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Nanotechnology for inflammatory bowel disease management: Detection, imaging and treatment

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ABSTRACT

Inflammatory bowel disease (IBD) is a group of intestinal disorders which cause prolonged digestive tract inflammation. The early diagnosis of IBD through the detection of its biomarkers (including tumor necrosis factor alpha, C-reactive protein, cytokines and microRNAs) and imaging agents is a challenge. Nanotechnology enabled biosensors and enhanced image contrasting chemicals for diagnosis offer promises for an affordable, early and reliable confirmation of the disease and type thereof. Moreover, engineered nanoparticles (NPs) can also be used to deliver active drug agents directly to the region of inflammation. Major advantages of the targeted drug delivery are low dosage drug requirement due to localized/guided delivery and minimal side effects to other organs by the drug. Here, we present a mini review about different engineered nanostructures (Au NPs, Graphene, Quantum dots, inorganic NPs, *etc.*) and plant-based nanoparticles for the detection, imaging and treatment of IBD.

1. Introduction

Inflammatory bowel disease (IBD) is also known as a chronic relapsing gastrointestinal (GI) condition that has two primary forms, ulcerative colitis (UC) and Crohn's disease (CD), associated with an imbalance in intestinal microbiota. As of today, neither of these two forms can be permanently cured [29]. This morbid condition causes severe gastrointestinal (GI) symptoms, including abdominal pain, bleeding, anemia, diarrhea, and weight loss [80].

Being a global disease, IBD has negative impacts on the quality of life and has an accelerating worldwide prevalence between 40 and 50 per 100,000 people-year [71]. It is hypothesized that in 2021, the coalescing prevalence of IBD might level off in Europe and America as the IBD population ages and, also probably due to an unanticipated rise in the death rate during the COVID-19 pandemic [45]. Still, this idiopathic condition remains a major challenge owing to the deteriorating impacts of the disease on the small intestine and colon. It has been estimated that more than 33% of IBD cases are struggling with complications farther than intestinal manifestations of the disease, such as arthritis, uveitis, ankylosing spondylitis, and a broad range of other inflammatory conditions [75,80].

Despite progress made, a definite diagnosis of IBD still poses challenges. Many enteropathogens have been implicated as causative agents for UC, making it difficult to discriminate between IBD entities and chronic infectious colitis (IC) [54]. Besides, with the changing epidemiology of intestinal tuberculosis (ITB) and CD, physicians have a hard time differentiating these two disorders, leading to delayed diagnosis or misdiagnosis [2].

On the other hand, current IBD treatments aim to maintain the patient in remission and alleviate complications of the disease, in preference over reversing the complex underlying pathogenic mechanisms [80]. Depending on the severity of symptoms, several drugs including

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immunomodulators, corticosteroids, aminosalicylates, monoclonal antibodies, and some broad-spectrum antibiotics are being used to treat IBD patients. Whereas, fish oil, methotrexate, bismuth, and arsenical salts are considered alternative pharmacotherapies [6,80]. Prolonged use of conventional medications was found to cause serious side effects such as pancreatitis, allergic reactions, nausea, and elevated liver enzymes, making the management of IBD challenging, specifically in elderly and vulnerable populations [3,100]. Surgery is another option of IBD treatment; nevertheless, several controversies exist in IBD surgery [51]. Specific delivery of a drug to the colon, termed colon delivery, has also gained much attention as an alternative therapeutic option [76]. Yet, some considerations have to be made for this purpose. For example, each GI tract segment has different pH conditions, and at unoptimized pH, drugs might be oxidized, deaminated, hydrolyzed, or completely inactivated. Moreover, drugs might be sensitive to enzymes of the GI tract, such as salivary amylase, pepsin, trypsin in the intestine, gastric lipase in the stomach, and other enzymes produced by microbiota of the gut [104]. As a physical barrier, the mucus produced by the intestinal epithelium limits the delivery of orally administered drugs. Likewise, the P-glycoprotein are efflux transporters that pump drugs out of the GI tract, thus, inhibits optimal drug delivery [121].

To overcome this therapeutic hurdle, in the last decade, IBD treatments has been enormously progressed, mostly as a result of advances in nanobiotechnology [108]. In this regard, nanoparticles (NPs), with various engineered properties suitable for biological applications, have been introduced as valuable tools revolutionizing disease diagnosis, treatment, and theranostics. Nowadays, NPs are widely used for the delivery of drugs, polypeptides, proteins, DNA, RNA, genes, and even vaccines [120]. Because of their nanometer-scale dimensions, specific delivery to inflamed tissue and controlled release, the nanomaterials (NMs) yield promising outcomes even at very low concentrations and have fewer side effects than conventional drugs [96]. This has made NMs an object of an even broader interest in light of successful optimization of designed nanocarriers as novel drug delivery systems (DDS) for targeted therapies [24].

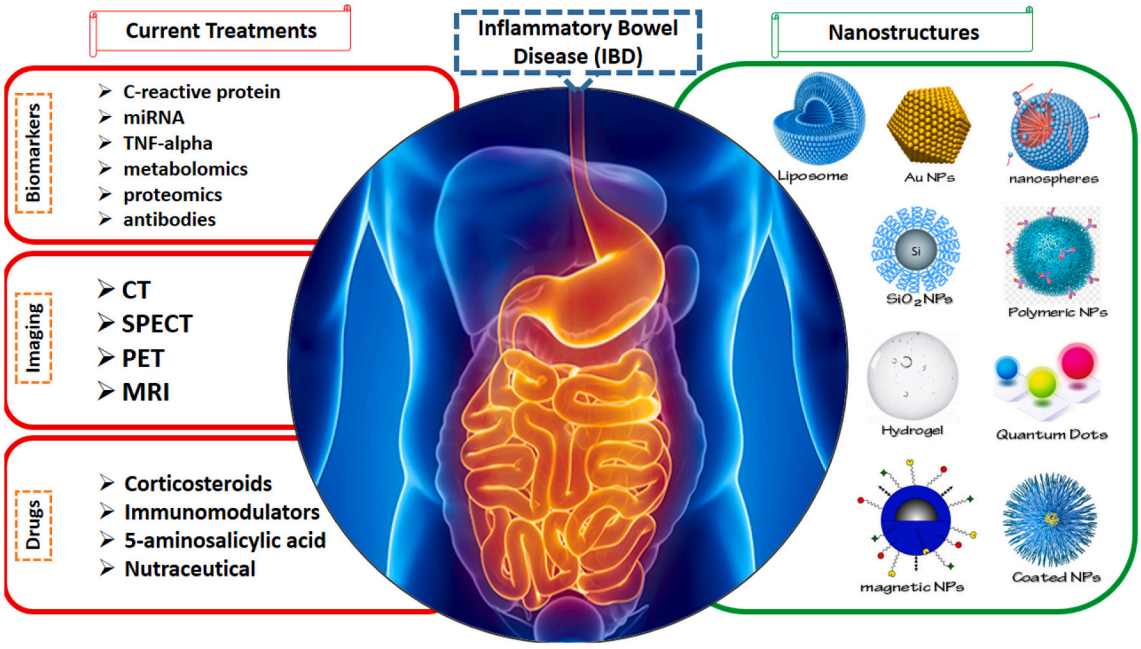
Recently, multiple targeted therapy approaches have been developed for IBD treatment, both *in-vivo* and *in-vitro* investigations. Several studies have focused on the pathophysiology of inflammatory responses in IBD patients through formulating a suitable carrier for colon delivery [100,121]. The application of nanocarriers for colon delivery improves their bioavailability and lessen the systemic complications seen in oral and intravenous administrations [58,100]. Some studies have suggested the use of NPs in forms of nanoemulsions, capsule and lipid-based nanocarriers, nanotubes, nanospheres, and solid lipid microparticles in a DDS [8,31,116]. These NPs could be derived from natural compounds [100] or natural products used in traditional Chinese medicine [31]. The majority of other studies have concentrated on the use of NPs as DDS in IBD treatment.

The use of NMs has improved IBD diagnosis as well. It has been shown that dextran-coated NPs could be utilized as computed tomography (CT) contrast agents for GI tract imaging in IBD patients. This could be very useful since conventional iodinated and barium-based CT agents are not specific for inflammatory sites of GI tract imaging [68]. Besides, polyethylene glycol-based nanocarriers, coupled with cell adhesion molecules and loaded with quantum dots, were generated as beneficial nanodevices for precise IBD diagnosis [109]. Based on our previous studies [10,19,33,67,83–85], in the current work, we reviewed different nanomaterials applied to diagnosis and treatment of IBD. Late advances in nanotechnology have made NMs, excellent tools to be deployed in the feisty fight against IBD (Scheme 1). In this review, we focus on different NMs applied to the treatment and diagnosis of IBD. (See Table 1.)

2. Challenges and nano-diagnosis approaches for inflammatory bowel disease

2.1. Serum biomarkers for inflammatory bowel disease and challenges

Better diagnosis assessment and therapeutic response prediction is a core issue in medical services. Also, due to the continuously growing epidemic, realistic and efficient diagnostic and clinical assessment techniques are required. In recent IBD studies, serum biomarkers have made considerable progress as they are non-invasive, convenient, and comparatively cheaper than indicators in colonoscopy tissue, urine, air, and other body fluids [18]. Tumor necrosis factor alpha (TNF-α) plays an important role in chronic problems such as cardiovascular diseases,



Scheme 1. Schematic representation of current approaches and use of nanostructures to enhance efficiency of these methods. Note: CT-Computed tomography SPECT-Single proton emission computed tomography, PET-positron emission tomography, and MRI- magnetic resonance imaging, miRNA: microRNA, TNF-alpha: tumor necrosis factor alpha.

Table 1
Recent biosensing investigations of various IBD biomarkers and their limit of detection (LOD).

Biosensor type	Material/active component	Marker/detected molecule	LOD	Reference
Electrochemical biosensor	VA-NCNT electrodes	lysozyme	100 fM	[112]
Electrochemical biosensor	functionalized CNTs with amino groups	5-ASA and FA	36 and 3.1 nM, respectively	[72]
Electrochemical immunoassay	iridium NPs-loaded graphene	CRP	3.3 pg mL-1	[61]
Electrochemical immunoassay	carbon electrode (SPE) loaded with AuNPs	CRP	0.15 nM	[105]
Endoscopy	Fecal immunochemical testing	fecal calprotectin (FCP); mucosal healing (MH)	100 ng/mL; 250 μg/g	[60]
FET sensor	anti-TNF-α/CNT-SiO_2	TNF-α	1 pg/L	[79]
Fiber optic-SPR bioassay	Functionalised Au coated optical fibers	infliximab	2.2 ng/mL (15 pM)	[56]
Fluorescent sensor	P1–4/AgNC/cDNA probe	miRNA (miR-223)	0.018 μM	[25]
Immunosorbent assay	CdSe/ZnS QDs	CRP	0.46 ng/mL	[59]
Impedance spectroscopy based sensor	Polyamide/ZnO	CRP, IL-1β	0.2 pg/mL	[41]
Optical absorption spectroscopy	ML@PDDA	lysozyme	0.5 μg mL −1	[22]
SERS quenching nanosensor	gold-coated copper oxide nanomaterial	TNF-α	173 pg/L	[34]
μQLIDA	PMMA microcapillary/MPO antibody/Quantum dots	myeloperoxidase	<5 nM	[118]
Waveguide-mode sensor	Streptavidin/AuNPs	CRP	10 pM	[7]

Abbreviations: 5-ASA: aminosalycilate drug mesalazine; CNT: carbon nanotubes; CRP: C-reactive protein; FA: folic acid; FET: field-effect transistor, IL-1β: interleukin-1β; miRNA: microRNAs; ML: Micrococcus lysodeikticus; PDDA: poly(diallyldimethylamonium); SERS: surface enhanced Raman spectroscopy; SPR: surface plasmon resonance; TNF-α: tumor necrosis factor alpha; μQLIDA: quantum dot-linked immuno-diagnostic assay, VA-NCNT: vertically aligned nitrogen-doped carbon nanotube.

muscular dystrophy, IBD, Parkinson's disease and cancer. C-reactive proteins, cytokines, antibodies, non-coding RNAs, metabolomics and proteomics are other well-established biomarkers that are commonly used [26,53,91]. There are still no accurate IBD serum biomarkers to date, with such an abundance of studies. Serum sampling (blood-based biomarkers) and non-coding RNAs are only starting to thrive but display tremendous promise for future clinical practice. Overall, integrating different approaches can improve the diagnosis quality of IBD.

2.2. Traditional IBD diagnostic methods and limitations

In patients with IBD, clinical symptoms are not necessarily associated with disease severity *i.e.* differentiating between the symptoms of a stable intestine and those of a chronic stage is non-trivial. Mucosal lesion practitioners can have no or just mild symptoms [78]. Precise measurements are needed to assess and monitor the development of IBD disease. While there is no established routine protocol for detecting the IBD but evaluating the symptoms of the disease or evaluating the reaction to prescription/therapy are helpful. Clinicians use a mixture of clinical symptoms, laboratory indicators, radiation monitoring, endoscopy, and histological analysis of tissue samples to assess disease occurrence and make treatment decisions [37]. In clinical IBD diagnostic, the use of one or more of the following imaging techniques is also applied. Computed tomography (CT), Single proton emission computed tomography (SPECT), positron emission tomography (PET), and magnetic resonance imaging (MRI) are most used techniques for imaging of IBD. Endoscopy can provide *in situ* imaging of mucosal lesions for IBD diagnosis. Nevertheless, it is painful, time-consuming, costly and associated with a chance of perforation. Transmural inflammation cannot be assessed by endoscopy [27].

2.3. Nanoparticle-based imaging of inflammatory bowel disease

Imaging techniques can offer promising features for imaging and evaluation of IBD [5,88,90,111]. Latest developments in multifunctional nanoparticles, use a multidisciplinary method to direct diagnosis of IBD. The combination of nanotechnology and imaging methodologies can allow early IBD diagnosis and disease severity monitoring and can also be used at the cellular or molecular level [55,115]. Wu et al. enhanced imaging quality of SPECT/CT and MRI by using indium (^{111}In)/ iron oxide nanoparticles labeled macrophages [114]. *Ex-vivo* mass spectrometry demonstrated high superparamagnetic iron oxide (SPIO) nanoparticle uptake (7.4 pg iron per cell). ^{111}In-labeled cells were present in all the tissues associated with reticuloendothelial area or in the mononuclear phagocyte system at 24 h.

Basirat et al. evaluated the accuracy of 99mTc(V)-dimercaptosuccinic acid (DMSA) and fecal calprotectin with ileocolonoscopy as new means for inflammation localization due to colonoscopy restriction in the evaluation of the whole intestine and patient discomfort in IBD [11]. In detecting active disease by colonoscopy, the calprotectin level had sensitivity, PLR (positive likelihood ratio), and PPV (positive predictive value) of 90%, 0.90, and 100% respectively. Naha et al. indicated that using dextran as a coating material on cerium oxide NPs would promote aggregation at IBD inflammation sites [68]. Dextran-coated cerium oxide NPs provided a good CT contrast and located it at the site of colitis in the intestine. To image hypoxia related with IBD, Zhou et al. developed an *in-vivo* hypoxia-activatable and cytoplasmic protein-powered fluorescence cascade amplifier (HCFA) [124]. A 4-aminobenzoic acid (azo)-modified mesoporous silica nanoparticle (MSN) was applied in their architecture as a container to load black hole quencher 2 (BHQ2) and cytoplasmic protein-binding squarylium dye (SQ). Then, through a host-guest interaction to form HCFA, the β-cyclodextrin polymer (β-CDP) combined with azo. The outcomes of the fluorescence imaging showed that HCFA could differentiate various levels of cellular hypoxia sensitively and monitor the variants of hypoxia *in-vivo*.

2.4. Nanosensors for the detection of inflammatory bowel disease

Since proper management of IBD is important with regard to disease prognosis, extensive studies have been carried out on non-invasive serum biomarkers to identify markers that are helpful for disease diagnosis, sub-classification, disease activity tracking and estimation of patient outcome and comorbidities [4,66]. Over the last few decades, nanosensors are being developed rapidly and are playing an increasing role in biological research, particularly in IBD [89]. In recent years, the application of nanostructures in diagnosis of IBD increased. Most recent studies about nano diagnosis of IBD will be discussed in the following paragraphs. Chemical sensors based on configurable molecularly modified Au NPs were reported by Karban et al. for the identification and discrimination between irritable bowel syndrome (IBS) and (IBD) [46]. The results showed an 81% accuracy of discriminative power between IBD and IBS and 75% between Crohn's and Colitis states.

Shepherd et al. implemented a stool analysis approach by using headspace gas chromatography coupled with chemiresistive metal oxide gas sensor. An artificial neural network software was fed with the variation in resistance over time data from different samples for IBD

detection [95]. The machine was able to separate samples from IBS and IBD with a sensitivity and specificity of 76% and 88%, respectively, with an overall mean predictive precision of 76%. Previously, miRNAs and silver NPs were used for fluorescence quenching diagnosis probe of inflammation [25]. However, theses probes have low limits of detection (LODs) due to interference of biomatrix. Fang et al. solved this problem by development of new DNA/AgNC-cDNA nanosensor that worked based on fluorescence enhancing approach [25]. They used miR-223 (IBD biomarker) to target IBD infection. The newly developed probe showed perfect specificity and sensitivity (10 times) compared to the conventional fluorescence approach.

An extremely sensitive surface enhanced Raman spectroscopy (SERS) quenching nanosensor (gold-coated copper oxide nanomaterial) for the identification of TNF-α in blood was developed by Gholami et al. [34]. TNF-α was measured down to $1*10^{-14}$ M (173 pg/L) using this SERS quenching sensor. The cytokine measurement by the SERS quenching approach was cross-validated against the enzyme-linked immunosorbent assay (ELISA) and 93.39% agreement was found between the two methods. C-reactive protein (CRP) is produced by the liver in response to the inflammation. A number of sensors utilizing various functional nanomaterials have been developed. A multimode SWEATSENSER for non-invasive ongoing analysis of C-reactive protein and interleukin-1β has been reported by Jagannath et al. [41]. Over a dynamic range of 3 log orders, the sensor detected interleukin-1β and C-reactive protein in sweat. A mean IL-1β concentration of ~28 pg/mL was reported by continuous on-body measurements in the healthy cohort. This study showed the first solid evidence of multimode cytokine and inflammatory marker identification in a portable and wearable form factor in passively expressed eccrine sweat that can be used for better IBD management. A straightforward, cheap, and label-free electrochemical nanosensor was developed by Thangamuthu et al. to measure CRP in a drop of serum sample using screen printed carbon electrode and immobilized AuNPs that covered by anti-CRP (See Fig. 1(a)) [105]. Near-perfect results for detection of CRP (LOD (0.15 nM), linear range (0.4–200 nM) and sensitivity (90.7 nA/nM)) was achieved.

A waveguide-mode sensor based on antibodies conjugated to streptavidin- and AuNPs was developed by Ashiba et al. for detection of CRP, as shown in Fig. 1(b). The one-step method was based on waveguide-mode resonance and evanescent wave [7]. The minimum detectable concentration of CRP of the nanosensor was 10 pM. In recent years, smartphones with a high-quality camera and an operating system have become common sensing devices, especially in point-of-care (POC) analyses. A portable smartphone-based diffusometry was developed by Chuang et al. for the analysis of the CRP concentration [17]. The 300 nm polymer fluorescent beads (polystyrene with $COOH^-$ functional group) were imaged by an optimized fluorescence microscopic add-on system for a smartphone. For a period, sequential nanobead data were captured and the image for the analysis of fluorescence correlation spectrometric (FCS) was used. The sensor demonstrates linearity in 1–8 μg/mL sensing range. A novel quantum dot-labeled immunosorbent assay has been developed by Lv et al. for rapid C-reactive protein detection [59]. The CRP detection assay provided a wide analytical range of 1.56–400 ng/mL with the LOD of 0.46 ng/mL and the limit of Quantitation (LOQ) of 1.53 ng/mL.

Ma et al. prepared ionic liquid-molybdenum disulfide /gold NPs hybrid and iridium NPs-loaded graphene to detect CRP [61]. The proposed nanosensor showed a LOD of 3.3 pg mL-1 and a linear range of 0.01 to 100 ng mL-1.

3. Nano-treatment of inflammatory bowel disease

Although the mechanism of action of IBD is still unclear, evidence indicate that genetic vulnerability, oxidative stress, chronic conditions, and changes in the microbiota can cause IBD [32,57,70]. Traditional IBD therapies have adverse side effects, including an elevated risk of infections and certain cancers [15]. In addition, patients must undergo long-term drug administration in order to prevent the disorder from relapsing [80,86]. It will be helpful for IBD patients to discover a drug that can be administered and localized to the inflamed tissues and preventing systemic side effects. Nanomedicine is a way of treatment that using nanocarriers or nanoparticles to deliver drug at targeted locations [92,93]. Miroliaee and colleagues reported the amelioratory role of newly synthesized selenium-NPs combined with silymarin in the experimental UC [64]. Laroui et al. opted to use engineered NPs to deliver KPV, an anti-inflammatory tripeptide, to the colon in a mouse model of UC. Based on their observation, by use of NP-based DDS, this tripeptide can be delivered to the inflamed site at a concentration much lower than that of the tripeptide alone [50]. Theiss and coworkers successfully delivered prohibitin, a ubiquitously expressed protein, to the colon *via* an encapsulated NP/hydrogel system and observed the promising ameliorating effects of NMs in drug delivery [106]. Ocansey et al. recommended the application of exosome-like NPs in IBD models for the delivery of synthetic molecules and drugs, proteins, and functional RNAs to the colon [73]. Similarly, exosome-like NPs derived from grapes induced favorable protection against UC in mice model [44]. Studies have also focused on using NPs for development of novel oral DDS in which release of drugs in GI tract is mainly triggered by pH or in the presence of enzymes or reactive oxygen species [65,104,121]. RNAi-

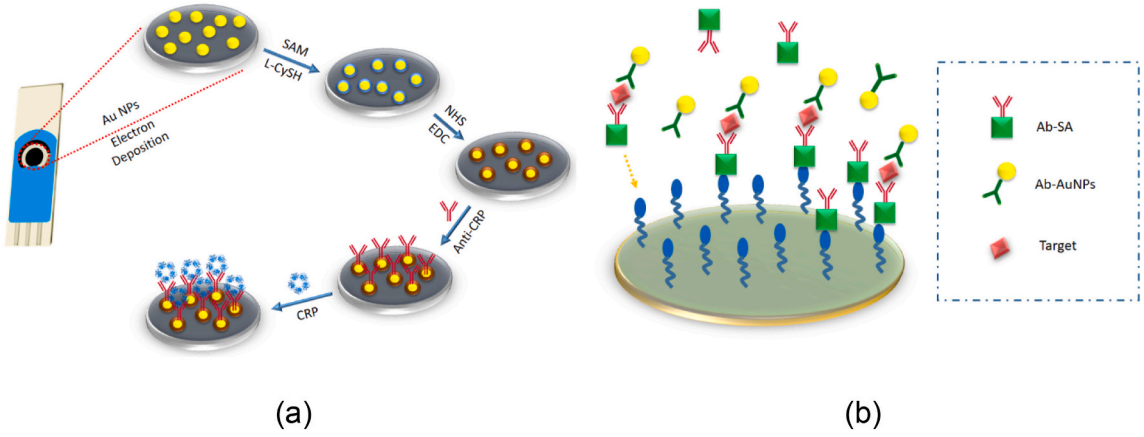


Fig. 1. (a). Schematic representation of the fabrication steps for the label-free C-reactive protein (CRP) immunosensor with anti-CRP functionalized AuNPs electrode, reproduced with permission from [105]. (b). Detection scheme of one-step method. Ab-SA: streptavidin-conjugated antibody, Ab-AuNP: gold nanoparticle-conjugated antibody, reproduced with permission from [7]. Here, SAM - self-assembled monolayer, L-CySH - L-cysteine, NHS - N-hydroxy succinamide, EDC - 1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide, Ab-SA - streptavidin-conjugated antibody.

based NPs with varied clinical applications have also been introduced as efficacious drug delivery systems for IBD treatment [39]. Fabricated chondroitin sulfate-curcumin NPs have also exhibited great biocompatibility and could be employed as a desirable strategy for IBD treatment [38]. Interestingly, intestinal organoids encompassing poly (lactide-*co*-glycolide)(PLGA) NPs has been regarded as a potential DDS to deliver conventional IBD medications to the inflamed areas [20].The following paragraph will address drug therapies used in the treatment of IBD and how the use of engineered NPs has enhanced their efficacy and safety profiles by offering local drug delivery, increasing drug concentration, and preventing systemic side effects.

3.1. 5-aminosalicylic acid (5-ASA)

Function of 5-ASA in management of IBD is well known. 5-ASAs are quickly absorbed in the small intestine, however, minimum quantity of drug reach to the colon [35,119]. Experts in this area have developed various NP formulations loaded with 5-ASAs to give a sustained, targeted and controlled release of drug. For example, chitosan-bound ginger nanocarriers were developed by Markam et al. for the slow and controlled release of the 5-ASA against IBD, [62]. The entrapment efficiency (EE%) of 5-ASA from nanocarrier was more than 50%. The controlled release of 5-ASA at gastrointestinal pH was favorable, which is desirably beneficial against IBD. In another report, poly(methoxyl ethylene glyc*o*l-caprolactone-*co*-methacrylic acid-co-poly(ethylene glycol) methyl ether methacrylate) (P(CE-MAA-MEG)) pH-sensitive hydrogels were developed by Bai et al. for 5-ASA delivery to IBD target [9]. Results of animal studies showed an observable effect on the healing of ulcerative colitis (UC). Tang et al. also prepared 5-ASA loaded SiO_2 NPs for nano treatment of IBD [101]. The colonic histopathology scores and disease activity index (DAI) of 5-ASA-loaded SiO_2 NPs improved compared to control mice group. Ultimately, they suggested that 5-ASA-SiO2 NPs have a selective drug release mechanism that targets the inflamed colon, UC features, and may significantly improve therapeutic efficacy in UC.

3.2. Corticosteroids

Corticosteroids such as budesonide, prednisolone and dexamethasone are another class of drugs, anti-inflammatory, used in IBD therapy. Due to global immunosuppression and various other systemic side effects, their use for long-term use is restricted. [63,97]. Shams et al. prepared prednisolone loaded Eudragit L100–55 polymer microparticles as a new drug delivery system to treat IBD [101]. It was reported that the use of pH-responsive Eudragit L100–55 in the acidic conditions of the stomach will reduce the release of prednisolone, followed by rapid release as the pH of the release medium was changed to 6.8 after the first 2 h. For the treatment of conditions like IBD and colon cancer, this feature can be useful. In three different nanocarriers (liposome coating aminoclay, liposome and Eudragit® S100-aminoclay double-coated liposome (EAC-Bud-Lip)), Kim et al. loaded budesonide (Bud) [48]. EAC-Bud-Lip gained excellent drug absorption in Caco-2 cells compared to the free Bud solution and demonstrated greater inhibition of TNF-a and IL-6 secretion in LPS-stimulated Raw264.7 cells. The role of TNF-α in inflammatory bowel disease (IBD) is shown in Fig. 2. In a similar study, Gite et al. prepared nanoparticles containing budesonide with the polymer Eudragit S100 and surfactant Poloxamer. It was determined that the optimized drug to polymer formulation ratio was 1:2 and the drug to surfactant ratio was 1:1 [36].

3.3. Immunomodulators

Immunomodulators are a type of drugs that weakens or modulates the function of the immune system and are also referred to as immunosuppressants. The use of Immunomodulators (tacrolimus, azathioprine, 6-mercaptopurine, and methotrexate) in IBD can decrease the

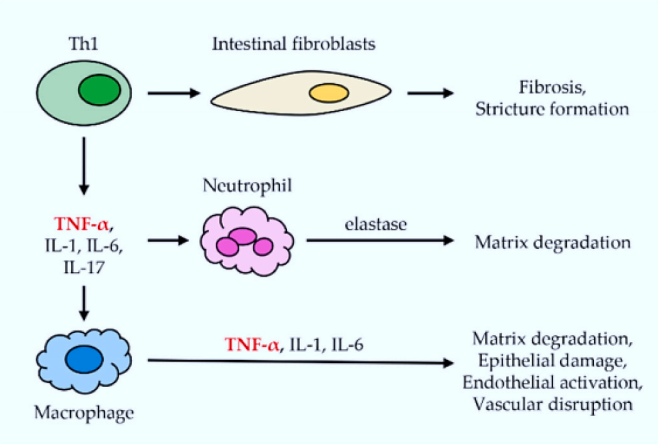


Fig. 2. The role of TNF-α in inflammatory bowel disease (IBD). TNF-α is secreted from Th1 cells along with other cytokines. These cytokines cause the accumulation of immune cells, including intestinal fibroblasts, neutrophils, and macrophages in the gut. Intestinal fibroblasts cause fibrosis and stricture formation. Neutrophils secrete elastase, which causes intestinal matrix degradation. Macrophages produce more inflammatory cytokines, which causes intestinal matrix degradation, epithelial damage, endothelial activation, and disruption [42].

inflammatory response of the body, which play a critical role in IBD flares [102,110]. An improved treatment efficacy can be achieve by using low cost and bio-available NPs. Regmi et al. suggested an oral drug delivery system (tacrolimus (FK506)-loaded microspheres) to treat inflammatory sites in the colon [87]. The oral administration of FK506-loaded thiocetal microspheres (FK506-TKM) resulted in a large aggregation of FK506 in inflamed colons. At the molecular level, the infiltration of CD4+ and CD8+ T lymphocytes in the colon and the differentiation of CD4+ T cells into Th1 and Th17 cells in colon-draining mesenteric lymph nodes were significantly inhibited by FK506-TKM thorough limiting colon dendritic cell migration. Pathak et al. proposed single-dose injection of FK506 (tacrolimus) loaded biodegradable microspheres (FK-Ms) [77]. The pharmacokinetics analysis showed the presence of FK506 for more than 20 days in the blood. Injection of FK-Ms blocked T cell infiltration into the colon and amplified the differentiation of T cells into Th1 interferon-γ secreting and Th17 interleukin-17A secreting cells in mesenteric lymph node colon-draining cells. Akhlaq et al. have developed a pH-responsive gelatin and poly(vinyl) alcohol (Gel/PVA) hydrogel that can achieve specific targeting of methotrexate to treat colorectal pathologies [1]. The kinetic model showed that methotrexate release from Gel/PVA hydrogel follows the process of non-Fickian diffusion. This research study concluded that the release of methotrexate gel/PVA hydrogel can be achieved in the intended colon region for the treatment of colorectal disorders.

3.4. Plant-based nanoparticles

The plant-derived molecules such as flavonoids, volatile oils, alkaloids, polyphenols, tannins, and polysaccharides are known for their broad biological functions and are of immense therapeutic potential in nanomedicines for treatment of different diseases [113]. Recently, the renewed attentiveness to the combinatorial approaches of nanotechnology with plant-based components has resulted in the development of nanomedicines for the treatment of inflammatory bowel disease [49]. Biological synthesis of nanoparticles *via* these natural phytochemicals particularly, curcumin (obtained from rhizome of *Curcuma longa* L.), silymarin (derived from seed of *Silybum marianum* (L.) Gaertn.), ginger (isolated from rhizome of *Zingiber officinale* Roscoe), berberine (obtained from the stem and root of *Berberis vulgaris* L.), embelin (derived from fruit of *Embelia ribes* Burm.f.), thymoquinone (isolated from seeds of

Nigella sativa L.), piceatannol (obtained from seed of *Euphorbia lagascae* Spreng.), Konjac glucomannan (a natural polysaccharide derived from the tubers of the plant *Amorphophallus konjac* K.Koch), quercetin (a polyphenol found in many plants, especially in onions), and resveratrol (RES, a polyphenol occur in many plants, especially in grapes), have shown a tremendous potential for IBD treatment [98]. For example, curcumin and embelin possesses pharmacological characteristics, including anti-inflammatory and antioxidant characteristics [99]. Green synthesis of nanoparticles with curcumin and embelin, are shown to be useful in treating mice with colitis [47,103]. *In-vivo* studies have demonstrated that curcumin and embelin nanoparticles were introduced for the protection of colon against dextran sodium sulfate (DSS)-induced colitis model in mice [103]. Another well-known example is ginger-derived nanoparticles which reduced the expression of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and IL-1β cytokines as well as elevated the expression of anti-inflammatory cytokines IL-10 and IL- 1β [107]. The results indicate that ginger-derived nanoparticles can be massively produced and developed for treatment of IBD and colitis associated cancer. The combination effect of selenium nanoparticles and silymarin decreased the production of nuclear factor kappa B (NF-κB) and showed a promising antioxidant profile, which is a potential candidate for treatment of IBD. Thymoquinone has several anti-inflammatory and immunomodulating activities targeting NF-κB, IL-1β and TNF-α signaling. Treatment of DSS-induced colitis in mice with thymoquinone has suppresses malondialdehyde (MDA) levels and myeloperoxidase (MPO) activity with concomitant increase in glutathione levels indicating improvement in colitis-associated tissue damage [52]. Moreover, there is significant reduction in the expression of inflammatory markers Cox-2, iNOS, Nrf2, KEAP1, and pro-inflammatory cytokines (IL-1β, IL-6, and TNF-α) both at the mRNA and protein levels [21,47,100].

Phytomolecules isolated from the plants, green synthesis of nanoparticles through natural proteins (for instance zein, a protein extracted from *Zea mays* L.) have shown great efficacy in IBD management [40]. Because of inherent hydrophobicity of zein, it could be a promising natural carrier specifically for the delivery of hydrophobic molecules [122]. It has been broadly used as a coating material to protect entrapped bio-actives from gastric acid and release them in intestinal environment. It has also received increasing attention as a protein-based carrier for the fabrication of delivery systems like microspheres, nanoparticles (NPs), hydrogels *etc.* due to its mucoadhesive, biodegradable properties and low cost [94].

Interest in the use of nutraceutical as a functional treatment has gained popularity over the last few years. Resveratrol is a nutraceutical for the treatment of IBD with promising anti-inflammatory properties. However, it's extremely poor solubility and poor stability impede the clinical efficacy of resveratrol as an oral anti-inflammatory agent [28,43,117]. In a novel analysis, in β-lactoglobulin (BLG) nanospheres, Pujara et al. encapsulated resveratrol, with 10% *w*/w loading, resveratrol complexation with β-lactoglobulin nanospheres (BLG) improved resveratrol aqueous solubility by ~1.7 times [81]. Dissolution of resveratrol-loaded NPs was higher than free resveratrol (90% in 8 h). Also, BLG-RES showed an increased disease activity index (DAI) compared to resveratrol. Notably, histological assessments showed a comparable trend of striking progress in colon pathology through a rise in the amount of goblet cells and colonic epithelium recovery. The expression level of cytokine interleukin-10 (Il10) was significantly increased by BLG-RES, which supports the decrease in inflammation, possibly due to increased dissolution and stabilization of resveratrol by BLG complexation [81].

It has been stated that curcumin is successful in inducing and sustaining remission in UC patients, indicating that nanoparticle curcumin can be used to treat IBD [117]. In this context, Ohno et al. stated that nanoparticle curcumin can boost experimental colitis through gut microbiota modulation and regulatory T cell induction [74]. In another study, Beloqui compared the *in-vitro* and *in-vivo* effectiveness of three curcumin (CC) –loaded nanocarriers (lipid core-shell protamine nanocapsules, nanostructured lipid carriers and self-nanoemulsifying drug delivery systems) for IBD treatments [12]. A 30-fold greater curcumin permeability across Caco-2 cell monolayers was obtained using nanostructured lipid carriers.

4. Challenges and future prospective

Due to the improved potency of the NPs and specificity accumulating in damaged tissue, nanotechnology provides revolutionary therapeutic options for IBD. Despite their advantages, none of the NPs has been licensed for the clinical use against IBD. Nanoparticles often have a complex formulation which involve encapsulation and modifications of the surface that may be necessary for human administration. Most notably, the side effects and toxicity of NPs in human cells have not been fully tested. NPs use antigen-presenting cells (APCs) as a target to deliver their cargo in most of the studies cited. In addition, most of the current detection methods for IBD are not suitable for *in-vivo* imagining, making APCs a more attractive target for NPs [23]. Finally, it is very difficult to translate results from animal models to humans, and it varies depending on the animal model used. Only a small number of targeted IBD NPs are currently being tested and established, as this analysis clearly demonstrated. However, there is an immediate clinical need to adopt nanoparticle technologies successfully used in other disease for IBD diagnostic. Despite a lot of study, existing IBD biomarkers are still far from ideal. Before they are introduced to clinical practice, newly identified markers should be verified in multicenter international collaborations. The increased sensitivity of imaging techniques and nanosensors may allow IBD targets that are currently inaccessible due to low cellular target expression and/or high NP concentrations needed for *in-vivo* detection and monitoring. Nanomedicine may help in treating medical conditions such as IBD, but due to inherent side effects, some drugs have minimal applications. Since this is an emerging area of research, further studies are needed to establish the pharmacokinetics, therapeutic effectiveness, and protection in humans of the NPs. The studies presented so far inspire researchers to continue discovering and experimenting with potential alternatives to medications. In addition, these experiments may serve as a tool for future human studies, with the ability to treat a wider variety of diseases safely by targeting their specific disease position and preventing systemic toxicity and side effects.

On the other hand, several nanotechnology based advanced sensing techniques such as surface enhanced Raman spectroscopy (SERS), localized surface plasmon resonance (LSPR), nanoparticle enabled potentiometric or amperometric sensors could potentially be used for the early detection of IBD [13,14,30,69]. Some of these techniques have recently been translated into whole blood EFA (Extraction, Filtration and Analysis) devices, in form of microneedles, which can potentially measure biomarkers of interest in a cost effective manner within less than a minute [82]. Moreover, new routes of IBD diagnosis based on detection of circulating tumor cells, cell surface protein recognition and mRNA could lead to the development of technologies which will vital to save human life in near future [16,125]. However, we identify few bottlenecks which has so limited the use of nanotechnology in the IBD diagnostics: 1) Low Reliability and Acceptability of Nanotechnology: Often the NP based detection is affected by non-specific binding of biomolecules, aggregation of nano probes and low signal-to-noise ratio in complex biosample such as whole blood. While many of the aforementioned issues are being addressed rapidly in literature, ensuring translational of nanosensors from academic to routine IBD diagnostics, still requires extensive investigations in large clinical sample pools; 2) large scale production of the nanosensors which have long shelf life. Often nanosensors involve several synthesis steps which can be non-trivial to integrate in an single automated process; and 3) Toxicity of the nanoparticles, especially for the *in-vivo* application in diagnostics, their biodistribution, biodegradability, and pharmacokinetic properties of nanoparticles should be considered [123].

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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