Sugar Based Biopolymers in Nanomedicine: A Review

By

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Department of Pharmacy

BRAC University

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Declaration

It is hereby declared that,

1. The thesis submitted is my/our own original work while completing degree at BRAC University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
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Approval

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Ethics Statement

No animal or human trial was conducted during this study.

Abstract

Since the last ten years, nanomedicine has recognized sugar-based biopolymers as potential materials for cancer imaging and therapy. Because of their robustness, biocompatibility, and adhesiveness, the molecules' molecular weights (MW) may be precisely adjusted, and because of their diversity, they can adopt a variety of conformations. Biocompatible sugar-based nanoparticles (SBNPs) can transport drugs to specific cells and also medicines and imaging carried out through the body. As demonstrated in several clinic phases, targeted strategies targeting cancer cells have been established and now include sugar-based indicators. These investigations create new biocompatible nanoparticles by chemically functionalizing biopolymers such chitosan, hyaluronic acid, mannan, dextran, levan, pectin, cyclodextrin, chondroitin sulphate, alginates, and heparin and adjusting their structural composition (NPs). Instead of taking a long time for each imaging and treatment step, these multipurpose sugar-based nanoparticles will have the benefit of quick detection, precise drug efficiency assessment, and the ability to immediately affect some dangerous diseases, particularly malignancies that are advancing quickly. To ensure that these nano-formulations are employed in clinical settings with effective pharmacological therapy and minimal overall toxicity, more work needs to be done and refined.

Keywords: Imaging, nanoparticle therapy, cancer, biopolymer, sugar.

Dedication

Dedicated to my beloved parents, friends and my instructors.

Acknowledgement

First of all, I would like to thank almighty Allah for granting me with countless blessings and opportunity to be able to complete this project.

Besides, I'd like to express my heartiest gratitude to my project supervisor Dr. Shahana Sharmin (Assistant Professor, School of Pharmacy, BRAC University) for providing me with the excellent opportunity to work on this fantastic project, which also allowed me to perform a lot of research and learn a lot of new things. I will be grateful to her for being so patient andsharing all those expert, valuable and sincere guidance throughout the entire phase which allowed me to accomplish this study.

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List of Acronyms

Np	Nanoparticle
Mw	Molecular Weight
BBB	Blood Brain Barrier
MRI	Magnetic Resonance Imaging
PLGA	Poly (lactic-co-glycolic acid)
DC	Drug Carrier
ASGP-R	Asialoglycoprotein receptor
FITC	Fluorescein Isothiocyanate
HA	Hyaluronic Acid
(RGD)	Arginyl-glycyl-aspartic Acid
FDA	Food and Drug Administration
MCF-7	Breast Cancer Cell
EPR	Electron Paramagnetic Resonance
CVD	Cardiovascular Disease
BCSF	Bone Cell Stimulating Factor
GAM	Gram Atomic Mass
TNF	Tumor Necrosis Factor

Chapter-1 Introduction

1.1 Background

A new generation of sugar-based polymers with complex structures, compositions, and well-defined molecular weights has emerged as a result of significant developments in polymer synthesis processes during the past few decades. All of these traits significantly increase polymer diversity and allow for a variety of biomaterials and biomedical applications (Matsumura et al., 2008). Sugar-based biomaterials are particularly well suited for in vivo therapeutic applications because they have the advantages of being biocompatible, biodegradable, and non-immunogenic when compared to other synthetic polymers. Significant interest has been shown in sugar-based polymers for medicinal applications, such as the administration of drugs, genes, proteins, and antigens, as well as diagnostic tools. In order to enclose bioactive compounds with variable hydrophilicities, they constitute one of the most promising delivery vehicles and may be easily synthesized into diverse formulations, such as nanoparticles, micelles, and hydrogels (Jain et al., 2012).

The development of biocompatible, sticky biopolymers that are easier to create and more affordable will probably lead to the creation of the next generation of cancer treatments. Therefore, polymers with high cell adhesion features and a variable MW have been establishing their promising use in the nano formulations (Kumari et al., 2010; S. Eroglu et al., 2017). These polymers are also multifunctional, bioactive, water soluble, biodegradable, anti-inflammatory, and they have these properties. In comparison to normal cells, cancer cells and their microenvironments require significantly more sugar-induced energy to proliferate and alter their morphology to improve extracellular adherence (Alfarouk et al., 2014; Almaraz et al., 2012; Schmaus et al., 2014) . In general, it is anticipated that cancer cells will prefer biopolymers as an energy source over normal cell. In contrast to the well-known cancer-targeting biopolymers chitosan and hyaluronan, mannan, dextran, and Levan have lately been employed for Cancer imaging and treatment using active nano-drug carriers (Kim et al., 2015; Ossipov, 2010; Park et al., 2010; Sezer et al., 2011; Yasar Yildiz & Toksoy Oner, 2014). They are intriguing materials for cancer targeting techniques because to their high avidity, supplied by their flexible conformations, changeable MW, and high sticky property [2022]. Hyaluronan NPs coated with mannose, for instance, can be created to target dendritic cells(Cui et al., 2011). However, they are easily

functionalized with various chemical groups to stop nanocarriers from adhering to healthy cells. The multivalent binding mechanism of carbohydrates may increase avidity between ligands and carbs. When tumours are inhibited and in vivo cellular imaging is being done, the multifaceted receptors of carbohydrates interact with special ligands of nanomaterials (Rao et al., 2015).

1.2 Aim of the study

The aim of this study is to provide an overall idea about the how biopolymer enhance the activity of nanomedicine specially focusing on its mechanism of action, clinical significance, limitations etc. The study is also performed to let people know how successful the sugar-based biopolymer is in terms of other drug activity and how curable it is in this journey.

1.3 Objective of the study

The objective of this study is to determine the efficacy, it's contribution towards advanced enhancement of the activity of nanomedicine and all the relevant factors affecting the activity of the sugar-based biopolymers. The study will also focus when and how sugar-based biopolymer impact on the overall treatment of a disease and how it can work more effectively. The other objectives are to show the significance of improving them by overcoming the shortcomings so that in future they can help increase the activity of biopolymer with their optimum efficacy.

1.4 Nanotechnology

Nanotechnology is characterized as the "deliberate plan, portrayal, creation, and utilizations of materials, designs, gadgets, and frameworks by manipulating their dimensions and form at the nanoscale (1 to 100 nm). Nanotechnology could be beneficial for therapeutic applications because nanoparticles can be created to have varied capacities while being comparable in scale to biologic

particles and frameworks. The goal of nanomedicine is to diagnose and cure illnesses at the atomic level by utilizing the characteristics and true qualities of nanoparticles.

Currently, nanomaterials are being developed to assist demonstration or restorative specialists' vehicles across biological barriers.; to get sufficiently close to particles; to intervene sub-atomic communications; and to distinguish sub-atomic changes in a delicate, high throughput way. Nanomaterials can be built to have a variety of sizes, forms, synthetic inventions, surface substance characteristics unlike molecules and naturally occurring materials, they can be created to have a high surface area to volume ratio. They can also be empty or robust structures. (Peer et al., 2007; Xia et al., 2009). Emerging generations of medicine, delivery tankers, contrast experts and demonstration tools are incorporating these qualities; some of these products are currently undergoing clinical testing or have received FDA clearance for use on people. The most typical nanomaterials utilized in medicine are illustrated in examples in Figure 1 and Table 1. The characteristics of nanomaterials, their significant clinical uses, and the potential for this developing discipline are all depicted in this sketch.

Table 1

Table 1 Representative examples of nanocarrier-based drugs on the market

Compound	Commercial name	Nanocarrier	Indications
Styrene maleic anhydride-neocarzinostatin (SMANCS)	Zinostatin/Stimalmer	Polymer–protein conjugate	Hepatocellular carcinoma
PEG-L-asparaginase	Oncaspar	Polymer–protein conjugate	Acute lymphoblastic leukemia
PEG-granulocyte colony-stimulating factor (G-CSF)	Neulasta/PEGfilgrastim	Polymer–protein conjugate	Prevention of chemotherapy-associated neutropenia
IL2 fused to diphtheria toxin	Ontak (Denilelukin diftitox)	Immunotoxin (fusion protein)	Cutaneous T-cell lymphoma
Anti-CD33 antibody conjugated to calicheamicin	Mylotarg	Chemo-immunoconjugate	Acute myelogenous leukemia
Anti-CD20 conjugated to yttrium-90 or indium-111	Zevalin	Radio-immunoconjugate	Relapsed or refractory, low-grade, follicular, or transformed non-Hodgkin's lymphoma
Anti-CD20 conjugated to iodine-131	Bexxar	Radio-immunoconjugate	Relapsed or refractory, low-grade, follicular, or transformed non-Hodgkin's lymphoma
Daunorubicin	DaunoXome	Liposomes	Kaposi's sarcoma
Doxorubicin	Myocet	Liposomes	Combinational therapy of recurrent breast cancer, ovarian cancer, Kaposi's sarcoma
Doxorubicin	Doxil/Caelyx	PEG-liposomes	Refractory Kaposi's sarcoma, recurrent breast cancer, ovarian cancer
Vincristine	Onco TCS	Liposomes	Relapsed aggressive non-Hodgkin's lymphoma (NHL)
Paclitaxel	Abraxane	Albumin-bound paclitaxel nanoparticles	Metastatic breast cancer

Table-1: Representative examples of nanocarrier-based drugs on the market

Throughout the course of recent many years, actual researchers have created methodologies to reproducibly orchestrate nanomaterials and to describe their one-of-a-kind, size-subordinate properties. (Peer et al., 2007; Xia et al., 2009). For the best use of nanomaterials in therapeutic applications, it is vital to comprehend these fundamental physical and chemical properties.

Generally referred to as metallic, natural, or semiconducting particles, separately, nanomaterials are made consisting of a mixture of metal and nonmetal molecules, nonmetal iotas, or metal molecules. The outer layer of nanomaterials is typically covered with polymers or biorecognition particles for improved biocompatibility and precise focussing of biologic atoms. The amount of salt and surfactant used, the reactant fixations, the response temperatures, and the dissolvable conditions used during their amalgamation all can have an impact on the final size and structure of nano materials.

This extensive surface to volume ratio that all nanomaterials share, which may be noticeably more notable than that of naturally observable materials, is one of their common characteristics. Similar overall volume and mass will result from splitting a 1-cm solid object into 1021 1 nm-square 3D cubes, however, there will be a 10-million-fold increase in surface area. In this way, both the benefit of using and the intensity of that impact were altered. For instance, all of the iron oxide's electron the electrons in iron oxide macroparticles (larger than 20 nm) rotate in the opposite direction from attracting nanoparticles, which rotate in the same direction. When these turns are modified in the same direction. The field becomes more substantial; however, when the electrons are adjusted in the opposite way, the fields are balanced. Because the total attractive field strength of a material is equal to the sum of the attractive fields of individual electrons, these nanoparticles have a stronger, more confined attractive field than larger particles. This larger attractive field can enhance the distinction in attractive reverberation imaging since more protons are cooperating in it (MRI).

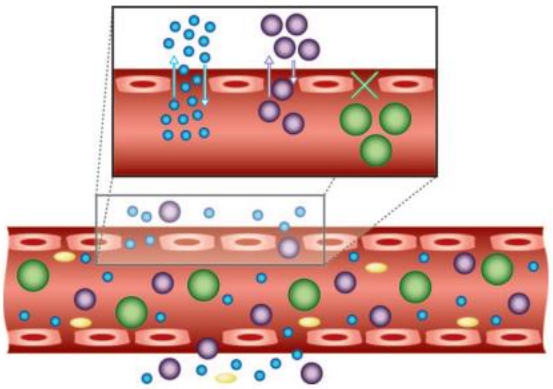

Figure 1: Efficacy of nanoparticles as delivery vehicles is highly size- and shape-dependent. The size of the nanoparticles affects their movement in and out of the vasculature, whereas the margination of particles to vessel wall is impacted by their shape. (Farokhzad & Langer, 2009)

1.5 Biopolymer

Innovative developments cantered on bio-based materials are currently of utmost importance since they have the potential to reduce reliance on fossil fuels (Mohanty et al., 2002). Biopolymers are gotten from normally happening matter, for example, shells of scavenger, mushrooms, or wood. The rationale for including biopolymers in this study is obvious in light of their inherent features, even though certain applications aim towards the usage of biopolymers for their maintainability, eco-effectiveness, current environment, and sustainable nature. Biopolymers are sustainable resources, yet additionally characteristically display antibacterial movement, biodegradability, and biocompatibility. (Rinaudo, 2006). Because of this, they are excellent for usage in a variety of industries, including ophthalmology, medicine, horticulture, materials, paper coatings, and automotive (Berger et al., 2004; Chirkov, 2002; Dodane & Vilivalam, 1998; Ravi Kumar, 2000; Subbiah et al., 2005; Vartiainen et al., 2004). Non-woven electro spun stringy mats made out of biopolymers could offer explicit applications including air filtration, defensive dress, substitutes for farming pesticides, and nanocomposites (Z. M. Huang et al., 2003). Section 3 has more discussion regarding the applications of nanofibrous mats. It means quite a bit to take note of that working with biopolymers can challenge. For instance, chitin can be extricated from, shellfish shells (Ravi Kumar, 2000; Tolaimate et al., 2000) bug cuticles (Zhang et al., 2000) or contagious

biomass (Pochanavanich & Suntornsuk, 2002; Wu et al., 2004). It's the sub-atomic weight (MW), amount of deacetylation (DD), immaculateness, and appropriation of charged groups which will vary depending on the source (Nwe & Stevens, 2004; Teng et al., 2001) and crystallinity (Jaworska et al., 2003; Ogawa et al., 2004). This variety turns out as expected for all biopolymers. Because of material irregularity, each mass material requires extraordinary handling conditions, which entangles controlled manufacturing. Despite the previously mentioned difficulties, the characteristic advantages can't be disregarded; it is hence that microfibers containing biopolymers, for example: chitosan, alginate, cellulose/chitin, alginate/carboxymethyl (CM) chitosan, 21–27 alginate, 28–30 Recently, alginate/soy34 and collagen/poly(lactide-co-glycolide) (PLGA)32 were produced utilizing conventional fiber handling techniques. Large-scale biopolymers and biopolymer composite filaments are the subject of active research. It is also interesting to develop nano-scale biopolymer filaments, which will be covered in Section 2.3 and throughout the rest of this study.

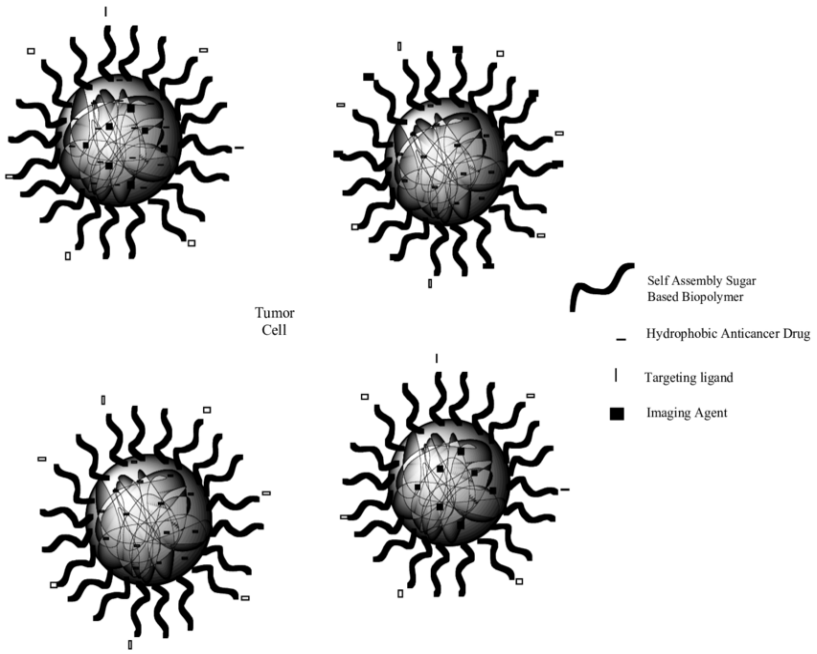

Figure 2: Sugar based biopolymer design for diagnose, imaging and therapy

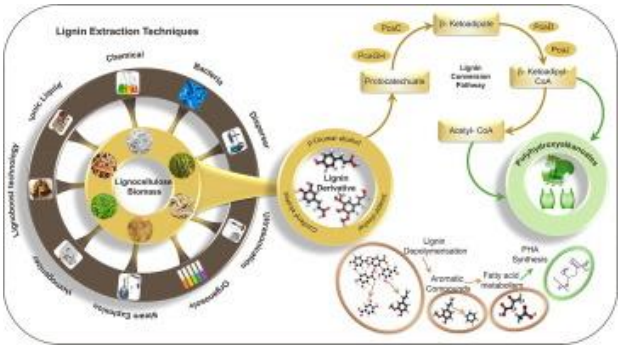

Figure 3:Different types of Biopolymers (Ling et al., 2018)

1.6 Sugar based (dextran) biopolymer nanomedicine

As per the figure polymeric nanoparticles can either covalently bond with or represent restorative payloads. Both synthetic polymers made from biodegradable materials and common polymers are used. Containers can be formed suddenly (micelles, Fig. 2C) through either drug and polymers have been combined, through self-association, or through emulsion processes as nanosized droplets. These nanospheres are made for controlled drug release, are quite stable, and have reasonably homogeneous sizes. They also feature a strong centre that is perfect for hydrophobic drugs. Drugs that can covalently attach to polymers that dissolve in water would surely lengthen their time of dispersion and reduce their toxicity to normal tissues (Boghossian, 2009). (Cho et al., 2008; Hu & Zhang, 2012; Mattheolabakis et al., 2012; Minko, 2005). Polymers have been improved in a variety of ways, including by concentrating on ligands, expanding PEG to prevent opsonization and extend dissemination time, and employing pH-sensitive or hypothermic polymer forms. Although several more are undergoing clinical exploratory testing, only two polymers, polylactide (PLA) and poly(lactide-co-glycolide) (PLGA), are now employed as polymeric biodegradable nanoplatforms for FDA-supported nanomedicines. (Mattheolabakis et al., 2012).

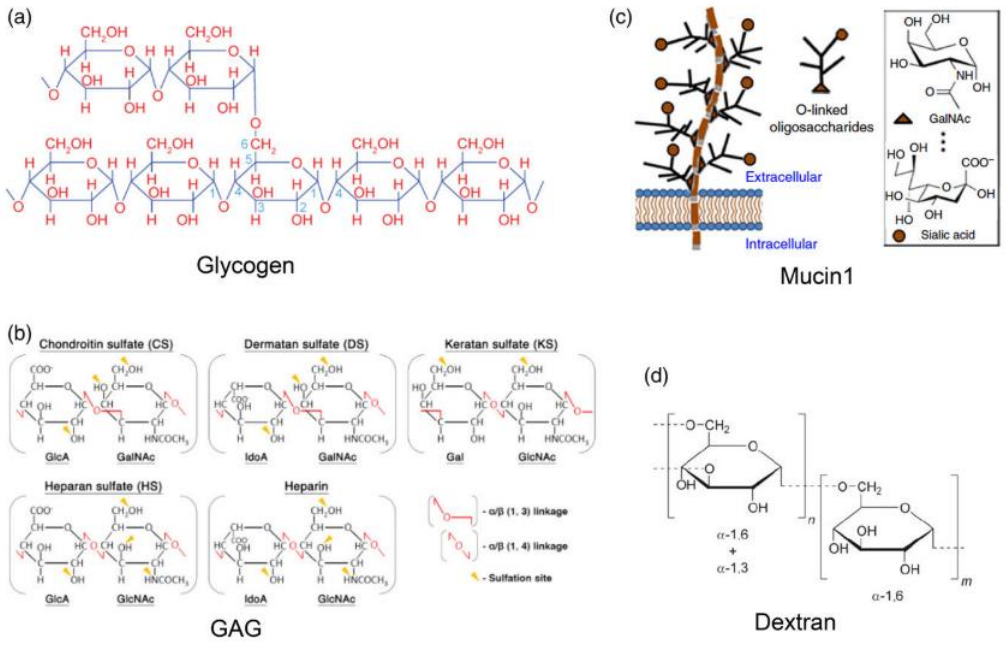

Figure 4: Structure illustration of four sugar-based biopolymers: (a) glycogen, (b) GAG, (c) Mucin1, and (d) dextran.

Dextran, which is clinically supported as plasma extender by FDA, is a water dissolvable non-ionic polysaccharide made out of α (1→6) connected glucose monomer build-ups. It very well may be disintegrated in natural mixtures, which is a significant benefit for the development of hydrophobic medication exemplified NPs. In spite of the fact that, it is biodegradable in blood, it can't be corrupted by lysozymes. It's essential and auxiliary hydroxyl bunches are qualified to tie proteins and malignant growth cell surfaces (Markovsky et al., 2012; Mehvar, 2000). Along these lines, self-collected dextran NPs are appropriate for anticancer medication conveyance. Dextran NPs can be delivered by uniting bile salts by means of acrylic corrosive copolymerization to acquire pH delicate NPs (Mehvar, 2000; Nichifor et al., 1999; Tang et al., 2006). Dextran can likewise be joined with other regular and manufactured polymers like poly (ε-caprolactone), hydroxyethyl and hydroxymethyl cellulose to acquire NPs (Lee et al., 2015).

Dextran has been utilized in radiolabelled and non-radiolabelled applications in clinical and attractive reverberation imaging since 1990s. Dextran-covered superparamagnetic iron oxide particles were utilized in solid workers for evaluating lymph hubs in head and neck aggregation (Anzai et al., 1994; Mehvar, 2000). In photodynamic treatment, dextran-chlorin e6 forms (DEXSS-

Ce6) could self-collect into NPs with uniform circles in watery arrangement and show cell redox-responsive switch conduct in regards to fluorescence signal (Liu et al., 2014). Dextran-covered superparamagnetic iron oxide NPs are known for the amalgamation of multifunctional imaging specialists (Fig. 6) (Donahoe, 2012).

As well as, β-cyclodextrin is additionally ordinarily utilized in SBNPs. Their alterations are broadly used for malignant growth treatment. Tamoxifen citrate stacked amphiphilic βcyclodextrin NPs showed sensible cytotoxicity against MCF-7 cells (Memisoglu-Bilensoy et al., 2005). In the other review, β-cyclodextrin curcumin self-gathering improved curcumin conveyance and its restorative viability in prostate malignant growth cells when contrasted with free curcumin (Yallapu et al., 2010). As the double focusing on treatment, attractive Fe3O4 NPs joined with single-chain counter acting agent (scFv) and docetaxel stacked β-cyclodextrin showed potential for ovarian malignant growth treatment, where polarization uncovered that these particles were superparamagnetic (Huang et al., 2014).

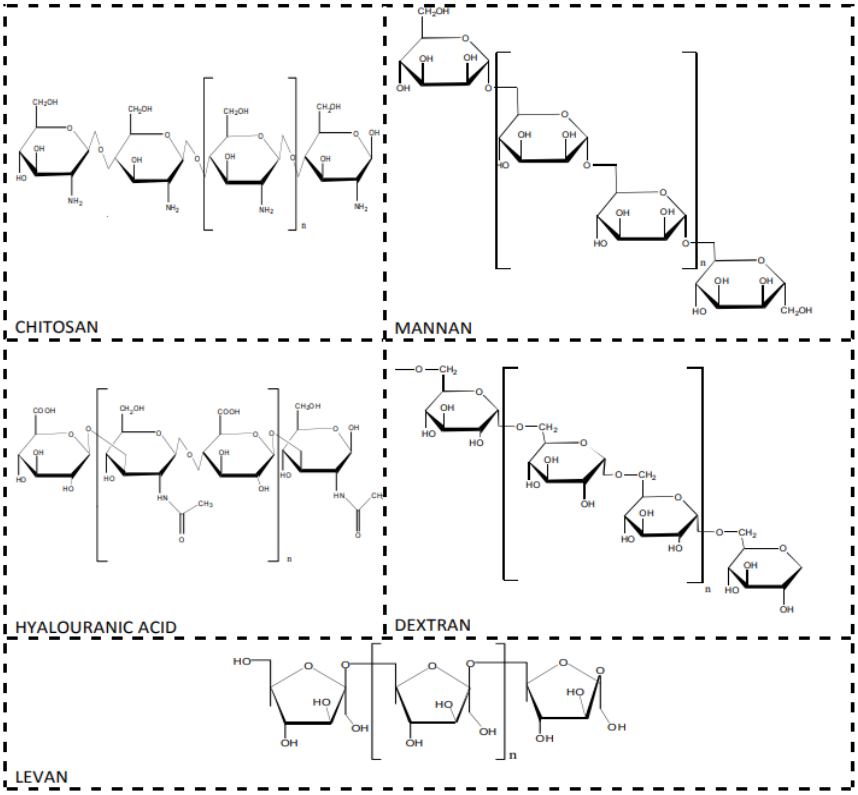

Figure 5: Chemical structures of sugar-based biopolymers (Ledet & Mandal, 2012)

Chapter-2 Methodology

This review aiming to discuss the potential of Sugar Based Biopolymer in Nanomedicine was conducted based on some recent and prominent research papers and articles from high impactful journals. A detailed and in-depth study was conducted through the peer reviewed journals, articles and official reports. Search engines such as Research Gate, PubMed, Google Scholar, Science Direct, Elsevier, and others were used to gather impactful information from them. Moreover, google search was also used to gather basic information from credible and impactful websites as well. Finally, to generate the optimum quality review, a thorough screening of those articles was conducted to extract the most recent and relevant information.

Chapter-3 Literature review

Nanomedicine is a quickly developing area of clinical exploration that is cantered around creating NPs for prophylactic, demonstrative, and restorative applications (Bhaskar et al., 2010). Nanomedicines capability on similar scale as numerous natural cycles, cell components, and natural particles, so they are remembered to give a particularly encouraging approach. There are now numerous tactics and norms for combining, functionalizing, and using NPs, which has resulted in the introduction of new techniques for sub-atomic focusing on, customized treatments, and negligibly obtrusive symptomatic techniques (Morigi et al., 2012). Nanotherapeutics, including therapies for macular degeneration, hepatitis, increased cholesterol, immune system illness, infectious contaminations, and a number of other illnesses, have been actively promoted by the FDA and made available for clinical use. (Table 1). for extra clinical implementation NPs remember use for immunizations, attractive reverberation imaging (X-ray) contrast specialists, fluorescent organic names, microorganism recognition, protein distinguishing proof, DNA structure examining, tissue designing, medication and quality conveyance specialists, and the detachment of natural particles and cells (Bhaskar et al., 2010). An examination of nanomedicine-based medications, equipment, and diagnostics that have received FDA approval as well as applications for nanomedical research.

3.1 Cancer

At present, malignant growth determination and therapy depend fundamentally on obtrusive demonstrative procedures like biopsies and medical procedure and nontargeted therapies like illumination and chemotherapy (Bharali & Mousa, 2010). Traditional nontargeted chemotherapy drugs need particularity and, in this manner, can make critical harm sound tissues, bringing about unfortunate incidental effects, like bone marrow concealment, going bald, and the sloughing of stomach epithelial cells (Bharali & Mousa, 2010). The conclusion of beginning phase malignant growth is additionally a huge test, in light of the fact that clinical side effects don't necessarily in every case show up so as to keep the sickness from spreading to a high-level stage. Consequently,

prior disease finding by negligibly obtrusive means and designated malignant growth therapies is desperately needed. NP-based therapies and diagnostics provide more delicate imaging techniques that result in prior identification and concentrate on, growth explicit specialists that give compelling, painless treatment. Keeping that in mind, to work on the capacity to analyse different malignant growths, numerous exceptionally unambiguous and profoundly delicate NP-based optical imaging stages are as of now being studied (Bharali & Mousa, 2010). Because they can be functionalized to selectively target growth cells, NP-based diagnostics offer a distinct advantage over other forms of experts in that imaging and restorative specialists may be supplied to those cells directly (Sambasivarao, 2013). Solitary particles lack the visual, alluring, and underlying qualities that these multipurpose NP constructions possess. Techniques for developing multifunctional NP edifices for malignant growth imaging and therapy include: (1) exemplification or potentially (2) covalent or noncovalent limiting the ability of the NPs to detect or recognize the cancerous development; a license for growth imaging; deliver a therapeutic "payload" and eradicate the cancer cells. By limiting or creating growth explicit concentrating is accomplished by coating the outer layer of NPs with a particle or biomarker that interacts with the receptors on cancer cells. The strategy of multifunctional NP buildings thusly needs information on growth explicit receptors, biomarkers, homing proteins, and compounds that can allow specific cell take-up of a symptomatic or helpful specialist and resulting collection in the growth microenvironment (Sambasivarao, 2013).

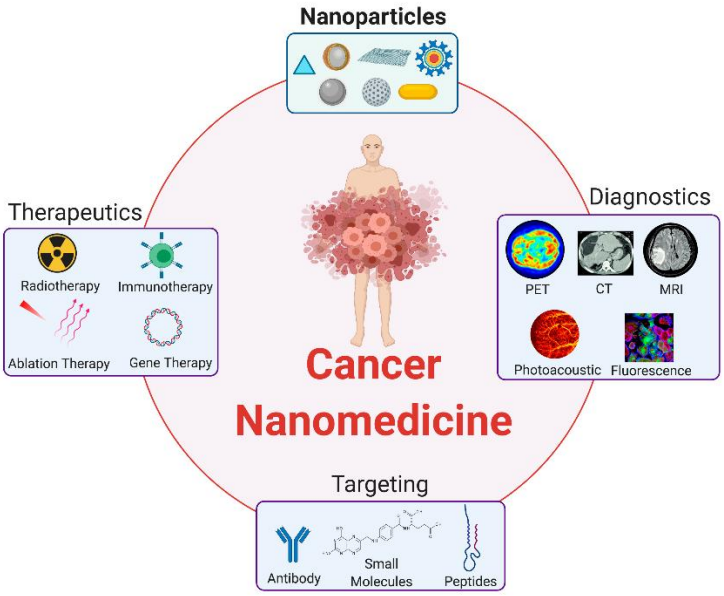

Figure 6: Nanoparticles in imaging and therapies in cancer (Damasco et al., 2020)

Peptides, proteins, and nucleic acids are among the particles and indicators frequently used for growth targeting, formation and little particle ligands. Both the inclusion of multidrug regimens and the development of the multifunctional NP complex with various peptides may result in synergistic effects. Confounded therapy regimens can also be developed using heat labile or protease-defenceless linkers that are corrupted by the tumor microenvironment to enable targeted drug release. Such multipurpose NP structures demonstrate a tremendous commitment to harmless growth imaging and diagnosis (17ffbac34bc2c4d5bdffa55d9d3f1d94.Pdf, n.d.). The disclosure of the "improved penetration and maintenance (EPR) impact" additionally adds to the progress of NPs in focusing on 582 P&T® • October 2012 • Vol.37 No.10 strong cancer tissues, contingent upon size and different qualities The EPR impact is the particular collection and maintenance of a specialist in strong cancer tissue for a drawn-out time frame. This impact is because of the intermittent epithelium and complication of the growth vasculature, expanded defectiveness of cancer veins, and diminished lymphatic drainage (Ledet & Mandal, 2012). Because there is little lymphatic freedom to remove them from the tumour, NPs are maintained inside the expanding tissue for a long time as a result of the EPR effect. Only NPs in a specific size range, however, may diffuse past the endothelium of developing tissues and take advantage of the EPR effect. The

particular size of the cancer vasculature surrenders depending on the type, location, and stage of the disease; however, the larger size range of the holes is frequently between 300 and 400 nanometres (nm) (Ledet & Mandal, 2012). NPs should also be larger than 10 nm to avoid kidney first-pass removal, but smaller than 150 to 200 nm to avoid liver and spleen elimination. In order to take advantage of the EPR effect, NPs between 20 and 100 nm in size are required. Due to their customizable size characteristics, functionalization, and capacity to take advantage of the EPR effect, among other things, 4 NPs have grown to be essential in the development of disease therapeutics. NP-based medication delivery can potentially enhance the bioavailability and poisonousness profiles of malignant growth therapies. The majority of anticancer medications are water-insoluble, so they need be broken down into an injectable solution using a naturally soluble prior organization (Bharali & Mousa, 2010). These organic solvents are toxic and frequently produce negative side effects. Numerous anticancer drugs' modest sub-atomic loads also contribute to rapid release and a poor restorative record, necessitating the organization of increasing parts, which increases cytotoxicity and other undesirable consequences. These chemotherapy specialists' nano formulations could reduce the need for unfavourable cytotoxic effects, increase bioavailability and maintenance time, work on the remedial file, get rid of the requirement for portion acceleration, use natural solvents instead of stents to cure restenosis and atherosclerosis, and do away with the need for portion acceleration. Investigation has shown that direct treatment delivery to plaque cells is made possible by the use of multifunctional NP structures built with cell-explicit ligands (Bharali & Mousa, 2010). The following therapies, among others, can be included in a specified NP complex to avoid restenosis or atherosclerosis: 5 • Cytotoxic specialists including paclitaxel, cytarabine, etoposide, and doxorubicin that prevent the growth of smooth-muscle cells. • Opponents of the platelet-determined development factor (PDGF) receptor (tyrphostins). • immunomodulators, including Cyclosporine A, bisphosphonates, and steroids. Anti-infection medications (fumagillin). Other exciting nano therapies for CVD centre on specific causes of apoplexy or intimal hyperplasia that can be identified (prostacyclin synthase and thymidine kinase). In order to achieve a prolonged discharge profile and provide insurance against enzymatic debasement, these therapies may deliver quality or other biomolecules.

Table 1. Summary of biopolymers, their advantages and possible polymeric complexes.

Biopolymer	Advantages	Polymeric Complexes	Drug	Route	Animal Model	Tumour Type	Therapeutic Target	Entrapment Efficacy	Oral vs. Intravenous Drug Uptake	References
Gelatin	- Non-toxic - Biodegradable - Inexpensive - Can be cross-linked	- Redox-responsive gelatin nanoparticles - EFGR targeted gelatin nanoparticles	- Gemcitabine - Doxorubicin	- Oral	- SCID beige mice - Nude mice	- pancreatic adenocarcinoma - breast cancer	- Panc-1 cells - MCF-7 cells	- not reported - 82%	- IG_{50} 17.08 ± 2.32 μM vs. IG_{50} value of 8.39 ± 1.79 μM	[7–18]
Collagen	- Naturally occurring - Non-antigenic - Biodegradable	- Collagen nanoparticles	- Doxorubicin	- Oral	- In vitro study	- liver cancer	- Hep G2 cells	- not reported	- 48% vs. 22%	[19–21]
PGA	- Hydrophilic - Non-toxic	- PGA nanoparticles - PEG-b-(PGA)-b-poly(phenylalanine) nanomicelles	- Cisplatin - Doxorubicin	- Oral	- Female BALB/c mice	- ovarian cancer - lung cancer	- A2780 cells - NCI-H460 cells	- not reported	- IG_{50} 0.14 nM vs. IG_{50} 1.5 nM - not reported	[22–27]
PLGA	- Biodegradable - Biocompatible	- Magnetic PLGA nanoparticles - PLGA nanoparticles	- Paclitaxel - Cetuximab	- Oral	- Strain mice	- breast cancer - lymphoma tumour	- MCF-7 and U-87 glioma cells - DLS cells	- 82.9% and 87.3%	- 64% vs. 18%	[28–35]
Chitosan	- Biocompatible - Biodegradable - Mucoadhesive - Abundantly available	- Lecithin-chitosan nanoparticles - Chitosan nanoparticles	- Tamoxifen - Doxorubicin	- Oral	- Study carried out ex vivo - Sprague–Dawley rats	- general tumours	- not reported	- 60%	- not reported	[36–44]
Alginates	- Biocompatible - Sol-gel transition properties - Mucoadhesive - Non-toxic	- Disulphide cross-linked sodium alginate nanoparticles - -pH-responsive alginate nanoparticles	- Paclitaxel - Doxorubicin	- Oral	- Kunming mice	- colon cancer - liver cancer	- HT-29 and CRL 1790 cells - H22 cells	- 77.1%	- not reported - 1216.7 ng/mL vs. 657.7 ng/mL	[45–49]
Hyaluronic acid	- Biocompatible - High viscoelasticity - Non-immunogenic	- Hyaluronic acid nanoparticles	- Doxorubicin - Cisplatin - Paclitaxel	- Oral	- Female BALB/c mice	- ovarian cancer - breast cancer	- A2780 cells - CD44-expressing MDA-MB-231 cells	- 87 ± 5.6% - 68.76 ± 5.67% - 28.1 ± 7%	- not reported	[50–55]
Pullulan	- Hydrophilic - Non-carcinogenic - Non-toxic	- pH-responsive pullulan nanoparticles - Pullulan nanoparticles	- Doxorubicin	- Oral	- Nude mice	- breast cancer	- 4T1 cells	- not reported	- not reported	[54–60]

Table 2: Summary of biopolymers, their advantages and possible polymeric complexes.

3.2 Neuro

Nanomedicine can provide a solution to the medication delivery problem across the blood-cerebral occlusion, which is arguably the greatest challenge the pharmaceutical industry has ever faced. (BBB). The BBB is a tightly packed layer of endothelial cells that surrounds the brain and blocks the entry of high-subatomic weight particles (Bawa, 2008). The BBB can only be penetrated by a small number of drugs or tiny particles with high lipid dissolvability and low subatomic mass (under 400 to 500 Daltons). Traditional medications exceed these dimensions and subatomic weight by over 98%, making them unsuited to penetrate this barrier (Bawa, 2008; Bhaskar et al., 2010). Therefore, in 2010, the market for the relatively few focused sensory system (CNS) tranquilizers that are readily available was only about one-fifth that of CVD medications. A considerable restorative benefit is provided by NPs' ability to cross the BBB due to their small size

and subatomic weight. In fact, it has been discovered that NPs can be delivered directly to the brain with hardly any functionalization or alteration (Bawa, 2008). However, a drug's pharmacological viability also depends on how well it is absorbed and how much sedate is available in the brain or CNS. Therefore, in addition to the actual obstruction brought on by the BBB and the blood cerebrospinal fluid, a number of other factors also play a role in this (BCSF). The preference for the explicit vehicle particle-specific nanocarrier substrates on the two sides of the BBB is one of these considerations (Bhaskar et al., 2010). Growth factors, insulin, and transferrin are a few examples of these delivery particles that can boost the effectiveness and energy of brain-specific nanotherapeutics. For the transport of nanomedicines through the BBB and the BCSF, similar thorough information on the variety of potential pathways to and from the CNS, lawful functionalization (where appropriate), and a method of evaluating if the nanocarrier has reached its final destination are required. Dynamic targeting can significantly boost drug penetration through the BBB. Through the process of receptor-intervened endocytosis, cells on the vascular side of the brain eventually take up the nanocarriers, which are created with ligands that bind to brain endothelial cell receptors. (Bawa, 2008). These nanocarriers, which can likewise be formed with ligands that perceive cerebrum growth cells, have arisen as a significant leap forward in CNS drug conveyance, particularly in neuro-oncology. Additionally, it is anticipated that nanomedical research will lead to the development of unique, fundamentally regulated demonstrative and restorative nanoprobes for the early identification and treatment of a range of chronic or age-related mental health conditions, such as epilepsy, dementia, stroke, and Alzheimer's disease. (Bhaskar et al., 2010).1 Nanoparticles designed with antimicrobial highlights may likewise have the option to cross the BBB, giving a successful therapy to cerebrum contaminations, including meningitis (Taylor & Webster, 2011).

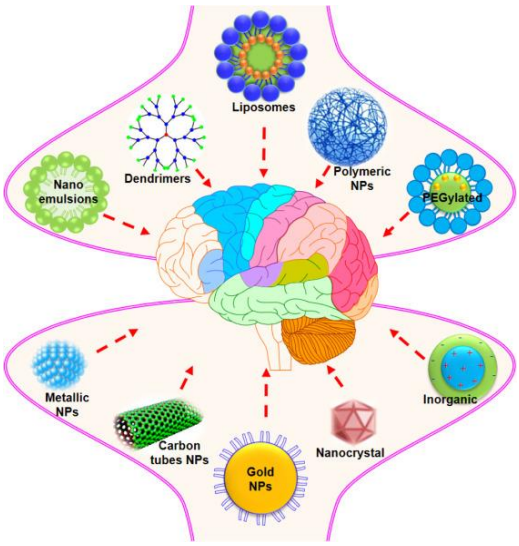

Figure 7: Nanotechnology-based drug delivery systems approaches on treatment of CNS disorders. (Nguyen et al., 2021)

3.3 Gene Therapy

Recently, several polymeric drug/quality stacked nanoparticles have been developed as drug delivery transporters, and their role in human body distribution has received extensive investigation (Adiseshaiah et al., 2010; Moghimi, 1995). When chemicals like medicines or quality-stacked nanoparticles are injected into the body, the pharmaceuticals must first cross epithelial barriers and loop through veins before they can reach the intended site. When tissues have fenestrated or are persistent, the nanoparticles exit the circulatory dispersion. The paracellular route, the intracellular cycle, or transmembrane transport through persistent vascular endothelium in healthy tissues are all ways that nanoparticles might leave the circulatory system. Contrary to the norm, the fenestrated vascular endothelium of porous tissues has holes that are substantially bigger (100 nm to 2 m) than those of solid tissues (2-6 nm). As a result, nanoparticles undergo fenestrations, which are known as "enhanced penetration and maintenance effect (EPR impact)" because they promote drug entry into tissues and aggregate pharmaceuticals in growth destinations (Adiseshaiah et al., 2010; Gaumet et al., 2008; Maeda et al., 2000). It should be mentioned that the fenestrations of the growth vasculature might differ based on the kind of malignant growth, the

severity of the sickness, and the location of the body. Additionally, the vasculature and fenestrations may change in a variety of compulsive situations (Gaumet et al., 2008; Maeda et al., 2000). For instance, the growth of cancer triggers the expansion of neo vasculature, which is characterized by intermittent endothelium with enormous fenestrations of 200-780 nm permitting nanoparticles transit (Hobbs et al., 1998). Toxicology has to be taken into account for the particles as well because of the many ways in which they might connect with liquids, cells, and tissues. Starting at the section's entrance, this should go via a number of different probable paths until it reaches the intended organs (Donaldson et al., 2004). Nanoparticles may activate intermediates at the site of conclusive maintenance in the target organ(s), which can then trigger provocative or immune reactions. Due to these circumstances, one of the essential requirements for the use of conveyance transporters is the creation of biopolymer-based nanoparticles with certain sizes. Nanoparticles may activate intermediates at the site of conclusive maintenance in the target organ(s), which can then trigger provocation or immunological reactions. Because of these factors, one of the necessary requirements for the use of conveyance transporters is the creation of biopolymer-based nanoparticles with certain sizes (Moghimi, 1995; Nakaoka et al., 1997). Because they all affect the process of cell assimilation via endocytosis, molecule shape, surface charge, and surface component also play a role in intercellular transport (Mizrahy & Peer, 2012; Petros & Desimone, 2010). Additionally, the kind of polymers, molecule sizes, dissolvability, biodegradability, and surface qualities should be taken into account in order to achieve the site-explicit conveyance and arrival of bioactive pharmaceuticals at the needed pace and quantity (Mohanraj & Chen, 2007). As an example, the growth of cancer (pH 7.2–7.4) and multiple powerful tumors stimulate the expansion of neo vasculature, which is characterized by intermittent endothelium with enormous fenestrations of 200–780 nm permitting nanoparticles passage (pH 6.2-6.9). A variety of illnesses, including malignant growth, Helps, and cardiovascular conditions, have received quality treatment based on the theory that human infection could be treated by the exchange of hereditary materials into specific cells of a patient to supply inadequate qualities necessary for infection improvement (Mansouri et al., 2004). The attributes should leave the cycles that affect how macro molecules behave in order to go to the specific place. Additionally, serum nucleases should not be used since they might degrade quality. In order to protect the quality till it reaches its destination, it is crucial to illustrate attributes in a conveyance carrier. The conveyance transports need to be little enough to fit into cells and divide to the centre. They should also be

capable of avoiding endosome-lysosome interaction and responding to endocytosis (Mansouri et al., 2004). Both viral and non-viral vectors for the transfer of characteristics have been developed, however because to their low immunogenicity and ease of administration, non-viral vectors have garnered the most attention (Taylor & Webster, 2011). interacting with DNA Cationic polymers may function in this way as non-viral vectors for uses in quality control. The creation of cell-explicit ligands for the outer layer of nanoparticles is taken into consideration as a deliberate transgene articulation to offer specificity to the surfaces. For instance, to address cell-explicit targeting and better-quality exchange, the cationic polymers and quality nanoparticles may be modified with proteins (handle, transferrin, or antibodies/antigens) (Dang & Leong, 2006). Methods for delivering nitric oxide (NO) have also been identified as prospective therapeutic strategies that take use of NO's important natural activities. Nitric oxide has been linked to wound healing and is known to have antibacterial properties. (2015) Wang et al (2009) Weller Numerous administrative, defensive, and detrimental impacts of nitric oxide (NO) have led to extensive study into its synthesis as well as modifications to the substances and drugs used in its manufacture. The potential for NO-delivering frameworks, such as nanoparticles, to store and deliver NO payloads in a more regulated and attractive manner is particularly fascinating (Carpenter & Schoenfisch, 2012). Numerous NO-producing substances have really been coupled with or immobilized in biocompatible polymer frameworks and used as patches, wound dressings, coatings on blood-reaching medical devices, and time-release NO medications (Eroy-Reveles & Mascharak, 2009). Dextran and chitosan, two biopolymers, have been used as frameworks for regulated NO arrival (Friedman et al., 2008).

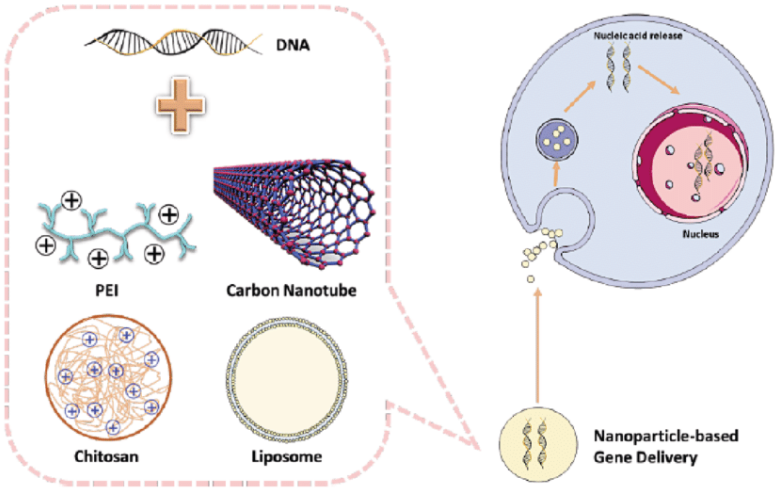

Figure 8: The applications of nanoparticles in gene delivery. (Shen et al., 2019)

3.4 Tissue Engineering

Tissue designing can be considered as an extraordinary instance of medication conveyance where achieving controlled cell transportation is the goal. The viability of tissue design is improved by the controlled introduction of restorative factors. By designing biomaterials with precise connections at the nanoscale, it is possible to significantly improve the natural components of shown drugs and cells (Bawa, 2008). The consolidation of quality conveyance components into the framework can possibly upgrade the transaction among cells with the extracellular milieu because the extracellular milieu acquaints cells with signals and prompts in a spatial and temporary fashion for tissue formation and support. In this manner, the restorative qualities can upgrade consolidation of a tissue develop, development and digestion with adjoining tissues. Additionally, the conveyance of qualities involving biopolymers can work as DNA complexing specialists as well as underlying frameworks for the purpose of developing tissues. This blend of quality treatment and tissue designing inside a solitary framework is believed to be another treatment for recovery medication (Dang & Leong, 2006). Neighbourhood quality conveyance framework utilizing quality-initiated lattice (GAM) mixes these two methodologies, filling in as a nearby

bioreactor with restorative quality articulation and giving an underlying layout to fix the glaring flaws in cell fusion, multiplication, and extracellular network combination (Peng et al., 2009).

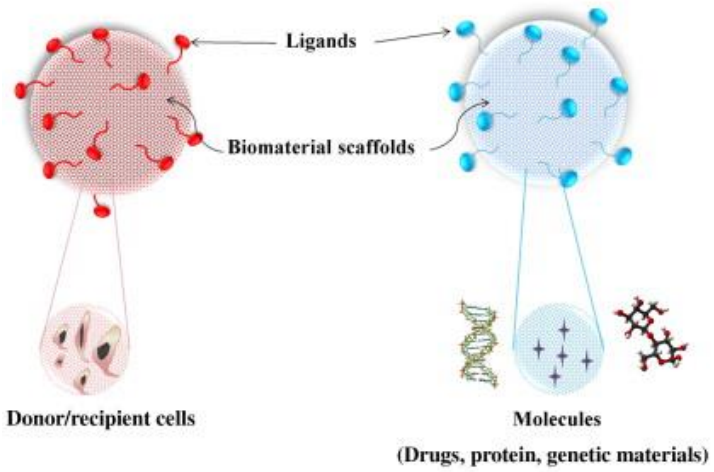

Figure 9:Approaches of tissue engineering. (Sudhakar et al., 2015)

Chapter-4 Discussion

4.1 Nanomedicine functions with polymer

Only the most important and pertinent information was provided in the previous section because the use of polymers and biopolymers in nanomedicine is widespread and effectively completes specialized applications. In like manner, it is difficult to credit appropriately undeniably distributed examinations and researchers in the area. The most current and closely related licenses to the aforementioned nanoparticle frameworks are discussed in this section, along with writing from logical diaries that illustrates various ways to arrange and use polymeric nanoparticles.

Polypeptide ligands were combined with nanoparticles containing healing agents, such as chondroitin sulfate, keratin sulfate, or hyaluronic acid, to deliver healing agents to ligament tissues (B. Goudoulas, 2012). Three ligands were effectively employed in the review; the term "ligand" refers to a polypeptide with a particular amino acid grouping that has the capacity to restrict to ligament tissue. The poly (propylene sulfide) (PPS) was the starting material, and the polypeptides on the particles confirmed that the production was successful. The tactics revealed by the patents expect to complete compelling designated conveyance of visco-supplementation (for example intra-articular infusion of medications), to limit intraarticular infusions and to expand the bioavailability of medications in articular ligament (B. Goudoulas, 2012). Recently, pGlu-PLA block copolymer nanoparticles that are synthesized with a ligand were generated using a similar method. These nanoparticles, as seen, have a hydrophilic outer shell and a hydrophobic inside core. The ligand is predisposed to bind to the asialoglycoprotein (ASGP) receptor, which is present on hepatocytes and several human hepatoma cell lines, therefore the liver is the transportation target in this case. (WO2011088562A1.Pdf, n.d.) likewise alludes to formed nanoparticles, which are contained a centre, including a glucose/polyethyleneglycol (PEG) form enclosing the centre, PEI, and a polynucleotide encoding p53. The methods developed for combining these nanoparticles hope to determine successful transporters for designated conveyance to cancer cells. The announced fundamental investigations of the application are empowering (WO2011088562A1.Pdf, n.d.).

One illustration of nanogel arrangement technique for oxidized dextrin has been as of late enrolled from the Minho University (PT). Due to their lack of poisonousness and immunogenicity, dextrin

and its subordinates are regarded as major polysaccharides in the biomedical sector. The development uncovers a readiness technique to get through a hydrogel straightforward and reasonable substance strategies, without utilizing poisonous pioneer or impetuses. These cycles, which also kick-start a helpful speed of gelification, enable the development of hydrogels with suitable mechanical properties, such as injectable material and simultaneously a medium for controlled drug conveyance frameworks, such as hydrophobic particles and reparative proteins. Gel structures made of oxidized dextrin that has been reticulated with adipic acid corrosive dihydrazide and contains mixes of, among others, chitosan, hyaluronic acid corrosive, collagen, and fibronectin. The inventors state that the maximum amount of dextrin that could dissolve in phosphate support at pH 6.0 was 30% (w/v), resulting in hydrogels that were very thick and virtually impossible to homogenize. Through the use of nanogel/FITC discharge, which is a fluorescent test often used in organic exams because of its biocompatibility, the corruption profile of the assembled nanogels was evaluated. Due of its biocompatibility, FITC is a fluorescence test commonly used in organic exams. According to mass misfortune investigations that were conducted, the debasement speed revealed that in about 25 days, dextrin nanogels had a mass misfortune of around 70%.

Another biopolymer used for mucosal conveyance of vaccine adjuvants and antigens is hyaluronic acid (HA), which has been used to transport microspheres. (Hagan et al., 2011). The development relates to the production of "microspheres," or nanoparticles from HA and its subordinates that are preferably between 500 nm and about 10 m in size the administration of an antigen to a mucosal surface, such as the sublingual or buccal surfaces, nasal, pneumonic, vaginal, rectal, or urethral surfaces is suggested by the term "mucosal conveyance." In a similar vein, any antigen for which humoral and cell resistance responses are required can be treated using the techniques demonstrated by the invention. According to the patent, antigens derived from bacterial, viral, infectious, and parasitic pathogens as well as T-cell cytotoxic and helper epitopes may be included. It is advised that the optimal sub-atomic weight for the esterified HA subsidiaries fall between 100 kDa and 150 kDa. Additionally, the depending on the antigen utilized, the ideal antigen to hyaluronic acid corrosive stacking proportion in a microsphere will range from about 2% to around 20% (w/w).

Due to their advantages, this vesicle has been put to use often in drug delivery in addition to the a forementioned clear application of liposomes (a centre shell lipid bilayer structure and so forth). Improvement, be that as it may, is required specifically perspectives, for example dependability so as (to forestall changes in molecule endlessly size appropriation), and momentary arrival of the medication. Regarding this, nanostructures that can contain a centre shell structure a permeable molecular centre encircled by a shell of lipid bilayer are introduced in patents (B. Goudoulas, 2012). Along these lines, the lipid bilayer and its combination on permeable molecule centre can be satisfactorily changed in accordance with control the medication stacking and discharge. Additionally, the targeting profiles may also be adjusted. These structures are used in ophthalmology medication conveyance, since consideration of medications into lipid-based definitions allows longer medication home on eye surface in contrast with watery arrangements presents a development of a liposome framework, by reaching mass material with a polyionic material solution, where the polyionic material has charges opposite to the charges of the vesicle, to produce a polyionic layer on top of the vesicle layer. It is suggested that the arranging phases be repeated several times in order to form layers of the polyionic substance that are sandwiched between each pair of adjacent vesicle layers. There is also a description of a liposomal delivery system that may transport several sorts of medications to the back of the eye. (B. Goudoulas, 2012). According to the patent, the disclosed techniques produce liposomes with an exceptional structure that comprise phospholipids, a charged material, and cholesterol or its derivatives. While the cholesterol works to build up the vesicle bilayers, the charged substance ideally one that is negatively charged will provide the real reliability of the liposomal solution.

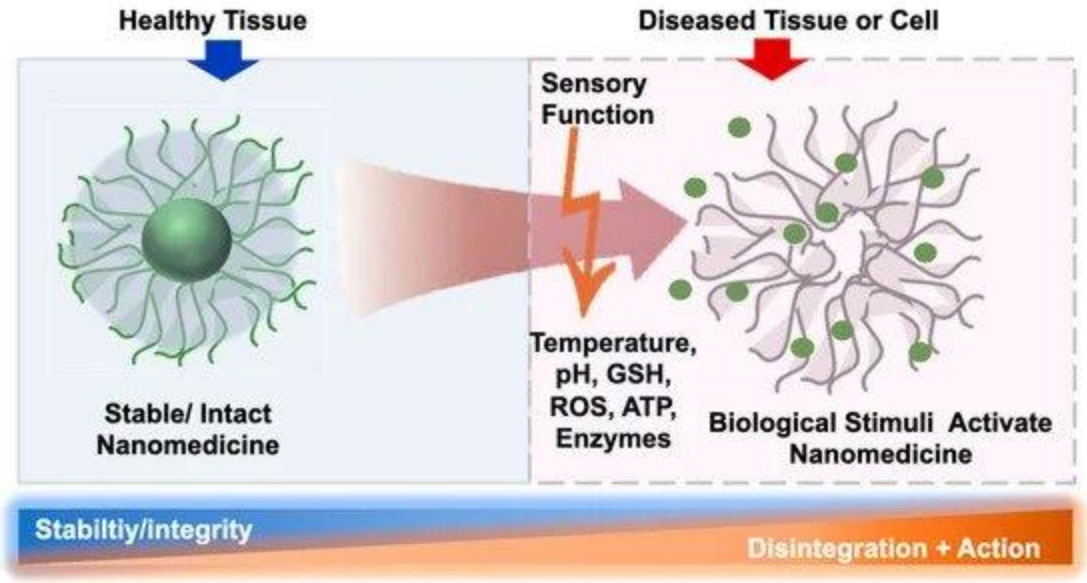

Figure 10: Nanomedicine function with polymer (Quader & Van Guyse, 2022)

4.2 How it's better than others

In the past 10 years, Nanomedicine has shown the fascinating potential of polymer- and biopolymer-related nanomaterials and nanotechnology. A few licenses still involve studies of drug delivery combined with novel assembly techniques for polymer assemblies such micelles, liposomes, dendrimers, and nanogels. In the event that appropriate copolymer mixes or the decision to commence polymeric mixtures are made, the final one may be productively regulated. The dependability of liposomes, practical multi-facet structures, and insightful upgrades responsiveness, to name a few, provide difficulties for development. Additionally, transitions from one type of nanoparticle to another or interactions of polymeric nanoparticles with a particular substrate for drug administration provide new insights on polymer nanotechnology and allow experts to continue their research. However, it should be highlighted that one issue with new licenses is the creation of a disproportionately large number of cases in them; a patent studied in the current work has encountered several abandoned claims.

One potential application for nanomedicine is the oral administration of chemotherapeutics. In contrast to the ongoing act of chemotherapy (i.e., intravenous infusion or implantation), which results in high peak drug fixation in the plasma and rapid discharge of the medication from the

circulatory system, oral chemotherapy can maintain a maintained and gentle medication focus in the dissemination to achieve a prolonged acceptance of carcinogenic cells to the medication. In this manner, oral medication conveyance is viewed as the most satisfactory technique for drug conveyance to the body (Saremi et al., 2011; Zhang et al., 2011).

One of the most difficult parts of nano-based diagnostics and medication delivery is the functionalization of NPs. In order to consolidate particular biomolecules to the top layer of NPs in a highly regulated manner, it is required to design new, potent forming processes (Bhaskar et al., 2010; Vinogradov et al., 2004). A multi-facet, PEGylated NP is depicted in. Functionalization in and of itself necessitates a substantial amount of knowledge regarding the target organ and its supporting tools, such as the management of brain growths.

However, on the other side, the BBB prevents Alzheimer's infection. The BBB, despite this, contains a few vehicle particles that could increase the potency and energy of nanocarriers directed at the brain (Bhaskar et al., 2010; Vinogradov et al., 2004). Another aspect of modern nanomedicine is the development of novel nanodevices for in vivo imaging. The ability to adjust factors such liposome size, surface charge, and particularity considers the possibility for imaging that is obsessional, such them in vivo imaging of aggressive tumours. Surface charges that keep an eye on impartiality are best suited for in vivo applications because they can reduce liposome particle identification by plasma proteins and the reticuloendothelial framework. This can be achieved by taking charged nonpartisan lipids into account while defining liposomes, such as NPs that concurrently consolidate gadolinium which completely immersed of a phospholipid part, for use as specialists to upgrade an attractive reverberation picture (MRI) of growths. In this manner, involving such NPs as differentiation specialists of the image, MRI seems more honed and offers effective demonstrative perusing. Another recently created nanocarrier framework has been proposed as a promising biocompatible and adaptable multifunctional stage for medicine and differentiation tailored conveyance for the treatment of the liver (containing functionalized RGD peptide by high thickness lipoprotein NPs) (Chen et al., 2010). The potential drug applications are various and at the same time accomplished in medicine conveyance, where nanomedicine can significantly provide solutions (for example, to tranquilize dissolvability and dependability issues) and work on particular conveyance to target destinations. In vivo and in vitro tests will show the viability of polymer nanoparticles, but more top to bottom examinations will be important to make

these frameworks advantageous to clinical investigations. The clinical preliminaries, be that as it may, will uncover the genuine advancement, since quite a long while and a great deal of preliminaries are needed from the final kind of a commercial medication, offered fresh techniques of combination.

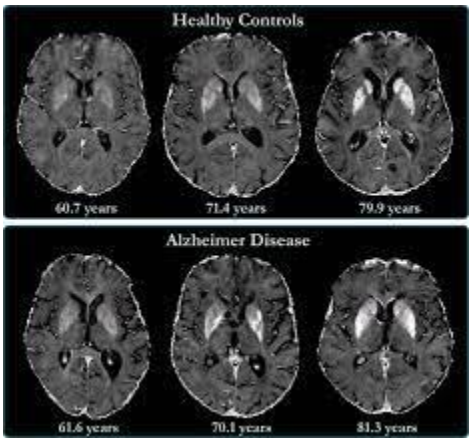

Figure 11: The Biomarkers of Alzheimer Disease Brain.

Chapter-5 Conclusion

5.1 Clinical Trial

Numerous clinical uses for NPs are being investigated in clinical preliminary studies, and much more concept validation work on in-cell societies or small animal models is in progress. An investigation that is focused on ClinicalTrials.gov, which is a data set of clinical trials that are both publicly and privately supported by the government in the United States and in other countries, currently records 111 clinical trials that include NPs. Table 3 provides a posting that was authorized for various NPs that are now the subject of investigation in clinical preliminary stages. BIND014 is a promising malignant growth nanomedicine in clinical trials (designated polymeric NP complex containing docetaxel, Tie Biosciences). The primary aims of the evaluation are to determine the most severe endured component of Tie 014 and to assess basic evidence of anticancer activity. Tie 014 accumulates at growth destinations and presents clinical viability at doses as low as 20% of standard docetaxel, even in illnesses that are not typically influenced by this medication, according to preliminary data in a patient population (n = 17) with cutting-edge or robust growths. Tie 014 was also shown to be very well tolerated, with no additional toxic levels recorded in the human clinical study to yet. The nanomedicine Aurimune (CytImmune Sciences) is another highly anticipated cancer treatment for individuals with advanced or metastatic cancers who have not responded to standard treatment. Aurimune comprises recombinant human growth putrefaction factor-alpha (TNF-a) functionalized strong gold NPs with a mean size of 30 nm (Seigneuric et al., 2010). The outer layer of the colloidal gold NPs in Aurimune is pegylated, allowing the therapeutic payload to avoid detection and transit safely through the circulation. Evidence from histopathology suggests that these NPs are selectively taken up by cancer cells and not by healthy tissues, unlike what is found with conventional TNF-a. Traditional definitions of cytokines, such as TNF-an, are limited in their therapeutic use due to the provocative responses they elicit, particularly when tissues are exposed to large levels. Patients have been able to tolerate 20 times the standard dose of traditional TNF-a with an IV injection of Aurimune. Patients with head and neck cancer are now being examined in clinical studies using AuroShell (Nanospectra Biosciences). The optically adjustable 28 AuroShell particles have a mean diameter of 150 nm, a silica core, and a very thin gold shell. Due to the EPR effect, these particles are intravenously

delivered into patients and gather in tumors. Following tumor formation, the region is irradiated with a near-infrared laser at wavelengths that allow penetration without damaging healthy tissues. AuroShell is being evaluated in clinical studies for people with head and neck cancer (Nanospectra Biosciences). The optically reconfigurable AuroShell particles comprise a silica core and an ultrathin gold shell, with a mean particle size of 150 nm. These particles, which are administered intravenously to patients, congregate in tumors due to the EPR effect. After aggregation in tumors, the region is illuminated using a near-infrared laser at wavelengths that can pass through healthy tissues without harming them. The metal in the AuroShell particles acts as a heat generator for thermal ablation treatment, which eliminates a tumor by heating it from the inside out. This technique has the potential to be used in the treatment of all solid tumors, such as those found in the breast, prostate, and lungs. Gold's toxicity, however, has not been well studied.

5.2 Challenges

Incorporated nanomedicine is the new arising period and can be accomplished by imaging and treatment. The job of sugar-based polymers has been extending in this field step by step due to their biocompatible and non-poisonous amphiphilic nature. By utilization of fundamental standards of science and materials science, multifunctional NPs are intended for malignant growth science and demonstrative imaging. The latest examinations in malignant growth treatment demonstrated that sugar-based biopolymers could likewise be applied for both medication conveyance and imaging frameworks. They have been giving unquestionable commitment to theragnostic by focusing on property. Furthermore, they have been utilized for sub-atomic imaging to envision cell capability or changes in malignant growth tissue, which mirror the movement and assign restorative reaction of malignant growth sickness(Massoud & Gambhir, 2003). Numerous SBNPs could be conveyed to cancers. Attributes of the particles like size, shape, dependability, unbending nature, and surface property have effect on the biodistribution of therapeutics(Omidi, 2011; Paquin et al., 2015; Peer et al., 2007). A solitary component cannot keep up with in that frame of mind of them. Additionally, their pharmacokinetics and in vivo conduct stay capricious and their course in body ought to be trailed by an imaging specialist. In this, we evaluated for the most part five different theragnostic NPs of sugar-based biopolymers, which could both convey designated restorative freight by the guide of their better properties and screen the reaction than treatment. Their cement, alterable and different nature make them extraordinary specialists in

nanomedicine for self-assembly and covering purposes. Then again, age of NPs for customized medication could be conceivable by investigation of natural microflora of malignant growth site and physicochemical construction of disease cells. According to this point of view, studies showed that clinical oncology ought to be coordinated with material science to foster novel NPs in not-so-distant future. As an outcome, plan of ideal NPs in malignant growth treatment can be laid out by effectively underway of multifunctional therapeutics; yet additionally seeing extraordinary cancer science and organic obstructions in human body. Be that as it may, dynamic and uninvolved focusing on methodologies address additionally broad growth types and the destiny of NPs must be seen by observing them by means of non-poisonous ways.

5.3 Future Aspects

Imaging and therapy can be used to achieve integrated nanomedicine, which is the new emerging field. Due to the following factors, the role of sugar-based polymers in this industry has been growing daily their amphiphilic character, which is biocompatible and non-toxic. Multifunctional NPs are created for imaging and cancer biology using fundamental chemistry and materials science concepts. Recent studies in the field of cancer treatment suggested that sugar-based biopolymers could be used for imaging and drug delivery. By focusing on property, they have made an unquestionable contribution to theragnostic. Molecular imaging has also been applied to them in order to see how cells behave or change in cancer tissue, reflecting the disease's course and identifying its therapeutic response (Massoud & Gambhir, 2003). Tumours could receive a lot of SBNPs. The biodistribution of medicines is influenced by the particle's size, shape, stability, rigidity, and surface properties(Mizrahy & Peer, 2012; Omidi, 2011; Pramod et al., 2014). They cannot sustain their in vivo fate due to a single cause. Moreover, an imaging agent should follow their course in the body because their pharmacokinetics and in vivo behaviour are still uncertain.

Here, we primarily evaluated five distinct theragnostic NPs made of sugar-based biopolymers that could deliver specific therapeutic cargo and track patient response to treatment. They are excellent self-assembling and coating agents in nanomedicine due to their sticky, modifiable, and diverse character.

On the other hand, examination of the biological microflora of the cancer location and the physicochemical structure of cancer cells may enable the creation of NPs for tailored therapy.

According to studies, clinical oncology and material science should be combined in the near future in order to produce innovative NPs. As a result, the design of perfect NPs for cancer treatment can be established by not only making multifunctional treatments readily, but also by understanding the specific biology of each tumour and the biological obstacles in the human body. However, both active and passive targeting methods reflect common tumour types, and the only way to determine the fate of NPs is to monitor them in non-toxic ways.

5.4 Conclusion

Nanomedicines have extraordinary properties that might possibly give novel arrangements in the treatment of numerous sicknesses. Various FDA-supported therapeutics, clinical gadgets, imaging specialists, and demonstrative gadgets containing nanomaterials have proactively opened up, propelling medication and further developing wellbeing care. Notwithstanding significant obstructions that hinder the turn of events and accessibility of nanomedical items, it is normal that examination and interest in this space will go on at a quick speed, making these items become a fundamental piece of standard medication later on.

Reference

Alfarouk, K. O., Verduzco, D., Rauch, C., Muddathir, A. K., Bashir, A. H. H., Elhassan, G. O., Ibrahim, M. E., Orozco, J. D. P., Cardone, R. A., Reshkin, S. J., & Harguindey, S. (2014). Glycolysis, tumor metabolism, cancer growth and dissemination. A new pH-based etiopathogenic perspective and therapeutic approach to an old cancer question. *Oncoscience*, *1*(12), 777–802. https://doi.org/10.18632/oncoscience.109

Almaraz, R. T., Tian, Y., Bhattarcharya, R., Tan, E., Chen, S. H., Dallas, M. R., Chen, L., Zhang, Z., Zhang, H., Konstantopoulos, K., & Yarema, K. J. (2012). Metabolic flux increases glycoprotein sialylation: Implications for cell adhesion and cancer metastasis. *Molecular and Cellular Proteomics*, *11*(7), 1–12. https://doi.org/10.1074/mcp.M112.017558

Cui, L., Cohen, J. A., Broaders, K. E., Beaudette, T. T., & Fréchet, J. M. J. (2011). Mannosylated dextran nanoparticles: A pH-sensitive system engineered for immunomodulation through mannose targeting. *Bioconjugate Chemistry*, *22*(5), 949–957. https://doi.org/10.1021/bc100596w

Damasco, J. A., Ravi, S., Perez, J. D., Hagaman, D. E., & Melancon, M. P. (2020). Understanding nanoparticle toxicity to direct a safe-by-design approach in cancer nanomedicine. *Nanomaterials*, *10*(11), 1–41. https://doi.org/10.3390/nano10112186

Farokhzad, O. C., & Langer, R. (2009). Impact of nanotechnology on drug delivery. *ACS Nano*, *3*(1), 16–20. https://doi.org/10.1021/nn900002m

Jain, K., Kesharwani, P., Gupta, U., & Jain, N. K. (2012). A review of glycosylated carriers for drug delivery. *Biomaterials*, *33*(16), 4166–4186. https://doi.org/10.1016/j.biomaterials.2012.02.033

Kim, S. J., Bae, P. K., & Chung, B. H. (2015). Self-assembled levan nanoparticles for targeted breast cancer imaging. *Chemical Communications*, *51*(1), 107–110. https://doi.org/10.1039/c4cc07679f

Kumari, A., Yadav, S. K., & Yadav, S. C. (2010). Biodegradable polymeric nanoparticles based drug delivery systems. *Colloids and Surfaces B: Biointerfaces*, *75*(1), 1–18.

https://doi.org/10.1016/j.colsurfb.2009.09.001

Ledet, G., & Mandal, T. K. (2012). Nanomedicine : Emerging Therapeutics for the 21st Century. *US Pharmacist*, *37*(3), 7–11.

Ling, S., Chen, W., Fan, Y., Zheng, K., Jin, K., Yu, H., Buehler, M. J., & Kaplan, D. L. (2018). Biopolymer nanofibrils: Structure, modeling, preparation, and applications. *Progress in Polymer Science*, *85*, 1–56. https://doi.org/10.1016/j.progpolymsci.2018.06.004

Massoud, T. F., & Gambhir, S. S. (2003). Molecular imaging in living subjects: Seeing fundamental biological processes in a new light. *Genes and Development*, *17*(5), 545–580. https://doi.org/10.1101/gad.1047403

Matsumura, S., Hlil, A. R., Lepiller, C., Gaudet, J., Guay, D., Shi, Z., Holdcroft, S., & Hay, A. S. (2008). Stability and Utility of Pyridyl Disulfide Functionality in RAFT and Conventional Radical Polymerizations. *Journal of Polymer Science: Part A: Polymer Chemistry*, *46*(April), 7207–7224. https://doi.org/10.1002/pola

Mizrahy, S., & Peer, D. (2012). Polysaccharides as building blocks for nanotherapeutics. *Chemical Society Reviews*, *41*(7), 2623–2640. https://doi.org/10.1039/c1cs15239d

Nguyen, T. T., Dung Nguyen, T. T., Vo, T. K., Tran, N. M. A., Nguyen, M. K., Van Vo, T., & Van Vo, G. (2021). Nanotechnology-based drug delivery for central nervous system disorders. *Biomedicine and Pharmacotherapy*, *143*(August), 112117. https://doi.org/10.1016/j.biopha.2021.112117

Omidi, Y. (2011). Smart multifunctional theranostics: Simultaneous diagnosis and therapy of cancer. *BioImpacts*, *1*(3), 145–147. https://doi.org/10.5681/bi.2011.019

Ossipov, D. A. (2010). Nanostructured hyaluronic acid-based materials for active delivery to cancer. *Expert Opinion on Drug Delivery*, *7*(6), 681–703. https://doi.org/10.1517/17425241003730399

Park, J. H., Saravanakumar, G., Kim, K., & Kwon, I. C. (2010). Targeted delivery of low molecular drugs using chitosan and its derivatives. *Advanced Drug Delivery Reviews*, *62*(1), 28–41. https://doi.org/10.1016/j.addr.2009.10.003

Pramod, P. S., Shah, R., Chaphekar, S., Balasubramanian, N., & Jayakannan, M. (2014). Polysaccharide nano-vesicular multidrug carriers for synergistic killing of cancer cells. *Nanoscale*, *6*(20), 11841–11855. https://doi.org/10.1039/c4nr03514c

Quader, S., & Van Guyse, J. F. R. (2022). Bioresponsive Polymers for Nanomedicine—Expectations and Reality! *Polymers*, *14*(17), 1–3. https://doi.org/10.3390/polym14173659

Rao, W., Wang, H., Han, J., Zhao, S., Dumbleton, J., Agarwal, P., Zhang, W., Zhao, G., Yu, J., Zynger, D. L., Lu, X., & He, X. (2015). Chitosan-Decorated Doxorubicin-Encapsulated Nanoparticle Targets and Eliminates Tumor Reinitiating Cancer Stem-like Cells. *ACS Nano*, *9*(6), 5725–5740. https://doi.org/10.1021/nn506928p

S. Eroglu, M., Toksoy Oner, E., Cansever Mutlu, E., & Sennaroglu Bostan, M. (2017). Sugar Based Biopolymers in Nanomedicine; New Emerging Era for Cancer Imaging and Therapy. *Current Topics in Medicinal Chemistry*, *17*(13), 1507–1520. https://doi.org/10.2174/1568026616666161222101703

Schmaus, A., Bauer, J., & Sleeman, J. P. (2014). Sugars in the microenvironment: the sticky problem of HA turnover in tumors. *Cancer and Metastasis Reviews*, *33*(4), 1059–1079. https://doi.org/10.1007/s10555-014-9532-2

Sezer, A. D., Kazak, H., Öner, E. T., & Akbua, J. (2011). Levan-based nanocarrier system for peptide and protein drug delivery: Optimization and influence of experimental parameters on the nanoparticle characteristics. *Carbohydrate Polymers*, *84*(1), 358–363. https://doi.org/10.1016/j.carbpol.2010.11.046

Shen, H., Huang, X., Min, J., Le, S., Wang, Q., Wang, X., Dogan, A. A., Liu, X., Zhang, P., Draz, M. S., & Xiao, J. (2019). Nanoparticle Delivery Systems for DNA/RNA and their Potential Applications in Nanomedicine. *Current Topics in Medicinal Chemistry*, *19*(27), 2507–2523. https://doi.org/10.2174/1568026619666191024170212

Sudhakar, C. K., Upadhyay, N., Verma, A., Jain, A., Narayana Charyulu, R., & Jain, S. (2015). Nanomedicine and Tissue Engineering. In *Nanotechnology Applications for Tissue Engineering*. Elsevier Inc. https://doi.org/10.1016/B978-0-323-32889-0.00001-7

Yasar Yildiz, S., & Toksoy Oner, E. (2014). Mannan as a Promising Bioactive Material for Drug

Nanocarrier Systems. *Application of Nanotechnology in Drug Delivery*. https://doi.org/10.5772/58413

Liu, G., Moake, M., Har-el, Y. E., Long, C. M., Chan, K. W., Cardona, A., … McMahon, M. T. (2012). In vivo multicolor molecular MR imaging using diamagnetic chemical exchange saturation transfer liposomes. Magnetic Resonance in Medicine, 67(4), 1106–1113. https://doi.org/10.1002/mrm.23100

Fang FC (2004) Antimicrobial reactive oxygen and nitrogen species: concepts and controversies. Nat Rev Micro 2:820–32

Friedman AJ, Han G, Navati MS, Chacko M, Gunther L, Alfieri A et al. (2008) Sustained release nitric oxide releasing nanoparticles: characterization of a novel delivery platform based on nitrite containing hydrogel/glass composites. Nitric Oxide 19:12–20

Stewart, B. W. & Kleihues, P. World Cancer Report (World Health Organization Press, Geneva, 2003).

Cancer Facts & Figures 2007 (American Cancer Society, Atlanta, 2007).

Duncan, R. Polymer conjugates as anticancer nanomedicines. Nat. Rev. Cancer 6, 688–701 (2006).

Ferrari, M. Cancer nanotechnology: opportunities and challenges. Nat. Rev. Cancer 5, 161–171 (2005).

Couvreur, P. & Vauthier, C. Nanotechnology: Intelligent design to treat complex disease. Pharm. Res.23, 1417–1450 (2006).

Alonso, M. J. Nanomedicines for overcoming biological barriers. Biomed. Pharmacother. 58, 168–172 (2004).

Matsumura, Y. & Maeda, H. A new concept for macromolecular therapeutics in cancerchemotherapy — Mechanism of tumoritropic accumulation of proteins and the antitumor agent smancs. Cancer Res. 46, 6387–6392 (1986).

Mancuso AA, Hanafee WN. Comp uted tomography and magnetic resonance imaging of the head and neck. 2nd ed. Baltimore: Williams and Wilkins, 1984:169- 240

Mancuso AA, Maceri D, Rice D, Hanafee WN . CT of cervical lymph node cancer. AJR Am J Roentgenol 1981; 136:38 1-385

Mancuso AA, Harnsberger HR, Muraki AS, Stevens MH. Computed tomography of cervical and retropharyngeal lymph nodes: normal anatomy, variants of normal and applications in staging head and neck cancer. Part 1: normal anatomy. Radiology 1983; 148:709-714

Som PM. Lymph nodes of the neck. Radiology 1987; 165:593-600

Som PM. Detection of metastasis in cervical lymph nodes: CT and MR criteria and differential diagnosis. AJR Am J Roentgenol 1992; 158:96 1-969

Bengele HH, Palmacci S, Rogers J, Jung CW, Crenshaw J , Josephson L. The biodistribution of an ultrasmall superparamagnetic iron oxide colloid, BMS 180549, by different routes of administration. Magn Reson Imaging (in press)

Lufkin RB, Larsson SG, Hanafee WN. Work in progress: NMR anatomy of the larynx and tongue base. Radiology 1983; 148:17 1-175

Teresi LM, Lufkin RB, Vinuela F, eta!. MR imaging of the nasopharynx and flsor of the m iddle cranial fossa. Part I. Normal anatomy. Radiology 1987; 164:811-816

Abdelkader H, Patel D, Mcghee C, Alany RG (2011d) New therapeutic approaches in the treatment of neurotrophic keratopathy. Clin Experiment Ophthalmol 39:259–270

Ahmed I, Patton TF (1985) Importance of the noncorneal absorption route in topical ophthalmic drug delivery. Invest Ophthalmol Vis Sci 26(4):584–587

Alany RG, Rades T, Nicoll J, Tucker IG, Davies NM (2006) Water in oil microemulsions for ocular drug delivery: evaluation of ocular irritation and precorneal retention. J Control Release 111:145–152

Bell SJD, He Q, Chu T, Potter DE (2004) Intraocular delivery compositions and methods. World

Patent 2004/050065

Bhadra D, Bhadra S, Jain S, Jain NK (2003) A PEGylated dendritic nanoparticulate carrier of fluorouracil. Int J Pharm 257(1–2):111–124

Bill A, Sperber G, Ujiie K (1983) Physiology of the choroidal vascular bed. Int Ophthalmol 6(2):101–107

Budai L, Hajdu´ M, Budai M, Gro´f P, Be´ni S, Noszа´l B et al (2007) Gels and liposomes in optimized ocular drug delivery: studies on ciprofloxacin formulations. Int J Pharm 343(1–2):34–40

Cavalli R, Morel S, Gasco MR, Chetoni P, Saettone MF (1995) Preparation and evaluation in vitro of colloidal lipospheres containing pilocarpine as ion pair. Int J Pharm 117(2):243–246

Cavalli R, Gasco MR, Chetoni P, Burgalassi S, Saettone MF (2002) Solid lipid nanoparticles (SLN) as ocular delivery system for tobramycin. Int J Pharm 238(1–2):241–245

P. Agostinis, K. Berg, K. A. Cengel, T. H. Foster, A. W. Girotti, S. O. Gollnick, S. M. Hahn, M. R. Hamblin, A. Juzeniene, D. Kessel, M. Korbelik, J. Moan, P. Mroz, D. Nowis, J. Piette, B. C. Wilson and J. Golab, Ca-Cancer J. Clin., 2011,61, 250–281.

P. Huang, J. Lin, X. Wang, Z. Wang, C. Zhang, M. He,K. Wang, F. Chen, Z. Li, G. Shen, D. Cui and X. Chen, Adv.Mater., 2012, 24, 5104–5110.

P. Huang, Z. Li, J. Lin, D. Yang, G. Gao, C. Xu, L. Bao,C. Zhang, K. Wang, H. Song, H. Hu and D. Cui,Biomaterials, 2011, 32, 3447–3458.

P. Huang, C. Xu, J. Lin, C. Wang, X. Wang, C. Zhang, X. Zhou,S. Guo and D. Cui, Theranostics, 2011, 1, 240–250.5 W. Miao, G. Shim, S. Lee, S. Lee, Y. S. Choe and Y.-K. Oh, Biomaterials, 2013, 34, 3402–3410

Ramberg JE., Nelson ED., Sinnott RA. Immunomodulatory dietary polysaccharides: a systematic review of the literature. Nutrition Journal 2010; 9(54).

Harris PJ., Stone BA. Chemistry and molecular organization of plant cell walls. In:Himmel ME. (ed.) Biomass recalcitrance. Blackwell: Oxford; 2008. pp 60–93.

Chauhan PS., Puri N., Sharma P., Gupta N. Mannanases: microbial sources, production, properties and potential biotechnological applications. Applied Microbiology and Biotechnology 2012;93(2) 1817–1830.

Mikkonen KS., Tenkanen M. Sustainable food-packaging materials based on future biorefinery products: xylans and mannans. Trends in Food Science & Technology 2012;28(2) 90-102.

Vu-Quang H., Muthiah M., Kim YK., Cho CS., Namgung R., Kim WJ., Rhee JH., Kang SH., Jun SY., Choi YJ., Jeong YY., Park IK. Carboxylic mannan-coated iron oxide nanoparticles targeted to immune cells for lymph node-specific MRI in vivo. Carbohydrate Polymers 2012; 88 780-788

National Cancer Institute, "NCI alliance for nanotechnology in cancer: understanding nanotechnology," in Learn About Nanotechnology, National Cancer Institute, Bethesda, Md, USA, 2010.

T. Flynn and C. Wei, "The pathway to commercialization for nanomedicine," Nanomedicine: Nanotechnology, Biology, and medicine, vol. 1, no. 1, pp. 47–51, 2005.

T. Niidome and L. Huang, "Gene therapy progress and prospects: nonviral vectors," Gene Therapy, vol. 9, no. 24, pp.1647–1652, 2002.

Z. Wang, G. Liu, H. Zheng, and X. Chen, "Rigid nanoparticlebased delivery of anti-cancer siRNA: challenges and opportunities," Biotechnology Advances, vol. 32, no. 4, pp. 831–843, 2014.

T. G. Park, J. H. Jeong, and S. W. Kim, "Current status ofpolymeric gene delivery systems," Advanced Drug Delivery Reviews, vol. 58, no. 4, pp. 467–486, 2006.

M. Arruebo, R. Fernandez-Pacheco, M. R. Ibarra, and J. ´Santamar´ıa, "Magnetic nanoparticles for drug delivery," NanoToday, vol. 2, no. 3, pp. 22–32, 2007.

G. G. D'Ayala, M. Malinconico, and P. Laurienzo, "Marine derived polysaccharides for biomedical applications: chemical modification approaches," Molecules, vol. 13, no. 9, pp. 2069–2106, 2008.

G. Crini, “Recent developments in polysaccharide-based materials used as adsorbents in wastewater treatment,” Progress in Polymer Science, vol. 30, no. 1, pp. 38–70, 2005.

Y. M. Du, L. Li, C. W. Leung, P. T. Lai, and P. W. T. Pong, “Synthesis and characterization of silica-encapsulated iron oxide nanoparticles,” IEEE Transactions on Magnetics, vol. 50, no. 1,2014.

M. S. Sadjadi, F. Fathi, N. Farhadyar, and K. Zare, “Synthesize and characterization of multifunctional silica coated magnetic nanoparticles using polyvinylpyrrolidone (PVP) as a mediator,”Journal of Nano Research, vol. 16, pp. 43–48, 2012.

M. Zhang, B. L. Cushing, and C. J. O’Connor, “Synthesis and characterization of monodisperse ultra-thin silica-coated magnetic nanoparticles,” Nanotechnology, vol. 19, no. 8, Article ID 085601, 2008.

Agnihotri SA, Mallikarjuna NN, Aminabhavi TM. 2004. Recent advances on chitosan-based micro- and nanoparticles in drug delivery. J Control Release 100: 5–28.

Ahmad Z, Sharma S, Khuller GK. 2007. Chemotherapeutic evaluation of alginate nanoparticle-encapsulated azole antifungal and antitubercular drugs against murine tuberculosis. Nanomedicine 3: 239–243.

Akagi T, Kaneko T, Kida T, Akashi M. 2005. Preparation and characterization of biodegradable nanoparticles based on poly (γglutamic acid) with l-phenylalanine as a protein carrier. J Control Release 108: 226–236.

Akagi T, Kaneko T, Kida T, Akashi M. 2006. Multifunctional conjugation of proteins on/into bio-nanoparticles prepared by amphiphilic poly(γ-glutamic acid). J Biomater Sci Polym Ed 17: 875–892.

Akiyoshi K, Deguchi S, Moriguchi N, Yamaguchi S, Sunamoto J. 1993. Self-aggregates of hydrophobized polysaccharides in water. Formation and characteristics of nanoparticles. Macromolecules 26: 3062–3068.

Davis, M. E., Chen, Z. & Shin, D. M. Nanoparticle therapeutics: an emerging treatment modality for cancer. Nature Rev. Drug Discov. 7, 771–782 (2008).

Zhang, L. et al. Nanoparticles in medicine: therapeutic applications and developments. Clin. Pharmacol. Ther. 83, 761–769 (2008).

Park, J. et al. PEGylated PLGA nanoparticles for the improved delivery of doxorubicin. Nanomedicine 5, 410–418 (2009).

Wang, X. et al. HFT–T, a targeting nanoparticle, enhances specific delivery of paclitaxel to folate receptor-positive tumors. ACS Nano 3, 3165–3174 (2009).

Torchilin, V. P. Recent advances with liposomes as pharmaceutical carriers. Nature Rev. Drug Discov. 4, 145–160 (2005).

Berry, G. et al. The use of cardiac biopsy to demonstrate reduced cardiotoxicity in AIDS Kaposi's sarcoma patients treated with pegylated liposomal doxorubicin. Ann. Oncol. 9, 711–716 (1998).

Ewer, M. S. et al. Cardiac safety of liposomal anthracyclines. Semin. Oncol. 31, 161–181 (2004).

Sharma, G., Anabousi, S., Ehrhardt, C. & Kumar, M. Liposomes as targeted drug delivery systems in the treatment of breast cancer. J. Drug Target. 14, 301–310 (2006).

Mohanty, A. K.; Misra, M.; Drzal, L. T. "Sustainable bio-composites from renewable resources: Opportunities and challenges in the green materials world", J. Polym. Environ.2002, 10, 19 –26.

Kaplan, D. L. Biopolymers from Renewable Resources; Springer: New York, 1998.

Rinaudo, M. "Chitin and chitosan: Properties and applications", Prog. Polym. Sci. 2006, 31,603–632.

Kayser O, Lemke A, Hernandez-Trejo N.the impact of nanobiotechnology on the development of new drug delivery systems. Curr Pharm Biotechnol 2005;6(1):3-5

Hawley AE, Davis SS, Illum L.targeting of colloids to lymph nodes:influence of lymphatic physiology and colloidal characteristics. Adv Drug Deliv Rev 1995;17(1):129-48

Ishida O, Maruyama K, Sasaki K, Iwatsuru M. Size-dependent extravasation and interstitial localization of polyethyleneglycol liposomes in solid tumor-bearing mice. Int J Pharm 1999;190(1):49-56

Kayser O, Lemke A, Hernandez-Trejo N. The impact of nanobiotechnology on the development of new drug delivery systems. Curr Pharm Biotechnol 2005; 6(1): 3-5.

Bawarski WE, Chidlowsky E, Bharali DJ, Mousa SA. Emerging nanopharmaceuticals. Nanomed-Nanotechnol 2008; 4(4): 273-82.

Moshfeghi AA, Peyman GA. Micro- and nanoparticulates. Adv Drug Deliv Rev 2005; 57: 2047-52.

Sajja HK, East MP, Mao H, Wang YA, Nie S, Yang L. Development of multifunctional nanoparticles for targeted drug delivery and noninvasive imaging of therapeutic effect. Curr Drug Discov Tech 2009; 6(1): 43-51.

Bhaskar S, Tian F, Stoeger T, et al. Multifunctional Nanocarriers for diagnostics, drug delivery and targeted treatment across bloodbrain barrier: Perspectives on tracking and neuroimaging. Part Fibre Toxicol 2010; 7:3

Vinogradov SV, Batrakova EV, Kabanov EV. Nanogels for oligonucleotide delivery to the brain. Bioconjugate Chem 2004; 15:50-60.

Cheng Y, Xu Z, Ma M, Xu T. Dendrimers as drug carriers: Applications in different routes of drug administration. J Pharm Sci 2008; 97(1): 123-43.

Voit BI, Lederer A. Hyperbranched and highly branched polymer architectures-synthetic strategies and major characterization aspects. Chem Rev 2009; 109(11): 5924-73.

Ambade AV, Savariar EN, Thayumanavan S. Dendrimeric micelles for controlled drug release and targeted delivery. Mol Pharm 2005; 2(4): 264-72.

Motornov M, Roiter Y, Tokarev I, Minko S. Stimuli-responsive nanoparticles, nanogels and capsules for integrated multifunctional intelligent systems. Prog Polym Sci 2010; 35: 174-211.

Novye perspektivy v issledovanii khitina i khitozana (New Prospects in Chitin and Chitosan Studies), Moscow: VNIRO, 1999.

Chitin Handbook, Muzzarelli, R.A.A. and Peter, M.G.,Eds., Grottammare: Atec, 1999.

Grigor'eva, T.M., Kochkina, Z.M., Chirkov, S.N., and Azizbekyan, R.R., Biotechnologiya, 1994, no. 5, pp. 14–16.

Kochkina, Z.M., Pospeshny, G., and Chirkov, S.N., Mikrobiologiya, 1995, vol. 64, no. 2, pp. 211–215.

Kochkina, Z.M., Pospeshny, G., and Chirkov, S.N., Prikl. Biokhim. Mikrobiol., 1996, vol. 32, no. 2, pp. 247–250.

Kochkina, Z.M. and Chirkov, S.N., Mikrobiologiya, 2000, vol. 69, no. 2, pp. 258–260.

Kochkina, Z.M. and Chirkov, S.N., Mikrobiologiya, 2000, vol. 69, no. 2, pp. 266–269.

Sudarshan, N.R., Hoover, D.G., and Knorr, D., Food Biotechnol., 1992, vol. 6, no. 3, pp. 257–272.

Tsai, G.J. and Su, W.H., J. Food Prot., 1999, vol. 62, no. 3, pp. 239–243.

Barrette, J., Champagne, C.P., and Goulet, J., Appl. Environ. Microbiol., 1999, vol. 65, no. 7, pp. 3261–3263.

Monsigny M, Roche AC, Midoux P, Mayer R. Glycoconjugates as carriers for specific delivery of therapeutic drugs and genes. Adv Drug Deliv Rev 1994;14:1e24.

Wang Q, Zhang L, Hu W, Hu ZH, Bei YY, Xu JY, et al. Norcantharidin-associated galactosylated chitosan nanoparticles for hepatocyte-targeted delivery. Nanomed 2010;6:371e81.

Jain K, Kesharwani P, Gupta U, Jain NK. Dendrimer toxicity: Let's meet the challenge. Int J Pharm 2010;394:122e42.

Nahar M, Dutta T, Murugesan S, Asthana A, Mishra D, Rajkumar V, et al. Functional polymeric nanoparticles: an efficient and promising tool for active delivery of bioactives. Crit Rev Ther Drug Carrier Syst 2006;23:259e318

Luo, Y., Perspectives on important considerations in designing nanoparticles for oral delivery 349 applications in food. Journal of Agriculture and Food Research 2020, 100031.

Carroll, R. J.; Thompson, M. P.; Nutting, G. C., Glutaraldehyde fixation of casein micelles for electron microscopy. Journal of Dairy Science 1968, 51 (12), 1903-1908.

Wusigale; Liang, L.; Luo, Y., Casein and pectin: Structures, interactions, and applications trends in Food Science & Technology 2020, 97, 391-403.

Huppertz, T.; Gazi, I.; Luyten, H.; Nieuwenhuijse, H.; Alting, A.; Schokker, E., Hydration of casein micelles and caseinates: Implications for casein micelle structure. International Dairy Journal 2017, 74, 1-11.

Elzoghby, A. O.; Abo El-Fotoh, W. S.; Elgindy, N. A., Casein-based formulations as promising controlled release drug delivery systems. Journal of Controlled Release 2011, 153 (3), 206-216.

Chen, C.; Liau, W.; Tsai, G. J Food Prot 1998, 61, 1124.

Helander, I. M.; Nurmiaho-Lassila, E.-L.; Ahvenainen, R.; Rhoades, J.; Roller, S. Int J Food Microbiol 2001, 71, 235.

Cuero, R. G.; Osuji, G.; Washington, A. Biotechnol Lett 1991, 13,441.

Muzzarelli, R. A. A. In Chitin in Nature and Technology; Muzzarelli, R. A. A.; Jeuniaux, C.; Gooday, G. W., Eds.; Plenum:New York, 1986; p 389.

Davies, D. H.; Elson, C. M.; Hayes, E. R. In Chitin and Chitosan; Skjak-Braek, G.; Anthonsen, T.; Sandford, P., Eds.; Elsevier Applied Science: London, 1989; p 467.

B. Speiser, Nanoparticles in organic production? in: Issues and Opinions, 16th IFOAM Organic World Congress, Modena, Italy, 2008.

F. Lai, et al., Artemisia arborescens L essential oil loaded, solid lipid nanoparticles for potential agricultural application: preparation and characterization AAPS Pharm. Sci. Tech. 7 (1) (2006) E2.

D. Huang, et al., Plastic compatible low resistance printable gold nanoparticle conductors for flexible electronics, J. Electrochem. Soc. 150 (2003) G412.

M.J. Choi, et al., Metal-containing nanoparticles and nano-structured particles in fingermark detection, Forensic Sci. Int. 179 (2–3) (2008) 87–97.

T.M. Liu, et al., Nanoparticle Electric Propulsion for Space Exploration in Space technology and Applications International Forum, STAIF, 2007.

Bartniki-Garcia S. Cell wall chemistry. Ann Rev Microbiol 1968;22:87–108.

Arcidiacono S, Kaplan DL. Molecular weight distribution of chitosan isolated from Mucor rouxii under different culture and processing conditions. Biotechnol Bioeng 1992;39:281–6.

Rane KD, Hoover DG. Production of chitosan by fungi. Food Biotech 1993;7:11–33.

Crestini C, Kovac B, Giovannozzi-Sermanni G. Production and isolation of chitosan by submerged and solid state fermentation from Lentinus edodes. Biotechnol Bioeng 1996;50:207–10.

Tan SC, Tan TK, Wong SM, Khor E. The chitosan yield of Zygomycetes at their optimum harvesting time. Carbohydr Polym 1996;30:239–42.

Bray, F.; Ferlay, J.; Soerjomataram, L.; Siegel, R.L.; Torre, L.A.; Jemal, A. Global cancer statistics 2018:GLOBACAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 2018, 68, 394–424. [CrossRef] [PubMed]

Cancer Incidence and Mortality Worldwide; International Agency for Research on Cancer: Lyon, France, 2011.

Nation Cancer Institute. Available online: https://www.cancer.gov/about-cancer/treatment/types/chemotherapy (accessed on 6 June 2019).

D'Souza, C.A.; Antony, S.; Thomas, B.; Murthy, S.G. Coping strategies used by cancer patients to deal with physical and psychological problems of chemotherapy. Int. J. Innov. Res. Dev. 2016, 5, 36–41.

Schoener, C.A.; Peppas, N.A. Oral delivery of chemotherapeutic agents: Background and potential of drug delivery systems for colon delivery. J. Drug Deliv. Sci. Technol. 2012, 22, 459–468. [CrossRef]

Mei, L.; Zhang, Z.; Zhao, L.; Huang, L.; Yang, X.-L.; Tang, J.; Feng, S. Pharmaceutical nanotechnology for oral delivery of anticancer drugs. Adv. Drug Deliv. Rev. 2013, 65, 880–890. [CrossRef]Alfarouk, K. O., Verduzco, D., Rauch, C., Muddathir, A. K., Bashir, A. H. H., Elhassan, G. O., Ibrahim, M. E., Orozco, J. D. P., Cardone, R. A., Reshkin, S. J., & Harguindey, S. (2014). Glycolysis, tumor metabolism, cancer growth and dissemination. A new pH-based etiopathogenic perspective and therapeutic approach to an old cancer

question. *Oncoscience*, *1*(12), 777–802. https://doi.org/10.18632/oncoscience.109

Almaraz, R. T., Tian, Y., Bhattarcharya, R., Tan, E., Chen, S. H., Dallas, M. R., Chen, L., Zhang, Z., Zhang, H., Konstantopoulos, K., & Yarema, K. J. (2012). Metabolic flux increases glycoprotein sialylation: Implications for cell adhesion and cancer metastasis. *Molecular and Cellular Proteomics*, *11*(7), 1–12. https://doi.org/10.1074/mcp.M112.017558

Cui, L., Cohen, J. A., Broaders, K. E., Beaudette, T. T., & Fréchet, J. M. J. (2011). Mannosylated dextran nanoparticles: A pH-sensitive system engineered for immunomodulation through mannose targeting. *Bioconjugate Chemistry*, *22*(5), 949–957. https://doi.org/10.1021/bc100596w

Damasco, J. A., Ravi, S., Perez, J. D., Hagaman, D. E., & Melancon, M. P. (2020). Understanding nanoparticle toxicity to direct a safe-by-design approach in cancer nanomedicine. *Nanomaterials*, *10*(11), 1–41. https://doi.org/10.3390/nano10112186

Farokhzad, O. C., & Langer, R. (2009). Impact of nanotechnology on drug delivery. *ACS Nano*, *3*(1), 16–20. https://doi.org/10.1021/nn900002m

Jain, K., Kesharwani, P., Gupta, U., & Jain, N. K. (2012). A review of glycosylated carriers for drug delivery. *Biomaterials*, *33*(16), 4166–4186. https://doi.org/10.1016/j.biomaterials.2012.02.033

Kim, S. J., Bae, P. K., & Chung, B. H. (2015). Self-assembled levan nanoparticles for targeted breast cancer imaging. *Chemical Communications*, *51*(1), 107–110. https://doi.org/10.1039/c4cc07679f

Kumari, A., Yadav, S. K., & Yadav, S. C. (2010). Biodegradable polymeric nanoparticles based drug delivery systems. *Colloids and Surfaces B: Biointerfaces*, *75*(1), 1–18. https://doi.org/10.1016/j.colsurfb.2009.09.001

Ledet, G., & Mandal, T. K. (2012). Nanomedicine : Emerging Therapeutics for the 21st Century. *US Pharmacist*, *37*(3), 7–11.

Ling, S., Chen, W., Fan, Y., Zheng, K., Jin, K., Yu, H., Buehler, M. J., & Kaplan, D. L. (2018). Biopolymer nanofibrils: Structure, modeling, preparation, and applications. *Progress in Polymer Science*, *85*, 1–56. https://doi.org/10.1016/j.progpolymsci.2018.06.004

Massoud, T. F., & Gambhir, S. S. (2003). Molecular imaging in living subjects: Seeing fundamental biological processes in a new light. *Genes and Development*, *17*(5), 545–580. https://doi.org/10.1101/gad.1047403

Matsumura, S., Hlil, A. R., Lepiller, C., Gaudet, J., Guay, D., Shi, Z., Holdcroft, S., & Hay, A. S. (2008). Stability and Utility of Pyridyl Disulfide Functionality in RAFT and Conventional Radical Polymerizations. *Journal of Polymer Science: Part A: Polymer Chemistry*, *46*(April), 7207–7224. https://doi.org/10.1002/pola

Mizrahy, S., & Peer, D. (2012). Polysaccharides as building blocks for nanotherapeutics. *Chemical Society Reviews*, *41*(7), 2623–2640. https://doi.org/10.1039/c1cs15239d

Nguyen, T. T., Dung Nguyen, T. T., Vo, T. K., Tran, N. M. A., Nguyen, M. K., Van Vo, T., & Van Vo, G. (2021). Nanotechnology-based drug delivery for central nervous system disorders. *Biomedicine and Pharmacotherapy*, *143*(August), 112117. https://doi.org/10.1016/j.biopha.2021.112117

Omidi, Y. (2011). Smart multifunctional theranostics: Simultaneous diagnosis and therapy of cancer. *BioImpacts*, *1*(3), 145–147. https://doi.org/10.5681/bi.2011.019

Ossipov, D. A. (2010). Nanostructured hyaluronic acid-based materials for active delivery to cancer. *Expert Opinion on Drug Delivery*, *7*(6), 681–703. https://doi.org/10.1517/17425241003730399

Park, J. H., Saravanakumar, G., Kim, K., & Kwon, I. C. (2010). Targeted delivery of low molecular drugs using chitosan and its derivatives. *Advanced Drug Delivery Reviews*, *62*(1), 28–41. https://doi.org/10.1016/j.addr.2009.10.003

Pramod, P. S., Shah, R., Chaphekar, S., Balasubramanian, N., & Jayakannan, M. (2014). Polysaccharide nano-vesicular multidrug carriers for synergistic killing of cancer cells. *Nanoscale*, *6*(20), 11841–11855. https://doi.org/10.1039/c4nr03514c

Quader, S., & Van Guyse, J. F. R. (2022). Bioresponsive Polymers for Nanomedicine—Expectations and Reality! *Polymers*, *14*(17), 1–3. https://doi.org/10.3390/polym14173659

Rao, W., Wang, H., Han, J., Zhao, S., Dumbleton, J., Agarwal, P., Zhang, W., Zhao, G., Yu, J., Zynger, D. L., Lu, X., & He, X. (2015). Chitosan-Decorated Doxorubicin-Encapsulated

Nanoparticle Targets and Eliminates Tumor Reinitiating Cancer Stem-like Cells. *ACS Nano*, *9*(6), 5725–5740. https://doi.org/10.1021/nn506928p

S. Eroglu, M., Toksoy Oner, E., Cansever Mutlu, E., & Sennaroglu Bostan, M. (2017). Sugar Based Biopolymers in Nanomedicine; New Emerging Era for Cancer Imaging and Therapy. *Current Topics in Medicinal Chemistry*, *17*(13), 1507–1520. https://doi.org/10.2174/1568026616666161222101703

Schmaus, A., Bauer, J., & Sleeman, J. P. (2014). Sugars in the microenvironment: the sticky problem of HA turnover in tumors. *Cancer and Metastasis Reviews*, *33*(4), 1059–1079. https://doi.org/10.1007/s10555-014-9532-2

Sezer, A. D., Kazak, H., Öner, E. T., & Akbua, J. (2011). Levan-based nanocarrier system for peptide and protein drug delivery: Optimization and influence of experimental parameters on the nanoparticle characteristics. *Carbohydrate Polymers*, *84*(1), 358–363. https://doi.org/10.1016/j.carbpol.2010.11.046

Shen, H., Huang, X., Min, J., Le, S., Wang, Q., Wang, X., Dogan, A. A., Liu, X., Zhang, P., Draz, M. S., & Xiao, J. (2019). Nanoparticle Delivery Systems for DNA/RNA and their Potential Applications in Nanomedicine. *Current Topics in Medicinal Chemistry*, *19*(27), 2507–2523. https://doi.org/10.2174/1568026619666191024170212

Sudhakar, C. K., Upadhyay, N., Verma, A., Jain, A., Narayana Charyulu, R., & Jain, S. (2015). Nanomedicine and Tissue Engineering. In *Nanotechnology Applications for Tissue Engineering*. Elsevier Inc. https://doi.org/10.1016/B978-0-323-32889-0.00001-7

Yasar Yildiz, S., & Toksoy Oner, E. (2014). Mannan as a Promising Bioactive Material for Drug Nanocarrier Systems. *Application of Nanotechnology in Drug Delivery*. https://doi.org/10.5772/58413