RECENT ADVANCES IN PHYTOCHEMICAL-BASED NANOPARTICLES FOR COLON-SPECIFIC DRUG DELIVERY

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Colon-specific drug delivery has emerged as a promising strategy for treating colonic diseases while minimizing systemic side effects. Recent advancements in nanotechnology have enabled the development of phytochemical-based nanoparticles that offer enhanced targeting, improved drug stability, and controlled release profiles. This review highlights the therapeutic potential of plant-derived phytochemicals, such as polyphenols, flavonoids, terpenoids, and alkaloids, and their application in nanoparticle systems for colon-targeted therapy. The unique bioactive properties, biocompatibility, and low toxicity of phytochemicals make them ideal candidates for nanoparticulate formulations. The review discusses various nanocarrier systems including liposomes, polymeric nanoparticles, dendrimers, micelles, and silica-based nanoparticles, emphasizing their role in enhancing the solubility, bioavailability, and therapeutic efficacy of encapsulated phytochemicals. It also explores preparative methods, such as nanoprecipitation, ionotropic gelation, and solvent evaporation. Moreover, synergistic combinations of phytochemicals with chemotherapeutic agents in multifunctional nanoparticles demonstrate improved outcomes against diseases like colorectal cancer and inflammatory bowel disease. Despite encouraging progress, challenges such as clinical translation, reproducibility, and large-scale manufacturing remain. Overall, phytochemical-based nanoparticles hold immense potential to revolutionize colon-specific drug delivery, offering a safe and effective platform for localized and personalized therapy.

Keywords: colon-specific drug delivery, phytochemicals, phytochemical-based nanoparticles

INTRODUCTION

The colon, constituting the proximal five feet of the large intestine, encompasses the ascending, transverse, descending, and sigmoid segments (Fig. 1). Although villi are absent in the colon, the presence of crescentic folds (*plicae semilunaris*) enhances its surface area, facilitating efficient absorption.[1] The colon performs the following primary functions (Fig. 2): (i) converts intestinal contents into faeces through water and electrolyte absorption, (ii) stores faecal matter until defecation, (iii) maintains an environment favourable for colonic bacterial growth, (iv) absorbs water and Na^+ while secreting K^+ and HCO_3^-, (v) removes water, electrolytes, and metabolites via mucosal movements, (vi) regulates stool consistency through variations in colonic motility.[1,2]

The colon is an ideal site for delivering drugs and labile molecules for treating local diseases, such as ulcerative colitis, Crohn's disease, and colorectal cancer (CRC). Colon-targeted systems enhance localized therapy, maximizing drug concentration at the site, while minimizing systemic side effects.[3,4]

Colon-targeted drug delivery systems (CTDDS) offer a promising approach for administering polar drugs prone to degradation in the gastrointestinal (GI) tract.[5] By preventing premature release in the upper GI tract, they enable precise delivery to the colon, where enzymatic activity and mucosal proteolysis are lower.[3] This environment enhances the stability and absorption of peptide- and protein-based drugs. Consequently, CTDDS improve systemic bioavailability, while minimizing enzymatic degradation in the small intestine.[6] The effectiveness of CTDDS is influenced by drug properties, delivery technology, GI transit, and drug-GI interactions.[7] The global rise in colonic disorders, including CRC is third most diagnosed and second leading cause of cancer deaths and increasing inflammatory bowel disease

(IBD) incidence in Asia, underscores the urgent need for targeted therapies.[8-11]

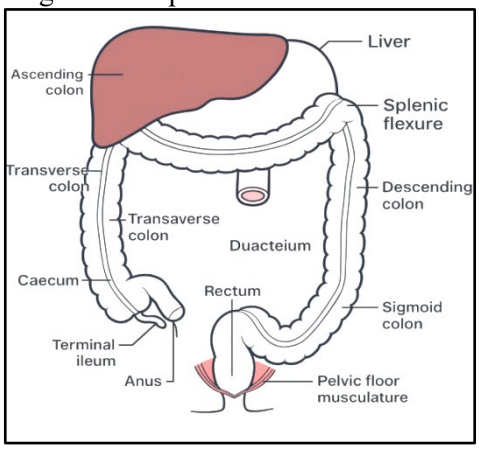

Figure 1: Anatomy of colon (concept based on[2])

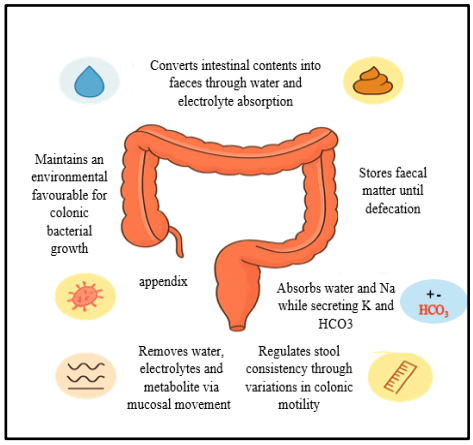

Figure 2: Function of colon (concept based on[2])

Colonic disorders, including IBD and CRC, represent major global health challenges. Conventional therapies, such as corticosteroids, non-steroidal anti-inflammatory drugs (NSAIDs), and chemotherapeutics, are widely used to manage these conditions. However, these treatments are often associated with significant limitations, including systemic side effects, poor target specificity, and reduced therapeutic efficacy due to premature drug absorption in the upper GI tract.[12,13] To overcome these challenges, attention has increasingly turned to naturally occurring phytochemicals, which offer multiple therapeutic advantages. Dietary phytochemicals, such as polyphenols, flavonoids, terpenoids, and plant organic sulphides exhibit anti-inflammatory, antioxidant, anticancer, antimicrobial, cardioprotective, and neuroprotective properties.[14-21] Many of these compounds also modulate gut microbiota, further enhancing their pharmacological effects and contributing to improved colonic health. Despite their promising bioactivities, phytochemicals often face limitations, such as low solubility, poor stability, and limited bioavailability. Recent advances in nanotechnology have enabled the development of nanoparticles (NPs) based CTDDS, which protect and stabilize encapsulated compounds, improve solubility and bioavailability, and allow controlled and localized release.[22] Incorporating phytochemicals into these NPs provides a synergistic approach, combining the inherent therapeutic potential of natural compounds with precise colon-targeted delivery, thereby enhancing efficacy and minimizing systemic side effects.

The design of nano formulations encompasses a diverse range of carrier systems, including organic nanocarriers, such as liposomes, polymeric NPs, micelles, and dendrimers, as well as inorganic nanocarriers that serve as efficient coating or delivery materials. In the context of CRC, numerous studies have explored various nanocarrier systems, such as silica, gold, silver, zinc oxide NPs, liposomes, polymeric NPs, micelles, and dendrimers, owing to their potential to improve drug accumulation and therapeutic efficacy within the tumour microenvironment.[22]

With a particular focus on CRC, numerous studies have demonstrated that nano-formulations of phytocompounds significantly enhance their antitumor efficacy. Various nanoparticle-based systems have been developed to improve the solubility, stability, and targeted delivery of bioactive plant constituents.[22] Examples include micronized resveratrol (RES) formulations,[23,24] quercetin-based nanoemulsions,[25] calcium phosphate NPs encapsulating esculetin and euphorbetin (curcumin derivatives),[26] PLGA NPs loaded with blueberry extract,[27] curcumin-loaded biodegradable polymeric micelles,[28] *Croton tiglium* nanoextracts,[29] RES loaded chitosan-based microcapsules,[30] curcumin encapsulated by solid binary lipid NPs.[31] These nanosystems exemplify the potential of plant-derived compounds incorporated into nanocarriers to enhance therapeutic outcomes in colon-targeted cancer therapy.

PHYTOCHEMICALS IN COLON DISEASE THERAPY

Phytochemicals, including polyphenols, flavonoids, terpenoids, and alkaloids, exhibit strong antioxidant, anti-inflammatory, and anticancer activities (Table 1) that support colon health. They act by modulating oxidative stress, inflammatory pathways, and gut microbiota balance, thereby maintaining epithelial integrity. Despite their potential, low bioavailability remains a challenge, encouraging the development of advanced delivery systems for targeted colonic therapy.

Polyphenols

Polyphenols are plant-derived secondary metabolites composed of one or more hydroxylated aromatic rings, which confer potent antioxidant and redox-regulating properties.[32,33] Within the colon, polyphenols help counter oxidative and inflammatory damage by scavenging reactive oxygen species and supporting the integrity of the epithelial barrier. Their biotransformation by gut microbiota yields smaller phenolic metabolites that modulate microbial composition and promote intestinal homeostasis.[34,35]

At the molecular level, polyphenols modulate major inflammatory signalling pathways, such as NF-κB, MAPK, and PI3K/AKT, thereby attenuating the expression of pro-inflammatory mediators, including TNF-α, IL-6, COX-2, and iNOS.[36,37] Polyphenols demonstrate anticancer activity by regulating key signalling pathways, such as Wnt/β-catenin, JNK, and p53, resulting in reduced proliferation and enhanced apoptosis in colon cancer cells. However, their clinical utility is limited by low solubility, chemical instability, and restricted colonic delivery, prompting the development of advanced delivery systems including polymeric NPs, lipid-based vesicles, and polysaccharide conjugates.[38,39] Key examples of bioactive polyphenols include curcumin, which reduces NF-κB and COX-2 activation in ulcerative colitis; epigallocatechin-3-gallate (EGCG), recognized for its ability to suppress colonic inflammation and inhibit tumour progression; and RES, which demonstrates epigenetic modulation and anticancer effects.[40-42] While clinical studies indicate that curcumin supplementation can lower inflammatory cytokine levels, evidence for its consistent efficacy in preventing adenomas or CRC is still inconclusive.[43]

Flavonoids

Flavonoids, a prominent subclass of polyphenols, possess a characteristic C6–C3–C6 carbon backbone, comprising two aromatic rings connected by a heterocyclic pyran ring. This structural framework classifies them into subgroups, such as flavones, flavanols, flavanones, isoflavones, and anthocyanins. In the colonic environment, flavonoids act as potent antioxidants by scavenging reactive oxygen species, chelating transition metals, and regenerating endogenous antioxidants like glutathione, thereby mitigating oxidative damage to epithelial tissues.[44-45] They enhance intestinal barrier integrity by increasing the expression of tight junction proteins, such as occludin, claudins, and ZO-1, thereby decreasing gut permeability and mitigating inflammation-related "leaky gut".[46]

Flavonoids can modulate immune responses in the colon by suppressing TLR4/NF-κB signalling in macrophages and dendritic cells, resulting in decreased production of pro-inflammatory cytokines, such as IL-1β, IL-6, and TNF-α, while enhancing regulatory T-cell activity.[47] In colon cancer models, flavonoids promote apoptosis through caspase activation, alter the Bax/Bcl-2 balance, induce cell cycle arrest, and inhibit angiogenesis and metastasis by regulating VEGF, MMPs, and signalling pathways including Wnt, MAPK, and PI3K.[48] Although flavonoids possess significant pharmacological effects, their clinical use is limited by low solubility and instability in gastrointestinal environments, leading to the development of advanced delivery systems, such as liposomes and NPs to improve colonic bioavailability.[49]

Key flavonoids include quercetin, which alleviates colitis, strengthens the epithelial barrier, and reduces colon tumour formation; kaempferol, which regulates gut microbiota and suppresses the LPS–TLR4–NF-κB pathway; naringenin, which diminishes intestinal inflammation through TLR4 inhibition; and apigenin, which lowers COX-2, iNOS, and MMP expression in models of colitis and colon cancer.[50-53] Collectively, these findings highlight flavonoids as promising agents for the prevention and management of inflammation-associated colorectal disorders.

Terpenoids

Terpenoids, also known as isoprenoids, are a diverse group of naturally occurring compounds built from repeating five-carbon isoprene (C_5) units and include subclasses, such as monoterpenes,

sesquiterpenes, diterpenes, triterpenes, and tetraterpenes.[54] Owing to their lipophilic properties, terpenoids readily penetrate cell membranes, allowing them to modulate intracellular signalling pathways in colonic epithelial cells. They demonstrate strong anti-inflammatory effects by suppressing pro-inflammatory cytokines, including TNF-α, IL-1β, and IL-6, and by inhibiting key signalling pathways, such as NF-κB and MAPK in the colon.[55,56] In CRC models, terpenoids promote apoptosis by activating mitochondrial and caspase-dependent pathways, induce cell cycle arrest through the p53/p21 signalling axis, and suppress angiogenesis and metastasis by downregulating VEGF, MMPs, and epithelial–mesenchymal transition (EMT) processes.[57-58] Terpenoids can regulate autophagy and oxidative stress by upregulating endogenous antioxidant enzymes, including superoxide dismutase (SOD), catalase, and glutathione. In addition, many terpenoids function as chemosensitizers, enhancing the efficacy of standard chemotherapeutic drugs, while mitigating their toxicity.[58-60] Although terpenoids possess significant therapeutic potential, their clinical use is restricted by low solubility and rapid metabolic clearance, highlighting the need for advanced formulation strategies, such as nanoencapsulation and prodrug designs to improve colonic delivery.[61] Notable terpenoids include maslinic acid, which diminishes preneoplastic lesions in the colon; plumericin, which mitigates DNBS-induced colitis; carvacrol, which shields the colon from acetic acid induced injury; and geraniol, which alleviates DSS-induced colitis and helps restore microbial balance.[62-65] Triterpenoids and limonoids have also demonstrated the ability to counteract multidrug resistance in CRC by regulating the activity of efflux transporters.[66]

Table 1
Sources of phytochemicals and their biological activity

Phytochemicals		Sources	Biological activities	Ref.
Polyphenols	Anthocyanins	Blackberries, mulberries, blueberries, raspberries, strawberries, red grapes, red wine	Anti-cancer, anti-inflammatory, antioxidant, anti-obesity, hypolipidemic, antibacterial, antiviral, anti-allergic, anti-mutagenic, anti-proliferative, anti-atherosclerotic, anti-platelet activity	[79,80]
	Apigenin	Apples, citrus fruits, parsley, and celery leaves	Anti-inflammatory, anti-cancer, anti-mutagenic, anti-proliferative, anti-tumor, anti-hyperglycemic, anti-allergic, antioxidant, anti-genotoxic, neuroprotective, cardioprotective, and antibacterial properties	[81]
	Catechin	Tea	Cancer prevention, anti-obesity, anti-hypertensive, anti-inflammatory, anti-proliferative, anti-thrombotic, anti-hyperlipidemic, antioxidant cardiovascular and neuroprotective effects	[82,83]
	Curcumin	Turmeric	Anti-inflammatory, antioxidant activity, anti-cancer, wound healing, antibacterial, controls angiogenesis, anti-proliferative, anti-platelet activity, hepatoprotective effects	[79,84,85]
	Ellagitannins	Pecans, chestnuts, pomegranates, strawberries, and blackberries	Anti-inflammatory, antioxidant, antibacterial, anti-proliferative, anti-cancer, anti-tumor, anti-	[86–89]

Phytochemicals		Sources	Biological activities	Ref.
			metastatic, anti-angiogenic, and immunomodulatory properties	
	Naringenin	Citrus, tomato peel, *Dendrobium officinale*	Anti-inflammatory, anti-cancer, bone regeneration, metabolic syndrome, antioxidant, genoprotective and neuroprotective effects	[90,91]
	Phytolignans	Flaxseed, asparagus, whole grains, vegetables, tea	Anti-inflammatory, antitumor, antioxidant, antiviral, antibacterial, antifungal, insecticidal, immunosuppressive, cardiovascular protective activities	[92-94]
	Proanthocyanidins Quercetin	Kale, cauliflower, grapes, cherries, string beans, apples, grains, stalks and leaves of buckwheat, sea buckthorn, hawthorn, onions, sapodilla leaves, galangal	Anti-inflammatory, antiviral, antibacterial, antioxidant, anti-cancer, anti-allergy, anti-diabetic, anti-proliferative, anti-atherosclerotic, neuroprotective, cardioprotective effects	[95-99]
	Resveratrol	Wine, grapes, and berries	Antioxidant, anti-inflammatory, anti-cancer and anti-viral properties	[100,101]
	Rutin	Vegetables like asparagus, tomatoes, and cucumbers, fruits like oranges, grapefruits, lemons, and limes, and herbs like acacia rice, astragalus and kudzu	Anti-inflammatory, antibacterial, anti-tumor, anti-asthmatic, anti-diabetic, anti-adipogenic, neuroprotective, and hormone therapy	[102–106]
Terpenoids	Beta-carotene	Orange and yellow vegetables and fruits	Antioxidant, anti-cancer, cardiovascular protective, anti-degenerative and anti-cataract effects	[107–109]
	Lycopene	Watermelon, tomatoes, pink grapefruit, apricots, and pink guava	Immunomodulatory, antitumor, anti-inflammatory, molluscicidal, antiviral, antifungal, hypoglycemic	[110–115]
	Saponin	*Glycine max*, *Cicer arietinum*, *Medicago sativa*	Hypocholesterolemic	
Plant organic sulphides	Isothiocyanate	Cabbage, broccoli, Brussels sprouts, and cauliflower	Antibacterial, anticancer, and antiplatelet aggregation properties	[116]

Alkaloids

Alkaloids are a class of nitrogenous heterocyclic compounds primarily synthesized from amino acids, such as tryptophan, tyrosine, and ornithine.[67] Alkaloids exhibit a wide range of pharmacological effects relevant to colon health, including anti-inflammatory, antioxidant, and cytotoxic activities. In IBD models, they reduce the levels of pro-inflammatory cytokines, such as TNF-α, IL-1β, and IL-6, inhibit NF-κB and MAPK signalling pathways, and upregulate antioxidant enzymes to protect against oxidative stress.[68-70] Alkaloids also support mucosal defence by enhancing tight junction protein expression and stimulating mucin production, which reinforces epithelial barrier integrity and reduces bacterial translocation.[71] Within the immune microenvironment, alkaloids influence

macrophage and T-cell functions, decrease neutrophil infiltration, and help re-establish the Th17/Treg balance. In CRC models, many alkaloids inhibit proliferation by intercalating DNA, blocking topoisomerase activity, inducing apoptosis, and causing cell cycle arrest. The combination of anti-inflammatory and cytotoxic properties in certain alkaloids makes them especially promising for preventing or treating inflammation-driven colon carcinogenesis.[68-70] Nevertheless, the inherent toxicity and limited therapeutic window of alkaloids emphasize the importance of developing targeted and controlled delivery approaches.[72-74] Notable alkaloids include berberine, which improves colitis outcomes by inhibiting NF-κB signalling and regulating gut microbiota; matrine, which alleviates inflammation in ulcerative colitis models; *Fumaria capreolata* alkaloid extract, which reinforces epithelial barrier integrity in DSS-induced colitis; and isatin, which mitigates TNBS-induced inflammation by lowering TNF-α and IL-1β levels while increasing IL-10 production.[75-78]

Potential of phytochemicals in colon targeting

Phytochemicals, derived from the Greek word *phyto* meaning "plant", are naturally occurring, biologically active compounds found in plants that provide additional health benefits beyond those offered by macronutrients.[117] Over the last few decades, phytochemicals found in many edible plants have demonstrated a convincing positive biological impact on human health.[123] Recently, it has become obvious that they play important functions in human health protection when their dietary intake is high. More than 4,000 phytochemicals have been collected and categorised according to their protective function, physical traits, and chemical properties.[117] Bacteria are vital in the absorption and processing of dietary phytochemicals in both the small and large intestines. However, the precise mechanisms by which dietary phytochemicals are absorbed and processed in the host colon remain unknown (Fig. 3).[116] Phytochemicals are mostly absorbed and metabolized in the colon, and variations in absorption and metabolism are largely related to variances in colonic microbiota.

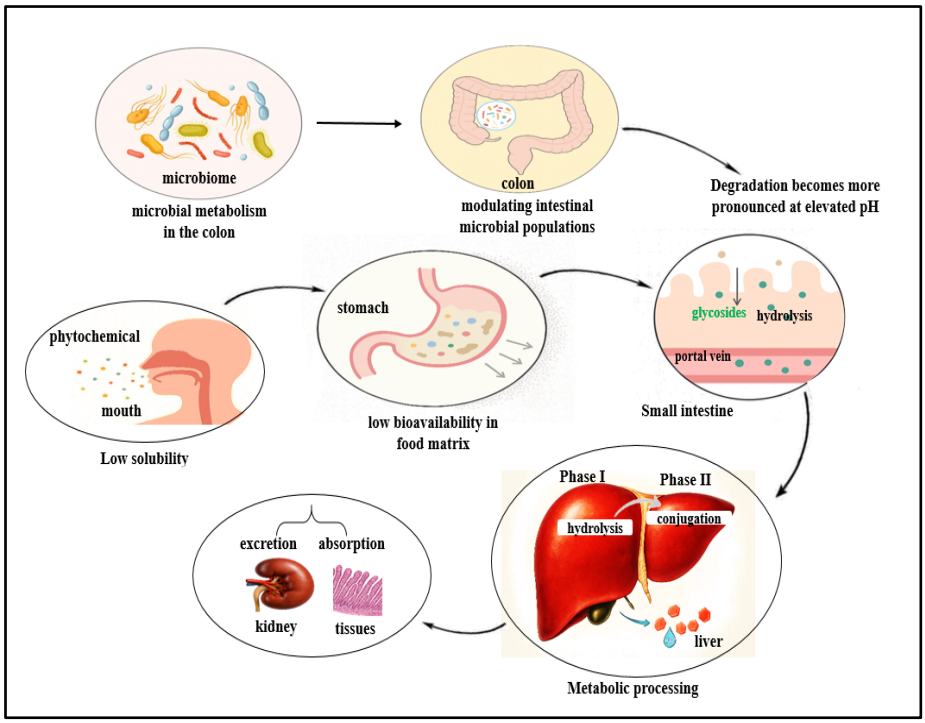

Figure 3: Metabolic pathways of phytochemicals in the human body (concept based on [116])

Furthermore, phytochemicals can be absorbed in the colon by acting on them via enzymes produced by intestinal cells and stem cells or by interacting with the intestinal flora, hence reducing related disorders. Phytochemicals, which are abundant in the human diet, might impact the gut microbiota ratio by boosting the growth and reproduction of beneficial microbiota, while suppressing the growth and reproduction of pathogenic bacteria. For example, cranberry

extract (CE) was effective in alleviating the metabolic syndrome induced by a high-fat/high-sucrose diet in obese mice, which could be attributed to the fact that CE treatment significantly increased the proportion of *Akkermansia* mucin-degrading microbiota in large genomic samples.[124]

After intake, phytochemicals with diverse activities undergo complicated biometabolism and change. The majority of polyphenols are poorly absorbed in the small intestine, about 90-95% of them being absorbed through microbial breakdown in the large intestine. The colon is the primary location of metabolism and absorption, where phytochemicals can be processed by bacteria and the enzymes they create via various metabolic pathways. Deglycosylation of anthocyanins is catalysed by the bacterial enzymes α-L-rhamnosidase and β-D-glucosidase.[125] There are inter-individual variances in phytochemical metabolism, and the majority of these changes are related to differences in the somatic gut microbiota. Finally, colonic bacteria have the greatest influence on phytochemical absorption and metabolism in the host.[116]

Extensive research has shown that a range of phytochemicals have excellent therapeutic potential in a variety of ailments. Most phytochemicals, on the other hand, have a high molecular weight, poor water solubility, restricted gastrointestinal permeability, substantial pre-systemic metabolism, and poor gastrointestinal stability. As a result, encapsulating these phytochemicals in biodegradable and biocompatible NPs may be an effective way to increase their bioactivity.[126] The actual *in vivo* bioactivity is exerted by the ultimate concentration of phytochemicals in the systemic circulation (*i.e.*, oral bioavailability of phytochemicals). As a result, maximizing phytochemical oral bioavailability is a critical aspect in obtaining great therapeutic efficacy/bioactivity. Extensive research has demonstrated that taking phytochemicals orally has excellent therapeutic efficacy in the treatment of a number of disorders.[126]

In recent decades, NPs based technologies have received considerable attention for tackling phytochemical delivery issues.[127] The development and application of numerous NPs based methods has improved the physicochemical properties of phytochemicals. As they enhance the aqueous solubility, colloidal stability, controlled release, intestinal absorption, and consequently, oral bioavailability of encapsulated phytochemicals, these nano-sized systems offer a wide range of benefits.[126] In addition, with specific phytochemicals, the quantity of other foods consumed has a large impact on their bioavailability and bioactivity.[128,129] Furthermore, phytochemicals differ greatly in terms of polarity, charge, functional groups, and molecular weights, which explains why they have such disparities in solubility, partitioning, stability in different environmental conditions, and physical states.[130]

PREPARATION METHODS OF NANOPARTICLE SYSTEMS FOR INCORPORATION OF PHYTOCHEMICALS

Nanoparticulate drug delivery systems have garnered significant attention due to their small size and adaptable surface chemistry. NPs are structures with at least one dimension ranging from 1 to 100 nm, though the term “nano” is often extended to include particles up to several hundred nanometres in size.[118] The “leaky” colon, characterized by increased intestinal permeability, facilitates passive accumulation of NPs at sites of inflammation, likely aided by uptake through immune cells. Their small size allows NPs to penetrate deeply into target tissues, enhancing their therapeutic potential. Moreover, NPs can improve a drug's solubility, stability, and immunogenicity, while surface modifications allow for targeted and controlled drug release. This ensures sustained therapeutic concentrations at the site of inflammation while reducing systemic side effects.[119] Nanotechnology further enhances drug bioavailability, solubility, absorption, and controlled release.[120-122]

The NPs can be manufactured by various methods. Mechanical milling, laser ablation, etching, sputtering, and electro-explosion are examples of top-down procedures, while bottom-up approaches include chemical vapor deposition, solvothermal and hydrothermal methods, sol-gel methods, soft and hard templating methods, and reverse micelle method. Figure 4 depicts the general process involved in the green synthesis of NPs using plant materials. Initially, plant parts are collected, cleaned, and subjected to extraction using suitable solvents, such as water or ethanol. The obtained extract is then combined with metal salt precursors (*e.g.*, $AgNO_3$, $HAuCl_4$, $CuSO_4$), where phytochemicals like flavonoids, phenolics, terpenoids, and proteins act as natural reducing and stabilizing agents. This leads to the conversion of metal ions into stable NPs, which are subsequently purified and characterized. Depending on the synthesis route, the formation of NPs may occur

either intracellularly within plant tissues or extracellularly in the extract. Parameters, such as extract composition, pH, and temperature, significantly influence the yield and morphology of NPs. Representative plants employed for this biosynthetic approach include *Aloe barbadensis*, *Acalypha indica*, *Jatropha curcas*, and *Magnolia kobus*.[132]

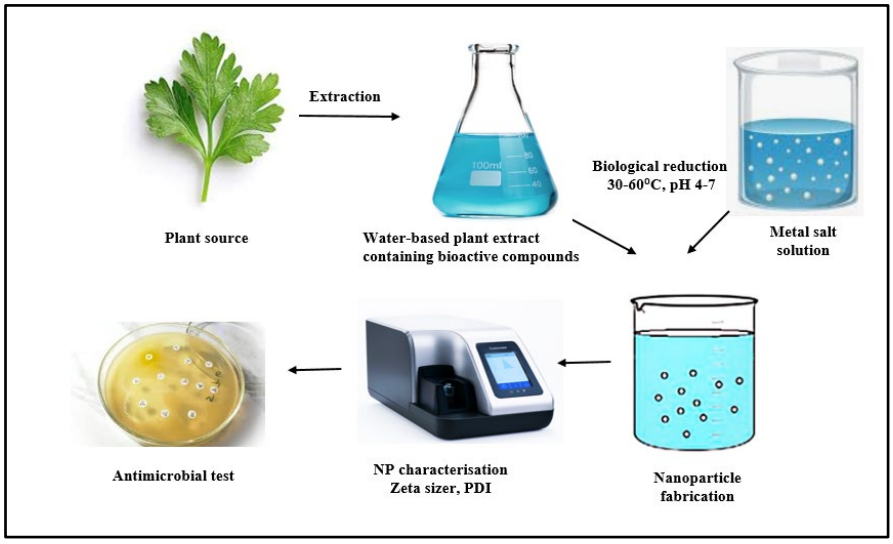

Figure 4: Schematic illustration of plant-mediated nanoparticle biosynthesis (concept based on [132])

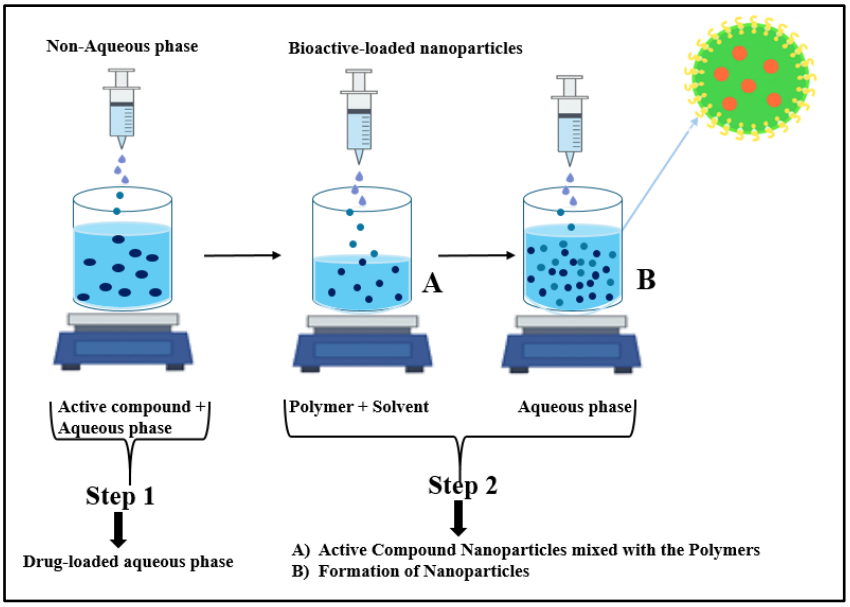

Figure 5: Nanoparticle formation using a two-step nanoprecipitation process (concept based on [137])

Nanoprecipitation method

The antisolvent nanoprecipitation technique (Fig. 5) has been effectively employed to prepare phytochemical-based NPs, including curcumin and silibinin, yielding particles approximately 100-200 nm in size with enhanced solubility, stability, and controlled *in vitro* release characteristics. For example, curcumin NPs were prepared using gelatin as a stabilizing agent, resulting in amorphous solid-state structures and improved release profiles.[133,134] Curcumin NPs were prepared from *Curcuma xanthorrhiza* extract using solvent–antisolvent precipitation, achieving an average size of ~164 nm under optimized stirring and pH conditions; comparable approaches have also been employed for silibinin to enhance its dissolution

and oral delivery potential.[135] These studies provide methodological precedents for applying antisolvent nanoprecipitation when designing colon-targeted delivery systems. Other researchers reported on the preparation of RES-loaded chitosan (CS) NPs by dissolving CS in 85% aqueous ethanol with a few drops of acetic acid, followed by addition of RES dissolved in ethanol. The mixture was then sonicated for 1 hour using an antisolvent precipitation method to obtain the NPs.[136,137]

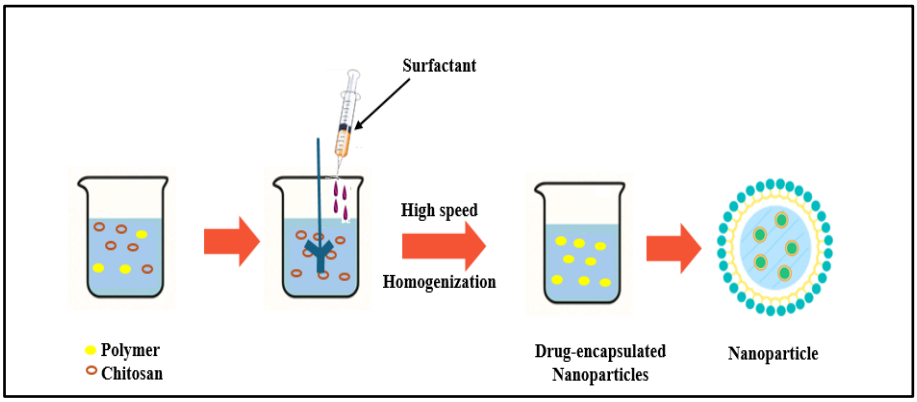

Figure 6: Ionic gelation method schematic representation (concept based on [137])

Ionotropic gelation method

Polymeric NPs and microparticles are being exploited in the search for new and improved treatments (Fig. 6). Because of the incorporation of biocompatible and biodegradable polymers, these formulations have various advantages.[138] Ionotropic gelation is one of the simplest and most cost-effective laboratory procedures.

NPs prepared via the ionotropic gelation technique were reported to enable efficient delivery of phytochemicals to the colon, highlighting their promise for colon cancer treatment. The potential of ginger extract-loaded CS NPs for targeted colon cancer therapy was investigated. For synthesis, a 0.5% (w/v) CS solution was prepared by dissolving CS in 1% acetic acid under magnetic stirring at 1500 rpm for 15 minutes, and the pH was adjusted to 5.0 using NaOH. The ginger extract was then incorporated into the CS solution with continuous stirring. Subsequently, a 0.1% (w/v) sodium tripolyphosphate solution was added dropwise to induce ionic crosslinking and nanoparticle formation. The obtained ginger-loaded CS NPs were separated by centrifugation at 3000 rpm for 30 minutes and washed with deionized water.[139,140]

The complexation of CS NPs with two oppositely charged macromolecules has sparked substantial interest due to its simplicity and mildness. As a result, electrostatic crosslinking has been employed rather than chemical crosslinking to reduce the likelihood of toxicity and other unwanted effects on the reagents. CS can electrostatically interact with polyanion tripolyphosphate (TPP). Several researchers began to look into the potential pharmaceutical applications of the TPP-CS complex. The cation of CS can be obtained by dissolving CS in an aqueous acidic solution and using the ionic gelation process. The solution is added dropwise while stirring continuously to generate a polyanionic TPP solution. Because CS molecules have an abundance of the NH_3 group, it is possible to cross-link them by interaction with the negatively charged phosphoric ions of TPP. The NPs were created through the processes of dissolution, aggregation, and opalescent suspension.[138]

Solvent evaporation method

The emulsion solvent evaporation technique is a methodology for producing NPs and nanocapsules that is well suited for applications requiring high purity and low toxicity materials, such as biomedicine or electronics. To dissolve polymers, such as PLA or PLGA, an organic solvent, such as chloroform, acetone, or ethyl acetate, is utilized. By dissolving the drug in a polymer solution, which is subsequently transferred to an aqueous phase including a surfactant, such as polyvinyl alcohol (PVA), an emulsion of an oil and water mixture is created. By extending the homogenization process, it is feasible to accelerate the evaporation of organic solvents.[141] At the end of the homogenization

stage, the NPs are collected using an ultracentrifuge. Figure 7 shows a schematic depiction of this method. The polymer-to-organic solvent ratio, organic solvent type, homogenization time, and speed can all be adjusted to get the desired particle size and other properties.

For a long time, the emulsion-solvent evaporation process has remained surprisingly understudied. Essentially, a polymer is dissolved in a good solvent and emulsified into an aqueous solution containing a surfactant. Because of the slow evaporation of the polymer-solvent, polymer nucleation occurs at the water-solvent interface.[137] In the literature, the preparation of resveratrol and ferulic acid-loaded solid lipid NPs (RES-FER-SLNs) using the solvent evaporation method has been reported. It was followed by CS coating via hot homogenization, and folic acid was subsequently conjugated to the CS layer. The resulting NPs exhibited a uniform spherical morphology, with an average diameter of 174 ± 5 nm and a polydispersity index (PDI) of 0.166, indicating good homogeneity. The zeta potential of the CS-RES-FER-FA-SLNs was measured at −25.9 mV, confirming excellent colloidal stability without aggregation. X-ray diffraction and FTIR analyses revealed that both RES and ferulic acid were uniformly dispersed within the lipid matrix and remained stable under encapsulation conditions.[142,143]

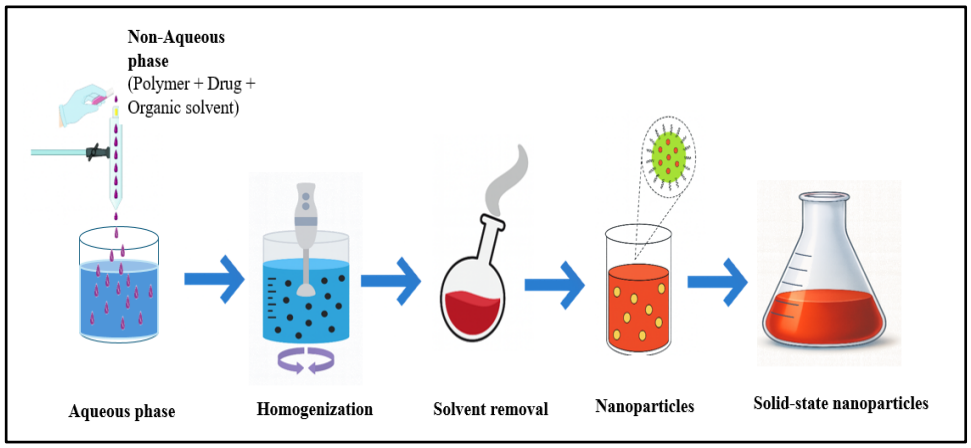

Figure 7: Schematic diagram of nanoparticles preparation by emulsification solvent evaporation method (concept based on [137])

Double emulsion evaporation method

The double emulsion evaporation method (Fig. 7) ($W_1/O/W_2$) involves forming a primary water-in-oil emulsion, followed by re-emulsification in an external aqueous phase, enabling efficient encapsulation of hydrophilic or hydrophobic drugs within polymeric NPs.

In the literature, RES-loaded polymeric NPs (5% RNP and 10% RNP) were prepared using this technique.[144] Briefly, poly(glycolide-co-ε-caprolactone) (PGA-co-PDL, 50 mg) and RES (2.5 mg or 5 mg, corresponding to 5% and 10% w/w loading, respectively) were dissolved in 2 mL of dichloromethane (DCM) and mixed using an ultrasonic water bath for 2 minutes. The mixture was then probe-sonicated at 65% amplitude for 2 minutes, while adding dropwise the first aqueous phase (10% w/v PVA, 0.5 mL) to form the primary emulsion. This emulsion was subsequently added dropwise into the secondary aqueous phase (1% w/v PVA, 20 mL) under sonication to produce the double emulsion. The resulting emulsion was stirred magnetically at 500 rpm for 3 hours to allow DCM evaporation. NPs were collected by ultracentrifugation at 35,000 rpm for 40 minutes at 4 °C using a 70.1 Ti rotor (Beckman Coulter Optima XPN-80), washed twice with deionized water, and recentrifuged to remove residual PVA.[144]

SELECTED PHYTOCHEMICAL BASED NANOPARTICLE SYSTEMS FOR COLON TARGETING

Nanotechnologies are the next exciting scientific field, with the potential to provide solutions for the prevention, diagnosis, and treatment of a wide range of human ailments. In the realm of medicine, NPs are of great interest due to their unique and complicated electronic, magnetic, optical, chemical, physical, and structural capabilities, which are difficult to acquire from any other materials, coupled or alone. As a result, there

is currently a significant deal of interest in the development of novel strategies for incorporating them into various drug delivery systems and studying their therapeutic efficacy in biological systems at all levels. Clinical trials have yet to investigate the systemic use of NPs for medical purposes.[145]

Liposomes

A PEGylated liposomal galbanic acid (terpenoid) – constituted of 56.2:38.3:5.3 molar ratios of hydrogenated soybean phosphatidylcholine/cholesterol/1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[amino (polyethylene glycol)-2000] – was investigated for the delivery of a treatment for colon cancer. To improve galbanic acid bioavailability, an integrin-targeted ligand (RGD peptide, cyclo [Arg-Gly-Asp-D-Tyr-Cys]) was inserted and evaluated onto the liposome (particle size: 100 nm; PDI of <0.150). *In vivo* tests on C26 tumour-bearing BALB/c mice indicated greater anticancer effects.[146] In another work, berberine (alkaloid)-loaded liposomes were recently studied to improve the phagocytic activity of liposomal imiquimod against LS180 I SW620 colon cancer cell lines. Liposomes were grafted using thin-film hydration and extrusion techniques. Liposomes were also created for CRC SW48 cell lines that were loaded with an aqueous-alcoholic aerial shoot portion extract of the plant *Dorema aucheri* (terpenoid). They were created using a lipid thin-film filtration approach, and their cytotoxic efficacy was determined using the MTT assay method. An effective reduction of roughly 41.5% in proliferating cells was detected in a dose- and time-dependent manner. In addition, a phase I/II clinical trial is underway to assess the efficacy of trifluridine/tipiracil hydrochloride in combination with nanoliposomal irinotecan in the treatment of patients with CRC that cannot be removed surgically. The combination acts by stopping the growth of tumour tissue, either by eliminating the cells, preventing them from developing, or reducing their spread (NCT03368963).[147]

L-RES NPs were prepared using the thin-film hydration technique. The average particle sizes of LIP and L-RES NPs were found to be 179.77 ± 5.67 nm and 167.30 ± 2.79 nm, respectively. The cytotoxic potential of L-RES was assessed through an MTT assay. Their impact on tumour spheroid growth was evaluated in L-RES-treated cancer-associated fibroblasts (CAF), while the effect on cell invasion was examined using a spheroid invasion assay. Additionally, the influence of L-RES on 5-fluorouracil (5-FU) sensitivity in CRC cells was studied using co-cultured tumour spheroids. A subtoxic concentration of L-RES was selected to investigate its potential in modulating CAF functions. The treatment with L-RES led to reduced expression of CAF markers, including α-SMA and IL-6, in activated fibroblasts. Notably, activated fibroblasts enhanced the invasiveness and drug resistance of CRC cells under both 2D and 3D co-culture conditions; these effects were mitigated by the L-RES treatment. These findings suggest that L-RES offers a promising drug delivery approach for CRC therapy by disrupting the communication between CRC cells and CAFs.[148]

Polymeric nanoparticles

Polymeric NPs with a reservoir system (nanocapsule) and a matrix system (nanosphere) can integrate hydrophilic/hydrophobic drug particles by coating inert materials in imaging, targeted drug delivery, and biological applications.[149] Polymeric NPs targeting functionality, both active and passive, enables them to selectively target certain tissue locations. The biodegradable polymer NPs have remarkable capabilities and can be used to provide a regulated and targeted DDS for CRC therapy.[150] Udompornmongkol *et al*. created curcumin (polyphenol)-loaded polymeric NPs for improved anti-CRC uses. Curcumin was added into polymeric NPs to improve anti-CRC activity. To make NPs, CS and gum arabic, two naturally occurring polysaccharides, were employed in the emulsification solvent diffusion process. According to the findings, curcumin was encapsulated in carriers with a +48 mV ZP, 136 nm size, and good encapsulation effectiveness (95%). Based on an *in vitro* release investigation, they determined that curcumin NPs could withstand hydrolysis by gastric fluid or small intestinal enzymes and hence should reach the colon fairly intact. Curcumin NPs revealed higher anti-CRC benefits than free curcumin due to improved cellular absorption.[137,151]

In another study, RES (polyphenol) was encapsulated within core–shell polymeric NPs composed of mPEG–PCL (poly(ethylene glycol)-block-poly(ε-caprolactone)) and evaluated against HT29 and HCT116 colorectal cancer cell lines. The NPs exhibited IC_{50} values of 47.85 ± 0.96 μg/mL and 23.65 ± 3.21 μg/mL, respectively ($p < 0.05$). The findings suggested that RES-induced

cytotoxicity was mediated through ferroptosis, an iron-dependent lipid peroxidation pathway. *In vivo* experiments using HT29 xenograft mice further demonstrated that tumour growth was significantly inhibited after 15 days of treatment with RES NPs co-administered with the tumour-penetrating peptide iRGD. Moreover, coating the NPs with an erythrocyte membrane enhanced circulation time by evading macrophage uptake.[152,153]

In a recent study, quercetin (flavonoid) and caffeic acid phenethyl ester (CAPE), two poorly soluble compounds, were successfully encapsulated into PLGA NPs using the single emulsion solvent evaporation method. The particle sizes of QuCaNP-1, QuCaNP-2, and QuCaNP-3 were 512.6 ± 3.41 nm, 378.2 ± 3.47 nm, and 237.8 ± 9.67 nm, respectively, with QuCaNP-3 selected for cell culture experiments. In HT-29 colorectal cancer cells, QuCaNP-3 exhibited enhanced cytotoxic, anti-proliferative, anti-migratory, and pro-apoptotic effects, compared to the free drugs. Notably, QuCaNP-3 activated the mitochondrial apoptotic pathway through caspase induction, suggesting its potential as a nanocarrier system for colorectal cancer therapy, though further studies are required to clarify the underlying molecular mechanisms.[154]

Dendrimers

Dendrimers are made from a variety of macromolecules, including polypropyleneimine, polyamidoamine (PAMAM), poly-L-lycine (PLL), melamine, triazine, and poly (ethylene glycol).[155] Dendrimers have been studied since Dr. Donald Tomalia first published his work on poly(amidoamine) (PAMAM) dendrimers in 1985. They are suitable for loading hydrophilic and hydrophobic drugs, and are characterized by branches, distinct molecular weights, and a globular assembly with a meticulous surface.[156] Recently, Mignani *et al*.[157] suggested that several anticancer phytochemicals, including daidzein (flavonoid), genistein (flavonoid), 7-ethyl-10-hydroxycamtothecin (SN-38) (alkaloid), colchicine (alkaloid), lamellarin D (alkaloid), digoxin (cardiac glycoside), biotin (water-soluble vitamin (B7)) and 10-hydroxycamptothecin (alkaloid), could be conjugated with dendrimers for enhanced anticancer activity. A growing body of research suggests that dendrimers mixed with phytochemicals can act as drug and gene carriers in cancer therapy, improving the solubility and bioavailability of hydrophobic medicines.[157-159]

Shi *et al*. explored an alternative strategy by formulating RES (polyphenol) within dendrimer-like structures derived from sugary maize (RES-SMDG). The RES-SMDG NPs exhibited a zeta potential of -9.5 mV, slightly lower than that of the plain sugary maize dendrimer-like glucan (SMDG, -6.7 mV), and a reduced particle size of 3.5 μm compared to SMDG. In Caco-2 cell studies, RES-SMDG demonstrated significantly enhanced cellular uptake and lower cytotoxicity. Within 30 minutes, RES was detected on the basolateral side with an apparent permeability (Papp) of 9.04×10^{-6} cm/s, and intracellular concentrations of RES dendrimers were 1.5-fold higher than those of free RES. These findings indicate that maize-derived RES dendrimers are absorbable and can improve bioavailability.[160]

Ben-Zichri *et al*. developed a synergistic strategy by co-encapsulating RES (polyphenol) and curcumin (polyphenol) in non-cationic dendrimers. The resulting NPs, with sizes below 200 nm, exhibited significant cytotoxicity against cancer cells by disrupting mitochondrial function. Intracellular calcium, essential for mitochondrial activity and ATP production, was elevated by approximately 25% in SH-SY5Y cells treated with the dendrimer formulation. This calcium overload impaired mitochondrial function, ultimately leading to cell death.[161]

Gallic acid (GA) is a phenolic compound that demonstrates significant anticancer activity across multiple cancer types, including colon, breast, lung, stomach, and liver cancers, and is considered a promising anticancer agent.[162] PAMAM G4 dendrimers have been shown to enhance the bioavailability of GA and its antitumor effects against HCT116 colon cancer cells by facilitating increased cellular uptake. Additionally, the dendrimers enable targeted release of GA and can act synergistically with other anticancer agents. In a CCl_4-induced oxidative liver damage rat model, oral administration of the GA-dendrimer conjugate significantly reduced liver enzyme levels and improved hepatoprotective effects. This enhanced efficacy is likely due to the dendrimers' ability to control the release rate of GA, allowing sustained drug release and maintaining effective concentrations for extended periods, thereby improving overall bioavailability.[163-164]

Polymeric micelles

Polymeric micelles (PMs) are self-assembled structures generated in water-based fluids by amphiphilic block copolymers. These micelles

have a hydrophobic core and a hydrophilic shell, making them ideal for encapsulating and enhancing the solubility of hydrophobic medicines.[165] PM-based carriers are simple to create and can be adjusted for drug delivery. They can also be functionalized with targeting ligands to improve their accumulation at tumour locations, minimize side effects, and enable regulated drug release over time.[166,167] A recent study focused on the development of pH-responsive copolymers for the optimal administration of anticancer medicines in the treatment of colon cancer. These micelles are pH sensitive and successfully target colon tissues, with regulated drug release rates exceeding 80%.[168] Hence, they are regarded as "smart" nanocarriers for delivering anticancer drugs and imaging agents, with potential applications in therapeutics and diagnostics. Notably, several PM formulations loaded with drugs have entered clinical trials for cancer treatment. PMs encapsulating quercetin (flavonoid) were developed using D-α-tocopheryl polyethylene glycol succinate (TPGS) as the carrier polymer. To enhance micellar stability, lecithin was incorporated to form a supportive lipid layer. The optimized formulation exhibited a mean particle size of 194 ± 0.25 nm, a polydispersity index (PDI) of 0.214 ± 0.02, and a zeta potential of 31.9 ± 0.31 mV. When evaluated in CT26 colon cancer cells, the quercetin-loaded micelles demonstrated a significantly lower IC_{50} value. Furthermore, *in vivo* studies using a Balb/c mouse model revealed a 360% improvement in oral bioavailability and a marked reduction in tumour volume compared to free quercetin.[153,169,170]

Sudha *et al*. demonstrated that RES (polyphenol)-loaded PMs effectively reduced tumour growth in an orthotopic colorectal tumour model in mice. The PLGA-based RES NPs, with an average size of 200-220 nm, showed significantly higher antitumor efficacy than free RES. Mice treated with the nanoparticle formulation exhibited approximately a 20% reduction in tumour mass. Moreover, the bioavailability of RES from the micellar NPs was nearly doubled compared to that of the free drug at an equivalent dose of 4 mg/kg, supporting their potential use as an effective therapeutic strategy for colon cancer management.[171]

Yang *et al.* developed curcumin (polyphenol) loaded amphiphilic block copolymer micelles using monomethyl poly(ethylene glycol)-poly(ε-caprolactone) (MPEG-PCL), with the addition of trimethylene carbonate (TMC) to form [MPEG-P(CL-co-TMC)] micelles. The incorporation of TMC enhanced micelle stability by reducing PCL crystallization. The resulting curcumin micelles exhibited a small particle size of 27.6 ± 0.7 nm, a polydispersity index (PDI) of 0.11 ± 0.05, drug loading of 14.07 ± 0.94%, and an encapsulation efficiency of 96.08 ± 3.23%. *In vitro* studies showed improved cellular uptake of curcumin micelles in CT26 cells, leading to cytotoxic effects and increased apoptosis, although the cytotoxicity was comparable to that of free curcumin. Importantly, *in vivo* experiments demonstrated that curcumin micelles significantly reduced tumour weight compared to free curcumin, indicating enhanced antitumor activity. The *in vivo* inhibition of subcutaneous CT26 tumour growth was attributed to suppression of tumour cell proliferation and angiogenesis, along with promotion of apoptosis. These results suggest that TMC incorporation improves micelle stability, making MPEG-P(CL-co-TMC) micelles an effective nanocarrier for curcumin in colon cancer therapy.[172]

Carbon-based nanoparticles

Carbon-based NPs are divided into two types: single-walled carbon nanotubes and multiple-walled carbon nanotubes,[159,173] which were first reported in 1991 by Sumio Iijima.[174,175] These CNTs have piqued the interest of researchers due to their unique physicochemical features, which allow them to cross the cell membrane,[176] as well as their versatility and tremendous biomedical application potential.[177]

The researchers developed a targeted delivery system by loading isolated lycopene (terprnoid) into nanotubes for colorectal cancer therapy. Phosphatidylcholine and Polyvinylpyrrolidone K30 were employed to enhance the stability of the formulation. The system was characterized for various physicochemical properties, including loading efficiency and *in vitro* release behavior. Cytotoxicity against HT29 and COLO320DM cell lines was assessed using multiple assays. The formulation was then encapsulated in enteric-coated gelatine capsules and evaluated for drug release profiles and *in vivo* localization using roentgenography. The lycopene loading efficiency was determined to be 90 ± 0.26%, with 93.81 ± 1.22% release observed at 60 minutes. The *in vitro* cytotoxicity results demonstrated enhanced activity against COLO320DM and HT29 cells compared to pure lycopene. Batch F2 exhibited 81 ± 0.55% drug release at 12 hours. Both *in vitro* and *in vivo* X-ray studies confirmed effective

colonic targeting, with minimal premature release.[178]

Quantum dots

Quantum dots (QDs) are one of the developing engineering nanomaterials that have showed promise as a platform for cancer detection and diagnosis. These include CdSe, ZnS, CdSe, ZnS, and CdS, all of which have distinct optical and chemical properties.[179] Colloidal QDs have been manufactured for diagnostic and therapeutic purposes in living systems via core development, shell expansion, solubilization, and biological binding.[180] However, one disadvantage of QDs is their toxicity, which is induced by the production of oxidative stress-inducing substances, such as ROS, inflammatory cytokines, and metal ions.[181] Curcumin quantum dots were recently discovered to improve the breakdown of bacterial biofilms, when compared to curcumin alone,[182] while folic acid[183] and chlorophyllin have also emerged as interesting QD NP imaging diagnosis possibilities.[159]

Recently, Ring *et al.* prepared curcumin quantum dots (Cur-NCDs) using a combination of mechanical milling and ultrasonic techniques. In this method, 10 g of zirconia beads were mixed with 600 mg of curcumin in 15 mL of ethanol and stirred for 15 minutes, followed by concentration using a rotary evaporator at 60 °C for 15 minutes. The concentrated solution was then ultrasonicated on an ice bath for 20 minutes (750 W, 20 kHz, 30 W/pulse, 50/10 s on/off) while adding 40 mL of hot water dropwise. This ultrasonication step was repeated, and the final product was dried at 70 °C, yielding Cur-NCDs with an average size of 13.7 nm and a zeta potential of +13.3 mV. The resulting Cur-NCDs exhibited promising antibacterial and antimicrobial activity.[184,185]

Another study evaluated the protective effects of berberine (alkaloid)-based carbon quantum dots (Ber-CDs) against 5-fluorouracil (5-FU)-induced intestinal mucositis in C57BL/6 mice. Ber-CDs improved body weight, reduced pro-inflammatory markers (IL-1, NLRP3), increased anti-inflammatory cytokines (IL-10, IgA), enhanced beneficial gut microbiota and short-chain fatty acids, and restored intestinal tight junction proteins (Occludin, ZO-1) more effectively than native berberine. Histological analysis confirmed improved mucosal integrity, indicating that Ber-CDs provide superior protection against 5-FU-induced intestinal injury and may serve as an effective alternative to natural berberine.[186]

Gold nanoparticles

Gold NPs are used in a range of medical applications, due to their distinct physical and chemical properties, and biocompatibility. Gold NPs can be used as carriers for various phytochemicals, leading to higher biological activity of the therapeutic agents.

Highly stable tannin-capped gold NPs were promptly synthesized from *Terminalia bellirica* fruit extract. They were tested for anticancer and anti-inflammatory efficacy against a colorectal cancer cell line (HT29) in a zebrafish model. The anti-inflammatory action was investigated by measuring the expression of inflammatory markers TNF-α, iNOS (induced nitric oxide synthase), and histological analysis. The treatment with NPs resulted in a significant decrease in the expression of inflammatory markers. The histopathological study of the NPs therapy group revealed no evidence of inflammation. The current study implies that *T. bellirica*-mediated gold NPs could be used as an effective therapeutic agent against a chronic inflammatory condition that progresses to cancer.[187]

Curcumin-coated gold NPs were synthesized via a simple and cost-effective one-pot green method and characterized for their effects on a human colorectal cancer cell line. Curcumin is known to exert anticancer activity by modulating key cancer-related genes and signalling pathways. The resulting NPs had an average size of 21.7 nm, displayed low cytotoxicity in MTT assays, and promoted apoptosis by upregulating Bax, P53, and P21 while downregulating the anti-apoptotic protein Bcl-2, demonstrating their potential as effective nanocarriers for curcumin in cancer treatment.[188,189]

The inclusion of quercetin within a gold nanoparticle core enhanced cytotoxicity 50-fold in SW-620 colon cancer cells. *In vivo* studies further demonstrated a reduction in tumour volume along with modulation of 27 apoptosis-related genes.[190] Kamal *et al.* developed a novel system of technetium-99m (Tc-99m) labelled RES-loaded gold NPs to assess their targeting efficiency in HT29 colon cancer cells. The study demonstrated that cellular uptake of 99mTc-Res-AuNP was significantly higher than that of 99mTc-AuNP or 99mTc-RES alone. *In vivo* experiments further showed that 99mTc-Res-AuNP achieved superior targeting of colon adenocarcinoma compared to free 99mTc-RES.[191]

Mesoporous silica nanoparticles

Mesoporous silica nanoparticles (MSNs) are a type of silica material that has received a lot of attention in drug delivery due to their unusual porous structure that can hold a lot of bioactive chemicals. MSNs have tunable cavity diameters ranging from 50 to 300 nm, decreased toxicity, simple cell absorption, and resilience to heat and varied pH conditions.[123] MSN-protamine (MSNPRM) is a hybrid system that has been designed to permit selective drug release in cancer cells, which can be activated by certain enzymes to commence anticancer action.[137]

Aminated mesoporous silica nanoparticles (MSN–NH_2) were synthesized and further modified by grafting alginate oligosaccharides (AOS) onto their surface to develop MSN–NH_2–AOS nanoparticles as a delivery system for the lipophilic drug curcumin. The resulting formulation exhibited a high encapsulation efficiency of 91.24 ± 1.23%. The AOS coating provided pH-responsive behavior, limiting curcumin release to 28.9 ± 1.6% under neutral pH and increasing it to 67.5 ± 1% under acidic conditions. *In vitro* studies using MTT and cellular uptake assays demonstrated that MSN–NH_2–Cur–AOS nanoparticles were more efficiently internalized by colon cancer cells compared to free curcumin, showing enhanced tumour-targeting ability. At a concentration of 50 μg/mL, the nanoparticles exhibited strong cytotoxic activity, suggesting that MSN–NH_2–AOS represents a promising carrier for the delivery of hydrophobic anticancer agents.[192]

A pH-responsive, multifunctional mesoporous silica nanoparticle (SBA-15) was developed for targeted delivery to human colorectal carcinoma (HCT-116) cells. The SBA-15 framework was functionalized with folic acid (FA) and loaded with the hydrophobic flavonoid quercetin. To enhance functionality, acid-labile magnetite (Fe_3O_4) NPs were incorporated onto the FA-functionalized, QN-loaded SBA-15, forming the composite FA–Fe–SBA15–QN. This nanocarrier demonstrated pH-sensitive drug release and significant anticancer activity both *in vitro* and *in vivo*. The formulation induced mitochondrial-mediated apoptosis via a redox-regulated signalling cascade, activating the JNK/H2AX/p53 apoptotic pathway. Additionally, inhibition of heat shock protein 27 (HSP-27) further promoted cell death through this signalling axis. MRI analysis confirmed the theranostic potential of the system, indicating that FA–Fe–SBA15–QN could serve as an effective dual-function material for targeted colon cancer therapy and diagnosis.[193]

Exosome-like nanoparticles

Grape exosome-like nanoparticles (GELNs), with a diameter of 380.5 ± 37.47 nm, were injected to protect the colon against DSS-induced colitis. GELNs targeted intestinal stem cells in this investigation, resulting in intestinal tissue remodelling and protection. Under physiological settings, GELNs were activated by lipids and promoted the proliferation of Lgr5+ stem cells. Only Lgr5 intestinal stem cells produced better intestinal organoid structure than the *in vitro* setting. Liposome-like nanoparticles (LLNs) in collaboration with GELNs are required for *in vivo* targeting of intestinal stem cells. The formation of Lgr5+ stem cells was inhibited by inhibiting the ß-cantenin signalling pathway of GELNs receiving cells. The GELNs system resulted in intestinal tissue regeneration remodelling and regulation.[194]

Kumquat-derived exosome-like nanovesicles (KNVs) were isolated and characterized to assess their therapeutic potential against colon cancer. KNVs were obtained via ultracentrifugation and further purified using a sucrose density gradient technique. Their size and particle concentration were analyzed by nanoparticle tracking analysis, while protein content was quantified using a BCA assay. Cytotoxicity against HCT116 colon cancer cells was evaluated using the MTT assay. The KNVs displayed uniform morphology with an average size of 153.1 ± 1.0 nm and a particle concentration of 6.67×10^{12} particles/mL. The total protein content was measured as 1.79 mg/mL. KNVs demonstrated significant, concentration- and time-dependent cytotoxic effects, reducing HCT116 cell viability by approximately 50% at 20 mg/mL after 48 hours.[195]

Mulberry, a deciduous plant, is valued for its diverse uses, including fruit production and providing leaves for silkworm cultivation. Beyond its agricultural significance, it also possesses notable therapeutic potential in clinical applications.[196-198] In IBD models, mulberry-derived exosome-like nanoparticles (MBDENs) have demonstrated protective effects against DSS-induced colitis in mice. These nanoparticles enhance the expression of heat shock protein 70 (HSP70) and activate the aryl hydrocarbon receptor (AhR) and constitutive photomorphogenic subunit 8 (COPS8) signalling pathways. Consequently, MBDENs effectively

mitigate inflammation, colon shortening, and weight loss associated with colitis.[199]

Broccoli-derived exosome-like nanoparticles (BDENs) represent a promising therapeutic platform, as broccoli and other cruciferous vegetables are rich in sulforaphane (SF), a bioactive compound known for its ability to suppress cytochrome P450 enzymes, induce apoptosis, inhibit cell cycle progression, and reduce inflammation. Research has shown that SF-loaded BDENs can selectively target colonic dendritic cells (DCs) and alleviate experimental colitis in mice. This effect is primarily achieved through the induction of tolerant colonic DCs, suppression of pro-inflammatory cytokines, and restoration of intestinal immune balance.[200]

Phytochemical-based nanoparticles present a novel and effective strategy for achieving precise and targeted drug delivery to the colon. These systems overcome the inherent drawbacks of conventional formulations, such as poor solubility, low stability, and limited site-specificity, while significantly enhancing therapeutic efficacy and bioavailability in the treatment of colon-associated disorders.

CONCLUSION

In conclusion, recent advances in phytochemical-based NPs for colon-specific drug delivery hold significant promise in the field of pharmaceutical research and development. The utilization of natural compounds derived from plants, such as polyphenols, flavonoids, terpenoids, and alkaloids, as building blocks for nanoparticle formulation offers several advantages. Phytochemicals not only exhibit inherent therapeutic properties, but also possess unique physicochemical characteristics that make them suitable candidates for nanoparticle synthesis. These characteristics include biocompatibility, biodegradability, and low toxicity, ensuring safe and effective drug delivery to the colon. The incorporation of phytochemicals into nanoparticle systems allows for enhanced drug stability, prolonged release, and targeted delivery to the colon region. By exploiting the physiological conditions of the gastrointestinal tract, such as variations in pH and enzymatic activity, these NPs can efficiently release drugs at the colon site, reducing systemic side effects and improving therapeutic outcomes. Furthermore, phytochemical-based NPs offer the potential for combination therapy, enabling the delivery of multiple drugs or therapeutic agents simultaneously. This capability can be beneficial in the treatment of complex diseases, such as inflammatory bowel disease and colon cancer. However, while significant progress has been made in the development of phytochemical-based NPs, challenges remain in terms of scalability, reproducibility, and clinical translation. The need for further research to optimize the nanoparticle formulation, improve drug loading capacity, and investigate long-term safety profiles is evident.

The recent advances in phytochemical-based NPs for colon-specific drug delivery have opened new avenues in personalized medicine and targeted therapy. These innovative drug delivery systems offer the potential to revolutionize colon-related treatments, providing patients with safer, more effective, and localized therapeutic interventions. With ongoing research and interdisciplinary collaboration, the integration of phytochemical-based NPs into clinical practice appears promising, contributing to improved patient care and better health outcomes.

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Abbreviations

CTDDS – colon targeted drug delivery system, CRC – colorectal cancer, IBD – irritable bowel disease, GIT – gastrointestinal tract, NP – nanoparticle, ROS – reactive oxygen species, TPP – polyanion tripolyphosphate, RGD – arginylglycylaspartic acid, MTT – (3-(4, 5-dimethylthiazolyl-2)-2, 5-diphenyltetrazolium bromide), RES – resveratrol, NF-κB – nuclear factor kappa-light-chain-enhancer of activated B cells, MAPK – mitogen-activated protein kinase, TNF-α – tumor necrosis factor-alpha, IL-6 – Interleukin-6, COX-2 – Cyclooxygenase-2, iNOS – inducible nitric oxide synthase, Wnt/β-catenin – wingless/integrated and beta-catenin signaling pathway, JNK – c-Jun N-terminal kinase, EGCG-epigallocatechin-3-gallate, ZO-1 – zonula occludens-1, TLR4 – toll-like receptor4, Bax/Bcl-2-regulate mitochondrial-mediated apoptosis, RES-FER-SLNs – resveratrol and ferulic acid-loaded solid lipid nanoparticles, RNP – resveratrol-loaded polymeric nanoparticles, L-RES – liposomal resveratrol nanoparticle, CAF – cancer-associated fibroblasts, QuCaNP – quercetin and caffeic acid NP, RES-SMDG – resveratrol sugary

maize dendrimer-like glucan, Cur-NCDs – curcumin quantum dots, CNT – carbon nanotubes, Ber-CDs – berberine-based carbon quantum dots, QD – quantum dots, DDS – drug delivery system, PAMAM – polyamidoamine, PM – polymeric micelles, MSNs – mesoporous silica nanoparticles, GELNs – grape exosome-like nanoparticles, KNVs – kumquat-derived exosome-like nanovesicles, MBDENs – mulberry-derived exosome-like nanoparticles, BDENs – broccoli derived exosome-like nanoparticles.

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