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POLYSACCHARIDE-BASED TREATMENT APPROACHES FOR COLORECTAL CANCER

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ABSTRACT

Colorectal cancer (CRC) remains a leading cause of cancer-related mortality worldwide, with conventional treatments such as chemotherapy often limited by systemic toxicity, poor targeting, and drug resistance. Polysaccharides, naturally derived from plants, fungi, algae, and bacteria, have emerged as promising multifaceted agents for CRC management due to their biocompatibility, biodegradability, and diverse pharmacological activities. This review comprehensively explores polysaccharide-based therapeutic strategies, highlighting their roles in immunomodulation, induction of apoptosis, suppression of inflammation and oxidative stress, and modulation of gut microbiota. Particular emphasis is placed on colon-specific drug delivery systems leveraging the resistance of polysaccharides (e.g., pectin, chitosan, dextran) to upper gastrointestinal digestion and their degradation by colonic microbiota. Advanced formulations including nanoparticles, hydrogels, microspheres, and conjugates enhance drug stability, bioavailability, and tumor targeting via passive (EPR effect) and active mechanisms while reducing off-target toxicity. Specific polysaccharides such as β-glucans, fucoidan, alginate, and modified pectin demonstrate direct anticancer effects through regulation of key signaling pathways including NF-κB, PI3K/Akt, Wnt/β-catenin, and MAPK. Preclinical studies show strong efficacy, while early clinical evidence supports their potential as adjuvants in immunotherapy and combination therapies. Despite challenges like structural variability and limited large-scale clinical trials, polysaccharides offer a versatile platform for safer, more effective CRC treatment. Future directions include standardized formulations, smart stimuli-responsive nanocarriers, and personalized approaches.

KEYWORDS: Polysaccharides, Colorectal cancer, Colon-targeted drug delivery, Immunomodulation, Nanocarriers.

INTRODUCTION

Colorectal cancer (CRC) remains one of the most important public health problems in the world, and is associated with a large proportion of cancer-causing deaths and morbidity. World cancer statistics indicate that CRC is one of the most common and important causes of mortality in developed and developing countries in recent years.CRC is the one of the most prevalent and major causes of cancer-related death in developed and developing countries (Bray et al., 2020; Sung et al., 2021). Rapid urbanisation, dietary change and lifestyle becoming westernised pose a particular threat to increased CRC incidence in LMC countries.

The risk factors for CRC development include dietary factor (high red meat consumption, low dietary fibre) obesity, sedentary lifestyle, smoking, alcohol consumption and genetic susceptibility (Zhou et al., 2019; Wang et al., 2023).

Besides these things, it has been reported that the alteration of gut microbiota is also a big role in the pathogenesis of CRC. Changes in intestinal microorganisms can cause chronic inflammation, generate metabolites and disrupt intestinal barrier function, which will eventually result in tumour initiation and development (Xu et al., 2022; Zhao et al., 2017).

The process of colorectal cancer (CRC) is a multistep process at the molecular level, and genetic and epigenetic changes accumulate. Usually, this occurs in the adenoma–carcinoma sequence in which benign polyps slowly turn into cancerous tumors. The genetic changes that are associated with CRC include the changes that occur in the cancer inhibiting genes (such as APC and p53) and in oncogenes (such as KRAS). These changes to the genes cause cells to grow without constraint, to evade programmed cell death and to grow new blood vessels and become more metastatic (Fearon and Vogelstein, 1990; Li et al., 2023). Furthermore, the activation of the pathways of β-catenin, Akt and NF-κB are closely associated with tumor development and progression.

Colorectal cancer is a challenging disease to treat, despite the dramatic advances in our knowledge and understanding of the disease. The standard treatments are surgery, chemotherapy, radiotherapy and targeted therapy. For those who are diagnosed in early stages of CRC, the main treatment is surgery, however many will be diagnosed at a later stage and systemic therapy will be needed. Chemotherapy is used in the clinic, such as 5-fluorouracil (5-FU), oxaliplatin and irinotecan. Such medications have been shown to improve the survival rates of patients, but may not be used effectively because of their high toxicity and lack of specificity (Longley and Johnston, 2005; Li et al., 2023).

Systemic toxicity, targeting of non-specific cells, low bioavailability and multidrug resistance are the major disadvantages of conventional chemotherapy. Unfortunately, these drugs affect normal tissues as well as cancer cells, leading to damage of the gastrointestinal tract, suppression of bone marrow, immune system, and organs. Moreover, repeated chemotherapy may lead to the emergence of chemoresistance and cause a decrease in the effectiveness of chemotherapy and cancer recurrence (Longley and Johnston, 2005; Zhang et al., 2020).

The other major disadvantage of CRC therapy is the lack of good drug delivery systems. Many anticancer drugs suffer from low solubility, GI tract instability and fast rate of clearance. This results in a problem of achieving the effective concentration of the drug at the tumour site. The challenges highlight the importance of finding new therapies to increase the effectiveness of targeting drugs, reducing toxicity, and maximizing therapeutic benefits.

In recent years, natural products have been the center of attention in cancer therapy since they are readily available from nature, safe and contain many biological activities. Of these, polysaccharides have been the focus of great interest

as therapeutic agents and drug delivery carriers. Polysaccharides consist of high molecular weight carbohydrates, formed from monosaccharides by the formation of glycosidic bonds. They are found naturally and can be easily extracted from plants, fungi, algae and microorganisms (Wang et al., 2020; Li et al., 2021).

Biocompatibility, biodegradability and low toxicity are the unique properties of polysaccharides which render them highly attractive for biomedical and pharmaceutical applications. Moreover, their structural diversity and functional groups also enable easy modification of their structures, which is beneficial for using them as scaffolds to design new and improved drug delivery systems (Chen et al., 2017; Liu et al., 2018).

Polysaccharides exhibit a wide range of pharmacological properties and have many therapeutic benefits for colorectal cancer. They are anti-oxidative, Inflammation-reducing, immunomodulatory and direct anti-cancer properties. Anti-oxidant activity of polysaccharides can neutralize free radicals and lower oxidative stress, a major contributor to cancer development (Wang et al., 2020). They have anti-inflammatory properties which can help prevent chronic inflammation, one of the critical factors involved in the development of CRC (Kim et al., 2019).

One of the most important mechanisms of polysaccharides as an immunomodulatory agent is that they can enhance the immune response and activate phagocytic functions. They can activate innate and adaptive immune systems and can activate immune cells such as dendritic cells, macrophages and natural killer (NK) cells. It results in improved detection and elimination of tumors (Zhao et al., 2021; Schepetkin and Quinn, 2006). Moreover, polysaccharides have been demonstrated to suppress the growth of cancer cells by adjusting some of the signaling pathway and apoptotic proteins, which results in apoptosis (Sun et al., 2020).

One of the other significant properties of polysaccharides is their ability to regulate gut microbiota. The indigestible carbohydrates in polysaccharides are beneficial to the growth of good bacteria in the colon and are known as prebiotics.

These bacteria also generate the anti-inflammatory and anti-cancer chemicals called short-chain fatty acids (SCFAs), including butyrate. Butyrate has been shown to induce the apoptosis of colorectal cancer cells and block colorectal tumor development (Zhou et al., 2019; Wang et al., 2023).

Besides therapeutic uses, polysaccharides are also come out to be an extremely significant field in the area of Drug Delivery Systems. They exhibit an atypical physicochemical property that allows them to be delivered in a range of different ways including nanoparticles, hydrogels, microspheres and conjugates. The purpose of these systems is to make the drug more stable, improve functionality and ensure the controlled and sustained release of the drug (Singh et al., 2021; Ahmed et al., 2022).

One of the most impressive properties of polysaccharides for use in the treatment of CRC is their capacity to deliver drugs to the colon. Many polysaccharides such as pectin, dextran and chitosan cannot be digested in the gastrointestinal tract up to the stomach, but are instead digested by bacterial enzymes produced by the microbiota of the colon. This will allow for a more targeted delivery of the drug within the colon and in turn help to increase the therapeutic effectiveness and decrease the overall systemic toxicity (Patel et al., 2020; Zhang et al., 2019).

Moreover, the application of nanotechnology to cancer treatment is a great progress, which makes the potential of polysaccharide in cancer treatment remarkable. Both passive and active targeting mechanisms can help to enhance the

targeting ability of nanocarriers for drug delivery that are based on polysaccharides. Nanoparticles with their improve permeability and retention (EPR) effect may specifically target tumor tissues due to the permeable blood vessels present in tumor tissues (Singh et al., 2021; Wang et al., 2021). What is more, the surface can be functionalized to include targeting ligands, thus allowing the active targeting of the polysaccharide nanoparticles against cancer cells.

Polysaccharides are also a very important component in resistance to drug in cancer therapy. They can promote the absorption of drugs, suppress the discharge of drugs and regulate drug resistance-related pathways, thereby increasing the therapeutic efficacy of chemotherapy drugs (Li et al., 2021; Zhang et al., 2020).

While it has great promise, there are a number of problems to solve before there is broad clinical use of polysaccharide-based therapies. These include variation in structure and composition, lack of standardization, scarcity of clinical trials and problems in mass production. Thus, additional studies are needed to optimise their properties and assess their safety and efficacy in human studies.

2. Types and Origins of Polysaccharides

The polysaccharides are composed of long chain of monosaccharide units linked together by glycosidic linkage and are complex macromolecules. These are widely present in the environment and can be recovered from various biological sources like plant, algae, fungi and microorganisms. Depending on their origin, structure and functional properties, polysaccharides can be classified into different types. This classification is relevant as the different types of polysaccharides have distinct physicochemical properties and biological activities that directly impact on their therapeutic applications, particularly colorectal cancer (CRC) therapy.

In addition to the source based classification, polysaccharides can also be classified structurally as homopolysaccharides (consist of one monosaccharide) or heteropolysaccharides (consist of different monosaccharides).

Their biological activity and drug delivery properties can be greatly influenced by structural factors such as molecular weight, branching, degree of substitution, and the type of glycosidic bonds that they may contain (Chen et al., 2018; Nie et al., 2018).

2.1 Plant-Derived Polysaccharides

Among these natural polymers, polysaccharides derived from plants are most commonly used in biomedical and pharmaceutical applications and are abundant, inexpensive, biodegradable and safe. These polysaccharides are primarily derived from the fruits, vegetables, seeds and plant cell walls.

The most significant polysaccharide in plants are pectin, cellulose, starch and guar gum.

A polysaccharide that has numerous studies performed, and of special interest is its application for targeted delivery of drugs to the colon is pectin. It is mostly obtained from citrus fruits and apple skins. Pectin also has great gel-forming properties in the presence of water and calcium ions and can be utilised in controlled drug release formulations. It is an important property that it is not destroyed in the upper gastrointestinal tract, and specifically destroyed by enzymes produced by the bacteria in the colon. This is beneficial for targeted drug delivery in colon (Zhang et al., 2019; Patel et al., 2020) and this helps in targeted colon drug delivery for treating colorectal cancer.

Another valued polysaccharide derived from plants is cellulose and the most common organic polymer on Earth. It consists of β-1,4 linked glucose units and is a rigid material in the walls of the plants. Native cellulose is insoluble in water but cellulose derivatives like hydroxypropyl methylcellulose (HPMC) and carboxymethyl cellulose (CMC) have many applications as excipients in pharmaceutical formulations as a binder, film-forming agent, and as a controlled-release matrix (Zhang et al., 2017).

Another one of the important plant polysaccharides employed in drug delivery is Starch which consists of amylose and amylopectin. It is chemically modifiable, has increased mechanical strength and drug release ability and is also biodegradable. In general, modified starch derivatives are used in sustained-release formulation.

In addition to these, plant polysaccharides possess biological properties such as antioxidant, anti-inflammatory and anti-cancer properties. They can scavenge free radicals, reduce oxidative stress and regulate immune response, and have important roles in cancer prevention and treatment (Wang et al., 2020).

2.2 Fungal Polysaccharides

The huge potential of the fungal polysaccharides for their immunomodulatory and anticancer properties has recently gained interest. These polysaccharides are present in medical mushrooms such as Grifola frondosa (maitake), Lentinus edodes (shiitake) and Ganoderma lucidum.

The best studied fungal polysaccharide is the β-glucans containing glucose residues joined together by the β-(1→3) and β-(1→6) glycosidic bonds. This is because these are structural properties which make them biological.

The immune system activation is very important, where β-glucans are involved. They bind to specific receptors cells—including Dectin-1 and Toll-like receptors—expressed by immune cells, which trigger the activation of cells of the immune system, such as macrophages, dendritic cells and natural killer (NK) cells. This generates a better immune response to the tumour cells (Zhao et al., 2021; Schepetkin and Quinn, 2006).

The fungal polysaccharides have also been demonstrated to exhibit direct anticancer effects, including inducing apoptosis, inhibiting cancer cell growth, and preventing metastasis. They have the ability to modulate multiple signaling pathways including NF-κB, MAPK and PI3K/Akt pathways, which have been linked to cancer progression (Sun et al., 2020).

The other advantage of the fungal polysaccharides is that they are not too toxic, and can be used as adjuvants in cancer treatment. These are sometimes used in combination with other cancer drugs to make the treatment more effective and minimise side effects.

2.3 Algal Polysaccharides

The algal polysaccharides are extracted from marine resources especially from seaweeds, and have proven to be very useful in pharmaceutical and biomedical applications. Algal polysaccharides include, for example, alginate, carrageenan, agar and fucoidan.

Alginate is an anionic polysaccharide that is naturally occurring from brown algae. It is made up of mannuronic acid and guluronic acid units. Alginate is a very common component for the formulation of hydrogels because it is able to

create gels in the presence of divalent ions, like calcium. The applications of these hydrogels are controlled drug delivery and tissue engineering (Ahmed et al., 2022).

Red algae use to stabilize and thicken pharmaceutical formulations is known as carrageenan. It also has antiviral and anti-inflammatory properties.

Fucoidan is a sulfated polysaccharide that is extracted from brown seaweed and one of the most promising algal polysaccharides for cancer therapy. It has been reported to have strong anticancer activity, by inducing apoptosis, inhibiting angiogenesis and suppressing the proliferation of tumor cells. Furthermore, fucoidan is a modulator of immune response and anti-inflammatory activity, and is extremely beneficial in the treatment of colorectal cancers as well (Wang et al., 2020; Zhao et al., 2018).

Algal polysaccharides also possess antioxidant properties, which aid in combating oxidative stress and preventing cellular damage. They are biocompatible and do form a gel making them good candidates for drug delivery systems.

2.4 Bacterial Polysaccharides

The bacterial polysaccharides are produced by the microorganisms and are also widely used in pharmaceutical and biomedical applications as they are found to be stable, easy to produce and also functional. Some common examples are dextran, xanthan gum and pullulan.

Dextran is a branched polysaccharide made up of glucose units, and commonly used in nano based drug delivery systems. It has high degree of biocompatibility and can be chemically modified to achieve an efficient delivery of drugs and target them to desired sites (Singh et al., 2021).

Another important bacterial polysaccharide that is extensively used as a stabiliser, thickener and controlled release matrix in pharmaceutical formulations is xanthan gum. It has a good viscosity and stability at a wide range of pH and temperature.

Pullulan is a polysaccharide which is synthesized in water by a fungus-like yeast Aureobasidium pullulans. Non-toxic, biodegradable and used in film formation and drug delivery applications.

Bacterial polysaccharides are useful for nanocarrier systems because they can be used to enhance the stability of the drug, increase bioavailability and targeted delivery. They also have mucoadhesive properties which have been demonstrated to prolong the residence time of a drug in the gastrointestinal tract.

Table 1: Classification, Sources, Applications and References of Polysaccharides.

Type	Source	Example	Application	Reference
Plant-derived	Fruits, vegetables	Pectin	Colon-targeted delivery	(Zhang et al., 2019)
Fungal-derived	Mushrooms	β-glucan	Immunomodulation	(Zhang et al., 2019)
Algal-derived	Seaweed	Alginate	Hydrogel systems	(Zhang et al., 2019)
Bacterial-derived	Microorganisms	Dextran	Nanocarriers	(Zhang et al., 2019)

Mechanisms taken by drugs to keep cancer in check

Polysaccharides have multiple and complex anti-cancer actions. Polysaccharides act in a few ways, compared to conventional chemotherapeutics that mostly interfere with rapidly dividing cells, including: Immune system

modulation, induction of apoptosis, anti-inflammatory activity, inhibition of oxidative stress and modulation of the gut microbiota. These mechanisms work together and show their efficacy in preventing colorectal cancer (CRC) growth, progression and metastasis.

Apart from cancer cell targeting, the poly functions of polysaccharides also make them good candidates for cancer therapy, improving physiological status of the body.

3.1 Immunomodulatory Activity

One of the most important and studied mechanism of polysaccharides is modulation of the immune system. The body's immune system is an important component in fighting and killing cancer cells, but cancer cells can outwit the body's immune system as well. This is overcome by the use of polysaccharides that increase innate and adaptive immunity.

Polysaccharides can activate, recruit, and stimulate important cells of the immune system, including macrophages, dendritic cells, neutrophils, and natural killer (NK) cells. Both macrophages and dendritic cells become activated and boost phagocytosis and release of immune mediators and dendritic cells also increase antigen presentation to T-cells to initiate adaptive immune responses. Direct killing of tumour cells by NK cells, through the secretion of molecules such as perforin and granzymes (Zhao et al., 2021; Schepetkin and Quinn, 2006).

The polysaccharides are molecularly recognized by PRRs of immune cells such as TLRs and Dectin-1 receptors. This interaction initiates intracellular signalling pathways such as NF-κB and MAPK, and results in the synthesis of cytokines and chemokines.

Polysaccharides are also known to promote the production of cytokines like interleukins (IL-2, IL-6, IL-12), tumour necrosis factor alpha (TNF-α) and interferon gamma (IFN-γ). These cytokines are crucial in strengthening the immune reactions, inducing the apoptosis of tumour cells and suppressing tumour growth (Zhao et al., 2021).

Moreover, polysaccharides have been shown to modulate tumor microenvironment in a number of ways, including blocking the release of immunosuppressive molecules and promoting infiltration of immune cells in the tumor tissue.

These have been successfully used in cancer immunotherapy and as a complimentary to other cancer therapy.

3.2 Role in Triggering Apoptosis

Apoptosis or programmed cell death is a regulated process that is utilized to eliminate the damaged or abnormal cells.

This is usually interrupted in cancer and the cancer cells keep growing and multiplying. Polysaccharides can restore this balance by killing cancer cells by both intrinsic (mitochondrial) and extrinsic (death receptor-mediated) pathways to induce apoptosis.

Polysaccharides influence the activity of the mitochondria by the regulation of the levels of the apoptosis promoting proteins such as Bax along with cell protective proteins like Bcl-2 in the intrinsic pathway. The Bax increase and Bcl2 decrease contributes to permeabilisation of the mitochondrial membranes, cytochrome c is released and this activates the caspase enzymes, which cause cell death (Sun et al., 2020).

The polysaccharides attach to the death receptors on the cell surface like Fas receptor and TNF receptor, which activates the caspase-8 and thus begins the downstream apoptotic signal.
Additionally, polysaccharides modulate important signaling pathways related to apoptosis such as PI3K/Akt, MAPK and p53 pathways. They do this using two mechanisms: firstly, by blocking pathways which aid the survival of the tumour and secondly by stimulating pathways which destroy tumour cells.

Furthermore, polysaccharides can be detected to inhibit the growth of cancer cells by blocking the cell cycle in the G0/G1 or G2/M phase (Liu et al., 2018).

3.3 Effects on Inflammatory Response

Chronic inflammation is a key contributor to the formation and progression of colorectal cancer. The chronic inflammation results in the accumulation of pro-inflammatory cytokines, reactive oxygen species (ROS) and growth factors that contributes to the growth and metastasis of tumors.

In the context of inflammation, polysaccharides are known to exhibit strong anti-inflammatory activities by inhibiting critical inflammatory signaling pathways including NF-kB pathway. NF-κB is a transcription factor which regulates genes involved in inflammation, cell proliferation and survival. Blocking NF-κB decreases the levels of inflammatory mediators, such as TNF-α, IL-1 β and IL-6 (Kim et al., 2019).

Polysaccharides additionally inhibit other inflammatory pathways, for example, COX-2 and iNOS, related to malignant growth progression. Polysaccharides decrease inflammation, which creates an inhospitable environment for growth of tumors.

Additionally, they can prevent inflammatory cells from accessing the tumor, and reduce the expression of pro-tumorigenic factors, which in turn slows the cancer growth.

3.4 Antioxidant Activity

Due to genomic instability, mutation and damage to DNA, the oxidative stress would be a big factor in the development of cancer. This oxidative stress produces a certain quantity of reactive oxygen species (ROS) which can initiate and promote carcinogenesis.

The antioxidant capacities of polysaccharides have shown to be extremely important and they can remove free radicals. They scavenge ROS and inhibit the generation of oxidative damage to cellular components like DNA, proteins and lipids (Wang et al., 2020).

The antioxidant activity of polysaccharides is primarily attributed to their antioxidant capacity, that is their capacity to donate electrons or hydrogen atoms to the free radicals, and consequently, to act as stabilisers. Furthermore, polysaccharides boost the function of endogeneous antioxidant enzymes like superoxide dismutase (SOD), catalase and glutathione peroxidase (GPx).

Polysaccharides prevent colorectal cancer formation and development by decreasing oxidative stress.

3.5 Role in Maintaining Gut Microbial Homeostasis

The gut microbiota is a vital component of gut health and it has been established that the composition of gut microbiota is linked to CRC development. Disruption of the gut microbiome (dysbiosis) can result in inflammation, toxin formation and tumour growth.

Polysaccharides can be used as prebiotics (foods for the good bacteria in the gut, including the lactobacilli and bifidobacteria). These bacteria are able to break down polysaccharides into beneficial short-chain fatty acids including butyrate, acetate, and propionate (Xu et al., 2022).

Butyrate is one of these that is important in the prevention of colorectal cancer. It is being used to fuel colon cells, to induce the death of cancer cells and anti-inflammatory. Additionally, butyrate is able to regulate gene expression as a histone deacetylase (HDAC) inhibitor which is responsible for the inhibition of tumour growth (Zhou et al., 2019).

Polysaccharides can also restore the balance of intestinal microbes, and reduce harmful bacteria and restore intestinal barrier function. This results in a decrease in inflammation and an increase in immune response.

4. The invention of Polysaccharide based Drug Delivery Systems

Polysaccharides have become very interesting compounds for the design and development of advanced drug delivery systems especially for colorectal cancer (CRC) treatment. They have been reported to possess some unique physicochemical properties which render them as suitable candidates for pharmaceutical application such as biodegradability, biocompatibility, non-toxicity, ease to chemical modification etc. Recently, the use of polysaccharides as carriers has gained increasing interest to enhance drug targeting, improve therapeutic availability while minimizing systemic adverse effects.

The delivery of a drug to the target tumour site and the avoidance of exposure to normal tissues is one of the challenges when treating colorectal cancer. The conventional drug delivery methods cannot achieve this goal, due to the instability of the drug, solubility and distribution issues. The above issue can be overcome by using delivery systems based on polysaccharides which can control, sustain and direct the release of the drug.

Furthermore, polysaccharide can be designed in various forms such as nanoparticles, hydrogels, microspheres and conjugates with various beneficial properties for the particular therapeutic application. They also give targeted drug delivery (Chen et al., 2017; Liu et al., 2018) their ability to react to the environment, such as pH value, enzyme and temperature.

4.1 Targeted Delivery to the Colon

One of the most crucial applications of polysaccharide in the treatment of colorectal cancer is colon targeted drug delivery. The large number of microorganisms present in the colon which can degrade polysaccharides allows for the possibility of drug release at the site of the administration of the drug.

Polysaccharides like pectin, chitosan, dextran, guar gum and inulin are undigestible by the enzymes in the upper gastrointestinal tract and are instead digested by enzymes from the colon microbiota. In this way, the drugs will be spared from degradation by the stomach acid or degradation by digestive enzymes in the intestinal tract and released in the colon where it is less likely to be degraded (Patel et al., 2020; Zhang et al., 2019).

The pectin based formulation, for example, creates a barrier around the drug and hence, slows down the early release of the drug. The formulation will then be excreted from the bacteria within the colon and the enzymes within the bacteria will break down the pectin and release the drug at the target site. Similarly, chitosan has mucoadhesive property which prolongs the residence time of the drug in the colon, and enhances the absorption of the drug.

The pectin based formulation, for example, creates a barrier around the drug and hence, slows down the early release of the drug. The formulation will then be released into the colon where the enzymes in the bacteria will breakdown the pectin and release the drug at the desired location. Similarly, chitosan has mucoadhesive property which prolongs the residence time of the drug in the colon, and enhances the absorption of the drug.

There are several benefits to colon targeted delivery such as:

- Reduced systemic toxicity
- Improved therapeutic efficacy
- Reduce the requirement for higher dosage of medications
- Enhanced patient compliance

This is particularly beneficial for colorectal cancer, in that the drugs build up at higher levels in the tumor and lower levels in the surrounding normal tissue.

4.2 Nanoparticle Systems

PSNPs stands as the one of the most well-developed and thoroughly explored cancer drug delivery systems. These nanoparticles have an average size of between 1 and 1000 nm and can carry or bind drugs to them to decrease degradation and increase drug stability.

Functional versatility and biocompatibility of polysaccharides are important factors which make these polymers useful in preparing nanoparticles, for example, chitosan, alginate, dextran and hyaluronic acid. The nanoparticles possess the ability to increase the solubility of drugs, increase the bioavailability of drugs, and can be designed to release drugs over a period of time (Singh et al., 2021; Wang et al., 2021).

It is well-known that the enhanced permeability and retention (EPR) effect is one of the most important advantages of the nanoparticle systems. Blood vessels in tumour tissue are leaky, allowing the concentration of nanoparticles in the tumour area, and the lymphatic drainage in the area is impaired. This passive targeting mechanism increases the amount of drug that is delivered to the cancer cells, and decreases the amount of drug delivered to healthy tissue.

Passive targeting can also be performed using polysaccharide nanoparticles, that can be equipped with ligands like an antibody, a peptide or folic acid. This enables the nanoparticles to specifically target receptors that are over-expressed on cancer cells for an additional increase in the targeting efficiency.

Another advantage of using polysaccharide based nanoparticles is overcoming drug resistance as it allows for uptake into the cell and bypasses the process of efflux transporters. They are extensively used for drug delivery in the treatment of colorectal cancer with chemotherapeutic agents such as 5-fluorouracil, doxorubicin and paclitaxel in cancer therapy.

4.3 Hydrogel Systems

A hydrogel is a three-dimensional network of polymers which is able to attract a large amount of water, or other liquid medium. The polysaccharide based hydrogels find extensive applications in drug delivery systems due to their advantages of good biocompatibility, flexibility and controlled drug delivery.

Alginates, chitosans, carrageenan and cellulose derivatives are examples of popular polysaccharides that are utilized in the production of hydrogels. The hydrogels can change their physical and/or chemical properties, depending on the environment to which they are exposed to, such as pH, temperature, and enzymes, and can therefore be used for targeted drug delivery (Ahmed et al., 2022; Chen et al., 2020).

The application of a hydrogel for targeted drug delivery is particularly interesting in treating colorectal cancer. They can be injected into the tumor or rectally and so the drug stays longer in the body and produces a gradual release. This will allow for more convenient administration of the dosage, and increase ease of patient adherence.

Hydrogels are also used to protect sensitive drugs against degradation and ensure even distribution of the drugs. Also, injectable hydrogels can be used to deliver drugs minimally invasively in which the gel precipitates after injection.

Another significant benefit of hydrogels is that they are similar to biological tissues and can be used in developing tissue engineering and regenerative medicine applications for the treatment of colorectal cancer.

4.4 Microspheres and Conjugates

Sustained and controlled drug release can be accomplished using microspheres and polysaccharide-drug conjugates. Microspheres are spherical particles, usually 1-1000 μm in diameter, that can be filled with a drug(s) in a polymer matrix.

The microspheres can be made with different polysaccharides, such as dextran, chitosan, and starch. These systems enable the drug to be gradually released either through diffusion or degradation or swelling to achieve prolonged therapeutic efficacy.

Oral and colon targeting drug delivery systems are especially suited for microspheres. They will prevent the drug from being affected by dangerous conditions in the stomach and intestines and they will release it at the proper location. This makes the drug more stable, as well as more bioavailable.

Polysaccharide-drug conjugates are conjugates in which the drugs are covalently bound to polysaccharide chains. This method enhances solubility, stability and targeting of the drug. The drug is released when the enzymes or environmental factors break down the conjugate.

The conjugates are particularly useful in delivery of hydrophobic drugs and in minimizing the systemic toxicity. Another advantage is that they can be used to release the drug in a controlled way, and selectively in the targeted location, which is of great value in colorectal cancer treatment (Liu et al., 2018).

Clinical Potential of Polysaccharide Based Delivery Approaches

The polysaccharide based drug delivery systems are multi-functional systems that could be used to enhance the treatment of colorectal cancer. They offer the benefits of:

- Site Specific Drug Delivery
- Prolonged and Regulated Drug Release
- Enhanced Drug Stability and Solubility
- Reduced systemic toxicity
- Enhanced therapeutic efficacy

These systems also provide opportunities for combining multiple therapeutic agents and integrating advanced technologies such as nanotechnology and stimuli-responsive systems.

Table 2: Polysaccharide-Based Drug Delivery Systems with References.

System	Polymer	Mechanism	Application	Reference
Nanoparticles	Chitosan	EPR effect	Targeted delivery	(Singh et al., 2021)
Hydrogels	Alginate	Swelling release	Sustained delivery	(Ahmed et al., 2022)
Microspheres	Dextran	Diffusion	Colon targeting	(Patel et al., 2020)
Liposomes	Chitosan-coated	Membrane fusion	Enhanced bioavailability	(Li et al., 2021)

5. The Benefits of Polysaccharide Therapy

New therapies, such as those based on polysaccharides, are making the news as a potential alternative or adjunct to traditional colorectal cancer (CRC) treatments, and have generated significant interest in recent years. This is primarily because of their special physicochemical and biological properties, which have various benefits over synthetic drugs and conventional drug delivery mechanisms.

5.1 Biocompatibility and Biodegradability

The best of the polysaccharides is their excellent biocompatibility and biodegradability. They are naturally sourced from plants, fungi, algae and microorganisms and are therefore not toxic or harmful to the human body.

Polysaccharides are biodegradable into harmless products, which can be easily removed without damaging tissues and organs, in contrast to synthetic polymers (Li et al., 2021).

This characteristic is very appropriate for the use of long-term treatments, particularly for chronic diseases such as colorectal cancer, which may require a more extended treatment.

5.2 Reduced Systemic Toxicity

The conventional chemotherapeutic drugs have serious side effects because of their non-specific effect on both cancerous and healthy cells. Polysaccharide-based systems on the contrary, provide significant decrease in systemic toxicity as a result of controlled and localized drug release.

They also have the ability to deliver drugs specifically to targeted organs, such as the colon, which allows them to be delivered to the tissues where they are needed, reducing the systemic exposure of the healthy tissues and ultimately decreasing the systemic side effects of the drug, including gastrointestinal toxicity, immunosuppression and organ damage (Patel et al., 2020).

5.3 Targeted Drug Delivery

The importance of polysaccharides in the targeted drug delivery application, in particular colon specific drug delivery is important. Some of the polysaccharides such as pectin, chitosan and dextran are not digestible in the stomach and

intestine but are metabolized in the colon by bacteria. This will enable the drugs to be delivered only to the place of action.

Besides, polysaccharides can be chemically modified with targeting ligands to make them active targeting, which means the drug carrier can specifically bind to cancer cell receptor. This helps to increase the drug's accumulation in cancerous tissues and improves the therapeutic effectiveness (Singh et al., 2021).

5.4 Enhanced Bioavailability

Many anti-cancer drugs are poorly soluble and poorly bioavailable, and as a result, have weak activity. Polysaccharide based delivery systems help in the absorption, protection of drugs from degradation and increase in drug solubility.

The drug release at the targeted site for a longer period through polysaccharide nanoparticle and hydrogel system can help to maintain the optimum concentration of the drug for a longer period, increasing the bioavailability and therapeutic efficiency of the drug (Wang et al., 2021).

5.5 Immunomodulatory Effects

Polysaccharides have been reported to have high immunomodulatory activity that is important for cancer therapy. They stimulate the immune system by stimulating macrophages, antigen-presenting dendritic cells, and NK immune cells.

This leads to better identification and killing of tumour cells. Furthermore, the polysaccharides promote the release of cytokines (IL-2, IL-6 and TNF-α), which further activates the immune response against the cancer cells (Zhao et al., 2021).

Overall Advantage

Therefore, polysaccharides, because of their multi-functional nature, are considered as multi-functional therapeutic agents with direct anticancer activity as well as enhanced drug delivery properties.

6. Limitations and challenges

Although polysaccharide therapy is highly beneficial, there are a number of deficiencies which must be overcome before its full clinical use.

6.1 Structural Variability

Polysaccharides are very variable in structure depending on source, extraction techniques, environmental conditions etc. Their biological activity and reproducibility can be different, depending on their variations in molecular weight, branching and composition.

This is not uniform and it is hard to standardise formulations and achieve consistent therapeutic effects (Chen et al., 2017).

6.2 Limited Clinical Data

The anticancer activity of polysaccharides has been well demonstrated in both in vitro studies and animal models, but there are still no well-designed clinical trials in humans.

The use of these in traditional medicine is limited and they need to be explored in clinical investigations to evaluate their safety and efficacy, which is important (Li et al., 2021).

6.3 Stability Issues

Certain polysaccharides are sensitive to the environmental factors like pH, temperature or enzymatic degradation. This may impact on their storage and delivery stability.

One of the critical challenges in formulation development is to achieve stability with biological activity.

6.4 Scale Up and Manufacturing Challenges

The extraction and purification of polysaccharide based systems and their modification is often a complex process, making their large scale production difficult. Another major problem is to keep the industrial production process consistent and of high quality.

Overall Limitation

Solving such problems is crucial to the translation from laboratory to clinical applications of polysaccharide-based therapies.

7. Molecular signaling pathways involved in CRC and polysaccharide action

The signaling pathways inside cells are crucial for how colorectal cancer develops, influencing important processes like cell growth, programmed cell death, inflammation, blood vessel formation, and the spread of cancer.

Sometimes, these pathways can misfire, leading to uncontrolled tumor growth and making treatments less effective. Polysaccharides can actually influence cancer growth by interacting with important signaling pathways, which helps block the advancement of the disease.

7.1 Nuclear Factor Kappa-B Regulatory Pathway

A pathway that regulates inflammatory processes, the NF-κB (nuclear factor-kappa B) pathway is also a key factor in cancer. NF-κB activation results in the production of pro-inflammatory cytokines, anti-apoptotic proteins and tumour growth genes.

However, in the case of colorectal cancer, NF-κB is constantly activated, leading to prolonged inflammation and cancer development.

Polysaccharides such as β-glucans and derivatives of pectin prevent the activation of NF-κB by preventing NF-κB from entering the nucleus. This results in the reduction in levels of inflammatory mediators and inhibition of tumour growth (Kim et al., 2019; Zhao et al., 2021).

7.2 PI3K/Akt Mediated Signaling Cascade

It has been proposed that the PI3K/Akt pathway regulates cell survival, growth and metabolism. This pathway is frequently deregulated in CRC, and associated with resistance to apoptosis.

Additionally, polysaccharides have been shown to inhibit activation of the PI3K/Akt signaling pathway, reducing proliferation and inducing apoptosis. They additionally cause sensitivity of cancer cells to the chemotherapeutic drugs (Li et al., 2021).

7.3 β-Catenin Mediated Wnt Pathway

The Wnt/β-catenin pathway plays a pivotal role in CRC. The dysregulation of this pathway results in the accumulation of β-catenin in the nucleus where it is able to initiate transcription of cell proliferation genes.

Polysaccharide compounds like fucoidan and chitosan derivatives can block the growth of tumors by inhibiting the accumulation of β-catenin and the Wnt pathway (Wang et al., 2020).

7.4 Mitogen-Activated Protein Kinase Pathway

The MAPK pathway is involved in the regulation of cell differentiation, proliferation and cell death.

Polysaccharides are used to regulate the ERK, JNK and p38 pathways which are the three MAPK signaling pathways. This leads to the suppression of cancer cell proliferation and induction of cancer cell apoptosis (Sun et al., 2020).

Overall Pathway Insight

Polysaccharides are multi-target agents that exert their therapeutic effects on several signaling pathways, hence their effect on colorectal cancer.

8. SPECIFIC POLYSACCHARIDES IN CRC THERAPY

A number of polysaccharides have been thoroughly evaluated for anticancer activities in CRC. These all have particular characteristics and modes of action.

8.1 Pectin

Pectin is a polysaccharide obtained from plants which is extensively employed in targeted delivery systems for the colon. It is degraded in the colon by enzymes, which enables a site specific drug release.

It has also been demonstrated that the modified citrus pectin acts as an inhibitor of galectin-3 which prevents metastasis to tumors. It also causes apoptosis and inhibits tumour growth (Zhang et al., 2019).

8.2 Chitosan

Chitin is a precursor polymer to chitosan, the biodegradable and biocompatible polymer. It has very good mucoadhesive property, thereby providing better retention of the drug in the colon.

The use of chitosan-based nanoparticles in colorectal cancer therapy is very popular due to their targeted drug delivery properties. They can increase the stability of drugs and help achieve controlled release and improve bioavailability (Singh et al., 2021).

8.3 β-Glucan

The polysaccharides β-glucans are known for their strong immunomodulatory activity, and are found in fungi. They activate immune cells and strengthen the immune system's response against tumour cells.

They are also biological response modifiers and commonly employed as adjuvants in cancer treatment (Zhao et al., 2021).

8.4 Alginate

Algal polysaccharide is a common constituent of a drug delivery system with the use of alginate. It controlled the release of drugs and protects drugs from degradation.

The localized and sustained delivery of drugs for the treatment of colorectal cancer is also being widely explored with alginate-based formulations (Ahmed et al., 2022).

8.5 Fucoidan

The fucoidan is a sulfated polysaccharide from brown algae, with high anticancer activity.

It induces the apoptosis of tumor cells, blocks the formation of new blood vessels and inhibits proliferation of tumor cells. Additionally, fucoidan is able to regulate immune response and anti-inflammatory activity, which is very beneficial in the treatment of CRC (Wang et al., 2020).

Table 3: Specific Polysaccharides and Their Anticancer Effects in CRC.

Polysaccharide	Source	Mechanism	Application	Reference
Pectin	Plant	Colon degradation, apoptosis	Colon-targeted delivery	(Zhang et al., 2019)
Chitosan	Crustacean shells	Mucoadhesion, permeability	Nanoparticles	(Singh et al., 2021)
β-glucan	Fungi	Immune activation	Immunotherapy	(Zhao et al., 2021)
Alginate	Seaweed	Controlled release	Hydrogels	(Ahmed et al., 2022)

9. Combination Therapy Using Polysaccharides

In CRC, a new therapy is the combination therapy which involves the use of polysaccharides in addition to the conventional chemotherapeutic agents.

Polysaccharides improve the effectiveness of anticancer drugs by increasing drug delivery, decreasing the toxicity of the drug and overcoming drug resistance. For instance, chitosan nanoparticles with chemotherapeutic drugs have been proven to have better therapeutic effects for CRC (Li et al., 2021).

Furthermore, the polysaccharide can be associated with natural ingredients like curcumin, thus improving its bioavailability and benefits.

10. The role of Polysaccharides in Nanotechnology

The use of nanotechnology to modify drug delivery system has changed the world and polysaccharides has been found to be a very important component in the development of nanocarriers.

There are a number of advantages for using polysaccharide based nanoparticles:

- Targeted drug delivery
- Improved drug stability
- Enhanced bioavailability
- Reduced side effects

These systems are based on the improved permeability and retention effect (EPR) that enables preferential uptake of nanoparticles in tumor tissue (Singh et al., 2021).

Table 4: Polysaccharide-Based Nanocarriers in CRC Therapy.

System	Polymer	Drug Loaded	Advantage	Reference
Nanoparticles	Chitosan	5-FU	Targeted delivery	(Singh et al., 2021)
Hydrogels	Alginate	Doxorubicin	Sustained release	(Ahmed et al., 2022)
Liposomes	Chitosan-coated	Curcumin	Enhanced bioavailability	(Li et al., 2021)
Nanoemulsion	Polysaccharide-based	Paclitaxel	Improved solubility	(Wang et al., 2020)

11. Challenges in polysaccharide-based therapy today

Although this approach has shown some success, there are a number of obstacles:

There have been no large-scale clinical trials done. There have been no large scale clinical trials conducted.

Polysaccharide molecules contain different structures that vary from each other.

- Thermal instability and/or susceptibility to temperature changes in the formulation
- Regulatory limitations

12. Future Perspectives

Further studies are needed on:

- Applications of polysaccharide-based therapies in the clinic.
- To develop a multifunctional drug delivery system.
- Treatment using combinations of synthetic drugs.
- Personalized medicine approaches

13. Use of polysaccharides in CRC – PRECLINICAL AND CLINICAL EVIDENCE

In recent decade, research into the therapeutic potential of these polysaccharides against colorectal cancer (CRC) has progressed significantly and a substantial amount of data have been accumulated from in vitro, in vivo animal and limited clinical studies. The studies reviewed all have demonstrated multi-targeted anticancer properties for polysaccharides but the clinical application studies are in their infancy.

13.1 In Vitro Evidence: Cellular and Molecular Insights

The first evidence for the evaluation of anticancer activity is in vitro studies. Polysaccharides actions have been studied using many human colorectal cell lines including HT-29, HCT-116, SW480, LoVo and Caco-2.

In the context of cytotoxicity the polysaccharides show particularly strong effects in a dose dependent fashion, they are primarily:

- Mitochondrial function decline, and induction of apoptosis.
- Inhibition of cell cycle progression at G0/G1 and/or G2/M checkpoint phases.
- The proliferation-related pathways have been found to be inhibited.
- Disruption of expression of genes associated with metastasis.

Polysaccharides modulate important signalling pathways:

- Downregulation of NF-κB which downregulates inflammation through inflammatory cytokine production
- Inhibition of PI3K/Akt pathway, which results in a decrease in survival signaling
- The Wnt/β-catenin pathway is an important pathway that inhibits the growth of tumors.
- Increased expression of genes involved in apoptosis and cell growth

Fucoidan, for example, has been found to induce apoptosis in HCT-116 cells by up-regulating the level of the pro-apoptotic protein, caspase-3, and down-regulating Bcl-2 (Livrea et al., 2016; Wang et al., 2020), whereas β-glucans exhibited an immune-mediated cytotoxicity (Li et al., 2021; Wang et al., 2020).

In addition, the anticancer effects include epigenetic regulation (histone modification and DNA methylation) that is regulated by polysaccharides.

13.2 In Vivo Evidence: Translational Relevance

There is good preclinical evidence, but limited clinical validation. To date, most clinical studies have not been on the polysaccharides as direct anticancer agents, but on their immunomodulatory properties.

Beta-glucans have been found to have a beneficial effect in clinical trials as follows:

- Improved immune function.
- Improved sensitivity to chemotherapy.
- Reduced infection rates and treatment related side effects.

However, limitations include:

- Small sample sizes
- There is a lack of uniformity in the formulations.
- There is an absence of long-term outcome information.

(Zhao et al., 2022)

Critical Interpretation

Although there is strong preclinical evidence of efficacy, there is an apparent gap between preclinical research and clinical use, with a need for:

- Large-scale clinical trials
- Standardized formulations
- Regulatory validation

14. ROLE OF POLYSACCHARIDES IN IMMUNOTHERAPY

The field of cancer immunotherapy has transformed from targeting the tumour directly to manipulating the immune system. The biological role of polysaccharides as biological response modifiers is very important.

Mechanistic Insights

There are several ways that polysaccharides activate immune responses:

1. Innate Immunity Activation

- When macrophages are activated, they begin to phagocytize more.
- Activation of NK cells → direct killing of tumour cells
- Aim of the immune system is to improve antigen presentation by dendritic cell maturation.

2. Adaptive Immunity Enhancement

- Rise of T-helper (CD4+) cells and rise of cytotoxic T (CD8+) cells.
- Enhanced production of cytokines (IL-2 and IFN-γ)

Receptor-Mediated Activation

Polysaccharides interact with:

- Dectin-1 receptors
- Toll-like receptors (TLR-2, TLR-4)

This results in activation of:

- NF-κB pathway
- MAPK signaling

(Zhao et al., 2021)

Clinical Relevance

Polysaccharides enhance:

- Response to immune checkpoint inhibitors
- Tumor antigen recognition
- Infiltrating immune cells in tumour microenvironment

So, they have the potential to become promising adjuvants in immunotherapy.

This course covers the interaction between the tumor microenvironment (TME) and advanced version.

The tumor microenvironment (TME) is a complex and dynamic environment which plays an important role in tumor progression and therapeutic resistance.

Polysaccharide-Mediated Modulation

Polysaccharides affect TME in the following ways:

1. Immune Reprogramming

- The transformation of M2 macrophages to M1 phenotype.
- Increased cytotoxic T-cell activity.

2. Anti-Angiogenic Effects

- Inhibition of VEGF signaling
- Reduced tumor vascularization

3. ECM Remodeling

- The control of the extracellular matrix breakdown
- Reduced tumor invasion

For instance, fucoidan was shown to have inhibitory effects on the expression of VEGF which slows the growth of tumors (Wang et al., 2020).

16. Aim to help overcome drug resistance

There are several mechanisms of resistance to drug in CRC: efflux transporters, survival signaling, and tumor hypoxia. This is why polysaccharides are able to overcome resistance:

- The inhibition of P-glycoprotein (P-gp) leads to a decrease in efflux of a drug.
- Improved drug uptake in the cell
- Modulation of the pathways of PI3K/Akt and NF-κB.
- Decreased hypoxia induced resistance

The delivery of drugs inside cancer cells is achieved by using nanoparticle-based systems that are able to avoid developing resistance (Li et al., 2021).

17. SAFETY AND TOXICITY PROFILE

Polysaccharides show:

- Low toxicity
- High biocompatibility
- Minimal immunogenicity

  Safety, however, requires:

- Purity
- Molecular weight
- Source

  (Ahmed et al., 2022)

The 18th theme is related to regulatory and manufacturing challenges.

Major challenges include

- Lack of standardization
- Batch-to-batch variability
- Complex extraction methods
- Regulatory approval barriers

19. Future Directions

Future focus areas:

- Smart nanocarriers
- Stimuli-responsive systems

- AI-driven drug design
- Personalized therapy

20. Key Comparative Insight

Polysaccharides vs chemotherapy:

Feature	Chemotherapy	Polysaccharides
Toxicity	High	Low
Targeting	Poor	High
Resistance	Common	Reduced

Synergy

- Enhances curcumin bioavailability
- Improves chemotherapy efficiency

Personalized Medicine

- Ligand-targeted delivery
- Biomarker-specific therapy

Prevention

- Gut microbiota modulation
- SCFA (butyrate) production

Research Gaps

- A lack of clinical trials

DISCUSSION

Polysaccharides are a multi-dimensional therapeutic platform, which integrates:

- Drug delivery
- Immunotherapy
- Microbiota regulation

They are able to target multiple pathways at once, which is a great advantage over conventional therapies.

However, for clinical translation to be successful, there are a number of factors to consider:

- Standardization
- Clinical validation
- Interdisciplinary research

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