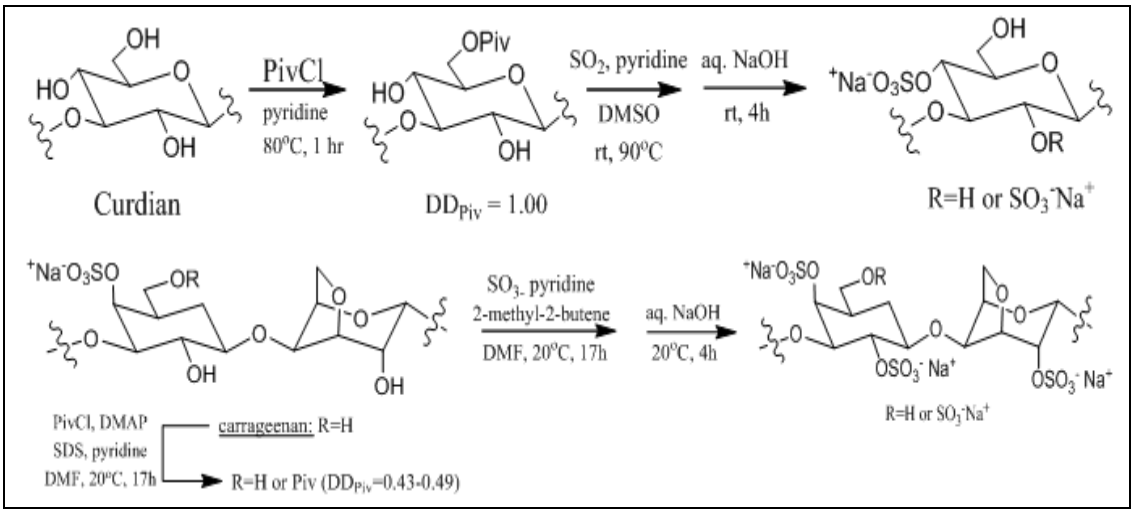

FIG. 5: SULFATION OF POLYSACCHARIDES

1.3.2 Carboxymethylation Modification: Carboxymethylation introduces carboxymethyl group withinside the polysaccharide chain. Aqueous medium and organic solvent-based strategies are extensively used for carboxymethylation. In the aqueous medium method, the polysaccharide is dispersed in an alkali solution, observed through the addition of monochloroacetic acid (MCA). The combined solution is permitted to react vigorously for several hours, since acetic acid is used as pH adjuster. Alcohol is introduced to the solvent to produce precipitate that is washed with ethanol and acetone. The washed precipitate is dried below the low-pressure situation to produce carboxymethyl derivatives of the polysaccharide. In the Solvent method, the polysaccharide is dispersed in isopropanol, ethanol, or any organic solvent; MCA is added for the etherification reaction at 2000C to obtain carboxymethyl derivatives. **Fig. 6** depicts the carboxymethylation of polysaccharides.

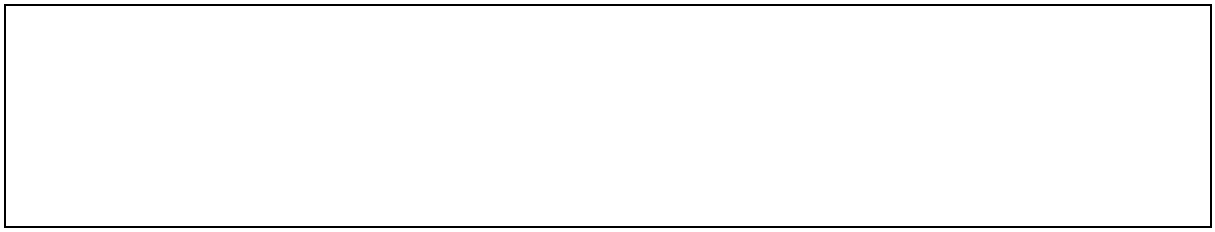

FIG. 6: CARBOXYMETHYLATION OF POLYSACCHARIDES

1.3.3 Phosphorylation Modification: Phospho-rylation introduces the phosphate group in the polysaccharide chain. Due to the presence of charged phosphate groups, phosphorylated polysaccharides have great medicinal value, which enables to enhance water solubility, change the molecular weight, and alter the chain conformation of polysaccharides. There are various methods

reported for polysaccharides phosphorylation. Of which the first method uses phosphoric acid or phosphoric anhydride. Polysaccharides are first dissolved in dimethyl sulfoxide (DMSO), and then phosphoric acid is added. The solution is saturated at room temperature and neutralized to pH 6.8. While in the second method, sodium tripolyphosphate, sodium hydrogen phosphate, sodium dihydrogen phosphate, sodium hexametaphosphate, or mixed salts are utilised to carry out phosphorylation without degradation of polysaccharides [1]. **Fig. 7** depicts the phosphorylation of polysaccharides.

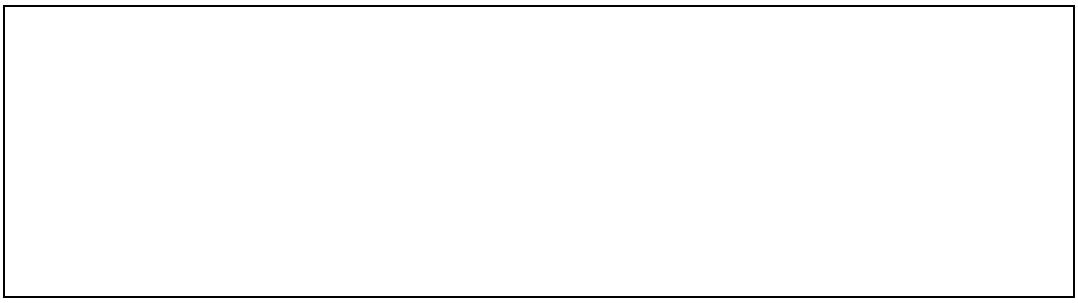

FIG. 7: PHOSPHORYLATION OF POLYSACCHARIDES

2.3.4 Acetylation Modification: Acetylation is an electrophilic substitution reaction in which acetic anhydride (electrophilic reagent) attacks polysaccharide molecules. The polysaccharide is dispersed in solvents, including DMSO, H_2O or formamide. After this, dropwise pyridine/Ac_2O or NBS/$Ac_2O$is added to the polysaccharide solution. This solution is then cooled, followed by the addition of three volumes of 95% ethanol for precipitation of acetylated polysaccharide [1]. **Fig. 8** illustrates the acetylation of polysaccharides.

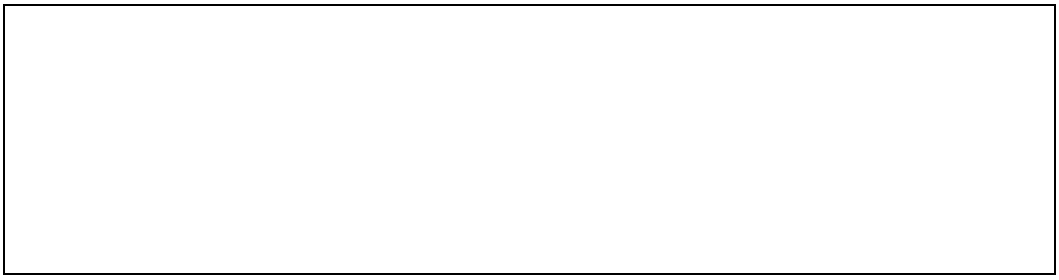

FIG. 8: ACETYLATION OF POLYSACCHARIDES

1.3.5 Alkylation: The alkylation of polysaccharides involves the addition of an alkyl group to the terminal end of the primary chain. Alkylating agents used particularly consist of halogenated alkanes, higher fatty aldehyde, and long-chain fatty acids. Alkylation decreases the viscosity and improves the solubility of polysaccharides that increases bioactivities such as antioxidant, anticoagulant, and antitumor activities [9]. **Fig. 9** depicts the alkylation reaction of glucopyranose. As we discussed various modification methods of polysaccharides, the effects of modified polysaccharides on properties are discussed below.

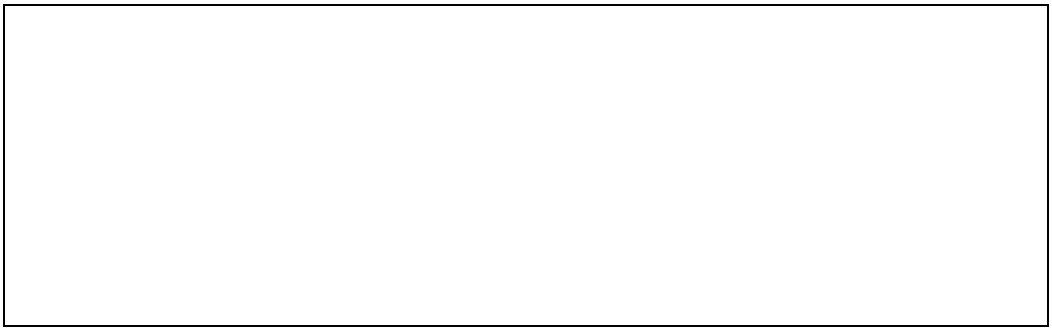

FIG. 9: ALKYLATION OF POLYSACCHARIDES

2. Effect of Modification on Properties of Polysaccharides: Modification has great effects on the polysaccharide's physical and chemical properties. This polysaccharide modification modifies the chemical and physical properties like its solubility, relative molecular mass, and intrinsic viscosity. It also enhances antitumor, antioxidant, anti-HIV, antibacterial, and anticoagulant activities.

Solubility: The polysaccharides show a wide range of solubility; some are insoluble in water like cellulose; some are soluble only in hot water example, starch, while some dissolve readily such as gum Arabic.

The molecular modification of polysaccharides increases the solubility rate in water. The introduction of ionic or hydrophilic groups within the polysaccharides will increase the water solubility. The increase in water solubility transforms the polysaccharides into ideal dosing forms that exert higher dissolution rates and faster absorption. The aqueous solubility of the eryngii polysaccharides in *Pleurotuseryngii* has sub-stantially enhanced by sulfation. The sulphation rate will increase as solubility increases by 56% to 86%. The number of ionic groups number increases due to sulfation increases water solubility. Similarly, the polysaccharides extracted from G. lucidum have poor solubility in water, increased by chemical modification to produce derivatives of carboxymethylations. Thus, carboxyl methylated polysaccharides had aqueous solubility of 100 mg/mL, which is 1000 times higher than the original polysaccharides.

Molecular Weight: The high molecular weight polysaccharides show low activity due to the decrease in the ability to cross the cell barrier and the difficulties in formulating dosage forms. Without difficulty, low molecular weight polysaccharides pass the multi-cell membrane barriers and show enhanced bioactivities. Physical modification is an efficient method to reduce the molecular weight of polysaccharides. The steam treatment is a physical modification technique used to modify the pectin extracted from thermally treated olive oil by-products. Due to this, treatment reduces the molecular weight by breaking the pectin chain, which facilitates its use in liposomal drug delivery for targeted action.

Viscosity: The polysaccharides with high intrinsic viscosity interfere with in-vivo absorption and in-vivo diffusion, limiting their bioactivity. Ulvan polysaccharide obtained from green algae Enteromorpha linza has a high intrinsic viscosity. When the degree of acetylation increases, intrinsic viscosity reduces from 34.67 to 22.92 mL/g of modified polysaccharides.

The decrease of hydrodynamic polymer volume reduces the viscosity. The addition of the acetyl group changed the directional and horizontal orders of polysaccharides exposing the hydroxyl groups of the polysaccharide, which increases the aqueous solubility of the polysaccharide and improves its antioxidant activity. Polysaccharides modified by acetylation methods show high antioxidant activity (30%) compared to the polysaccharide that is not modified (15%).

Biological Activity: S-RPS3 and P-RPS3 are polysaccharides extracted from *R. panacisjaponici*, and phosphorylation modification method is used. It shows antitumor activities in *in-vitro* also *in-vivo*. By adding more negative charges in the polysaccharide chain, the water solubility of polysaccharides was improved. S-RPS3 and P-RPS3 have increased their ability to interact with the macrophage receptor so that antitumor activity has increased. The phosphorylated derivatives show great inhibitory activity on the growth of B16 and MCF-7 tumor cells due to improved water solubility.

Haibo Feng examined that the Radix *Cyathulae officinalis* Kuan polysaccharides (pRCPS) are phosphorylated and have an immunomodulatory effect in the immunosuppressed mice and improve the activity of humoral as well as cellular immunity. These are extracted in water and observed through ethanol precipitation. The phosphorylation of RCPs to form pRCPs is being explored for its cellular and humoral immunity activities in the mice to the subunit of the hepatitis B vaccine. pRCPS will greatly increase the serum immunoglobulin (IgG, IgA, IgM) concentrations, thereby having better splenocyte proliferation and the spleen and thymus indices. Additionally, they promote peritoneal macrophage phagocytosis and improve cytokine (IFN-γ, IL-2, -4, -5, -6, and -10) serum levels. pRCPS also improves the selected T

cell subpopulations proportion ratios (CD3+, CD4+, and the CD4+ to CD8+ ratio). These outcomes indicate that the phosphorylation of the polysaccharides improves their immunological effects. The sulfate group is an effective electron-withdrawing group which it enhances the antioxidant activities.

To eliminate DPPH radicals, a greater degree of sulphated polysaccharide is used efficiently. The sulfate-modified polysaccharide has scavenging activity nearly doubled that of the untreated polysaccharide. The modified polysaccharides from Sargassum horneri have intermediate molecular weight and a very high sulfate content and excellent antioxidant activity. The negatively charged (sulfate groups) are combined with the positively charged groups (coagulation protease inhibitor antithrombin) to activate antithrombin and produce the anticoagulation activity. After carboxymethylation, acetylation and sulphation, the negative charge density and solubility in water, as a result, the anticoagulant activity of polysaccharides is improved [11].

Sulfated polysaccharides (SPS) are generally considered safe as well as biologically compatible substances used in modern pharmaceutical research. Due to non-toxic and immunomodulating effects, natural SPS nanoparticles have replaced several chemicals in medicine and Pharma-cotherapy, which induces harmful side effects; therefore, the treatment cost is reduced and patient compliance is improved. SPS coated metallic and magnetic nanoparticles under research studies for application in deep tissue imaging with enhanced targeting efficiency additionally is evaluated for better disease understanding and enhanced strategies related to treatment [12].

Wang *et al.* reported the effects of antitumor in the sulfated Artemisia sphaerocephala polysaccharides (ASPs) on H22 tumor-bearing mice and three cancer cells. ASPs exhibited superior in vitro antiproliferative activity on HepG2 and Hela cells, respectively, IC50 of 172.03 and 161.42 g/mL. In vivo studies illustrated that these sulphated polysaccharides considerably inhibited tumor growth in the H22 tumor-bearing mice. The inhibitory nature of low-dose ASPs (200 mg/kg) and high-dose ASPs (400 mg/kg) were 60.85% and 49.03%, respectively. The histological morphology, cell cycle, and immunohistochemistry analysis confirmed that ASPs should induce H22 cells cycle arrest by suppressing the expression of mutant p53 protein. Hence results confirmed that sulphated ASPs had advanced antitumor activity in vitro as well as *in-vivo* studies. After modification of polysaccharides, their biological, physical, and chemical properties are enhanced, making the modified polysaccharides widely available in diverse fields.

3. Applications of Functionalized Poly-saccharides: The modified polysaccharide derivatives have extensive applications in drug delivery, tissue engineering, gene therapy, targeted cancer therapy, and diagnostics. Many modified polysaccharides have anticoagulant, antioxidant, antitumor, and anti-HIV activities. Nanogels based on polysaccharides are often used because of their properties such as biological degradability, biocompatibility, stimulus-sensitive behaviour, smoothness, and swelling properties, often used as carriers for anti-cancer medicines; ensuring a controlled control and activated response to the target site [13]. Polysaccharides have an intrinsic capacity for the detection of certain cells whereby the system is directed by receptor-mediated endocytosis [14]. The modified polysaccharides-based hydrogels are used in wound healing, implantable devices, coatings, and biosensors to diagnose various biological components like glucose, uric acid, proteins, and nucleic acids. **Fig. 10** depicts various applications of modified polysaccharides in diverse fields,

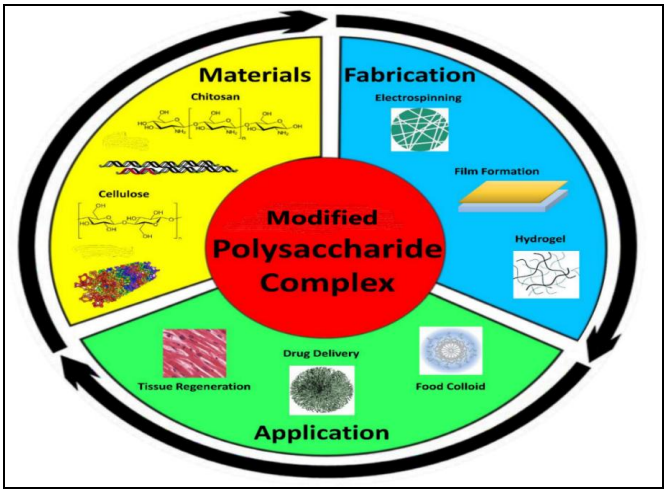

FIG. 10: APPLICATIONS OF FUNCTIONALIZED POLYSACCHARIDES

3.1. Drug Delivery: The poor bioavailability of molecules, drugs, and hydrophobic proteins makes them a bad candidate for administration and delivery. Therefore, modifications of natural polysaccharides as carrier systems are examined by improving their solubility of the active ingredient, bioavailability, and stability.

Modified polysaccharides of natural origin are often used as substituents for synthetic polymers to develop new drug delivery systems. By adding a variety of functional groups on the polysaccharide chain, modified polysaccharides are used to produce polymeric microspheres, nanostructures, self-assembled micelles that improve the release of drugs into tumour areas [15]. The modified polysaccharides are used to design sensitive controlled released systems such as transdermal films, oral tablets, matrix tablets, microspheres, hydrogel bead systems, and nanoparticle systems. The modified polysaccharides are often used in micelles, liposomal and hydrogel-based systems and are analyzed below. **Fig. 11** illustrates various drug delivery systems based on modified polysaccharides.

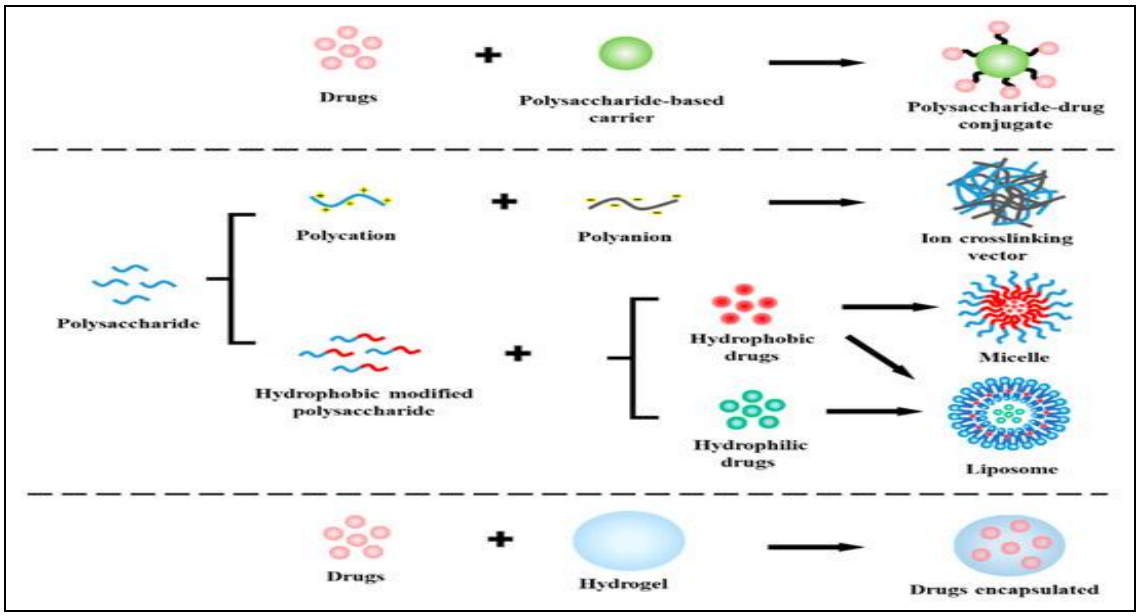

FIG. 11: POLYSACCHARIDES BASED DRUG-DELIVERY SYSTEMS

3.1.1 Micelles and Liposomal Delivery System: Micelles are supramolecular core-shell structures that are caused by the self-assembling of amphiphiles if their concentration is above critical micellar concentration. Polymeric micelles have hydrophobic and hydrophilic groups, which form micellar arrangements in an aqueous solution for drug encapsulation. The hydrophobic center core acts as a drug carrier, while the hydrophilic shell helps drug-loaded micelles escape the phagocytosis process. Molecules of polysaccharides are not amphiphilic and thus cannot form polymeric micelles. Introducing hydrophobic groups in the hydrophilic polysaccharide chain by modification, the resulting amphiphilic molecules have the ability to self-assemble in an aqueous solution as nanoscale micelles. Polymeric liposome of amphiphilic polymers having a bilayer membrane structure [16]. Hydrophobic molecules such as cholesterol, steroid acid, deoxycholic acid, and hydrophobic polymers are commonly used to change polysaccharide molecules. Minimizing interface free energy allows amphiphilic polysaccharides to be combined in micelles or liposomes. Liposomes can transport both hydrophilic drugs and hydrophobic drugs. The water-soluble drugs are present in the hydrophilic cavity, while the hydrophobic drugs are present between the phospholipid bilayers of the liposome. These liposomes and micelles are used in controlled and targeted drug delivery [17].

3.1.2 Hydrogel Delivery System: The hydrogel consists of hydrophilic polysaccharides covalently cross-linked to avoid their dissolution. The hydrogel can quickly absorb and store a large amount of water due to its hydrophilicity. The modified polysaccharides are useful for the

preparation of polysaccharide-basedhydrogels loaded with drugs. The chemical modification introduces hydrophilicity into polysaccharides that can be used as hydrogels [18]. The drug molecules are encapsulated in the gel matrix through non-covalent binding, and the expansion of the gel matrix releases the drug. The molecules of prodrug form hydrogels by self-assembly, providing sustained drug release like doxorubicin hydrogel when injected into cancer tissues, isolated in cancer cells, and achieved long-term drug release in the cancer region. The modified polysaccharide hydrogels are used in the controlled delivery of various bioactive agents such as contraceptives, ophthalmic, antibacterial, anti-cancer drugs, enzymes, and antibodies [19].

3.2. Wound Healing: The use of modified polysaccharides in wound healing is increasing due to their nontoxicity, biocompatibility, biological degradability, and adsorption capacity [20]. Alginate gel dressings are highly absorbent, which restricts and minimizes bacterial contamination. Wound secretions are readily biodegraded [21]. The dressings retain the moist environment and promote healing and tissue granulation. The alginates are easily rinsed with sterile saline water, making dressing removal painless and not interfering with healing granulation. These dressings are very useful for the treatment of moderate to heavily exudating wounds [22]. For the treatment of wound infection due to *E. coli* crossed linked hyaluronic acid hydrogel complexed with Ethylene diamine tetraacetic acid-Fe^{3+} is used. This complex is installed with the platelet factor to reduce the inflammation of the wound and avoid bacterial growth. Chitosan acetate used in bandages provides high healing activity due to its haemostatic and antimicrobial activity. Silver, an antimicrobial agent used to treat skin infections, a combination of chitosan acetate, shows synergistic effects against MRSA, *Pseudomonas aeruginosa,* and *Staphylococcus aureus*. These modified polysaccharide-based hydrogels provide sufficient moisture for the wound and act as shielding against bacteria. Therefore they are used as an effective adjuvant for wound healing [23].

3.3. Tissue Engineering: Tissue Engineering is a part of biomedical engineering that uses biochemical and physicochemical factors to recover, maintain, and improves different types of tissues. The modified polysaccharides are widely used in tissue technology by grafting the polysaccharides because they are remarkable materials for stimulating cells, biosensing, and bioengineering applications [24]. The grafted polysaccharides have improved miscibility with cellular components, and when injected *in-vivo,* it gets converted into a gel. In addition, the modified polysaccharide has improved mechanical properties to carry cell loads and is used as the carrier for stem cells. The functionalized polysaccharides used include starch, cellulose, chitin, alginate, agar, dextran, pullulan, and xanthan [25]. Chemically modified starch microfibers are combined with collagen nanofibers to create an extracellular matrix equivalent to bone tissue engineering [26]. The modified starch-polycaprolactone provides favourable growth support for macro-and microvascular endothelial cells *in-vitro* 27. The purified plant cellulose is chemically converted from short fibers into long fibers used to build three-dimensional vascularized tissue *in-vitro*. These cells form multilayers in the fibers and are enzymatically eliminated by cellulase. The remaining SMC maintains the lumen and therefore imitates the newly formed blood vessels [25, 28].

Gelatin methacrylate hydrogels are a type of methacrylamide-modified gelatin that was first reported by Van Den Bulcke *et al.* (2017). They are made by reaction of gelatin with methacrylic anhydride. Gelatin methacrylate hydrogels are applied in tissue engineering due to their physicochemical properties and good biocompatibility. Another example of a modified polysaccharide is the modified polysaccharide of tamarind kernel. A biomaterial is synthesized from the polysaccharide of tamarind kernel that is grafted with hydrophilic acrylic acid by radical polymerization. They are used for the growth of osteoblasts derived from mesenchymal stem cells. The TKP acrylic acid can be substantially used as a framework for various types of cells, particularly for cost-effective bone tissue engineering [29].

3.4. Targeted Cancer Therapy: It is reported that polysaccharides have activities against cancer and can increase the effectiveness of chemotherapeutic drugs [30]. Pectin, complex polysaccharides of plant origin, consisting of a galacturonic structure and side chains of neutral sugars. It prevents colon

cancer because it is dietary fiber. Pectin is modified into low molecular weight mass fragments to improve bioavailability and bioactivity [31]. The modified pectin fibers inhibit tumour growth, induce apoptosis, suppress metastasis and immunological reactions. The anti-cancer activity of the modified pectin is due to the ligand recognition by galectin-3 [32]. The anti-tumour activity is responsible for triggering the activity and is useful in reverse tumour resistance to several chemotherapeutic agents. Modified pectin is a suitable vehicle for anti-cancer drug delivery systems and functions like a biological response modifier used in the immunological system regulation [33]. Hyaluronic acid is formed byan alternate chain of D-glucuronic acid and N-acetyl-D-glucosamine, which mainly exists in vivo as sodium hyaluronate. HA is chemically modified in three functional groups; carboxylic, hydroxyl and acetamido groups. Activation of the paclitaxel hydroxy group with carbodiimide for conjugation with 4-bromobutyric acid to form ester-linked 4-bromobutyric-paclitaxel. The IV delivery of paclitaxel is complicated due to hydrophobicity and side effects. To overcome the limitations of paclitaxel, it is combined with hydrophilic HA. Hyaluronic acid-based nanomaterials effectively treat many cancers such as colon, ovarian, and breast carcinoma. The use of nanomaterials based on hyaluronic acid is used in drug delivery systems and molecular images. Nanomaterials increase the pharmacological activities of many hydrophobic anti-cancer drugs, such as paclitaxel. doxorubicin, and irinotecan [34].

3.5. Biosensors: A biosensor is an analytical device used to detect chemical substances by combining a biological with a physicochemical detector. Biosensor consists of three parts: (1) Bio-recognition elements, (2) a transducer [35] (3) a signal processing system [36]. The recognition elements include receptors, enzymes, antibodies, nucleic acids, microorganisms, and lectins [2]. The modified polysaccharides offer many advantages such as high sensitivity, diagnosis, and durability in the production of biosensors and, therefore, help detect [37] various biological components. Modified chitin-chitosan, cellulose, and alginate-based biosensors are discussed here. **Fig. 12** illustrates various components of biosensors.

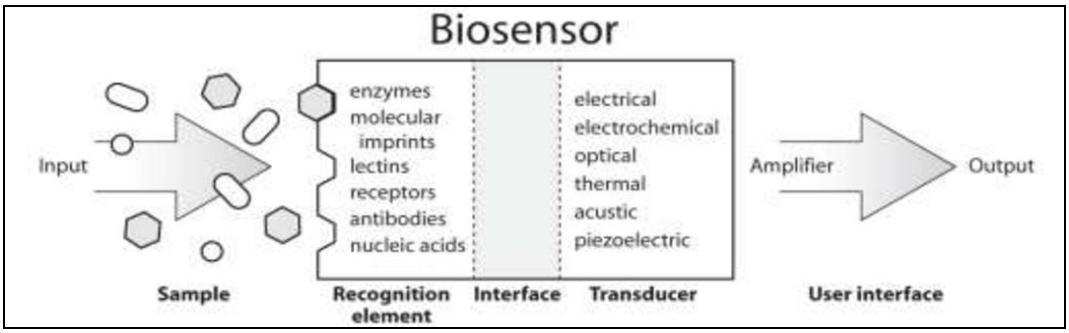

FIG. 12: COMPONENTS OF BIOSENSORS, VARIOUS MODIFIED POLYSACCHARIDES ARE USED IN BIOSENSORS

3.5.1 Modified Chitinchitosan-based Biosensor: Chitin and chitosan have good biocompatibility and can form films and hydrogels. It contains nitrogen and oxygen-based functional groups, which can be modified chemically [2]. While electrochemical research *in-vitro* determines the integrity and lifetime of the entrapped macromolecules that allow analyte recognition and quantification [38]. The response achieved when the matrix-induced degradation of the immobilized BRE (B recognition element) occurs leads to the formation of a stable and reproducible reaction. The compatibility of the immobilizing layer with the BRE gene is critical for durable sensor performance. The tip and sensor design should not trigger a local inflammatory host response. The tissue compatibility and low immunogenicity of chitin and chitosan are validated in many clinical trials [39]. Chitin and chitosan under gophosphorylation, cyclodextrin linked, thiolation, sulfation, and ferrocene-branched to obtain functionalized derivatives. Functionalization of amino groups of chitosan with electron-donating or –withdrawing groups changes the charge on the biomaterial [40]. The use of modified chitin chitosan films in electrochemical biosensors provided

excellent sensitivity, and precision in detecting the BRE and enhanced the performance of the biosensor [38].

3.5.2 Modified Cellulose-based Biosensor: Nanocellulose (NC) is a distinct nature-based nanomaterial that attracts attention in numerous fields like biomaterials, bioengineering, biomedicine, and digital gadgets, nanocomposites, textiles, cosmetics, and food products. It gives a great properties such as biodegradability, inherent renewability, low density, commercial availability, flexibility, optical transparency high porosity also has extraordinary thermal, mechanical, and physiochemical properties [41]. Nanocellulose is modified and applied in biosensing technology and exhibits analytical data that relates to diverse fields, including medical diagnostic, environment monitoring, food safety, bioimaging, and physical and mechanical sensing applications. Cellulose derivatives such as of block copolymers are used as stimuli and responsive mediators. Regio, selectively modified through the dissolution of cellulose by ionic liquids via radical polymerization, is used as a polyethylene glycol derivative that produces honeycomb-patterned films. Fluorescent molecules are also connected to films, signifies the potential for site particular biosensor functionality [42].

3.5.3 Modified Alginate-based Biosensor: Polychlorinated biphenyls (PCBs) are the foremost pollution in soil and the aquatic environment. The possible treatment method used is Rhizoremediation by removing the PCBs from the sediment and contaminated soils. Pseudomonas fluorescens F113Rifpcb is a rhizosphere bacterium obtained from genetically engineered processes that have the potential to deteriorate the polychlorinated biphenyls (PCBs). F113L:1180gfp and F113 Rifpcbgfp are the biosensor strains that are capable of detecting PCB biodegradation and bioavailability. Alginate is used for the encapsulation process of microorganisms for environmental and commercial applications. The modified alginate beads formed by the encapsulation process are uniform, easily handled, non-toxic and biodegradable. Alginate beads consist of a large bacterial population and release bacteria over a long period. Encapsulating whole-cell biosensors in modified alginate shows a useful detection tool for environmental pollutants. Modified alginate beads remarkably increase inoculant robustness and shelf-life, reducing the associated cost and handling labour [52]. The biosensor cell has containment within the modified alginate beads that allows for easy recovery and visualization of the biosensor cells from the environmental matrices and provides an approach for assessing the biodegradation potential of PCB contaminated soils [38]. Varied modified polysaccharides such as dextran, starch, and pectin are utilized in varieties of biosensors for diverse biomedical applications to a lesser extent. Biosensors are applied in different biomedical functions such as pathogen detection and cell metabolite, wound healing, cancer monitoring, and tissue engineering and detecting small biomolecules such as urea, glucose, cholesterol, and lactate.

CONCLUSION: Polysaccharide chemistry has an essential class of polysaccharides molecular modification because it plays an essential function as natural polysaccharides offer desirable physiochemical properties, various bioactivities, augmentation of innate biological activity, and decreased side effects. These modifications modify the molecular weight of polysaccharides, thereby alternating the physical and chemical properties and biological activities. Modification done by chemical methods is an extensively used functionalization method; it will increase the water solubility and bioactivities of polysaccharides by grafting diverse functional groups. Natural polysaccharide modification scaffolds in the polymeric carrier structures are investigated to enhance drug stability; solubility also decreases the induced toxicity.

It is widely used for synthetic polymer substitution due to toxicity and immunogenicity limitations withinside the development of new drug-delivery systems. The polysaccharide backbone is conjugated with different ligands to yield materials that find utility in the fabrication of self-assembled micelles, coated polymers microspheres, and self-reorganized nanostructures, improving drug release in target areas. The features of polysaccharides associated with structures include glycoside bond linkage, monosaccharide composition, molecular weight, solution conformation, and degree of

substitution play a crucial role in their bioactivity profile. The functionalization of bioactive native poly-saccharides to extend their application landscape is a rapidly growing research area. The functionalized polysaccharides are synthesized using various methods such as acetylation, sulphation, carboxymethylation phosphorylation, and hydroxylation, which have been reported for diverse polysaccharides of plant and marine origin.

The functionalized polysaccharides find application in biosensors, drug delivery, wound healing, diagnostics, and the food industry. The route of synthesis in terms of reagents and reaction conditions (reagent types, reagents ratio, reaction conditions, and process feasibility) for the synthesis of these polysaccharides is wide open for intensive research and can result in the genesis of a diverse array of functionalized materials with superior attributes and applications.

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