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Targeted Colon Cancer Therapy Using Bio-Polymers-Mechanisms, Delivery Systems, And Recent Advances

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ABSTRACT:

One of the main and most causes of morbidity and mortality in the world is colon cancer. Surgery, chemotherapy, and radiation are examples of conventional therapeutic approaches that frequently have drawbacks like systemic poisoning, non-specific drug activity, and limited drug concentration within tumour tissue. Polymeric drug delivery systems have become a viable approach for colon cancer management. Chemotherapeutic agents or bio-active compound can be mixed with natural and synthetic polymers to produce sophisticated colon delivery systems like hydrogels, nanoparticles, microspheres, and polymeric coatings that allow for targeted and regulated drug release in the colon site. These systems improve therapeutic bio-availability, cellular uptake, and tumour focused targeting while shielding medications from early gastrointestinal breakdown. Additionally, polymer-mediated delivery methods have the ability to alter important molecular signalling pathways like PI3K/Akt/mTOR, NF-κB, MAPK, and apoptosis-related pathways involved in colonic carcinoma and can be modulated by polymer-driven delivery systems. The mechanisms of action of several natural and synthetic polymeric matrices utilized for colon-directed drug delivery are covered in this review, along with how they can improve therapeutic outcomes.

1. Introduction

Colon cancer is among most prevalent cancers in the world and continues to be leading cause of carcinoma-related death. If left untreated, can progress to tumours that are malignant. Although whole-body chemotherapy treatment frequently results in Standard cancer management strategies, including surgical intervention, chemotherapy, and radiotherapy, are extensively used but often suffer from high toxicity, non-specific drug action, and suboptimal tumour drug accumulation. These limitations, lower the effectiveness of treatment and could result in acquired resistance to therapeutic drugs and harm to healthy tissues. Among all other novel drug delivery systems, ppolymer-based drug delivery systems have become a viable approach for colon cancer treatment in order to overcome these limitations. This method employs natural or synthetic polymers in combination with the anticancer compounds/bio-active compound to construct targeted delivery vehicles including hydrogels, nanoparticles, microspheres, and polymer coatings. Specific grades of synthetic polymer and some of natural polymers can facilitate controlled or site-specific drug release in the colon and shield therapeutic agents from premature gastrointestinal tract degradation. When polymers are combined with chemotherapeutic agents, systemic toxicity is reduced while drug stability, bioavailability, and accumulation at the tumor site are all improved. Additionally, polymer-based therapeutic delivery platforms can improve therapeutic efficacy by promoting cellular uptake and prolonged drug release. Such systems can also have an impact on key molecular pathways that contribute to the development of colon cancer, such as apoptosis-related mechanisms and growth-regulating signalling cascades. Many studies have looked into polymer–drug combinations for the treatment of colon cancer in recent years, with an emphasis on increasing anticancer efficacy, decreasing side effects, and improving targeted delivery. . Natural and synthetic polymers are the two main categories of polymeric carriers used for colon-

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targeted therapeutic delivery Biocatalysts generated by bacteria in colon can break down natural polymers like chitosan, pectin, alginate, guar gum, and dextran, which are biodegradable and well-tolerated substances. The embedded medication is released directly into the colon as a result of this enzymatic breakdown. Conversely, industrial important polymers that provide exact rregulation of drug release characteristics and cconformational stability include Eudragit, PLGA, PCL polymer, and polyethylene glycol (PEG). For an example, the aalkaline environment of the colon dissolves pH-sensitive polymers like Eudragit S100 and L100, enabling targeted drug release in the distal gut. Promoting effective cellular drug absorption and prolonged ssystemic drug availability at the tumour site, polymers combined with anticancer medications iimprove drug transport and subsequently enhance therapeutic effectiveness. Increased intracellular drug levels in cancer cells may result from polymeric nanoparticles' improved penetration of tumour tissues and their potential to take advantage of biological phenomena like enhanced permeability and retention (EPR). Additionally, the medications that are administered have the ability to alter important molecular pathways that contribute to the development and spread of tumours, such as those that control inflammation, apoptosis, and cell division. Polymer-drug delivery systems can prevent tumour growth and encourage colon cancer cells to undergo programmed cell death by affecting these signalling pathways. Consequently, a promising avenue for colon cancer treatment is the creation of polymer-assisted drug delivery systems. These systems provide new ways to improve treatment effectiveness and patient outcomes by combining developments in polymer science, nanotechnology, and cancer biology. Emphasizing the kinds of polymers used, current advancements in polymer-based drug delivery techniques, colon targeting mechanisms, and therapeutic pathways implicated for enhanced anticancer therapy are thoroughly reviewed in this review of polymer–drug combination strategies for colon cancer treatment.

2. POLYMERS FOR COLORECTAL CANCER

Because of their ability to protect drug in the stomach & small intestine and in site-triggered mechanism in the distal gut these polymers increase local exposure (Figure 1). In colorectal tumours while reducing systemic toxicity, polymeric systems are often used for anticancer medication delivery to the colon. Usually, the response of the polymers to the tumour microenvironment depends on mucus interactions, colonic enzymes/microbiota, and gastrointestinal pH. Employing polymers that are still insoluble under acidic stomach conditions, and start to ionize/dissolve at a higher intestinal pH allowing for delayed release in the distal intestine or in the colon is prerequisite. Because of their simplicity of preparation, reproducibility, and scalabilityy, these systems are often used as coatings, matrices, or shell layers in microparticles and nanoparticles. Because the colon has a high concentration of microflora, several polymeric systems are developed to undergo enzymatic decomposition or microbial-triggered bond cleavage, therefore targeting drug release and disintegration selective to the colon. For oral targeting, this technique is attractive; however, the release could vary according to the microbiota composition, diet, and health condition, all of which are crucial translational variables. Biopolymeric carriers have mucoadhesive, biodegradability, and biocompatibility, rresistant to upper-GI deterioration but sensitive to enzymatic breakdown in the colon, and its matrices/coatings over API can enhance local delivery through oral colon delivery.

These polymers can be used to produce nanoparticles, beads, hydrogels, and nano-in-micro architectures. Mucoadhesive polymers raise local exposure and may raise absorption at tumour sites by lengthening residence time near the colonic mucosa. Mucoadhesion also encourages regulated release; hence, design usually offers a balance between adhesion and diffusion even if higher mucus affinity could sometimes restrict penetration into deeper tissues. The drug loaded polymeric nanocarriers responding to tumour-relevant signals like redox state, enzymes, and inflammatory environment after coming into the colon provide more targeted release at tumour locations, often presented as next-generation strategies when used with oral targeting.

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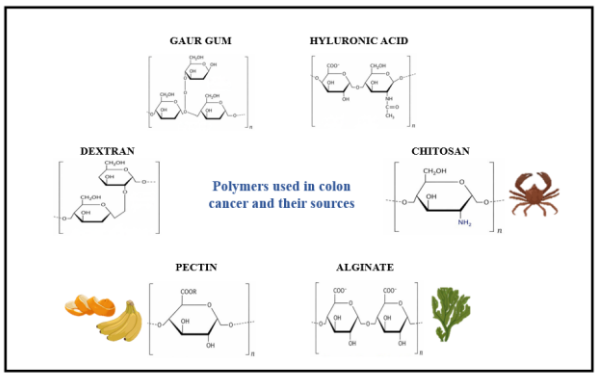

Figure 1 Polymer used for colon targeted drug delivery

2.1 NATURAL POLYMERS

Chitosan:

Chitosan which is linear polycationic (positively charged) amino polysaccharide. produced by deacetylation of chitin, Non-toxic, Non-immunogenic, well tolerated by tissues, which is left behind in crustacean shells of shrimp, crab, insect cuticles, fungal cell walls and some marine sources and the iindustrial chitosan is commonly made from crustacean shell chitin **[1]**. Low–molecular-weight chitosan (LCH) and the medium–molecular-weight chitosan (MCH) are used to encapsulate yarrows extract rich in chlorogenic acid which shows effects of cytostatic agents on colon adenocarcinoma cells. In this study two techniques were used i.e ion gelation and spray drying. Spray-drying technology has highest %EE and chitosan can be proposed as a promising vehicle to increase the colon delivery of yarrow phenolics compounds (mainly chlorogenic acid and DCQAs) against colorectal cancer. Comparatively to native polymers, surface modified polymer performs more efficiently. Cchitosan surface-modified PLGA nanoparticles (CS-PLGA NPs) for encapsulating **C**cranberry powder extract (CBPE) inhibit colon cancer cell growth and proliferation by modulating its release rate, permeation, and cell targeting **[2].** Using an emulsification method, chitosan-coated poly (lactic-co-glycolic acid) nanoparticles were formulated for the oral administration of ferulic acid. The therapeutic effectiveness of the ferulic acid-loaded nanoparticles was on par with that of the free drug, suggesting that ferulic acid's biological activity like antioxidant or cytotoxic was unaffected by chitosan encapsulation. Similarly folic acid (FA) loaded nanoparticles revealed higher transport efficiency across the Caco-2/HT29-MTX/Raji co-culture model. According to these results, chitosan-coated PLGA nanoparticles show promise as a delivery method for folic acid taken orally **[3].** In another study, sulfide-conjugated sodium alginate nanoparticles were prepared to precisely deliver docetaxel to colon cancer cells. DMP2 (Docetaxel-loaded thiolate sodium alginate disulfide cross-linked nanoparticle formulations) was chosen for surface functionalization with fWGA because it demonstrated the highest drug-loading efficiency (17.8%) among several nanoparticle formulations where docetaxel was successfully encapsulated (DMP1, 2, 3, and 5). The conjugation efficiency of the resulting fDMP2 formulation was 14.1%. Its potential for targeted anticancer drug delivery was demonstrated by cellular studies showing preferential selectivity toward HT-29 colon cancer cells compared to L929 normal fibroblast cells. After two hours of incubation, fluorescence and confocal microscopy confirmed that fDMP2 achieved a cellular uptake of approximately 29%, indicating successful intracellular internalization. Overall, fDMP2 appears to be a promising nanocarrier for the sustained and controlled delivery of anticancer drugs to colon cancer cells **[4].**

Alginate:

Alginate extracted from brown seaweeds consists of D-mannuronic and L-guluronic acids and has a linear (unbranched) structure. These monomers can be arranged in alternating, sequential, or random patterns, depending on their synthesis method. Key features of the polymer include biocompatibility, non-toxicity, biodegradability, and functional versatility **[5][6].** Alginate-derived nano- and micro-systems with specific characteristics and enhanced functionality have been explored for cancer-targeted therapy and drug delivery applications. Regulated and sustained drug release significantly improves the efficacy of anticancer treatments. New alginate-based targeted cancer therapies using nano systems and modern oral drug delivery methods offer a non-invasive approach, increasing patient acceptability and simplifying drug administration **[7].** Calcium alginate combined with an imidazolium ionic liquid via ion exchange has been used to produce alginate/imidazolium-based ionic liquid nanocomposites. These dual drug-loaded nanocomposites, with an average particle size of about 70 nm, demonstrated clear pH-responsive release behaviour for methotrexate and

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ciprofloxacin, with greater release at pH 5.8 than at pH 7.4. The antibacterial activity of ciprofloxacin-loaded nanocomposites was significantly higher than that of the free drug ($P < 0.001$). Similarly, in another study, methotrexate-loaded nano formulations showed substantially higher cytotoxicity against MCF-7 breast cancer cells ($P < 0.001$) and induced notable S-phase cell-cycle arrest ($P < 0.001$) compared to untreated cells **[8].**

Pectin:

Pectin is a broad class of plant-derived polysaccharides mainly found in the cell walls of higher plants. It is widely used as a stabilizing, gelling, and emulsifying agent and also functions as a drug carrier in the food and pharmaceutical industries. Citrus peels, apples, and various botanical sources are utilised in its extraction **[9].** A study optimized thymoquinone-loaded pectin beads for colon-specific delivery using an electrospray method. These beads exhibited rate-controlled and localized drug release, with minimal release in the intestinal and gastric environments and increased release in the colon, making them suitable for targeted colon delivery. The formulation effectively improved thymoquinone's bioavailability and therapeutic potential against colorectal cancer **[10].** Additionally, a newly isolated apple pectin, showed potent anticancer properties compared to modified citrus pectin. This pectin reduced the availability of irinotecan, increased intracellular reactive oxygen species, induced apoptosis, and decreased the viability of colon cancer cells. It also demonstrated strong anti-inflammatory qualities, reduced bacterial β-glucuronidase activity, and prevented E. coli from adhering to colon cancer cells; however, these results are only supported by in-vitro studies **[11].**

Guar gum:

The endosperm of the cluster bean is used to produce guar gum, a novel agrochemical. Flurbiprofen (FLB) is a nonsteroidal anti- inflammatory drug employed to treat pain and inflammation related to the colon. Regular intake of FLB can lead to gastrointestinal issues such as gastric ulceration and bleeding **[12][13].** Certain gut microorganisms, including Bacteroides ovatus (about 25% of the strains studied), Bifidobacterium adolescentis (one strain), and Bifidobacterium dentium (all tested strains showed fermentative activity), have been reported to ferment guar gum **[14]** and in this case colon targeted drug delivery system will be useful. In another study, Tween 80 was used as the surfactant, and Transductal P served as the co- surfactant in developing a colon-targeted solid self- nanoemulsifying drug delivery system (S- SNEDDS) for xanthohumol (XH). The solid S- SNEDDS powder was created by adsorbing the liquid SNEDDS (L- SNEDDS) onto pectin and guar gum. The optimized formulation produced nano emulsion droplets with a high drug- loading efficiency (~94%), a negative zeta potential (~- 19 mV), and an average size of approximately 119 nm. Colon- specific release was confirmed through dissolution tests in media containing rat cecal contents; less than 10% of XH was released in the first five hours, followed by a rapid release phase between five and ten hours, caused by polysaccharide degradation. Cytotoxicity tests indicated that XH- loaded S- SNEDDS had significantly stronger cytotoxic effects on Caco- 2 cells than free XH, demonstrating its potential as an effective colon- targeted delivery system **[15].** Using emulsion polymerization, 5- ASA- loaded guar gum microspheres were fabricated. Particle size, drug entrapment efficiency, and in- vitro release was optimized under colonic- like conditions. FTIR, PXRD, and DSC analyses characterized drug–polymer interactions. With an average particle size of 150. 3 ± 11. 8 μm and a high entrapment efficiency of 82. 39% (mean ± SD: 1. 06), the optimized formulation was deemed suitable for targeted colonic drug delivery. In- vitro release tests showed 9. 32 ± 0. 63% drug release in SGF (pH 1. 1.2, without pepsin), 13. 13.93 ± 0. 90% in SIF (pH 7. 5), and 32. 11 ± 2. 80% in SCF (pH 7. 7.0, without rat cecal contents), while a notable increase in drug release (94. 62 ± 4. 50%) was observed in SCF (pH 7.0. 0) containing 4% rat cecal material after six days of enzyme induction. As guar gum- based microspheres can enhance localized drug delivery and treatment outcomes, they represent a promising therapeutic approach for managing ulcerative colitis **[16].**

Dextran:

Dextran is an exopolysaccharide produced by lactic acid bacteria (LAB) or their extracellular enzymes when sucrose is available as a substrate. Dextran's structure mainly consists of a linear chain of D-glucose units linked by alpha-1,6 glycosidic bonds. Additionally, glucose residues connected in various ways form branches of different sizes. This structural flexibility

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makes it useful in a wide range of biomedical and physicochemical fields **[17].** To evaluate its efficacy as a drug delivery system, 5-fluorouracil (5-FU) was encapsulated in dextran-coated iron oxide nanoparticles (IONPs), which were subsequently characterized in detail. All formulations showed a gradual increase in hydrodynamic size over time; however, extended storage did not affect the overall stability of the colloidal system. Zeta potential measurements indicated that the nanoparticle suspensions remained stable for at least 28 days. Early data from this study indicate that Caco-2 cells treated with dextran-functionalized IONPs bearing 5-FU significantly lowered MCM-2 expression. The sample with an IONP: 5-FU ratio of 1.5: 1 among those tested had the most effective antitumor activity. This activity was linked to increased cellular nanoparticle uptake, more reactive oxygen species production, and a more noticeable suppression of cell proliferation. **[18].**

Hyaluronic acid

A mucopolysaccharide, hyaluronic acid (HA) is a carbohydrate found naturally in a variety of living things. Hyaluronan is a linear, negatively charged polymer composed of repeating β-D-N-acetylglucosamine and β-D-glucuronic acid disaccharide units. Mostly found in the pericellular and extracellular matrices, hyaluronic acid (HA) is very important for keeping tissues in good shape and working properly **[19].** To enable good tumour targeting, CUBs were coated with a HA–SA composite. Release studies of drugs in vitro showed a controlled diffusion pattern like the tumour microenvironment; more release happened under acidic conditions. The system displayed good physicochemical stability even throughout stability studies. In cytotoxicity tests, HA-REG-CAP-CUBs had the strongest antiproliferative effects against HCT-116 and HT-29 colorectal cancer cell lines, so showing that they can make drugs work better and target tumours better **[20].** HA-based nanomaterials are becoming somewhat well-known in cancer treatment. In a number of tests, drug-loaded HA-functionalized nanoparticles showed promising in vitro and preclinical results. Conjugation with HA enhances targeting performance by means of HA–CD44 receptor-mediated endocytosis, therefore boosting nanocarrier biocompatibility and efficient tumour cell uptake **[21].**

Chondroitin sulfate:

Chondroitin sulfate is a sulfated acidic polysaccharide. The molecule's strongly anionic nature results from numerous sulfate and carboxyl groups along the polymer backbone, largely defining its surface-related structural properties. N-acetyl galactosamine connects to a uronic acid residue in each of the hundreds of repeating disaccharide units that make up CS. Its unique physicochemical and biological characteristics arise from this repetitive architecture. GalNAc residues, substituted to varying degrees with sulfate linked to the 4- or 6-hydroxyl positions, alternate in glycosidic linkages with glucuronic acid (GlcA), which is substituted with sulfate at the 2- and (more rarely) 3-hydroxyl positions **[22].** In vivo anticancer experiments in HCT-116 xenograft mice demonstrated that Bor/Cs/Chs-FA mediated a greater suppression of xenograft tumors with less harm to usual organs and tissues compared to controls, including those treated with free medicines and nano formulations lacking a folate-based targeting moiety. Thus, this improved formulation is promising for folate-specific receptor chemotherapy, leading to potential effective strategies for treating folate receptor–positive colorectal tumors **[23].**

Cyclodextrin:

Cyclodextrins (CDs) are natural cyclic oligosaccharides. They consist of six, seven, or eight glucose units linked by α-1,4-glycosidic bonds, forming α-, β-, and γ-CDs. These molecules have a water-resistant internal surface and a hydrophilic exterior surface [24]. In a study regarding curcumin nanoparticles, the average particle diameter of the FA-Cur-NPs was approximately 152 nm, with a drug loading capacity of 20%. Release studies indicated that curcumin was released significantly faster in mildly acidic conditions (pH 6.4) than at physiological pH (7.4), suggesting that the tumor microenvironment favours drug release. The ability of FA-Cur-NPS to accumulate in tumors and demonstrate strong anticancer effects was confirmed by in vivo studies, highlighting their potential for targeted cancer therapy. In another study, A cRGD-functionalized β-cyclodextrin–caprolactone conjugate has a diameter of around 140.2 nm and a zeta potential of -11.3 millivolts. The formulation showed satisfactory physicochemical stability. Both Scu and the cRGD-functionalized β-cyclodextrin–caprolactone significantly reduced HT-29 cell proliferation and viability, as demonstrated by MTT assay. The cRGD-modified system exhibited improved

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in vitro efficacy. Colony formation and flow cytometry analyses confirmed these findings by showing that the cRGD-functionalized β-cyclodextrin–caprolactone more effectively induced apoptosis and more strongly inhibited cell growth [25].

Cellulose:

Fibers in cellulose are generally derived from various natural sources, such as wood, bark, cotton, leaves, and jute. It can be found as pulp in natural fibres or as chemically modified derivatives that form synthetic fibers. Cellulose is made up of repeating anhydrous D-glucose units linked by β-1,4-glycosidic bonds. Strong hydrogen bonds between these chains give them a semicrystalline structure, making the material stiff, water-insoluble, and capable of forming long, parallel fibrillar structures **[26][27].** To assess their antitumor potential against colorectal cancer cells, cellulose nanocrystals (CNCs) were designed as carriers for 5-fluorouracil (5-FU). The CNC/5-FU nano formulation demonstrated significant cytotoxic activity, primarily by inducing cell death and damaging mitochondrial membrane integrity. All these results suggest that CNC/5-FU is a promising nanocarrier system that can enhance therapeutic outcomes and improve drug delivery efficiency in colorectal cancer treatment **[27].**

Starch:

Starch is a plant storage polysaccharide based on glucose, composed mainly of two types of polymers: amylose, which is linear, and highly branched amylopectin. It is produced in plastids (amyloplasts or chloroplasts) and functions as the main carbohydrate store in seeds, roots, and tubers. Two well-known gut bacteria that degrade resistant starch, Ruminococcus bromii ATCC 27255 and Bifidobacterium adolescentis L2-32, were used to evaluate the microbial fermentation capacity of intrinsic RS-3. The samples included two substrates with an A-type crystalline form, enabling assessment of strain-specific utilization patterns (N16-A, P21-A), and two with a B-type form (N32-B, N76-B). N16-A, N32-B, and N76-B were made from narrowly dispersed enzymatically synthesized α-1,4-glucans, while P21-A was derived from polydisperse debranched waxy rice starch **[28].** Starch nanoparticles made by emulsification-crosslinking have high drug loading efficiencies, often over 75% for chemotherapeutics like 5-Fluorouracil." The use of pH-responsive coatings, such as pectin or Eudragit S100, guarantees these cores reach the colon intact. In the stomach's acidic environment, only about 10% of the cargo is released; this two-step method prevents premature release. When the coating dissolves in the acidic colon, microbial enzymes degrade the starch matrix, optimizing the drug concentration precisely at the tumour location **[29].**

Gelatin:

Gelatin, which can be produced from various types of collagens, is derived from different biological sources, primarily porcine skin, hides, bovine bones, and marine organisms like fish [30]. According to an IR-assisted self-assembly technique, gelatin nanoparticles carrying carboplatin exhibit potent anticancer properties against colorectal cancer cell lines. Smaller nanoparticles exhibit better cellular absorption and prolonged drug release than larger ones. The gelatin matrix's biodegradability and stability translate into great medicine entrapment efficiency. The study ultimately determined that IR-light-triggered synthesis results in highly controllable, non-toxic polymer carriers that improve carboplatin's cytotoxic properties. Targeted colon cancer treatment and localized treatment seem very promising from this **[31].**

2.2 SYNTHETIC POLYMERS

PLGA (poly lacticco glycolic acid);

Poly (lactic-co-glycolic acid) is a biodegradable co-polymer derived from 2-hydroxypropionic acid and glycolic acid. It is typically produced by polymerising cyclic dimers, lactide (LA), and glycolide (GA), through ring-opening polymerization of LA and GA **[32].** Sunitinib malate has been effectively encapsulated within PLGA-based polymeric nanoparticles to enable sustained drug release. These optimized PLGA nanoparticles demonstrate enhanced cytotoxic effects against HT-29 cell lines compared to the free drug, indicating their potential as efficient carriers for targeted colon cancer therapy **[33].** Furthermore, wheat germ agglutinin (WGA)-conjugated PLGA nanoparticles have shown a significant increase in the bioavailability and colonic retention of 5-fluorouracil (5-FU). Gamma scintigraphy studies confirmed prolonged retention of the drug in the colonic region for over 24 hours in vivo, in contrast to the rapid systemic clearance observed with the free drug. The WGA ligand enhances mucoadhesion

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and facilitates interaction with cell membranes, thereby improving drug delivery to target cells and exhibiting superior cytotoxicity against HT-29 and COLO-205 cell lines. Overall, this nano formulation effectively protects 5-FU from degradation in the gastric environment and provides a targeted oral drug delivery system that enhances therapeutic efficacy while reducing systemic toxicity in colorectal cancer treatment **[34].**

PLA:

Lactide polymerises through a ring-opening process, producing three stereoisomers: D-lactide, L-lactide, and DL-lactide. Their main difference lies in optical activity. These stereoisomers directly influence the properties of the resulting polymers. Therefore, D-lactide forms poly(D-lactide) (PDLA), L-lactide forms poly(L-lactide) (PLLA), and DL-lactide forms poly (DL-lactide) **[35].** PLA (or PLGA/PLA cores) offers predictable hydrolytic drug release and is not inherently responsive to microbiota. To add microbiota responsiveness and enable colon targeting, PLA/PLGA cores are coated with materials such as alginate, pectin, or dextran. These coatings are broken down or fermented by bacteria that can utilise alginate **[35].** Rifampicin and ciprofloxacin are two antibiotics often co-encapsulated within PLA-based systems to combat multidrug-resistant bacterial infections and biofilms **[36].**

PCL (polycaprolactone)

Poly(ε-caprolactone) (PCL) is a synthetic, semi-crystalline aliphatic polyester produced through the ring-opening polymerization of ε-caprolactone (ε-CL). Microbial degradation, where the process is mediated by extracellular esterase/depolymerase enzymes derived from bacteria and fungi. Furthermore, dual-modified PCL-PEG nanoparticles have been shown to enhance the accumulation of docetaxel in colorectal tumours compared to non-targeted PCL and PEG nanoparticles. The PCL-PEG block copolymer forms nanoparticles with a stable amphiphilic shell, improving the solubility of docetaxel and prolonging its circulation half-life, as demonstrated in cell studies **[37].**

Polyethylene glycol)

PEGylated cisplatin nanoparticles are noted for their high stability and pH-responsive drug release behaviour, which allows for drug release in the acidic microenvironment of colorectal cancer cells. The PEG polymer layer functions as a “stealth” coating, extending blood circulation and lowering systemic toxicity. Experimental studies demonstrated increased apoptosis in colon cancer cells compared to free cisplatin. The study concluded that this nano formulation effectively uses the tumour pH gradient to trigger drug release **[38].**

Eudragit S 100 (pH-sensitive methacrylate):

Eudragit polymers are extensively used in pharmaceutical drug delivery systems. Eudragit-based hydrogels, when combined with other polymers, enable controlled drug release, plastic deformation, rapid responsiveness, and increased drug-loading capacity. These hydrogels demonstrate good adhesion to the skin without causing irritation and are commonly employed in cutaneous, vaginal, and ophthalmic delivery applications. As a positively charged polymer, Eudragit enhances mucoadhesive formulations by improving mucosal drug adherence. Hydrogels further enhance drug retention at mucosal sites **[39].** Citrus pectin nanoparticles coated with Eudragit S100 effectively protect 5-fluorouracil from gastric acidity, releasing less than 20% of the drug in the upper gastrointestinal tract. Upon reaching the colonic pH of 7.4, the Eudragit layer dissolves, enabling the pectin core to target galectin-3 receptors on HT-29 cells. The study concluded that this pH-dependent, ligand-mediated system significantly improves cellular uptake and cytotoxicity, providing a superior therapeutic window for colorectal cancer compared to traditional oral chemotherapy **[40].**

Eudragit L100-55 (enteric / pH-dependent) In each grade, the cationic copolymers Eudragit E100, E12, and E5 consist of methyl methacrylate, diethylaminomethyl methacrylate, and butyl methacrylate. Their chemical composition includes methacrylate, 2-dimethylaminoethyl methacrylate, and methyl methacrylate. The molecular weight is approximately 47,000 g/mol, with an alkali value of about 0.18 g KOH g^{-1}, and they exhibit low-viscosity solubility at gastric pH 5. Anionic copolymers such as Eudragit S100 and S12.5 are synthesized using methacrylic acid and methyl methacrylate. These polymers have molecular weights, acid values, and glass transition temperatures exceeding 125 kDa, 190 mg KOH/g, and 150°C, respectively, and are freely soluble at neutral to basic pH conditions. Eudragit L100, in particular, dissolves at pH > 6 in the intestine,

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independent of microbial activity **[39].** Curcumin-loaded Eudragit S100/PLGA nanoparticles have demonstrated significantly enhanced cytotoxicity against CT26 colon carcinoma cells compared to free curcumin. The formulation achieved a markedly lower IC_{50} value of 0.25 µg, compared to 1.43 µg for the free drug. This dual-polymer system uses Eudragit S100 for pH-dependent release and PLGA for sustained biodegradability. The study concluded that this approach effectively overcomes curcumin's poor solubility and bioavailability, providing a highly potent, site-specific drug delivery system that maximizes therapeutic efficacy in the colonic region **[41].**

3. MOLECULAR MECHANISMS UNDERLYING OF SOME NATURAL POLYMER-MEDIATED TARGETING OF SIGNALING PATHWAYS AND MECHANISM IN COLORECTAL CANCER

Naturally occurring polymers used in colon-targeted drug delivery systems break down selectively in the colon because it contains many microorganisms that can digest them. Many other bacteria found in the colon, including Bacteroides, Bifidobacterium, and Ruminococcus, produce a wide range of carbohydrate-active enzymes, including glycosidases, lyases, and esterases. More specifically, these enzymes break down tough polysaccharides, such as pectin, guar gum, alginate, dextran, and resistant starch, into easier-to-digest oligosaccharides and fermentable compounds. Consequently, these polymers are converted into secondary metabolites, primarily short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate **[42]**, as well as other bioactive oligosaccharides, including pectin-derived oligosaccharides (POS). This microbiota-induced disintegration not only facilitates site-specific drug delivery but also maximises the colon's natural therapeutic benefits. **[43] (Figure 2)**

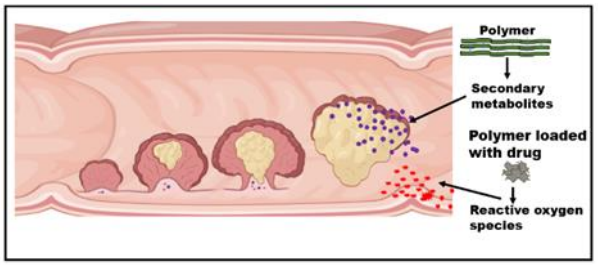

Figure. 2 Molecular mechanisms of Biomaterial in the colon cancer

Particularly, SCFAs, the generated secondary metabolites, are very important in colorectal cancer prevention via several molecular processes. The strongest SCFA, butyrate, inhibits histone deacetylase (HDAC), therefore causing epigenetic alteration that induces apoptosis and suppresses colon cancer cell development. Furthermore, SCFAs control essential signalling channels such NF-κB, PI3K/Akt, and MAPK, therefore lowering inflammation and oxidative stress, two colorectal carcinogenesis's most important drivers. Furthermore, improving gut barrier integrity, they regulate immune responses by supporting regulatory T-cell differentiation. Moreover, oligosaccharides such as POS have prebiotic activity, which means that they selectively stimulate good bacteria and inhibit harmful species, so contributing to the maintenance of microbial homeostasis. Together, these activities help to inhibit tumour initiation and development, emphasizing the dual function of natural polymers as drug carriers and microbiota-mediated therapeutic substances. **[44, 45]**

POLYMER	COLON CANCER	ENZYMES INVOLVED	MECHANISM OF DEGRADATION	METABOLITES PRODUCED	REFERENCE
Chitosan	General colonic microbiota	Chitosanase, β-glucosidase	Enzymatic hydrolysis	Oligosaccharides	**[1]**
Alginate	Bacteroides ovatus	Alginate lyase	β-elimination of glycosidic bonds	Alginate oligosaccharides	**[6]**
Pectin	General gut microbiota	Pectinase, polygalacturonase	Depolymerization of galacturonic acid chains	Pectin oligosaccharides (POS)	**[43]**

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Guar gum	Bacteroides ovatus, Bifidobacterium spp.	β-mannanase	Fermentation of galactomannan	SCFAs	**[14]**
Dextran	LAB-associated microbiota	Dextranase	Hydrolysis of α-1,6 bonds	Glucose/oligosaccharides	**[17]**
Starch	Ruminococcus bromii, Bifidobacterium adolescentis	Amylase, pullulanase	Hydrolysis of α-1,4 and α-1,6 bonds	SCFAs	**[28]**
Cellulose	General microbiota	Cellulase	β-1,4 glycosidic bond hydrolysis	Glucose (imited)	**[27]**
Hyaluronic acid	Host enzymes	Hyaluronidase	Cleavage of β-1,4 linkages	Disaccharides	**[19]**
Chondroitin sulfate	Non-specific	Chondroitinase	Desulfation & depolymerization	Sulfated disaccharides	**[22]**
Cyclodextrin	Limited microbiota	Amylase-like enzymes	Ring-opening hydrolysis	Oligosaccharides	**[24]**
Gelatin	Proteolytic bacteria	Proteases	Protein hydrolysis	Peptides/amino acids	**[30]**

Table 1. Natural polymer–microbiota interactions and formation of anticancer metabolites in the colon

Since hyaluronic acid's major receptor is CD44, hyaluronate nanoparticles were designed to specifically target colon cancer cells that overexpress CD44. By affecting epigenetic regulators, especially long non-coding RNAs (lncRNAs) and microRNAs (miRNAs), the system improves the intracellular transport of raloxifene and regulates tumour growth. These modifications impact downstream signalling pathways involved in metastasis, apoptosis, and proliferation. The formulation exhibits enhanced targeting efficiency, suppression of oncogenic signalling, and regulation of epigenetic cascades that govern tumour growth **[46].**

The complex plant polysaccharide, pectin, has been studied for its potential in treating colon cancer. In the gut, it is broken down into oligosaccharides called POS. As prebiotics, POS are believed to regulate

inflammation and oxidative stress, two major factors in colorectal cancer. According to the literature, POS enhances antioxidant and anti-inflammatory responses and promotes cancer cell death by influencing many signalling pathways, particularly AMP-activated protein kinase (AMPK), Nrf2, and NF-κb. By modulating these pathways, it may reduce inflammation and oxidative damage in the colon, potentially preventing the growth of colon cancer. However, more research is needed because some POS could activate other pathways like STAT1/3, which might counteract these benefits **[43].**

To address the symptoms of colorectal cancer in HT29 cells, alginate was utilised as a biodegradable polymer to formulate nanogels containing oxaliplatin. Additionally, hyaluronic acid was integrated into the alginate-based nanogel system and coupled with folate to improve selective absorption through CD44 and folate receptor-mediated endocytosis. The drug's intracellular accumulation increased, enhancing its cytotoxic and pro-apoptotic effects at specific doses. By activating intrinsic apoptotic pathways—characterised by increased caspase activity and changes to pro- and anti-apoptotic proteins—the formulation mechanically induced apoptosis. Therefore, the alginate nanogel platform improved anticancer efficacy and functioned as a tumour-targeting delivery system and a sustained drug carrier by amplifying oxaliplatin-induced apoptotic signalling in colorectal cancer cells **[47].**

Procaine dramatically inhibits the ability of colon cancer cells to proliferate and migrate. RhoA, a small GTPase involved in cytoskeletal structure and cell motility, is mechanistically downregulated by procaine. Inhibition

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of rhoA results in decreased phosphorylation of key signalling molecules in the FAK and ERK/MAPK pathways, which are both critical for tumour development, survival, and metastasis. Procaine interferes with cellular functions necessary for the invasion and spread of cancer cells by weakening these signalling cascades. The results suggest that procaine's potential as a therapeutic agent in colon cancer treatment lies in its ability to target RhoA-mediated stimulation of the ERK/MAPK and FAK signalling pathways to produce antitumor effects **[48].** Dextran sulphate sodium is used not as a therapeutic agent but as a chemical inducer of colitis to simulate chronic intestinal inflammation, which promotes colitis-associated colorectal cancer. Due to disruption of the colonic epithelial barrier, DSS causes immune cell infiltration, an overabundance of inflammatory cytokines, and the activation of signalling pathways involved in tumour development and spread. In addition to immune cell infiltration and excessive inflammatory cytokine production, DSS disrupts the colonic epithelial barrier and activates signalling pathways linked to tumour progression. The study shows that DSS-induced inflammation activates Nfatc3 signalling, which intensifies inflammatory reactions and encourages epithelial-mesenchymal transition (EMT). Overexpression of NFATc3 promotes tumour development, spread, and metastasis by increasing pro-inflammatory mediators and EMT-related markers. The AOM/DSS model demonstrates a significant reduction in tumour size and number when NFATc3 is blocked. Because inhibiting NFATc3 decreases inflammatory cytokine production and downregulates EMT markers, it is clear that NFATc3 plays a crucial role in linking colorectal carcinogenesis to ongoing inflammation. NFATc3-mediated inflammatory signalling and pathways associated with EMT are involved. DSS-induced inflammation enhances the migratory and invasive capabilities of colorectal cancer cells by inducing downstream molecular mechanisms that regulate transcription factors related to EMT. Inhibition of NFATc3 reduces inflammatory responses and prevents epithelial cells from transforming into mesenchymal cells by blocking these signalling cascades. Dextran sulphate sodium primarily functions as a pro-inflammatory agent to create a model of colorectal cancer associated with colitis **[49].**

Chitosan blocks PI3K/Akt/mTOR pathway activation in colon cancer, thereby inducing apoptosis via the mitochondrial pathway and initiating the caspase cascade. It also modulates NF-κB inflammatory cascades and EMT progression, effectively increasing chemosensitivity using nanoencapsulation **[50].** Through electrostatic contact with epithelial membranes, chitosan-coated PLGA nanoparticles improve oral absorption of 7-ethyl-10-hydroxycamptothecin by mucoadhesion and transiently opening tight junctions in the gut. Chitosan suppresses P-glycoprotein-mediated efflux, thereby enhancing transcellular transport. Sustained release from PLGA protects SN-38 from breakdown, improving systemic bioavailability and therapeutic exposure **[51].**

Tumour-targeting nanocarriers, such as alginate-based systems, promote AMPK activation, induce apoptosis, and enhance chemotherapeutic efficacy in colon cancer by suppressing NF-κB signalling and TLR4/MyD88-driven inflammation **[49].** The calcium ion–exchange crosslinking method creates an alginate–clay nanocomposite that exhibits pH-responsive drug release, leading to improved cellular uptake and increased cytotoxicity. While ciprofloxacin inhibits DNA gyrase and topoisomerase IV, disrupting bacterial DNA replication, methotrexate inhibits dihydrofolate reductase in the folate metabolism pathway, causing S-phase cell-cycle arrest **[52].**

Guar gum functions as a colon-targeted delivery platform to improve the delivery of anticancer compounds (e.g., 5-FU) to tumour cells, promoting localized apoptotic activity and tumour growth suppression through sustained release in colon carcinoma models. Guar gum itself does not directly influence cancer signalling pathways. It enables 5-ASA to be delivered solely to the colon by preventing its release in the stomach and small intestine and allowing breakdown by colonic bacteria, which then release the drug in the colon. 5-ASA acts locally to reduce inflammation by blocking pro-inflammatory pathways like NF-κB that are linked to ulcerative colitis **[53].**

By influencing MAP kinase–mediated signalling (ERK/JNK/p38), chondroitin sulfate reduces CDK expression, thereby restricting proliferative capacity and facilitating apoptosis in colon cancer cells, demonstrating anticancer potential **[54].** Chondroitin

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sulfate-modified nanoparticles attach to CD44 receptors that are overexpressed on malignant cells, making it easier for the cells to absorb drugs through receptor-mediated endocytosis. Bortezomib inhibits the 26S proteasome, preventing NF-κB activation, inducing caspase-dependent apoptosis, and inhibiting tumour growth. Chondroitin sulfate enhances targeted delivery via the CD44 pathway **[55].**

Cyclodextrin itself does not directly cause tumour-specific signal transduction but enhances targeted drug delivery to colon cancer cells, aiding chemotherapeutic internalization and inducing apoptosis via caspase activation while reducing NF-κB-linked treatment resistance **[56].** By forming inclusion complexes, Cyclodextrin–PCL hybrid polymer NPs increase drug solubility and provide sustained release through biodegradable PCL matrices. Endocytosis promotes cellular uptake, raising intracellular drug levels. Depending on the loaded drug, the therapeutic pathway generally inhibits proliferative signalling in cancer cells and triggers apoptosis through caspase activation **[57].**

Eudragit S100 has no direct effect on cancer signalling mechanisms; it provides pH-controlled delivery to the large intestine, releasing drugs (e.g., 5-FU) in regions with higher intestinal pH to increase chemotherapeutic-driven apoptosis and improve neoplastic tissue uptake **[58].** Through pH-dependent dissolution in the distal gut and prolonged polymer-mediated drug release, curcumin-loaded Eudragit S100/PLGA nanoparticles enable colon-targeted delivery. After internalisation via endocytosis, curcumin inhibits the PI3K-driven Akt/mTOR signalling pathway and NF-κB signalling, downregulates Bcl-2, and triggers Bax-mediated caspase-3 apoptosis. In colon cancer cells, this mechanism increases cytotoxicity, restrains tumor cell growth, and causes cell cycle arrest **[59].** Colon-specific delivery is achieved with Eudragit S100-coated calcium pectinate microspheres, which dissolve pH-dependently at neutral colonic pH and are enzymatically degraded by colonic microorganisms, releasing curcumin. In colorectal cancer cells, released curcumin inhibits proliferation and promotes programmed cell death by suppressing the pro-inflammatory NF-κB/COX-2 signalling network, downregulating Bcl-2, and activating caspase-3–mediated apoptosis **[60, 61].**

4. Conclusion:

Polymer-drug combination systems are emerging as promising drug delivery platforms for colon cancer therapy. Natural polymers such as chitosan, alginate, pectin, dextran, and hyaluronic acid show considerable promise regarding biocompatibility and response to microflora. Synthetic polymers such as PLGA, PLA, PCL, PEG, and Eudragit provide drug release, structural integrity, and targeting ability. Combining polymers and drugs may lead to advanced systems that improve stability, targeting, and reduce systemic toxicity. These delivery systems can regulate critical molecular pathways involved in colon cancer therapy, including PI3K/Akt/mTOR, NF-κB, MAPK, and apoptosis. Polymer-assisted delivery may enhance therapeutic outcomes and overcome the limitations of conventional chemotherapy. Further research may help establish the significance of these systems for colon cancer therapy.

DECLARATION

The authors disclose no conflict of interest.

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