BioChem

MDPI

Review

Oxidative Stress-Induced Gastrointestinal Diseases: Biology and Nanomedicines—A Review

Maryam Rezvani [1,2]

[1] Department of Life and Environmental Sciences, Drug Science Division, University of Cagliari, 09124 Cagliari, Italy; rezvani.mary@yahoo.com
[2] Advanced Nanobiotechnology and Nanomedicine Research Group (ANNRG), Iran University of Medical Sciences, Tehran 14496-4535, Iran

Abstract: Gastrointestinal diseases have been among the main concerns of medical and scientific societies for a long time. Several studies have emphasized the critical role of oxidative stress in the pathogenesis of the most common gastrointestinal diseases. To provide a comprehensive overview of gastrointestinal diseases caused by oxidative stress, their biological aspects, molecular mechanisms and specific pathways, the results of the most recent published articles from the online databases were studied considering both the upper and lower parts of the digestive tract. The results revealed that although the oxidative stress in each part of the digestive system manifests itself in a specific way, all these diseases arise from the imbalance between the generation of the reactive intermediates (especially reactive oxygen species) and the antioxidant defense system. Annual incidence and mortality statistics of gastrointestinal diseases worldwide emphasize the urgent need to find an effective and non-invasive treatment method to overcome these life-threatening problems. Therefore, in the next step, a variety of nanomedicurfines developed to treat these diseases and their effect mechanisms were investigated precisely. Furthermore, the most important nanomedicines responsive to endogenous and exogenous stimuli were evaluated in detail. This review could pave the way to open a new horizon in effectively treating gastrointestinal diseases.

Keywords: gastrointestinal diseases; oxidative stress; nanomedicine; stimuli-responsive nanoparticles; reactive oxygen species

check for updates

Citation: Rezvani, M. Oxidative Stress-Induced Gastrointestinal Diseases: Biology and Nanomedicines—A Review. *BioChem* **2024**, *4*, 189–217. https://doi.org/10.3390/biochem4030010

Academic Editor: Nidhi Jalan-Sakrikar

Received: 26 April 2024
Revised: 5 July 2024
Accepted: 22 July 2024
Published: 29 July 2024

Copyright: © 2024 by the author. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (https://creativecommons.org/licenses/by/4.0/).

1. Introduction

Oxidative stress (OS) in living organisms occurs arising from the excessive generation of reactive intermediates such as reactive oxygen species (ROS), reactive nitrogen species (RNS) and reactive sulfur species (RSS) that cannot be neutralized by the endogenous antioxidant system [1]. ROS at appropriate physiological concentrations plays a prominent role in intracellular homeostasis, gene expression, cell proliferation and differentiation, signal transduction and apoptosis [2]. Various external triggers including trans-fatty acids and acrylamide in processed foods, radiation, alcohol, drugs, organic solvents, heavy metals, smoking and pollutants can induce OS [3]. Plasma membrane, cytosol, lysosomes, peroxisomes, endoplasmic reticulum and mitochondria are intracellular sources of chemical reactive intermediates. Chemical reactions for ROS generation are catalyzed by a variety of enzymes including the enzymes of the mitochondrial electron transport respiratory chain (the most important ones) and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (with homologs of dual oxidase (DUOX) 1-2 and NOX1-5), cyclooxygenases (COXs), lipoxygenases (LOXs), xanthine oxidase (XO), phospholipase A2, glucose oxidase, myeloperoxidase (MPO) and uncoupled nitric oxide synthase (NOS) [4]. Hydroxyl radical ($^{\bullet}OH$), superoxide anion radical ($O_2^{\bullet-}$), hypochlorous acid (HOCl) and hydrogen peroxide (H_2O_2) are the major ROS, and nitric oxide (NO) and peroxynitrite radicals ($ONOO^-$) are the main RNS. Amongst the RSS, $GSSG^{\bullet-}$, reactive sulfur substances (SO_2, SO_3) and reactive sulfane species (RSR) are the most important

ones [5,6]. Endogenous antioxidants can counteract and remove the reactive species by oxidizing themselves, delaying/inhibiting the oxidation of other compounds, chelating metal ions and blocking radical formation. Superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx) and glutathione reductase (GSR) are the major endogenic enzymatic antioxidants [7]. Glutathione (GSH) and thioredoxin (Trx) are the prominent non-enzymatic endogenous antioxidants [8]. GSR converts oxidized glutathione (GSSG) to GSH by transferring electrons from NADPH to GSSG [9]. The thioredoxin system is composed of Trx and thioredoxin reductase (TrxR) [10]. Figure 1 demonstrates the generation of reactive intermediates and the function of the antioxidant defense system under normal physiological conditions. The imbalance between ROS generation and the neutralizing ability of the antioxidant system can cause various diseases resulting from damage to the vital molecules and cellular structures including DNA, proteins and lipids [11].

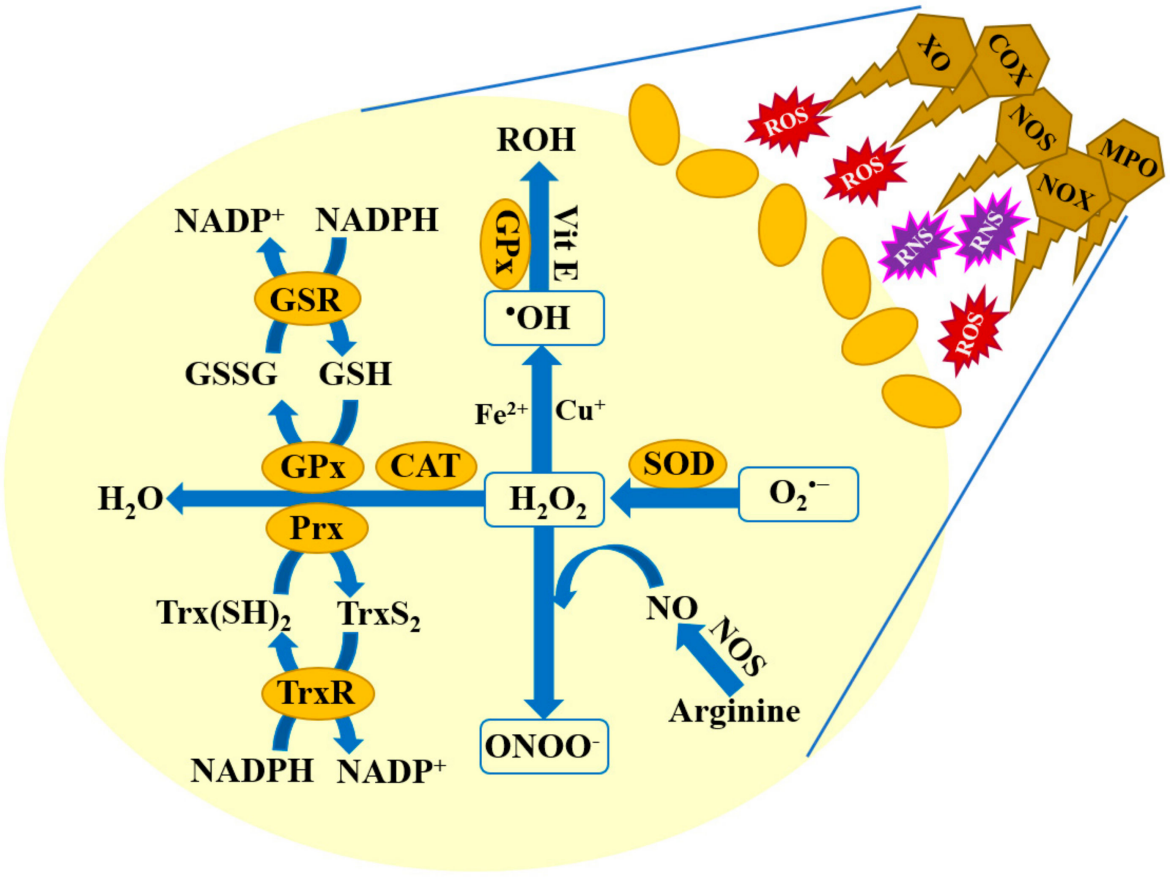


Figure 1. Generation of the reactive intermediates and the mechanisms of their neutralization by the antioxidant defense system. The orange ovals illustrate the antioxidant enzymes, the rectangles demonstrate the reactive intermediates and the brown hexagons refer to some of the enzymes generating reactive oxygen species (ROS) and reactive nitrogen species (RNS): NOX: nicotinamide adenine dinucleotide phosphate oxidase, NOS: nitric oxide synthase, COX: cyclooxygenase, XO: xanthine oxidase and MPO: myeloperoxidase. The generated $O_2^{\bullet -}$ can be converted to H_2O_2 by superoxide dismutase (SOD). H_2O_2 can be converted to $^{\bullet}OH$ through the Fenton reaction with Fe^{2+}, which can initiate lipid peroxidation. Glutathione peroxidase (GPx) and vitamin E (Vit E) can neutralize the free radicals and result in ROH formation as the product. Nitric oxide (NO) can be generated from arginine by NOS, which results in $ONOO^-$ production through its reaction with H_2O_2. Catalase (CAT), peroxiredoxin (Prx) and GPx can convert H_2O_2 to water. Glutathione reductase (GSR) and thioredoxin reductase (TrxR) keep glutathione (GSH) and thioredoxin (Trx) in their reduced forms by transferring the electrons from NADPH to their oxidized forms. GSSG is the oxidized form of GSH and $Trx(SH)_2$ and $TrxS_2$ are the reduced and oxidized states of Trx, respectively.

ROS can activate the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway, which can contribute to regulating the generation of proinflammatory cytokines and the inflammatory response. ROS (especially H_2O_2) can stimulate the activation of NF-κB by promoting IkBα phosphorylation and its subsequent degradation, which causes the transrelocation of the dimerized NF-κB proteins into the nucleus to start the transcription of their target genes. It can promote the expression of proinflammatory cytokines including Interleukin-8 (IL-8), IL-1 and tumor necrosis factor-α (TNF-α), and lead to inflammation and carcinogenesis [12]. Another ROS-activated pathway is mitogen-activated protein kinase (MAPK). This pathway is activated by mitogen cascades including JNK (c-Jun N-terminal kinases), p38 (p38 kinase), ERK1/2 (offline cell-related kinases) and BMK1/ERK5 (significant MAP kinase 1 pathway). During the OS, H_2O_2 induces the oxidation of the cysteine residue of Trx, resulting in apoptosis signal-regulated kinase-1 (ASK-1) dissociation for activating JNK and p38 cascade-inducing apoptosis. Translocation of the activated MAPKs into the nucleus and phosphorylation of transcription factors can lead to the generation of pro-inflammatory mediators, enhancing the inflammatory response. Excessive ROS demonstrates a positive correlation with arresting the cell cycle, senescence and apoptotic condition through the signaling cascade of ASK1/JNK/p38 [13].

The gastrointestinal (GI) tract, as a passageway for delivering, swallowing, digesting and absorbing food and liquids and excreting waste from the body, consists of the oral cavity, esophagus, stomach, small and large intestines and rectum. The GI tract plays a prominent role in modulating energy homeostasis, providing vital nutrition, defending against infectious stimuli, secreting hormones and neurotransmitters and regulating body physiology [14]. All parts of the GI tract must be in normal condition to carry out their work. Otherwise, the food cannot be processed properly, and the health is adversely affected. OS-induced disease and inflammation in the GI tract can effectively influence the total homeostasis of the body, threatening life.

Conventional medical treatments including drug administration and clinical surgical solutions have possessed several shortcomings including the need to use high doses, poor bioavailability and the lack of effective targeted delivery of drugs, off-target toxicity and adverse side effects, drug resistance, low therapeutic efficacy and high recurrence rate. Nanomedicines with large surface-to-volume ratios, nanoscale dimensions and biocompatibilities have been developed to overcome the obstacles in treating OS-induced diseases. High drug loading capacity, providing synergistic effects of multi-loading, prolonging drug circulation time, specific targeting capability, improving bioavailability, promoting drug accumulation at diseased sites, controlled drug release and reducing drug resistance and systemic toxicity are some benefits of using nanomedicines in treating the GI diseases [15]. Furthermore, these nanomedicines can be designed and developed to respond to endogenous/exogenous stimuli for on-demand controlled release in the target tissues. Active targeting and passive targeting are two categories of targeting mechanisms. Active targeting provides selective drug delivery to the target area through affinity between nanomedicine ligands and the receptors of the target cells, which facilitates the internalization of nanomedicines and the selective release of the drugs into the target cells. Passive targeting exploits the differences between the tumor tissues and the normal ones. Blood vessels of the tumor tissue have large gaps between their endothelial cells, through which nanomedicines can leak and penetrate the tumor. Because of the poor lymphatic drainage, the accumulated nanomedicines are retained within the tumor microenvironment for a prolonged duration, providing sustained drug delivery. This is known as the enhanced permeability and retention (EPR) effect [16]. A wide range of nanomedicines has been developed to treat the GI disorders caused by OS, including nanovesicles, micelles, carbon nanotubes, polymeric nanoparticles (NPs), quantum dots, silica NPs, exosomes, dendrimers, lipid NPs and metallic (such as gold (Au), copper (Cu) and silver (Ag)) NPs. This study aimed to provide a comprehensive overview of how OS affects the biology and pathophysiology of each part of the GI tract from the mouth to the anus, involving specific molecular mechanisms and pathways and the nanomedicines developed to combat

diseases. Some of the most common diseases caused by OS in the GI tract are illustrated in Figure 2, which will be discussed in detail in the following sections.

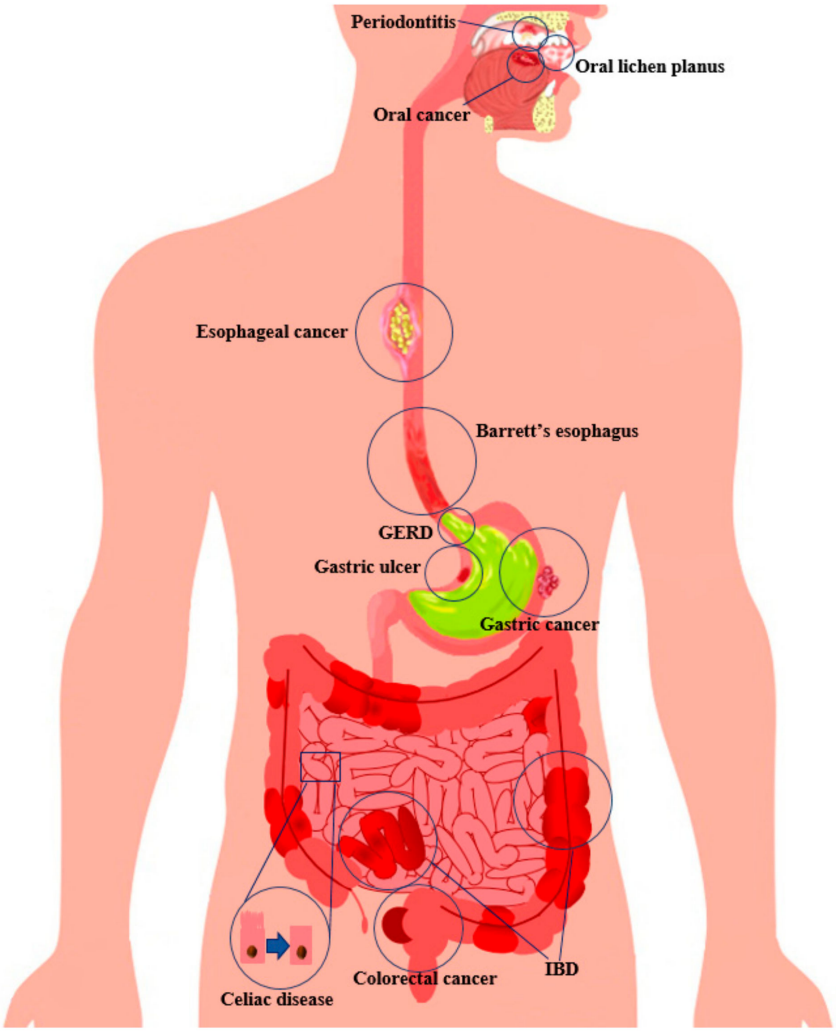


Figure 2. The most common oxidative stress-induced gastrointestinal diseases. GERD and IBD are the abbreviations of gastroesophageal reflux disease and inflammatory bowel disease, respectively.

2. Methodology

English language articles published from 2016 to 2024 were selected from online databases, particularly PubMed, MEDLINE, Google Scholar and Scopus. Publications on OS-induced GI disease, the involved mechanisms and nanomedicines developed for the treatment of GI diseases were separately searched for each of the related diseases including oral lichen planus, oral cancer, periodontitis, gastroesophageal reflux disease, Barrett's esophagus, esophageal cancer, *H. pylori*-induced gastric diseases, gastric ulcers, gastric cancer, celiac disease, inflammatory bowel disease and colorectal cancer. Each of the found articles was independently screened for quality, validity and eligibility, and finally, the best papers were precisely selected for the preparation of this review. The inclusion criteria were longitudinal studies, *in vitro* and *in vivo* studies, observational studies, book chapters, review articles, case reports and systematic reviews with special attention to more recent works published in high-impact international journals. The exclusion criteria included conferences, expert opinions, letters to the director, compendiums and symposia.

3. OS-Induced GI Diseases and Developed Nanomedicines

3.1. Oral Diseases

The mouth is the first part of the GI tract and is composed of the teeth (surrounded with the gums), tongue and salivary glands as the accessories. OS-induced oral diseases including oral cancer, lichen planus and periodontitis impose a significant economic burden on society and cause high mortality and morbidity worldwide [17,18]. In many cases, the colonization of bacteria in the oral cavity can stimulate the defense systems to combat pathogens by ROS generation. However, ROS targets both microorganisms and host cells [19]. In addition to salivary enzymes such as CAT, SOD and peroxidase, the non-enzymatic molecules including uric acid, glutathione, ascorbic acid and albumin play antioxidant roles. Among these molecules, most of the total antioxidant capacity is provided by uric acid as the main salivary antioxidant, which plays a crucial role in monitoring OS [20]. In a weakened antioxidant system, OS in the mouth results in various inflammatory diseases, which can affect mucosal, gingival and even underlying bone tissues. One of the relatively common chronic inflammatory diseases with unknown etiology is oral lichen planus (OLP), which can be developed by the activation of signaling pathways and autoimmune reactions caused by excessive OS products. Despite the unclear mechanism of OS in OLP incidence, various studies have revealed that ROS-induced OS can especially contribute to the inflammatory signaling and metabolic dysregulation of OLP [21]. The detection of a decreased level of total antioxidant activity and increased levels of salivary ROS, malondialdehyde (MDA) and NO in OLP patients compared to the healthy control group are the proofs for this claim [22,23]. Research demonstrated several possible pathomechanisms for ROS in OLP. The antigen-specific mechanism through lipid peroxidation and antigen-nonspecific mechanism via the Fas/FasL pathway, Bcl-2 family proteins, matrix metalloproteinase-9, TNF-α, granzyme B and p53 participate in OLP pathogenesis, leading to lymphocyte infiltration and keratinocyte apoptosis. On the other hand, ROS can cause tissue damage and the release of DAMPs (damp-associated molecular patterns), which can lead to inflammation and tissue dysfunction. OS in OLP exhibits a close correlation with the activation of NF-κB [21]. A current treatment strategy for OLPs is the local administration of corticosteroids, often for a long period and a subsequent increasing dose or systemic applications in recalcitrant cases, which cannot show necessary effectiveness many times and are followed by side effects [24]. Mucus as a strong barrier prevents the adherence and penetration of the topical corticosteroids prescribed in the forms of gel, lotion, cream and ointment to reach the epithelial surface and causes their rapid clearance during the first seconds of the application [25]. The use of nanoformulations has demonstrated promising results in this regard, possessing biodegradability and mucoadhesiveness. Sadeghian et al. revealed the effect of mucoadhesive nano-triamcinolone acetonide gel on the recovery acceleration of OLP, pain severity, lesion size and appearance compared to the conventional gel formulation. However, they reported statistically significant improvement just for ulcer appearance on the 6^{th} and 14^{th} days of treatment with the nanoformulation in comparison to the non-nano one [24]. Studies have shown the healing effects of nanoformulations containing curcumin on oral mucosal lesions. Curcumin exposes its antioxidant and anti-inflammatory activities by preventing free radical-induced damage and the downregulation of the pro-inflammatory cytokines (such as TNF-α, IL-8, IL-6 and IL-1), inflammatory transcription factors (like NF-κB) and some enzymes (such as LOX, COX-2 and COX-5) [26]. Kia et al. proposed oral nanomicellar soft gel capsules loaded with curcumin as an alternative strategy in treating OLP patients with contraindications on the use of corticosteroids and reoccurrence of the disease. They reported a reduction in lesion size, burning sensation and pain severity in OLP patients by oral administration of nano-curcumin with no significant differences with the prednisolone administration. [27]. Similar results were obtained by oral administration of the nanomicelle containing curcumin which significantly improved the clinical appearance of oral lesions and decreased pain intensity in OLP patients [28]. Combination therapy with 1% nanomicelle curcumin gel and 0.1% triamcinolone acetonide caused a higher reduction in the reticular-erosive-ulcerative clinical score and higher effi-

cacy in reducing the extent of oral lesions than the triamcinolone acetonide alone in OLP patients [29]. Popovska et al. recommended the topical application of the nano-bio fusion gingival gel, a nanoemulsion form of propolis and vitamins E and C, as a substitute for the topical or systematic administration of steroids in the treatment of OLP. They reported significant clinical improvements during 5 weeks of treatment with stable achievements even after 3 months [30].

Dysbiosis in periodontal tissues results in periodontitis, destructing the supporting structures of teeth, chronic inflammation and tooth loss. OS plays a vital role in the pathogenesis of periodontitis. Gram-negative anaerobic bacteria on the dental plaque can activate neutrophils, which causes an excessive release of ROS through the NADPH oxidase pathway and subsequent damage of periodontal tissues, apoptosis of gingival fibroblasts, osteoclastogenesis and alveolar bone resorption [31]. ROS can lead to direct damage to periodontal tissues through damaging the nucleic acid (including base pair mutations or strand breaks), the denaturing of proteins, the deactivating of enzymes, the peroxidation of lipids, cell membrane destruction and mitochondrial damage. The analysis of the biological samples prepared from patients with chronic periodontitis showed higher levels of MDA and 8-isoprostane (as biomarkers of lipid peroxidation) and 7,8-dihydro-8-oxoguanine (as a biomarker of OS-mediated DNA damage) [32,33]. Furthermore, ROS can lead to periodontal pathogenesis by regulating the signaling pathways of the c-Jun N-terminal kinase (JNK), NOD-like receptor family, pyrin domain-containing protein 3 (NLRP3) inflammasomes and NF-κB. Activated JNK signaling can lead to the E-cadherin dissociation and disruption of the periodontal junctional epithelium. Furthermore, activation of this pathway can lead to the initiation of the apoptosis cascade through the caspase-3-dependent pathway. ROS-mediated NLRP3 inflammasome activation can result in IL-1β secretion and pyroptosis. Excessive levels of IL-1β can lead to periodontal destruction. ROS-induced activation of NF-κB can cause periodontal destruction by triggering inflammatory responses, the expression of pro-inflammatory cytokines and osteoclastic differentiation [34]. Various metal NPs have been developed to treat periodontitis, exhibiting anti-inflammatory, antibacterial and photothermal enhancement effects. ROS generated by metal NPs can damage the bacterial cell membranes and destroy their nucleic acids and proteins. Furthermore, these NPs can physically interact with bacterial cell walls, interrupting the electron transfer. The released positive ions from metal NPs adversely affect bacterial proteins and DNA [35]. Chlorhexidine/metronidazole-conjugated Ag NPs were evaluated for their effects on periodontal diseases. They showed an inhibitory effect on fungi and bacteria and also reduced the concentration of metalloproteinases MMP3 and MMP8 and the generation of the TNF-α, IL-1β, IL-6 and IL-8 [36]. Castangia et al. developed a mouthwash to counteract the OS-induced and bacterial damage in the oral cavity. This mouthwash formulation included quercetin and mint oil co-loaded liposomes improved with glycol and ethanol and demonstrated antioxidant activity against hydrogen peroxide-induced cell damage. The vesicles with 200 mg/mL mint oil in their formulations exerted an antibacterial effect on cariogenic bacteria (*Lactobacillus acidophilus* and *Streptococcus mutans*) [37]. Surfactin-loaded κ-carrageenan oligosaccharides linked cellulose nanofibers NPs diminished the generation of ROS and pro-inflammatory cytokines and exhibited an anti-inflammatory effect on lipopolysaccharide (LPS)-stimulated human gingival fibroblast cells. Furthermore, these NPs induced OS, reduced the viability of *Pseudomonas aeruginosa* and *Fusobacterium nucleatum* and prevented biofilm formation. However, these results were obtained from the *in vitro* studies and needed to be evaluated by the animal clinical ones [38]. Local injection of the curcumin-loaded NPs reduced the inflammatory infiltrate and osteoclast numbers and completely prevented bone resorption in the LPS-induced periodontal rat model. These NPs attenuated the activation of NF-κB and p38 mitogen-activated protein kinases in the gingival tissues [39].

Reduced antioxidants and increased lipid peroxidation have also been reported in oral cancers, indicating the OS contribution to this disease [32]. Furthermore, ROS-induced OS can damage DNA, proteins and lipids to develop oral cancer [40]. Oral squamous cell

carcinoma (OSCC) is amongst the most common cancers worldwide, in which OS and the accumulation of ROS play key roles in carcinogenesis and progression. An overexpression of LOX, COX, NOX and NOS in oral cancer leads to an increase in the reactive intermediates (ROS and RNS) levels, which regulates the activity of NF-κB, p53 and STAT (signal transducer and activation of transcription), affecting cancer progression [41]. A variety of NPs have been developed to treat oral cancer. Shi et al. developed hyaluronic acid (HA)-based mesoporous silica NPs for the delivery of TH287 (protein MutT homolog 1 inhibitor) and P-glycoprotein 1 siRNA to treat OSCC. These NPs possessed a controlled release of the drug and uptake by CAL27 cells, an inhibitory effect on the function of P-glycoprotein 1 and a killing effect on oral cancer tissue. Treating the CAL27 xenograft model with NPs caused a significant reduction in the tumor burden in comparison to the free TH287 and control [42]. Arabic gum-encapsulated Au NPs demonstrated a reduction in cell viability, c-Myc antibody levels and the expression of hypoxia-regulating miRNAs (miR-21 and miR-210). They suppressed the expression of the hypoxia-inducible factor-1α protein, showed a dose-dependent inhibitory effect on hypoxia in CAL27 and caused death in tongue squamous carcinoma cells [43].

3.2. Esophageal Diseases

Gastroesophageal reflux disease (GERD), Barrett's esophagus (BE), eosinophilic esophagitis and esophageal cancer are the most common diseases induced by OS in the esophagus. Repeated backflow of the stomach acid and other gastric contents into the esophagus causes esophagitis. This problem is called GERD, which is characterized by regurgitation and heartburn [44]. Studies have revealed the involvement of OS in the development and progression of GERD, which in turn plays a pivotal role in the induction of other OS-related esophageal diseases [45]. As shown in Figure 3, GERD can lead to BE and replacement of the normal esophageal squamous epithelium with metaplastic columnar epithelium that may develop into esophageal adenocarcinoma, a rare cancer [46].

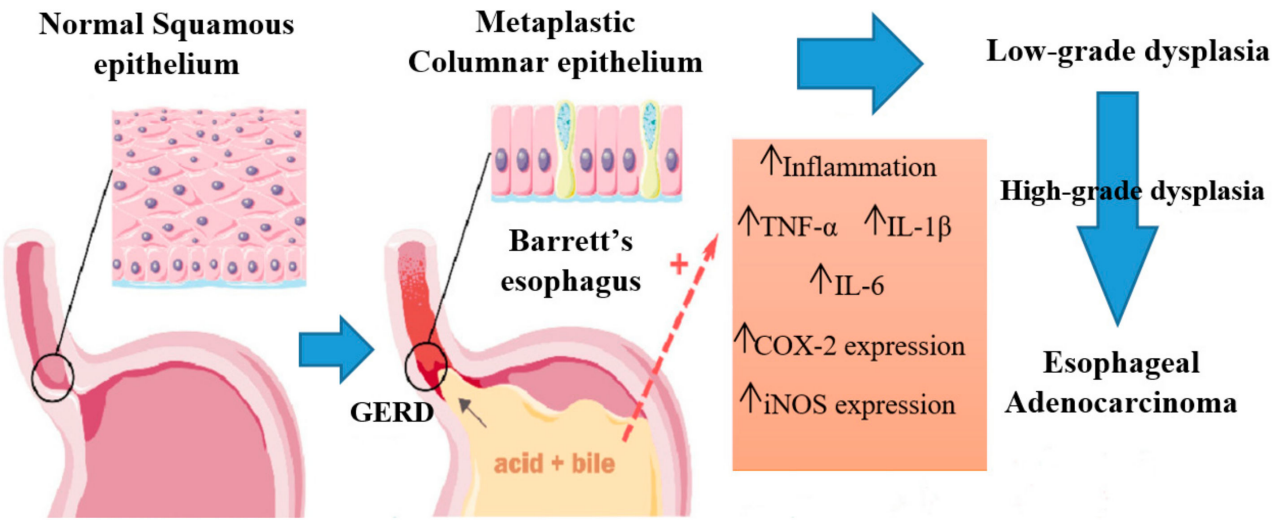


Figure 3. Gastroesophageal reflux disease (GERD) and its consequences as Barrett's esophagus and esophageal adenocarcinoma. TNF-α: tumor necrosis factor-α, IL-1β: interleukin-1β, IL-6: interleukin-6, COX-2: cyclooxygenase-2 and iNOS: inducible nitric oxide synthase. Reproduced from [46].

Unconjugated bile acids as potent COX-2 inducers and acidic pH cause ROS increase and the stabilization of HIF-2α (hypoxia-inducible factor 2 alpha) in BE. The inflammatory response to reflux injury is regulated by HIF-2α in association with NF-κB signaling. The activation of NF-κB in the distal esophagus causes persistent inflammation. From esophagitis to BE and esophageal adenocarcinoma, the levels of IL-1β, IL-8 and NF-κB increase, which results in epithelial cell proliferation, apoptosis inhibition and carcinogenesis. IL-6 is

another pivotal cytokine in the BE pathogenesis. The generation of IL-6 in the metaplastic epithelium activates and translocates STAT3 to the nucleus, which leads to the synthesis of Bcl-xL and Mcl-1 as antiapoptotic proteins in cancer cells. The activation and interaction of NF-κB and IL-6/STAT3 pathways results in persistent inflammation and cancer progression [47,48]. In BE, Rho kinase ROCK2 is activated in a calcium-dependent manner and causes the overexpression of NOX5 and NOX5-S, which leads to the overproduction of $O_2^{\bullet -}$ and H_2O_2, respectively. SOD inactivation and lipid peroxidation have been reported in BE. The production of ROS is enhanced by esophageal epithelial cells under high gastric acid, which activates macrophages, platelet-activating factor and proteinase-activated receptor 2 and causes OS, inflammation and mucosal damage [49]. Preventing the incidence of GERD has been evaluated as an effective treatment strategy for other OS-induced diseases in the esophagus. Dysfunction of the lower esophageal sphincter (LES) contractility is one of the contributors to GERD pathogenesis. The use of nano-based delivery systems for the controlled release of therapeutic agents to regulate the LES tone or neutralize gastric acid is one of the strategies for effectively treating GERD [50]. Hydrogen sulfide (H_2S), a gastrotransmitter, has been reported as a probable key agent in the regulation of LES contractility [51]. The design and development of the NPs exploiting this regulatory role of H_2S can be a promising approach for treating GERD. The oral delivery of therapeutics to the esophagus faces several challenges including rapid clearance and short transit time [52]. Hammad et al. proposed an alternative to the oral administration of drugs in GERD treatment. Intranasal administration of the surface-modified nanostructured lipid carriers loaded with mosapride citrate showed great potential in enhancing the bioavailability of the drug for treating GERD (4.54-fold more than oral marketed tablets and 2.44-fold more than drug suspension). A strong relationship between the *in vivo* absorption in rabbits and the *in vitro* permeation of the nanostructures across sheep nasal mucosa was shown by a point-to-point correlation [53]. GERD in advanced stages can lead to esophageal cancer. The combined administration of Cu–cysteamine NPs and disulfiram in xenograft nude mice showed a noticeable inhibitory effect on the growth of esophageal tumors. This strategy led to ROS accumulation, cell apoptosis and blocking of the translocation of NF-κB into the nucleus in esophageal squamous cell carcinoma [54]. Zhuang et al. synthesized Cu NPs via an eco-friendly method using the extract of *Mentha piperita* as a reducing/stabilizing agent to treat esophageal cancer and attributed their anticancer effects to their high antioxidant activity [55]. Exploiting the overexpression of PI3K in esophageal squamous cell carcinoma, a combination of the disulfide cross-linked micelle loaded with docetaxel and the disulfide cross-linked micelle loaded with AZD8186 (PI3K inhibitor) was developed for tumor-specific targeting. Evaluating these formulations *in vitro* and in KYSE 70 xenograft mouse models showed potent synergistic anticancer activity of the nanoformulations with reduced hemato-toxicity [56].

3.3. Gastric Diseases

Consumption of alcohol and nonsteroidal anti-inflammatory drugs, smoking, stress and especially *Helicobacter pylori* (*H. pylori*) infection are among the OS-causing factors in the stomach, which can result in gastric inflammation, ulcers and cancer [57]. *H. pylori*, a microaerophilic and Gram-negative bacterium, possesses antibiotic resistance and has been reported as the major inducer of gastric cancer [58]. The lack of an effective treatment and unsuccessful attempts of the host to eradicate the infection of *H. pylori* lead to bacterial colonization and generation of ROS and RNS by epithelial and immune cells. This condition results in continued OS, chronic inflammation, DNA damage and gastric carcinogenesis [59]. Activated gastric epithelial cells produce ROS to combat the *H. pylori* infection. Reactive species such as $O_2^{\bullet -}$ and H_2O_2 are produced by NOX and spermine oxidase, respectively. DUOX2 and NOX1 play vital roles in gastric inflammation caused by *H. pylori*, which can lead to peptic ulcers and gastric cancer [60]. *H. pylori* causes OS in gastric epithelial cells and the activation of several signaling pathways including NF-κB, AMPK (AMP-activated protein kinase), ERK, NF-κB-mediated NLRP3 inflammasomes,

JAK/STAT3, PI3K/Akt/mTOR and PTEN/MAPK. NF-κB can result in angiogenesis and inflammation. AMPK and PI3K/Akt/mTOR are involved in cell survival and cell proliferation, respectively. The JAK/STAT3 pathway contributes to cell migration. ERK is involved in cell proliferation and gene expression. PTEN/MAPK can lead to inflammation and apoptosis [61].

Various nanomedicines have been developed to counteract this bacterial infection and its complications. Metal-based NPs have been studied as long-lasting antimicrobial agents to resolve the antibiotic resistance of *H. pylori*. Three main mechanisms have been proposed for this antibacterial activity of metal NPs including ROS generation, the release of metal ions and contribution to phototherapy [62]. Green synthesized zinc oxide NPs using *Quercus infectoria* gall extracts (as reducing/capping/stabilizing agents) demonstrated potent and dose-dependent antibacterial activity against *H. pylori* with a greater inhibitory effect than clarithromycin and amoxicillin (standard antibiotics). The combination of these nanoformulations with amoxicillin decreased MIC_{90}, demonstrating the synergistic effect between NPs and antibiotics against *H. pylori* [63]. Nanovesicles with an outer lipid layer of rhamnolipid and loaded with cholesterol–PEG, calcitriol and clarithromycin showed antibacterial efficacy against *H. pylori* in the classical infected mice model. These vesicles could reach the infected region by rapidly penetration through the mucosal layer. They demonstrated their anti-*H. pylori* effect by destroying the bacterial biofilms, exposing the interior bacteria, killing dispersed bacteria, preventing residual bacteria from re-adhesion and blocking the regeneration of biofilms. These nanovesicles activated downstream immune responses by releasing cholesterol–PEG from collapsed vesicles, repairing lipid rafts and reconstructing cytokine receptors. Furthermore, they killed intracellular bacteria by contributing to the regulation of H^+ and Ca^{2+} balance and restoring lysosomal acidification and degradation capabilities [64]. Activity of NOXs and especially infiltration of the neutrophils and leukocytes lead to the overproduction of $O_2^{\bullet -}$ and H_2O_2 in peptic ulcers. Damage in gastric mucosa is often followed by a decrease in H_2S levels. Therefore, one of the therapeutic strategies for gastric ulcers could be the administration of H_2S [65]. Studies have shown the antioxidative and anti-inflammatory effects of H_2S. Chitosan NPs loaded with tetrathiomolybdate and omeprazole released H_2S and molybdenum in a sustained manner and showed a healing effect on gastric ulcers in rat models, which was approved by the reduced gastric juice content, stimulated catalase activity and increased nitrite levels and histopathological evaluations [66]. The other member of the gasotransmitter family, carbon monoxide (CO), has also been proposed to treat gastric ulcers. Elsisi et al. reported the gastroprotective and healing effects of CO on gastric ulcers. CO released from its donor (CORM-2) activated the nuclear factor erythroid 2-related factor 2 (NRF2)/heme oxygenase-1 pathway and reduced OS, lipid peroxidation and COX-2 in indomethacin-induced gastric ulcer models. They highlighted that the PEGylated CORM-2 NPs could outperform CORM-2 in prophylaxis against gastric ulcers, indicating the promoted bioavailability of their payloads [67]. Chitosan–bilirubin conjugate NPs demonstrated a protective effect against OS and inflammatory-induced gastric injuries, an inhibitory effect on the secretion of TNF-α and IL-6 and improved cellular uptake. They accumulated in the stomach and provided long-lasting therapeutic effects and anti-ulcer activity in the ethanol-induced acute gastric ulcer model [68]. Metallic nanosystems such as Ag NPs exhibited a protective effect against gastric ulcers in rats, which could be attributed to the capability of NPs to scavenge free radicals and decrease lipid peroxidation and OS. These NPs were prepared using a combination of *Melissa* extract and Arabic gum and reduced ulcer index, MDA levels and Bax protein expression. An increase in the pH of stomach content, mucus secretion, CAT and SOD activities and HSP70 expression was observed upon using Ag NPs [69]. Studies revealed the effect of upregulated spermine oxidase and NOX1 activity in the oxidative damage of DNA and gastric oncogenesis induced by *H. pylori* infection [60,70]. *In vitro* and *in vivo* studies demonstrated the strong efficiency of glucosamine-decorated 7-ethyl-10-hydroxycamptothecin-poly lactic acid-loaded NPs in targeted gastric cancer therapy. Intravenous injection of these NPs into

the MKN45 xenograft mouse model effectively prevented tumor growth. NPs possessed the capability of accumulation in the gastric tumor site through both EPR effect (passive targeting) and specific binding to the overexpressed glucose transporters on the tumor cells (active targeting) with no probable off-target effect and enhanced cytotoxicity against gastric cancer cells [71]. Poly (lactic-co-glycolic acid) (PLGA) NPs loaded with curcumin demonstrated strong anti-gastric cancer and anti-*H. pylori* activity with emphasis on the greater effectiveness of nanocurcumin than the native curcumin [72].

3.4. Intestinal and Rectal Diseases

OS in the lower part of the GI tract can lead to a variety of diseases such as colorectal cancer, inflammatory bowel disease (IBD) and celiac disease [73,74]. In celiac disease, gluten peptides can induce cytotoxic effects on the epithelial cells of the small intestine through OS induction, which causes total villous atrophy (a flat mucosa with no villi) [73,75]. An increase in the ROS level and inducible NOS (iNOS) and COX-2 expression and the activation of NF-κB signaling pathways and inflammatory cascade have been reported in celiac disease [75]. An injection of gliadin-encapsulated PLGA NPs into the celiac disease mouse models effectively caused immune tolerance to gliadin and decreased inflammatory markers and gluten-induced enteropathy [76]. Similar results were reported in another study where gliadin-encapsulated PLGA-antigen NPs inhibited gluten-induced immune activation in celiac patients [77]. These findings revealed that restoring T cell tolerance to gliadin could be used as a promising strategy to treat celiac disease. The administration of an NP-in-microsphere oral system encapsulating IL-15 and tissue transglutaminase-2 silencing siRNA sequences to the polyinosinic/polycytidylic acid-based celiac disease mouse model led to a decrease in the infiltration of neutrophils and expression of pro-inflammatory cytokines. These systems also improved the healing process and restored barrier function in the small intestine [78].

IBD is a complex and multifactorial disease manifesting in relapsing and chronic inflammation at different sites of the GI tract [79]. Despite the unknown exact etiopathology of IBD, the pivotal role of OS in the pathogenesis of IBD has been emphasized by both local and systemic detection of oxidative damages in the intestinal mucosa and peripheral blood leukocytes of the patients, respectively [80,81]. Based on the nature of the histological disorders and the location of the inflammation, IBD can be differentiated into two common types including ulcerative colitis (UC) and Crohn's disease (CD) [82]. In most cases, ulceration and inflammation in UC are limited to the mucosal and submucosal layers of the colon and rectum, while CD can extensively affect the GI tract and lead to inflammation in all wall layers from mouth to anus in a discontinuous fashion. However, the incidence of CD mostly occurs in the perianal site or terminal ileum [83]. The genesis and progression of UC are affected by NOS, ROS, pro-inflammatory cytokines, an increased concentration of MPO and a loss of mucosal antioxidant defense. The iNOS increases the synthesis of NO and stimulates the expression of TNF-α, activates the generation of the intercellular adhesion molecule (ICAM) and P-selectin and causes neutrophil infiltration, leading to cellular damage in the colon [84]. An association has been observed between the elevated activity of Mn-SOD, XO, iNOS and TNF-α in CD patients and decreased antioxidant levels. Memory T cells and major histocompatibility complex class II molecules (MHC) are increased in CD [85]. Despite the similar properties of both types of IBD, $O_2^{\bullet -}$ and $^{\bullet}OH$ plays a prominent role in CD occurrence, while HOCl and H_2O_2 have been reported as major players in the pathophysiology of UC [86]. The overproduction of ROS induced by mitochondrial dysfunction, a complicated balance between redox-sensitive pro-inflammatory pathways (NF-κB and NLRP3 inflammasome) and the adaptive upregulation of GPX2 and Mn-SOD determine the development of IBD [87]. Signaling pathways including extracellular signal-regulated kinase, RTKs, JNK and PKC (protein kinase-C) are activated by ROS, which can result in inflammation in IBD [88]. MAPK pathways have also been reported to be involved in initiating or developing IBD [89]. To overcome the obstacles of efficient IBD treatment, various nano-based strategies have been developed. Polymeric nanocarriers

are amongst the most studied colonic delivery systems. Application of the PEGylated polyesterurethane NPs loaded with infliximab, an anti-TNF-α antibody, resulted in a higher cellular uptake and interaction in inflamed epithelial cells compared with polycaprolactone NPs and PLGA NPs. These NPs reduced the level of cytokines in inflamed monocytes, provided a rapid recovery of the epithelial barrier function and showed good potential to treat GI inflammation [90]. Tragacanth–whey liposomes loaded with gingerol possessed a high protective effect on intestinal cells against hydrogen peroxide-induced damage [91]. Biotechnological hyalonutriosomes fabricated by using the bioactive whey prepared by dark fermentation effectively internalized the colonic cells and showed great potential to counteract OS. The application of these nanoformulations proposed a strategy to promote intestinal health through their antioxidative effect on intestinal cells and proliferative effect on *Streptococcus salivarius*, a human commensal bacterium possessing an inhibitory effect on pathogen-induced inflammatory pathways [92]. Intrarectal administration of HA NPs loaded with budesonide, a second-generation glucocorticoid, diminished MPO activity and TNF-α concentration. These NPs targeted the inflamed tissues via interactions with overexpressed CD44 receptors, relieved inflammation, alleviated colitis and improved endoscopic appearance in an acetic acid-induced colitis rat model [93]. Oral delivery of tacrolimus by using cationic lipid-assisted NPs could alleviate lesions in dextran sodium sulfate (DSS)-induced colitis through the ability of NPs to accumulate in the colon, increase retention time and pass through the enterocytes [94]. Silencing and inhibiting the pro-inflammatory pathways is one of the strategies used to treat IBD and inhibit the development of colorectal cancer. Cationic liposomes loaded with NLRP3 siRNA efficiently delivered siNLRP3 into peritoneal macrophages and prevented activation of the NLRP3 inflammasome. They also exhibited an inhibitory effect on the secretion of IL-18 and IL-1β from macrophages and infiltration of the immune cells. Modulating the macrophage polarization, downregulating the $CD4^+$ T cell production, proper anti-inflammatory effects and alleviating intestinal injury in DSS-induced UC mouse models were achieved by using these nanocarriers [95]. Inflammatory mediator S100A9 correlates with the severity of UC and can be used as a target molecule to treat UC. An evaluation of the macrophage membrane-coated PLGA NPs developed for oral delivery of tasquinimod demonstrated drug accumulation in the inflamed tissue, decreased S100A9 and other cytokines, attenuated the symptoms of UC and reduced systemic toxicity in chemically induced UC mouse models [96]. Immunomodulators and corticosteroids have been employed for the treatment of IBD. However, various systemic side effects and immunosuppression limit their long-term use. 5-aminosalicylate (5-ASA), as a nonsteroidal drug, is commonly prescribed to treat mild to moderate IBD, especially UC [97]. However, a small amount of this therapeutic agent can reach the colon because of its rapid absorption by the small intestine [98]. To overcome this obstacle, various nanocarriers have been developed to deliver the 5-ASAs into the colon. For instance, 5-ASA-loaded silicon dioxide NPs with lower drug dosage showed therapeutic effects similar to high dosages of free drug, improved colonic histopathology scores and disease activity index and decreased the severity of mucosal injury in DSS-induced UC mouse models. Furthermore, lower levels of TNF-α and IL-6 in serum and expression of the related mRNA in colonic mucosa were reported with the administration of these NPs [99]. It has been reported that a combination of ZnO NPs with 5-ASA could improve the therapeutic efficacy of 5-ASA in a DSS-induced colitis mouse model. Metal oxide NPs such as SiO_2 and ZnO NPs have been used for treating IBD. ZnO NPs increased the length of the colon, decreased the histological lesion score and disease activity index and attenuated the colitis in the mouse model. Their therapeutic effect was attributed to their antioxidant and anti-inflammatory properties. They elevated the level of GSH, activated the NRF2 pathway and suppressed IL-1β, TNF-α, MPO, MDA and ROS generation. It was reported that released Zn^{2+} ions from the NPs likely possessed an attenuating effect on colonic injuries [100]. Another common OS-induced disease involving the colon and rectum is colorectal cancer. Activation of the NF-κB and MAPK pathways involves the expression of carcinogenesis-related genes, which increases the risk of colorectal cancer

development [89]. 5-Fluorouracil is a standard chemotherapy drug for colorectal cancer. However, its treatment efficacy is hindered by its short half-life and rapid metabolism. The development of nanoformulations for loading this therapeutic agent has been proposed as a solution to overcome this limitation. Intragastric administration of bacteria bioinspired NPs composed of zinc gallogermanate mesoporous silica coated with *Lactobacillus reuteri* biofilm was carried out to target the colorectal tumor by 5-fluorouracil. Chemotherapy with these nanosystems diminished the number of tumors per mouse by one-half compared to the use of 5-fluorouracil alone. The targeted delivery of the drug to the colorectal site was supported by the ability of these NPs to withstand the gastric acid. These nanosystems localized to the colorectal tumor, prevented the tumor growth and systemic toxicity and increased the survival time of mice [101]. PEGylated solid lipid NPs loaded with 5-Fluorouracil caused high toxicity in HCT-116 cells. In subcutaneous xenograft mouse models, these NPs improved the pharmacokinetic parameters of the drug, prevented the growth of the tumor and downregulated the expression of human epidermal growth factor receptor 2, a key oncogenic driver in the progression of colorectal cancer [102].

3.5. Stimuli-Responsive Nanomedicines for Treatment of OS-Induced GI Diseases

In recent decades, a variety of nanomedicines have been developed and characterized for treating GI diseases, which can react to stimuli in a special predictable manner. This reaction can be in response to the exogenous (laser irradiation, ultrasound, magnetic field, changes in temperature) or endogenous (ROS, changes in pH values) stimulus or a combination of them. OS-induced diseases in the GI tract are characterized by an excessive level of ROS arising from an imbalance between ROS generation and the antioxidant system. Therefore, various ROS-responsive nanomedicines have been developed to treat GI diseases, especially for IBD. A prodrug as a pharmacologically inactive compound can be metabolized into a pharmacologically active drug by *in vivo* biotransformation through enzymatic or chemical cleavages [103]. NPs self-assembled from aromatized thioketal-linked budesonide and tempol prodrugs could be hydrolyzed via exposure to H_2O_2 in a time- and concentration-dependent manner. ROS-responsive NPs showed a simultaneous and almost complete release of drugs in inflammatory macrophages. These NPs accumulated in the inflamed colon and enhanced the maximum concentration of the drugs, preventing the expression of proinflammatory cytokines and oxidative mediators and relieving colitis in the IBD mouse model [104]. D-α-tocopherol polyethylene glycol succinate-b-poly(β-thioester) copolymer NPs loaded with luteolin alleviated the UC symptoms in the DSS-induced colitis murine model. They suppressed TNF-α, IL-6, IL-17A and interferon-γ and upregulated IL-4, IL-10 and GSH. A decrease in the numbers of T helper 1 (Th1) and Th17 cells and an increase in the numbers of Th2 and regulatory T cells were observed by the administration of these nanosystems, which regulated the inflammatory environment and accelerated intestinal wound healing. These NPs released the drug through size change in response to ROS due to the thioether bond in the polymer main chain [105].

Another endogenous stimulus for the targeted delivery of nanomedicines is changes in the pH value arising from a different condition in the specific tissues or cells or different parts of the GI tract. Administration of the clustered carbon dot NPs to dental biofilm rodent models reduced the viability of *Streptococcus mutans* without adverse effects on oral microbiota balance. Furthermore, these NPs showed an anti-biofilm activity that could be attributed to the interactions between NPs and bacterial membranes, the excessive production of ROS and the fragmentation of DNA [106]. Some pH-responsive nanodelivery systems have been developed to overcome the difficulties of drug delivery to the esophagus arising from short transit time and rapid clearance. Self-assembled chitosan–eggshell membrane NPs loaded with famotidine showed a controlled drug release up to 12 h at pH 1.2, indicating their great potential to treat GERD [107]. Curcumin and docetaxel co-loaded T7 peptide-modified targeted nanosystems exerted the pH-responsive drug release behavior. They promoted biodistribution to the esophageal tumor, increased the

concentration of drugs in the tumor tissue and led to the synergistic therapeutic effect in the esophageal cancer cells of xenograft mice [108].

The harsh gastric environment leads to physiological obstacles for effectively treating *H. pylori* and the delivery of some therapeutic agents including antibiotics and proteins. The application of nanomotors, as a novel strategy for temporarily neutralizing the harsh acidic environment and adjusting the local physiological parameters, can inhibit decreasing the drug efficacy and avoid irreversible damage. Nanomotors can convert acid fuel into kinetic energy and propulsive force, and they can be an alternative to commonly used proton pump inhibitors. The application of a nanomotor composed of silica nanobottles loaded with Pt NPs, clarithromycin and nano-calcium peroxide in mouse models led to a reduction in *H. pylori* burden by 2.6 orders of magnitude compared with the negative control. The chemical reaction between CaO_2 and gastric fluid led to the rapid consumption of protons, temporarily neutralizing gastric acid. Pt NPs catalytically decomposed the product of this reaction (hydrogen peroxide) to a huge amount of oxygen. The resulting gas efflux through the narrow opening of the nanobottles caused them to push forward, providing maximum prodrug release and efficacy [109]. The pH-responsive NPs composed of Zn-based zeolitic imidazolate frameworks loaded with hydrogen-absorbed palladium were encapsulated in ascorbate palmitate hydrogel and used for treating *H. pylori* infection. The outer hydrogel could target the inflammatory site, was hydrolyzed by matrix metalloproteinase and released NPs. Hydrogen and Zn^{2+} resulted from the decomposition of these NPs by gastric acid, which effectively killed *H. pylori* by disrupting the cell membrane permeability of bacteria by hydrogen, accelerating the entrance of Zn^{2+} into the cells, promoting the cell leakage, interfering with the metabolism of bacterial cells and preventing urease activity. In this nanosystem, gastric acid invasion of the bacteria was accelerated by Zn^{2+}. Released hydrogen from NPs prevented hyperactive inflammatory response by regulating the secretion of inflammatory factors in macrophages, scavenging excessive oxygen free radicals and alleviating OS-induced damages to epithelial cells. It also restored the impaired gastric mucosa by upregulating the expression of mucosal repair protein. This anti-*H. pylori* treatment strategy had no adverse side effects on gut flora homeostasis [110].

Colon targeting via the oral route necessitates developing nanodelivery systems that can release therapeutic agents in a weak basic environment but not in acidic pHs. NPs coated with Eudragit L100, Eudragit S100, chitosan and other pH-responsive polymers can facilitate the delivery of the drug into the lower sites of the GI tract and increase the concentration of the drug in the colon with minimized side effects, which can be used in the effective treatment of IBD. One of the promising treatment strategies for IBD was loading the anti-miR-301a into an oral delivery system developed by using Eudragit S100, HA, PLGA and chitosan (Figure 4). These components ensured the targeted delivery of the payload without its degradation during its journey to the intestine. The epithelial cells and macrophages are the key factors in the progression of intestinal inflammation. Therefore, the CD44 receptor, which is overexpressed on the inflammatory epithelial cells and macrophages, was used as the target for this drug delivery. Eudragit S100 and HA endowed NPs with pH responsiveness and a high affinity to CD44 receptors. Coating the NPs with Eudragit S100 led to minimizing the release of the drug in the stomach. However, increasing the pH in the colon dissolved Eudragit S100 and led to the release of the payload. As shown in Figure 4, HA on the surface of the NPs promoted their cellular uptake through CD44 receptors at the inflamed site. NPs accumulated in the colon and improved the IBD symptoms in DSS-treated mice by relieving inflammation, restoring colon length, repairing the intestinal barrier and reducing the levels of IL-6, IL-1β, TNF-α and MPO [111].

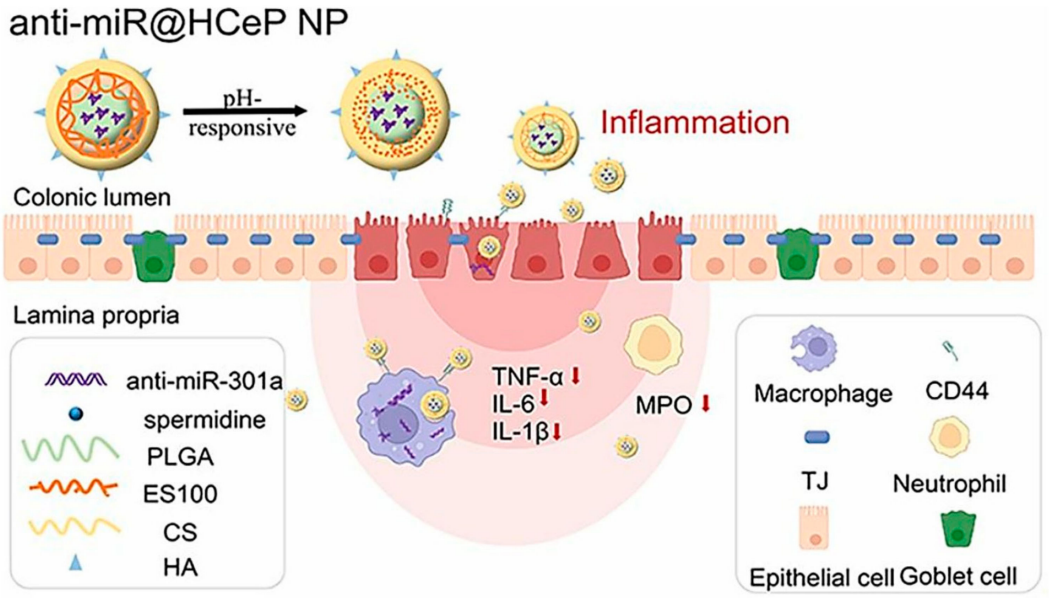


Figure 4. The pH-responsiveness and colon-targeting of anti-miR-301a-loaded nanoparticles with the high affinity of HA to the CD44 receptors at the inflamed site and ES100 dissolvability and releasing the payload in the colon. PLGA: poly (lactic-co-glycolic acid) copolymer, ES100: Eudragit S100, CS: chitosan, HA: hyaluronic acid. TJ: tight junction proteins. Reproduced from [111].

Eudragit–nutriosomes co-loaded with tocopherol and ascorbic acid demonstrated great potential for intestinal-targeted delivery, treating OS-induced diseases and healing intestinal wounds [3]. In another study, hydroxypropyl methylcellulose phthalate was used as a cross-linker in synthesizing chitosan NPs loaded with 5-ASA and berberine to treat UC and inhibit drug release in the upper parts of the GI tract. These NPs exhibited a reduction in the wet weight of the colon and an increase in the length of the colon. They improved the ulcer index and disease activity parameters and led to a proper drug release in the simulated intestinal fluid without release in simulated gastric fluid. They were effective in treating the acetic acid-induced UC in rats [112]. The pH-responsive nanocomposites composed of poly (acrylic acid) brushes anchored on the pore channels of mesoporous silica SBA-15 were designed for the colon-targeted delivery of doxorubicin. In this nanodelivery system, poly (acrylic acid) brushes acted as gatekeepers, which capped the pore outlets and kept the drug encapsulated in acidic pH (gastric environment). In colonic conditions, these brushes were swelled to allow for the release of doxorubicin through the open outlet [113].

The application of responsive nanomedicines to external stimuli such as electromagnetic field, ultrasound and laser irradiation in the treatment of the OS-induced GI disease has brought promising therapeutic results. Magnetic sphingomyelin-containing liposomes encapsulated with cisplatin used a combination of an external magnetic field and an endogenous disease marker (sphingomyelinase enzyme) to release the drug only at the tumor site and at the correct time. They prolonged the survival of the OSCC mouse model [114]. The application of the magnetic microbot was proposed as an effective strategy for treating esophageal cancer, which facilitated targeted locoregional drug delivery in response to the external magnetic field. These magnetic soft microbots were composed of mussel adhesive protein microparticles embedded with iron oxide magnetic NPs and doxorubicin and possessed a potent underwater adhesive capability and long-lasting retention in the hydrodynamic fluid of the esophagus. A sustainable release of doxorubicin and an effective anticancer activity were achieved by these microbots [115].

Sonodynamic therapy (SDT) by combining low-intensity ultrasound irradiation with sonosensitizers to produce ROS can be used as a noninvasive strategy to treat deep target tissues [116]. Verteporfin-preloaded lecithin bilayer-coated PLGA NPs neutralized the secreted virulence factor by *H. pylori*, vacuolating cytotoxin A. Localized ultrasound

(0.5 W/cm^2 for 10 min) exposure of the skin over the stomach of the infected mouse models decreased the *H. pylori* infection by these NPs as strong as the triple therapy (Figure 5).

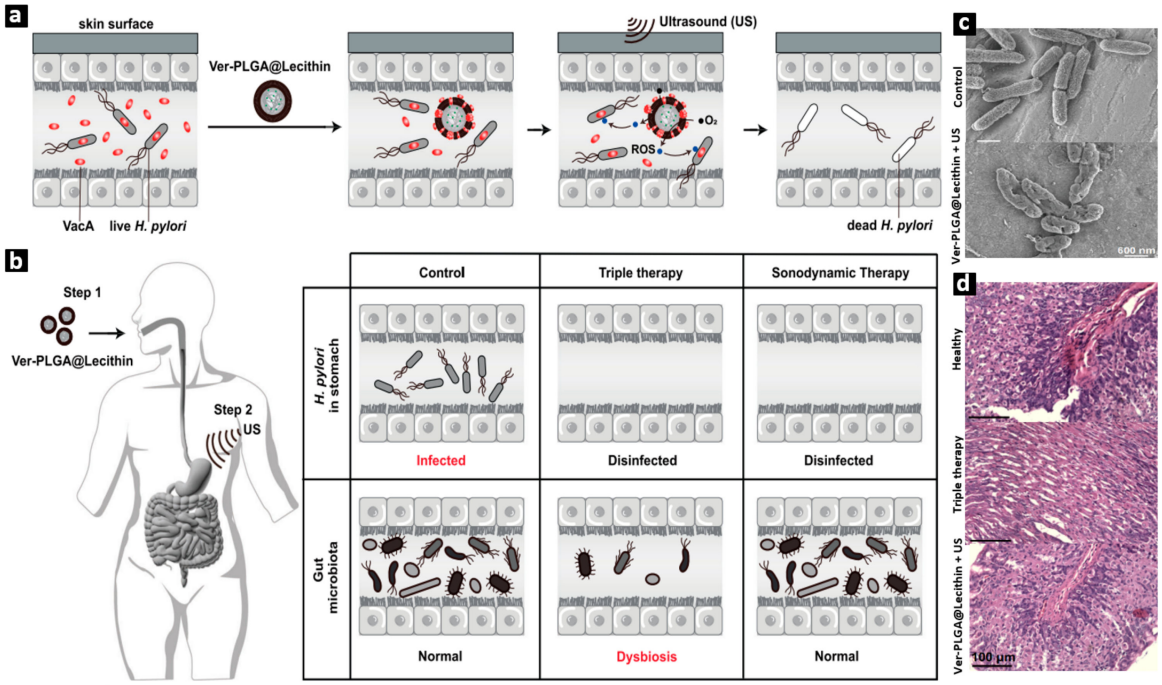


Figure 5. The effect of sonodynamic therapy on gastric *H. pylori* infection: the effect of the Ver-PLGA@Lecithin (verteporfin-preloaded lecithin bilayer-coated PLGA NPs) on VacA (vacuolating cytotoxin A) and *H. pylori* in the absence and presence of US (ultrasound) (**a**); the superior effect of sonodynamic therapy in treating the *H. pylori* infection compared to triple therapy (**b**); *H. pylori* cells after sonodynamic therapy in comparison to the control (**c**); stomach tissues of *H. pylori*-infected mouse models treated with triple therapy or the combination of NPs and US (**d**). Healthy tissues were used as the references. Reproduced from [117].

This effect was attributed to the generation of singlet oxygen ($^1O_2$) (neither $O_2^{\bullet-}$ nor $^\bullet$OH) as the ROS. This strategy revealed useful results in non-antibiotic-based therapy for the eradication of *H. pylori*, indicating not only no disruptive effect on the gut microbiota but also *Lactobacillus* upregulation. Stomach tissues in mouse models treated by this technique showed a similar appearance to the healthy ones. The results of the study revealed that cell apoptosis was increased due to the infection by *H. pylori*. The apoptotic condition became worse by triple therapy, while SDT by NPs decreased the relative ratio of TUNEL-positive cells in the *H. pylori*-infected stomach back to normal [117]. The combination effect of SDT and chemotherapy on the orthotopic colorectal cancer mouse model was evaluated by the oral administration of pH/ultrasonic dual-responsive enteric-coated granules produced via enwrapping the nanoprobes by carboxymethyl chitosan. Nanoprobes were fabricated by co-loading the chlorin e6 and doxorubicin hydrochloride into the mesoporous silicon-coated Au NPs and encapsulating the resulting structure in the folic acid-modified phospholipid. Carboxymethyl chitosan ensured the stability of granules in the gastric acidic environment and rapidly disintegrated in the colorectum, leading to the release of nanoprobes from the granules. Highly expressed folate receptors on the surface of the colon cancer cells facilitated tumor targeting by folic acid. Breaking down of the phospholipids could occur under ultrasound leading to the release of sonosensitizers and chemotherapy drug. Treatment guidance was provided by CT imaging using the Au NPs in mesoporous silicon, which showed the highest concentration of enteric-coated granules 7–9 h post-administration in the colorectum of the mouse model. The results revealed a better anticancer effect of combination therapy than the single treatment [118].

Phototherapy including photothermal therapy (PTT) and photodynamic therapy (PDT) is a light-induced therapeutic strategy using photothermal conversion agents and photosensitizers. In PTT, the energy of light is converted to heat and local hypothermia plays a pivotal role in the therapeutic effect [119]. PDT is used as an effective technique with minimal invasiveness for treating inflammatory and cancerous diseases, in which a photosensitizer is applied to a target site to be exposed to the light of a specific wavelength, preferentially in the red spectral region ($\lambda \geq 600$ nm), and conducts photochemical reactions leading to the generation of singlet oxygen and other ROS [120]. Phototherapy has been studied for the treatment of different GI diseases. Various limitations hinder the *in vivo* application of a single phototherapy method, particularly for deep-targeted cells. Dendritic Au Ag NPs coated with procyanidin–Fe networks photothermally eradicated the biofilm of periodontal pathogens under NIR irradiation and reduced OS and inflammation. They activated the phosphoinositide 3-kinase/protein kinase B signaling pathway, enhanced the polarization of M2 macrophages, upregulated NRF2, scavenged ROS and prevented the NF-κB signaling pathway. The combination of these nanosystems with NIR irradiation was proposed as an effective therapeutic strategy against periodontitis, which could repair periodontal damage by modulating tissue regeneration [121]. The application of doxorubicin–Ag NPs under laser irradiation resulted in the chemo-PTT dual effect on esophagus cancer cells, downregulated the expression of antiapoptotic genes and increased the level of caspase-3 mRNA in nanocomposite-treated cancer cells compared to the control cells [122]. Under NIR laser irradiation, pH-sensitive Au nanostars conjugated with *H. pylori*-antibodies nanoprobes could photothermally eradicate *H. pylori* isolated from clinical patients possessing antibiotic resistance and also in mice models. These nanoprobes did not disturb the intestinal microbiome within therapeutic doses and caused the restoration of gastric lesions to normal status one month after PTT [123]. Intraluminal PDT treatment using fiber-covered esophageal stents prolonged the survival of orthotopic esophageal cancer rabbit models. The electrospun fibers were embedded with albumin-Chlorin e6-manganese dioxide NPs, which were gradually released and diffused into the tumor. Chlorin e6 acted as a photosensitizer, and manganese dioxide significantly increased the generation of the $^1O_2$ by reacting with endogenous H^+ and H_2O_2 at the tumor site to produce O_2 and Mn^{2+}, promoting the PDT efficacy [124]. Combination therapy (photothermal-, photodynamic- and chemo-therapy) using photonic nanoporphyrin micelles loaded with 7-ethyl-10-hydroxycamptothecin (SN-38) exhibited higher antitumor efficacy than single treatments in HT-29 colon cancer xenograft mouse models. The enhancement of *in vitro* antitumor activity of this trimodal therapy was 350 and 78 times more than single phototherapy and single chemotherapy with SN-38, respectively [125]. The combination of PDT and ROS-responsiveness has been extensively studied for OS-induced diseases of the GI tract. Platinum nanozyme-loaded prodrug NPs consisting of thioketal bond-linked camptothecin and 2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide-a were developed for chemo-PDT of colon cancer. In these nanosystems, NIR irradiation (660 nm) in the presence of 2-(1-hexyloxyethyl)-2-devinyl pyropheophorbide-a as a photosensitizer led to ROS generation, which not only possessed a PDT effect but also caused the camptothecin release, providing chemotherapeutic effect. The catalyzing activity of platinum nanozymes decomposed hydrogen peroxide and produced oxygen, promoting PDT and the on-demand release of camptothecin [126]. A similar therapeutic strategy was used for the targeted treatment of oral tongue squamous cell carcinoma. The synthesized PEGlated doxorubicin prodrug through thioketal linkage and cyclo-arginine-glycine-aspartic acid-d-phenylalanine-cysteine peptide modification was used to produce NPs for encapsulating hematoporphyrin (a photosensitizer). NPs internalized cancer cells, and under laser irradiation, they induced ROS production for PDT and the ROS-responsive release of doxorubicin. They could target the tumor and diminish its growth in the mouse model [127].

A summarized list of nanomedicines developed and evaluated for the treatment of GI diseases is illustrated in Table 1.

Table 1. Nanomedicines developed for treating oxidative stress-induced GI diseases.

GI Diseases	Nanomedicines	Stimulus	Study Design/Experimental Cells/Animal Model	Results	Ref.
Oral lichen planus	Gliadin/Ethylcellulose-based nanofibrous mats loaded with mycophenolate mofetil, ZnO NPs and aloe vera	-	*In vitro* study: Inflamed human gingival fibroblasts, *S. aureus* and *E. coli* Clinical study: RCT on patients suffering from OLP lesions	Nanofibrous mats showed antimicrobial activity and anti-inflammatory effects with a decrease in TNF-α, IL-6 and ROS of stimulated human gingival fibroblasts. The symptoms of patients were significantly improved with the mats compared to the treatment with commercial ointment.	[128]
	0.1% triamcinolone acetonide with nanoliposomal carriers in Orabase	-	Clinical study: RCT on patients suffering from OLP lesions with treatment duration of 1 month (3 times a day)	Nanoformulation effectively reduced the lesion size and pain intensity with 33.3% fully resolved lesions after 4 weeks.	[129]
Periodontitis	0.02% Ag NPs gel	-	Clinical study: RCT study on patients with chronic periodontitis for 3 months	The effectiveness of silver NPs gel with SRP was the same as sub-gingival delivery of tetracycline gel in chronic periodontitis patients, proposing a non-toxic therapeutic strategy with no increase in bacterial resistance, no side effects and no need for complicated armamentarium with good acceptance by the patients. Differences in microbiological (colony forming units) and clinical parameters (Plaque Index, Gingival Index, Probing Pocket Depth and Clinical Attachment Level were statistically significant from baseline (just before gel placement) to 3 months of gel application.	[130]
	Epigallocatechin gallate-modified Au NPs-loaded hydrogel	NIR (PTT)	*In vitro* study: *S. aureus*, *E. coli*, human umbilical vein endothelial cells and bone marrow mesenchymal stem cells *In vivo* study: Periodontitis rat model	Application of the NIR light spectrum effectively regulated the release of epigallocatechin gallate, increased the antibacterial effect, stimulated angiogenesis and boosted bone and periodontal tissue regeneration. This strategy caused a preventive effect on *E. coli* and *S. aureus* and its biofilm. The combination of NIR light irradiation and these nanomedicines inhibited the dental plaque biofilm and repaired the alveolar bone in the rat periodontitis model.	[131]

Table 1. Nanomedicines developed for treating oxidative stress-induced GI diseases.

GI Diseases	Nanomedicines	Stimulus	Study Design/Experimental Cells/Animal Model	Results	Ref.
	Methylene blue-loaded PLGA NPs	NIR (PDT)	*In vitro* study: Human dental plaque microorganisms (in planktonic and biofilm phase) *In vivo* study: Clinical pilot study on patients with chronic periodontitis	NP-mediated PDT showed a killing effect on the dental plaque bacteria and biofilms. The gingival bleeding index was more improved in the patients treated by NPs and ultrasonic scaling + SRP + PDT than in the cases just treated by ultrasonic scaling + SRP.	[132]
	Glutathione-stabilized Ag NPs	-	*In vitro* study: Human gingival fibroblast cells (HGF-1) and oral pathogens (*Porphyromonas gingivalis*, *Fusobacterium nucleatum*, and *Streptococcus mutans*	NPs showed an inhibitory effect on the growth of periodontal pathogens, increased the generation of cytokines and activated the inflammatory response in the oral epithelial model.	[133]
Oral squamous cell carcinoma	AE105-decorated dendritic mesoporous silica NPs encapsulating Rose Bengal and ultrasmall $Cu_{2x}S$ NPs	NIR(PTT)/ US(SDT)/pH	*In vitro* study: OSC-19 cells *In vivo* study: OSCC xenografts mouse model	NPs targeted urokinase plasminogen activator receptors overexpressed in the tumor cell membrane and accumulated in the tumor site, and payloads were released by slowly biodegrading dendritic mesoporous silica NPs in the tumor acidic microenvironment and providing synergistic PTT/SDT nanotherapeutics and eradicated tumor cells/xenografts.	[134]
GERD and peptic ulcer	Montmorillonite famotidine/chitosan bio-nanocomposite hydrogels	pH	*In vitro* study: Sheep gastric mucosal tissue	The optimized bio-nanocomposite hydrogel formulation exerted proper mucoadhesion, long-lasting gastric retention time and sustainable release of the famotidine with potential therapeutic effect on GERD and peptic ulcers.	[135]
Esophageal cancer	DOX/Au-coated nanoturf esophageal stent	NIR (PTT)	*In vitro* study: Human Caucasian esophageal carcinoma cell *In vivo* study: Esophageal cancer mouse model	Nanoturfs provided a long-lasting DOX reservoir, sustained release and reproducible hyperthermia induced by localized surface plasmon resonances under NIR irradiation, promoting on-demand drug release (chemo-PTT). An *in vivo* application of thermo- and chemo-stents induced significant esophageal tumor apoptosis by the synergistic effect of the released drug and hyperthermia in response to NIR irradiation.	[136]

Table 1. Nanomedicines developed for treating oxidative stress-induced GI diseases.

GI Diseases	Nanomedicines	Stimulus	Study Design/Experimental Cells/Animal Model	Results	Ref.
	Trastuzumab-decorated cisplatin and fluoropyrimidine co-encapsulated lipid–polymer hybrid NPs	-	*In vitro* study: Human esophageal cancer cell line *In vivo* study: Esophageal adenocarcinoma-bearing xenograft mouse model	Trastuzumab-decorated NPs showed higher uptake by the esophageal cancer cell lines and more cytotoxicity than the non-decorated NPs. Cisplatin and fluoropyrimidine dual-loaded NPs prevented the growth of tumor cells more effectively than the single drug-loaded NPs *in vivo*. The cisplatin to fluoropyrimidine ratio (*w*/*w*) of 1/1 in the preparation of NPs led to the best synergistic effect. This nanosystem caused a sustained drug release with no systemic toxicity or side effects.	[137]
Gastric *H. pylori* infection	Superparamagnetic iron oxide NPs and amoxicillin co-loaded chitosan–poly (acrylic acid) particles	Magnetic field	*In vitro* study: Human gastric adenocarcinoma cell line, mammalian mouse fibroblast cell line, *H. pylori* strains (127–4, 125–54 and 125–57) *In vivo* study: Pathogen-free BALB/c mice, *H. pylori*-infected mouse model	The combination of these nanomedicines with the magnetic field caused an increase in mucopenetration and the residence time of the drug in the stomach for more effective *H. pylori* eradication therapy. Mucoadhesive properties, antibacterial and anti-biofilm activities and the sustained release of amoxicillin from the NPs were reported in this study.	[138]
Gastric cancer	GX1-modified nanostructured lipid carriers loaded with paclitaxel	-	*In vitro* study: Human umbilical vein endothelial cells (HUVEC cells), human gastric carcinoma cells (MKN45 cells), immortalized fetal gastric mucosal cells (GES-1) *In vivo* study: Tumor-bearing nude mouse model	GX1-modified nanocarriers exhibited higher uptake rates in CoHUVEC cells and a greater inhibitory effect on these cells compared to the unmodified nanocarriers and free paclitaxel. The minimum cytotoxicity effect of GX1-modified nanocarriers was observed in GES-1 cells. A potent antitumor effect with lower side effects in the mouse model was achieved by using GX1-modified nanocarriers.	[139]

Table 1. Nanomedicines developed for treating oxidative stress-induced GI diseases.

GI Diseases	Nanomedicines	Stimulus	Study Design/Experimental Cells/Animal Model	Results	Ref.
	AuNPs modified with the AS1411 aptamer and hairpin DNA loaded with DOX	pH/NIR	*In vitro* study: AGS cells, L929 cells	The nanosystem targeted AGS cells through the interaction of AS1411 with nucleolin on the AGS cytomembrane and more selectively entered the AGS cells than the L929 cells. These NPs showed dual responsiveness for laser irradiation and pH (pH 5), indicating more drug release after the internalization of NPs into the lysosomes or tumor intracellular environment. NIR laser irradiation enhanced the anticancer activity of the NPs on AGS cells.	[140]
IBD	Ginger-derived lipid NPs loaded with siRNA-CD98	-	*In vitro* study: Caco-2BBE cells, RAW 264.7 cells, colon-26 cells *In vivo* study: FVB mice	NPs possessed good biocompatibility and highly efficient cellular uptake, specifically targeting the colon and decreasing the expression of the colonic CD98 gene to treat ulcerative colitis.	[141]
	Glycyrrhizic acid-loaded Eudragit S100/PLGA NPs	pH	*In vivo* study: Dextran sodium sulfate-induced colitis mouse model	These NPs possessed anti-inflammatory and antioxidant activity, diminished the colitis progression, improved the retention time of the drug and its accumulation in the inflamed area and alleviated the symptoms of the disease.	[142]
Colorectal cancer	PEGylated hyaluronic acid–DOX NPs	pH	*In vitro* study: CT26 cells *In vivo* study: CT26 tumor-bearing mouse model	NPs increased the circulation time of DOX by 12.5 times and showed strong antitumor activity in the tumor-bearing mice model. They targeted CD44-positive cancer cells and accumulated in the tumor. The PEG shell of the NPs was dissolved in the acidic environment of the tumor and promoted the cellular endocytosis of NPs. The interaction of released DOX with the nucleus inhibited the growth and proliferation of CT26 cells.	[143]
	DOX-loaded magnetic mesoporous silica core-shell nanocarrier modified with gold gatekeepers, PEG and EpCAM aptamer	pH	*In vitro* study: Human colon cancer cell line (HT-29), Chinese hamster ovary (CHO) cell line *In vivo* study: C57BL/6 mice bearing HT-29 tumors	NPs specifically targeted cancer cells and released the drug at the acidic pH as a result of the functionality of aptamer and gold gatekeepers on their surfaces. EpCAM-positive HT-29 cells showed greater uptake of the NPs than EpCAM-negative CHO cells. These nanomedicines prevented tumor growth with a decrease in off-target toxicity in mouse models.	[144]

RCT: randomized clinical trial, SRP: scaling and root planing, US: ultrasound, NIR: near-infrared, PLGA: poly(lactic-co-glycolic acid), PDT: photodynamic therapy, PTT: photothermal therapy, SDT: sonodynamic therapy, GERD: gastroesophageal reflux disease, DOX: doxorubicin, PEG: polyethylene glycol, EpCAM: epithelial cell adhesion molecule.

4. Safety Issues of Nanomedicines

As mentioned previously, traditional pharmaceutical treatments require frequent administration and more drug dosages due to their non-selectivity, which can lead to severe side effects as well. The low solubility, poor biodistribution and disability to penetrate through different biological barriers adversely affect the efficacy of the traditional drug molecules. Targeted delivery, controlled release, reduced toxicity and the promoted solubility, lipophilicity, penetration proficiency, half-life and bioavailability of drugs achieved by the use of nanomedicines have overcome the obstacles of the traditional treatments and enhanced the efficacy of nanomedicine-based treatments [145]. For instance, in the treatment of tumor tissues where traditional pharmaceutical molecules face penetration difficulties, nanomedicines can provide effective penetration, prolonged circulation time and targeted accumulation in the tumor tissue with reduced off-target toxicity [146]. Despite these potent beneficial effects, our knowledge regarding the effects of long-term administration of nanomedicines, their probable toxicity and negative consequences is restricted. It is necessary to pay more attention to the pharmacodynamics and pharmacokinetics aspects of nanodrugs and nanomaterials used in the construction of nanomedicines. Prediction and inhibition of their potential toxicity may not be completely feasible because of their unknown interaction mechanisms with biological tissues, limited detection techniques and the difficulties of monitoring the nanomaterials' metabolism and deposition in the body [147]. Long-term oral administration of nanomedicines even prepared with safe substances approved by the FDA (Food and Drug Administration) may adversely influence gut microbiome homeostasis [148]. Some studies have reported genotoxicity, immunogenicity and irreversible changes and malfunction of the intracellular organelles due to the administration of nanomedicines [149]. Some of the nanomaterials may damage DNA, break its strands, fragment chromosomes, cause point mutations and increase the risk of cancer. Nanomedicines may induce this genotoxicity directly through their interaction with chromosomes or DNA, inhibiting its transcription or replication. They can also act indirectly via releasing toxic ions or ROS generation, which interfere with involved proteins in the genetic functions or oxidize nitrogenous bases and cause their mispairing and mutation [150]. Nanomedicines may cause immunogenicity, regional inflammation or allergic-like responses. The immunogenicity potential of nanomedicines depends on their type, dose and exposure time. The biocompatibility of nanomaterials cannot eliminate the risk of immunotoxicity [151]. Homeostasis of intracellular organelles such as the mitochondria, endoplasmic reticulum and plasma membrane may be negatively affected by nanomedicines. Especially, negatively charged NPs can induce lysosome membrane permeabilization, cytosolic acidification, cellular component disintegration and apoptosis. Positively charged NPs may damage the intracellular organelles and cause cell death [152]. Extensive *in vivo* studies and the use of artificial intelligence can help evaluate and predict the pharmacotoxicological, pharmacokinetic and toxicological characteristics of nanoparticles [153]. In this regard, a multidisciplinary collaboration of scientists, regulatory bodies and clinicians along with efforts for the cost-effective and safe clinical transformation of nanomedicines are required as well. Despite the current activities of WHO (World Health Organization), FDA, EMA (European Medicines Agency) and ICH (International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use), it seems more regulation, standards and supervision are needed to ensure the production of nanomedicines with long-term safety.

5. Concluding Remarks

Despite the critical role of ROS in various physiological processes in the GI tract, excessive generation of ROS that cannot be neutralized by the antioxidant defense system leads to OS and the incidence of different GI diseases. In this regard, the role of prooxidants, reactive intermediates and antioxidants in each part of the alimentary canal was elucidated in the current review paper. Mitochondrial dysfunction, lipid peroxidation and DNA and tissue damage are the consequences of OS in the GI tract. This review revealed

the great strides made in the treatment of GI diseases by application of nanomedicines including targeted and stimuli-responsive NPs. The results of the studies showed that nanomedicines can treat GI diseases by inducing antioxidant activity, anti-inflammatory effects, antibacterial and anti-biofilm activity and tissue repair, and promoting immune tolerance according to the specific conditions of each disease and the related GI environment. However, there is still a long way to go to find a potent strategy for the comprehensive management of GI diseases caused by OS. Further studies are needed to gain more insight into the oxidative pathway involved in the pathogenesis of each GI disease, the therapeutic mechanisms of nanomedicines and their potential risks. Future perspectives for more effective treatment of GI diseases may include the design and development of bioinspired and biomimetic smart multifunctional nanomedicines including nanomotors and nanobots by exploiting the specific environment of different GI organs.

Funding: This research received no external funding.

Data Availability Statement: No new data were created in this study.

Conflicts of Interest: The author declares no conflict of interest.

References

1. Medrano-Macías, J.; Flores-Gallegos, A.C.; Nava-Reyna, E.; Morales, I.; Tortella, G.; Solís-Gaona, S.; Benavides-Mendoza, A. Reactive Oxygen, Nitrogen, and Sulfur Species (RONSS) as a Metabolic Cluster for Signaling and Biostimulation of Plants: An Overview. *Plants* **2022**, *11*, 3203. [CrossRef] [PubMed]
2. Zhang, B.; Pan, C.; Feng, C.; Yan, C.; Yu, Y.; Chen, Z.; Guo, C.; Wang, X. Role of mitochondrial reactive oxygen species in homeostasis regulation. *Redox Rep.* **2022**, *27*, 45–52. [CrossRef] [PubMed]
3. Rezvani, M.; Manca, M.L.; Caddeo, C.; Escribano-Ferrer, E.; Carbone, C.; Peris, J.E.; Usach, I.; Diez-Sales, O.; Fadda, A.M.; Manconi, M. Co-Loading of Ascorbic Acid and Tocopherol in Eudragit-Nutriosomes to Counteract Intestinal Oxidative Stress. *Pharmaceutics* **2019**, *11*, 13. [CrossRef] [PubMed]
4. Juan, C.A.; de la Lastra, J.M.P.; Plou, F.J.; Pérez-Lebeña, E. The Chemistry of Reactive Oxygen Species (ROS) Revisited: Outlining Their Role in Biological Macromolecules (DNA, Lipids and Proteins) and Induced Pathologies. *Int. J. Mol. Sci.* **2021**, *22*, 4642. [CrossRef] [PubMed]
5. Ali, S.S.; Ahsan, H.; Zia, M.K.; Siddiqui, T.; Khan, F.H. Understanding oxidants and antioxidants: Classical team with new players. *J. Food Biochem.* **2020**, *44*, e13145. [CrossRef] [PubMed]
6. Giles, G.I.; Nasim, M.J.; Ali, W.; Jacob, C. The Reactive Sulfur Species Concept: 15 Years On. *Antioxidants* **2017**, *6*, 38. [CrossRef] [PubMed]
7. Al-Sheikh, Y.A.; Ghneim, H.K.; Alharbi, A.F.; Alshebly, M.M.; Aljaser, F.S.; Aboul-Soud, M.A. Molecular and biochemical investigations of key antioxidant/oxidant molecules in Saudi patients with recurrent miscarriage. *Exp. Ther. Med.* **2019**, *18*, 4450–4460. [CrossRef] [PubMed]
8. Ren, X.; Zou, L.; Zhang, X.; Branco, V.; Wang, J.; Carvalho, C.; Holmgren, A.; Lu, J. Redox Signaling Mediated by Thioredoxin and Glutathione Systems in the Central Nervous System. *Antioxid. Redox Signal.* **2017**, *27*, 989–1010. [CrossRef] [PubMed]
9. Dobreva, A.; Camacho, E.T.; Miranda, M. Mathematical model for glutathione dynamics in the retina. *Sci. Rep.* **2023**, *13*, 10996. [CrossRef] [PubMed]
10. Hasan, A.A.; Kalinina, E.; Tatarskiy, V.; Shtil, A. The Thioredoxin System of Mammalian Cells and Its Modulators. *Biomedicines* **2022**, *10*, 1757. [CrossRef]
11. Lee, D.; Jo, M.G.; Kim, S.Y.; Chung, C.G.; Lee, S.B. Dietary Antioxidants and the Mitochondrial Quality Control: Their Potential Roles in Parkinson's Disease Treatment. *Antioxidants* **2020**, *9*, 1056. [CrossRef] [PubMed]
12. Sarmiento-Salinas, F.L.; Perez-Gonzalez, A.; Acosta-Casique, A.; Ix-Ballote, A.; Diaz, A.; Treviño, S.; Rosas-Murrieta, N.H.; Millán-Perez-Peña, L.; Maycotte, P. Reactive oxygen species: Role in carcinogenesis, cancer cell signaling and tumor progression. *Life Sci.* **2021**, *284*, 119942. [CrossRef] [PubMed]
13. Kirtonia, A.; Sethi, G.; Garg, M. The multifaceted role of reactive oxygen species in tumorigenesis. *Cell. Mol. Life Sci.* **2020**, *77*, 4459–4483. [CrossRef] [PubMed]
14. Monteiro, M.P.; Batterham, R.L. The Importance of the Gastrointestinal Tract in Controlling Food Intake and Regulating Energy Balance. *Gastroenterology* **2017**, *152*, 1707–1717.e2. [CrossRef] [PubMed]
15. Liu, Q.; Zou, J.; Chen, Z.; He, W.; Wu, W. Current research trends of nanomedicines. *Acta Pharm. Sin. B* **2023**, *13*, 4391–4416. [CrossRef] [PubMed]
16. Ashique, S.; Garg, A.; Hussain, A.; Farid, A.; Kumar, P.; Taghizadeh-Hesary, F. Nanodelivery systems: An efficient and target-specific approach for drug-resistant cancers. *Cancer Med.* **2023**, *12*, 18797–18825. [CrossRef] [PubMed]
17. Peres, M.A.; Macpherson, L.M.; Weyant, R.J.; Daly, B.; Venturelli, R.; Mathur, M.R.; Listl, S.; Celeste, R.K.; Guarnizo-Herreño, C.C.; Kearns, C.; et al. Oral diseases: A global public health challenge. *Lancet* **2019**, *394*, 249–260. [CrossRef] [PubMed]

18. Subramanian, A.K.; Narayan, V.; Navaneethan, R. Oxidative Stress and Oral Diseases. In *Book Role of Oxidative Stress in Pathophysiology of Diseases*; Springer: Singapore, 2020; pp. 1–12. [CrossRef]
19. Sardaro, N.; DELLA Vella, F.; Incalza, M.A.; DI Stasio, D.; Lucchese, A.; Contaldo, M.; Laudadio, C.; Petruzzi, M. Oxidative Stress and Oral Mucosal Diseases: An Overview. *In Vivo* **2019**, *33*, 289–296. [CrossRef] [PubMed]
20. Čižmárová, B.; Tomečková, V.; Hubková, B.; Hurajtová, A.; Ohlasová, J.; Birková, A. Salivary Redox Homeostasis in Human Health and Disease. *Int. J. Mol. Sci.* **2022**, *23*, 10076. [CrossRef] [PubMed]
21. Li, X.; Wang, Z. Mechanisms of reactive oxygen species in oral lichen planus: A literature review. *Eur. J. Inflamm.* **2022**, *20*, 1721727X221104389. [CrossRef]
22. Dalirsani, Z.; Shirzaiy, M.; Salehian, M. Salivary antioxidants levels in patients with oral lichen planus. *Indian J. Dermatol.* **2022**, *67*, 651–656. [CrossRef]
23. Tvarijonaviciute, A.; Aznar-Cayuela, C.; Rubio, C.P.; Tecles, F.; Ceron, J.J.; López-Jornet, P. Salivary Antioxidant Status in Patients with Oral Lichen Planus: Correlation with Clinical Signs and Evolution during Treatment with *Chamaemelum nobile*. *BioMed Res. Int.* **2018**, *2018*, 5187549. [CrossRef] [PubMed]
24. Rohani, B.; Sadeghian, R.; Golestannejad, Z.; Sadeghian, S.; Mirzaee, S. Comparison of therapeutic effect of mucoadhesive nano-triamcinolone gel and conventional triamcinolone gel on oral lichen planus. *Dent. Res. J.* **2019**, *16*, 277–282. [CrossRef]
25. Jurczyszyn, K.; Trzeciakowski, W.; Kozakiewicz, M.; Kida, D.; Malec, K.; Karolewicz, B.; Konopka, T.; Zborowski, J. Fractal Dimension and Texture Analysis of Lesion Autofluorescence in the Evaluation of Oral Lichen Planus Treatment Effectiveness. *Materials* **2021**, *14*, 5448. [CrossRef] [PubMed]
26. Da Anunciação, T.A.; Garcez, L.S.; Pereira, E.M.; Queiroz, V.A.d.O.; Costa, P.R.d.F.; de Oliveira, L.P.M. Curcumin supplementation in the treatment of patients with cancer: A systematic review. *Braz. J. Pharm. Sci.* **2021**, *57*, e18008. [CrossRef]
27. Kia, S.J.; Basirat, M.; Mortezaie, T.; Moosavi, M.-S. Comparison of oral Nano-Curcumin with oral prednisolone on oral lichen planus: A randomized double-blinded clinical trial. *BMC Complement. Med. Ther.* **2020**, *20*, 328. [CrossRef]
28. Kia, S.J.; Basirat, M.; Estakhr, L. The effect of oral curcumin on pain and clinical appearance of oral lichen planus. *J. Dentomaxillofac.* **2017**, *6*, 1–7.
29. Bakhshi, M.; Gholami, S.; Mahboubi, A.; Jaafari, M.R.; Namdari, M. Combination Therapy with 1% Nanocurcumin Gel and 0.1% Triamcinolone Acetonide Mouth Rinse for Oral Lichen Planus: A Randomized Double-Blind Placebo Controlled Clinical Trial. *Dermatol. Res. Pract.* **2020**, *2020*, 4298193. [CrossRef] [PubMed]
30. Popovska, M.; Fidovski, J.; Mindova, S.; Dirjanska, K.; Ristoska, S.; Stefanovska, E.; Radojkova-Nikolovska, V.; Mitic, K.; Rusevska, B. The Effects of NBF Gingival Gel Application in the Treatment of the Erosive Lichen Planus: Case Report. *Open Access Maced. J. Med. Sci.* **2016**, *4*, 158–163. [CrossRef] [PubMed]
31. Shang, J.; Liu, H.; Zheng, Y.; Zhang, Z. Role of oxidative stress in the relationship between periodontitis and systemic diseases. *Front. Physiol.* **2023**, *14*, 1210449. [CrossRef] [PubMed]
32. Kumar, J.; Teoh, S.L.; Das, S.; Mahakknaukrauh, P. Oxidative Stress in Oral Diseases: Understanding Its Relation with Other Systemic Diseases. *Front. Physiol.* **2017**, *8*, 693. [CrossRef] [PubMed]
33. Mohideen, K.; Chandrasekar, K.; Ramsridhar, S.; Rajkumar, C.; Ghosh, S.; Dhungel, S. Assessment of Oxidative Stress by the Estimation of Lipid Peroxidation Marker Malondialdehyde (MDA) in Patients with Chronic Periodontitis: A Systematic Review and Meta-Analysis. *Int. J. Dent.* **2023**, *2023*, 6014706. [CrossRef]
34. Liu, C.; Mo, L.; Niu, Y.; Li, X.; Zhou, X.; Xu, X. The Role of Reactive Oxygen Species and Autophagy in Periodontitis and Their Potential Linkage. *Front. Physiol.* **2017**, *8*, 439. [CrossRef] [PubMed]
35. Nasiri, K.; Masoumi, S.M.; Amini, S.; Goudarzi, M.; Tafreshi, S.M.; Bagheri, A.; Yasamineh, S.; Alwan, M.; Arellano, M.T.C.; Gholizadeh, O. Recent advances in metal nanoparticles to treat periodontitis. *J. Nanobiotechnol.* **2023**, *21*, 283. [CrossRef] [PubMed]
36. Steckiewicz, K.P.; Cieciórski, P.; Barcińska, E.; Jaśkiewicz, M.; Narajczyk, M.; Bauer, M.; Kamysz, W.; Megiel, E.; Inkielewicz-Stepniak, I. Silver Nanoparticles as Chlorhexidine and Metronidazole Drug Delivery Platforms: Their Potential Use in Treating Periodontitis. *Int. J. Nanomed.* **2022**, *17*, 495–517. [CrossRef] [PubMed]
37. Castangia, I.; Manconi, M.; Allaw, M.; Perra, M.; Orrù, G.; Fais, S.; Scano, A.; Escribano-Ferrer, E.; Ghavam, M.; Rezvani, M.; et al. Mouthwash Formulation Co-Delivering Quercetin and Mint Oil in Liposomes Improved with Glycol and Ethanol and Tailored for Protecting and Tackling Oral Cavity. *Antioxidants* **2022**, *11*, 367. [CrossRef] [PubMed]
38. Johnson, A.; Kong, F.; Miao, S.; Thomas, S.; Ansar, S.; Kong, Z.-L. In-Vitro Antibacterial and Anti-Inflammatory Effects of Surfactin-Loaded Nanoparticles for Periodontitis Treatment. *Nanomaterials* **2021**, *11*, 356. [CrossRef] [PubMed]
39. Zambrano, L.M.G.; Brandao, D.A.; Rocha, F.R.G.; Marsiglio, R.P.; Longo, I.B.; Primo, F.L.; Tedesco, A.C.; Guimaraes-Stabili, M.R.; Junior, C.R. Local administration of curcumin-loaded nanoparticles effectively inhibits inflammation and bone resorption associated with experimental periodontal disease. *Sci. Rep.* **2018**, *8*, 6652. [CrossRef] [PubMed]
40. Iqbal, M.J.; Kabeer, A.; Abbas, Z.; Siddiqui, H.A.; Calina, D.; Sharifi-Rad, J.; Cho, W.C. Interplay of oxidative stress, cellular communication and signaling pathways in cancer. *Cell Commun. Signal.* **2024**, *22*, 7. [CrossRef]
41. Ionescu, C.; Kamal, F.Z.; Ciobica, A.; Halitchi, G.; Burlui, V.; Petroaie, A.D. Oxidative Stress in the Pathogenesis of Oral Cancer. *Biomedicines* **2024**, *12*, 1150. [CrossRef]
42. Shi, X.-L.; Li, Y.; Zhao, L.-M.; Su, L.-W.; Ding, G. Delivery of MTH1 inhibitor (TH287) and MDR1 siRNA via hyaluronic acid-based mesoporous silica nanoparticles for oral cancers treatment. *Colloids Surf. B Biointerfaces* **2019**, *173*, 599–606. [CrossRef] [PubMed]

43. Gamal-Eldeen, A.M.; Baghdadi, H.M.; Afifi, N.S.; Ismail, E.M.; Alsanie, W.F.; Althobaiti, F.; Raafat, B.M. Gum arabic-encapsulated gold nanoparticles modulate hypoxamiRs expression in tongue squamous cell carcinoma. *Mol. Cell. Toxicol.* **2021**, *17*, 111–121. [CrossRef]
44. Chapelle, N.; Ben Ghezala, I.; Barkun, A.; Bardou, M. The pharmacotherapeutic management of gastroesophageal reflux disease (GERD). *Expert Opin. Pharmacother.* **2021**, *22*, 219–227. [CrossRef] [PubMed]
45. Franceschelli, S.; Gatta, D.M.P.; Pesce, M.; Ferrone, A.; Di Martino, G.; Di Nicola, M.; De Lutiis, M.A.; Vitacolonna, E.; Patruno, A.; Grilli, A.; et al. Modulation of the oxidative plasmatic state in gastroesophageal reflux disease with the addition of rich water molecular hydrogen: A new biological vision. *J. Cell. Mol. Med.* **2018**, *22*, 2750–2759. [CrossRef] [PubMed]
46. Bilski, J.; Pinkas, M.; Wojcik-Grzybek, D.; Magierowski, M.; Korbut, E.; Mazur-Bialy, A.; Krzysiek-Maczka, G.; Kwiecien, S.; Magierowska, K.; Brzozowski, T. Role of Obesity, Physical Exercise, Adipose Tissue-Skeletal Muscle Crosstalk and Molecular Advances in Barrett's Esophagus and Esophageal Adenocarcinoma. *Int. J. Mol. Sci.* **2022**, *23*, 3942. [CrossRef] [PubMed]
47. Hu, Y.; Ye, X.; Wang, R.; Poon, K. Current research progress in the role of reactive oxygen species in esophageal adenocarcinoma. *Transl. Cancer Res.* **2021**, *10*, 1568–1577. [CrossRef] [PubMed]
48. Maslenkina, K.; Mikhaleva, L.; Naumenko, M.; Vandysheva, R.; Gushchin, M.; Atiakshin, D.; Buchwalow, I.; Tiemann, M. Signaling Pathways in the Pathogenesis of Barrett's Esophagus and Esophageal Adenocarcinoma. *Int. J. Mol. Sci.* **2023**, *24*, 9304. [CrossRef] [PubMed]
49. Imro'Ati, T.A.; Sugihartono, T.; Widodo, B.; Nefertiti, E.P.; Rovian, I.; Wibawa, I.G.N. The Relationship between Serum Total Oxidant Status, Total Antioxidant Status, and Oxidative Stress Index with Severity Levels of Gastroesophageal Reflux Disease: A Literature Review. *Open Access Maced. J. Med. Sci.* **2021**, *9*, 584–589. [CrossRef]
50. Herdiana, Y. Chitosan Nanoparticles for Gastroesophageal Reflux Disease Treatment. *Polymers* **2023**, *15*, 3485. [CrossRef] [PubMed]
51. Bai, X.; Ihara, E.; Hirano, K.; Tanaka, Y.; Nakano, K.; Kita, S.; Iwamoto, T.; Ogino, H.; Hirano, M.; Oda, Y.; et al. Endogenous Hydrogen Sulfide Contributes to Tone Generation in Porcine Lower Esophageal Sphincter Via Na^+/Ca^{2+} Exchanger. *Cell. Mol. Gastroenterol. Hepatol.* **2018**, *5*, 209–221. [CrossRef] [PubMed]
52. Krause, J.; Brokmann, F.; Rosenbaum, C.; Weitschies, W. The challenges of drug delivery to the esophagus and how to overcome them. *Expert Opin. Drug Deliv.* **2022**, *19*, 119–131. [CrossRef] [PubMed]
53. Hammad, R.W.; Sanad, R.A.B.; Abdelmalk, N.S.; Aziz, R.L.; Torad, F.A. Intranasal Surface-Modified Mosapride Citrate-Loaded Nanostructured Lipid Carriers (MOS-SMNLCs) for Treatment of Reflux Diseases: *In vitro* Optimization, Pharmacodynamics, and Pharmacokinetic Studies. *AAPS PharmSciTech* **2018**, *19*, 3791–3808. [CrossRef] [PubMed]
54. Chang, Y.; Wu, F.; Pandey, N.K.; Chudal, L.; Xing, M.; Zhang, X.; Nguyen, L.; Liu, X.; Liu, J.P.; Chen, W.; et al. Combination of Disulfiram and Copper–Cysteamine Nanoparticles for an Enhanced Antitumor Effect on Esophageal Cancer. *ACS Appl. Bio Mater.* **2020**, *3*, 7147–7157. [CrossRef]
55. Zhuang, X.; Kang, Y.; Zhao, L.; Guo, S. Design and synthesis of copper nanoparticles for the treatment of human esophageal cancer: Introducing a novel chemotherapeutic supplement. *J. Exp. Nanosci.* **2022**, *17*, 274–284. [CrossRef]
56. Wang, X.-S.; Ding, X.-Z.; Li, X.-C.; He, Y.; Kong, D.-J.; Zhang, L.; Hu, X.-C.; Yang, J.-Q.; Zhao, M.-Q.; Gao, S.-G.; et al. A highly integrated precision nanomedicine strategy to target esophageal squamous cell cancer molecularly and physically. *Nanomed. Nanotechnol. Biol. Med.* **2018**, *14*, 2103–2114. [CrossRef] [PubMed]
57. Lee, J.; Kim, M.-H.; Kim, H. Anti-Oxidant and Anti-Inflammatory Effects of Astaxanthin on Gastrointestinal Diseases. *Int. J. Mol. Sci.* **2022**, *23*, 15471. [CrossRef] [PubMed]
58. Reyes, V.E. *Helicobacter pylori* and Its Role in Gastric Cancer. *Microorganisms* **2023**, *11*, 1312. [CrossRef] [PubMed]
59. Salvatori, S.; Marafini, I.; Laudisi, F.; Monteleone, G.; Stolfi, C. *Helicobacter pylori* and Gastric Cancer: Pathogenetic Mechanisms. *Int. J. Mol. Sci.* **2023**, *24*, 2895. [CrossRef] [PubMed]
60. Gobert, A.P.; Wilson, K.T. Polyamine- and NADPH-dependent generation of ROS during Helicobacter pylori infection: A blessing in disguise. *Free Radic. Biol. Med.* **2017**, *105*, 16–27. [CrossRef] [PubMed]
61. Sah, D.K.; Arjunan, A.; Lee, B.; Jung, Y.D. Reactive Oxygen Species and *H. pylori* Infection: A Comprehensive Review of Their Roles in Gastric Cancer Development. *Antioxidants* **2023**, *12*, 1712. [CrossRef] [PubMed]
62. Franco, D.; Calabrese, G.; Guglielmino, S.P.P.; Conoci, S. Metal-Based Nanoparticles: Antibacterial Mechanisms and Biomedical Application. *Microorganisms* **2022**, *10*, 1778. [CrossRef] [PubMed]
63. Attia, H.G.; Albarqi, H.A.; Said, I.G.; Alqahtani, O.; Raey, M.A.E. Synergistic Effect between Amoxicillin and Zinc Oxide Nanoparticles Reduced by Oak Gall Extract against *Helicobacter pylori*. *Molecules* **2022**, *27*, 4559. [CrossRef] [PubMed]
64. Chen, X.; Zou, Y.; Zhang, S.; Fang, P.; Li, S.; Li, P.; Sun, Y.; Yuan, G.; Hu, H. Multi-functional vesicles improve Helicobacter pylori eradication by a comprehensive strategy based on complex pathological microenvironment. *Acta Pharm. Sin. B* **2022**, *12*, 3498–3512. [CrossRef] [PubMed]
65. Shen, M.-F.; Wang, Z.; Shen, F.; Zhao, C.-S.; Chen, G. The role of hydrogen sulfide in gastric mucosal damage. *Med. Gas Res.* **2019**, *9*, 88–92. [CrossRef] [PubMed]
66. Manivannan, S.; Sivaraman, H.; Murugesan, R.; Narayan, S. Omeprazole and H_2S releasing agents encapsulated in chitosan nanoparticles to enhance healing process against indomethacin-induced gastric ulcer model. *J. Mater. Res.* **2023**, *38*, 3089–3109. [CrossRef]

67. Elsisi, A.E.; Mekky, E.F.; Abu-Risha, S.E. Potential effects of carbon monoxide donor and its nanoparticles on experimentally induced gastric ulcer in rats. *Inflammopharmacology* **2023**, *31*, 1495–1510. [CrossRef] [PubMed]
68. Huang, Z.; Shi, Y.; Wang, H.; Chun, C.; Chen, L.; Wang, K.; Lu, Z.; Zhao, Y.; Li, X. Protective Effects of Chitosan-Bilirubin Nanoparticles Against Ethanol-Induced Gastric Ulcers. *Int. J. Nanomed.* **2021**, *16*, 8235–8250. [CrossRef] [PubMed]
69. Ibrahim, I.A.A.; Hussein, A.I.; Muter, M.S.; Mohammed, A.T.; Al-Medhtiy, M.H.; Shareef, S.H.; Aziz, P.Y.; Agha, N.F.S.; Abdulla, M.A. Effect of nano silver on gastroprotective activity against ethanol-induced stomach ulcer in rats. *Biomed. Pharmacother.* **2022**, *154*, 113550. [CrossRef]
70. Butcher, L.D.; Hartog, G.D.; Ernst, P.B.; Crowe, S.E. Oxidative Stress Resulting from Helicobacter pylori Infection Contributes to Gastric Carcinogenesis. *Cell. Mol. Gastroenterol. Hepatol.* **2017**, *3*, 316–322. [CrossRef] [PubMed]
71. Ding, N.; Xu, S.; Zheng, S.; Ye, Q.; Xu, L.; Ling, S.; Xie, S.; Chen, W.; Zhang, Z.; Xue, M.; et al. "Sweet tooth"-oriented SN38 prodrug delivery nanoplatform for targeted gastric cancer therapy. *J. Mater. Chem. B* **2021**, *9*, 2816–2830. [CrossRef] [PubMed]
72. Alam, J.; Dilnawaz, F.; Sahoo, S.K.; Singh, D.V.; Mukhopadhyay, A.K.; Hussain, T.; Pati, S. Curcumin Encapsulated into Biocompatible Co-Polymer PLGA Nanoparticle Enhanced Anti-Gastric Cancer and Anti-Helicobacter Pylori Effect. *Asian Pac. J. Cancer Prev.* **2022**, *23*, 61–70. [CrossRef] [PubMed]
73. Veres-Székely, A.; Bernáth, M.; Pap, D.; Rokonay, R.; Szebeni, B.; Takács, I.M.; Lippai, R.; Cseh, Á.; Szabó, A.J.; Vannay, Á. PARK7 diminishes oxidative stress-induced mucosal damage in celiac disease. *Oxid. Med. Cell. Longev.* **2020**, *2020*, 4787202. [CrossRef]
74. Wang, Y.; Chen, Y.; Zhang, X.; Lu, Y.; Chen, H. New insights in intestinal oxidative stress damage and the health intervention effects of nutrients: A review. *J. Funct. Foods* **2020**, *75*, 104248. [CrossRef]
75. Yu, T.; Xie, Y.; Yuan, J.; Gao, J.; Xiao, Z.; Wu, Y.; Chen, H. The Nutritional Intervention of Resveratrol Can Effectively Alleviate the Intestinal Inflammation Associated with Celiac Disease Induced by Wheat Gluten. *Front. Immunol.* **2022**, *13*, 878186. [CrossRef] [PubMed]
76. Freitag, T.L.; Podojil, J.R.; Pearson, R.M.; Fokta, F.J.; Sahl, C.; Messing, M.; Andersson, L.C.; Leskinen, K.; Saavalainen, P.; Hoover, L.I.; et al. Gliadin Nanoparticles Induce Immune Tolerance to Gliadin in Mouse Models of Celiac Disease. *Gastroenterology* **2020**, *158*, 1667–1681.e12. [CrossRef] [PubMed]
77. Kelly, C.P.; Murray, J.A.; Leffler, D.A.; Getts, D.R.; Bledsoe, A.C.; Smithson, G.; First, M.R.; Morris, A.; Boyne, M.; Elhofy, A.; et al. TAK-101 Nanoparticles Induce Gluten-Specific Tolerance in Celiac Disease: A Randomized, Double-Blind, Placebo-Controlled Study. *Gastroenterology* **2021**, *161*, 66–80.e8. [CrossRef] [PubMed]
78. Attarwala, H.Z.; Suri, K.; Amiji, M.M. Co-Silencing of Tissue Transglutaminase-2 and Interleukin-15 Genes in a Celiac Disease Mimetic Mouse Model Using a Nanoparticle-in-Microsphere Oral System. *Mol. Pharm.* **2021**, *18*, 3099–3107. [CrossRef]
79. Elhag, D.A.; Kumar, M.; Saadaoui, M.; Akobeng, A.K.; Al-Mudahka, F.; Elawad, M.; Al Khodor, S. Inflammatory Bowel Disease Treatments and Predictive Biomarkers of Therapeutic Response. *Int. J. Mol. Sci.* **2022**, *23*, 6966. [CrossRef] [PubMed]
80. Alemany-Cosme, E.; Sáez-González, E.; Moret, I.; Mateos, B.; Iborra, M.; Nos, P.; Sandoval, J.; Beltrán, B. Oxidative Stress in the Pathogenesis of Crohn's Disease and the Interconnection with Immunological Response, Microbiota, External Environmental Factors, and Epigenetics. *Antioxidants* **2021**, *10*, 64. [CrossRef] [PubMed]
81. Tian, T.; Wang, Z.; Zhang, J. Pathomechanisms of Oxidative Stress in Inflammatory Bowel Disease and Potential Antioxidant Therapies. *Oxidative Med. Cell. Longev.* **2017**, *2017*, 4535194. [CrossRef] [PubMed]
82. Sahoo, D.K.; Heilmann, R.M.; Paital, B.; Patel, A.; Yadav, V.K.; Wong, D.; Jergens, A.E. Oxidative stress, hormones, and effects of natural antioxidants on intestinal inflammation in inflammatory bowel disease. *Front. Endocrinol.* **2023**, *14*, 1217165. [CrossRef] [PubMed]
83. Kellermann, L.; Riis, L.B. A close view on histopathological changes in inflammatory bowel disease, a narrative review. *Dig. Med. Res.* **2021**, *4*, 3. [CrossRef]
84. Ashique, S.; Mishra, N.; Garg, A.; Sibuh, B.Z.; Taneja, P.; Rai, G.; Djearamane, S.; Wong, L.S.; Al-Dayan, N.; Roychoudhury, S.; et al. Recent updates on correlation between reactive oxygen species and synbiotics for effective management of ulcerative colitis. *Front. Nutr.* **2023**, *10*, 1126579. [CrossRef] [PubMed]
85. Guan, G.; Lan, S. Implications of Antioxidant Systems in Inflammatory Bowel Disease. *BioMed Res. Int.* **2018**, *2018*, 1290179. [CrossRef] [PubMed]
86. Miranda, M.R.; Vestuto, V.; Moltedo, O.; Manfra, M.; Campiglia, P.; Pepe, G. The ion channels involved in oxidative stress-related gastrointestinal diseases. *Oxygen* **2023**, *3*, 336–365. [CrossRef]
87. Pérez, S.; Taléns-Visconti, R.; Rius-Pérez, S.; Finamor, I.; Sastre, J. Redox signaling in the gastrointestinal tract. *Free. Radic. Biol. Med.* **2017**, *104*, 75–103. [CrossRef] [PubMed]
88. Rauf, A.; Khalil, A.A.; Awadallah, S.; Khan, S.A.; Abu-Izneid, T.; Kamran, M.; Hemeg, H.A.; Mubarak, M.S.; Khalid, A.; Wilairatana, P. Reactive oxygen species in biological systems: Pathways, associated diseases, and potential inhibitors—A review. *Food Sci. Nutr.* **2024**, *12*, 675–693. [CrossRef] [PubMed]
89. Lin, S.; Li, Y.; Zamyatnin, A.A., Jr.; Werner, J.; Bazhin, A.V. Reactive oxygen species and colorectal cancer. *J. Cell. Physiol.* **2018**, *233*, 5119–5132. [CrossRef] [PubMed]
90. Pabari, R.M.; Mattu, C.; Partheeban, S.; Almarhoon, A.; Boffito, M.; Ciardelli, G.; Ramtoola, Z. Novel polyurethane-based nanoparticles of infliximab to reduce inflammation in an in-vitro intestinal epithelial barrier model. *Int. J. Pharm.* **2019**, *565*, 533–542. [CrossRef] [PubMed]

91. Rezvani, M.; Manca, M.L.; Muntoni, A.; De Gioannis, G.; Pedraz, J.L.; Gutierrez, G.; Matos, M.; Fadda, A.M.; Manconi, M. From process effluents to intestinal health promotion: Developing biopolymer-whey liposomes loaded with gingerol to heal intestinal wounds and neutralize oxidative stress. *Int. J. Pharm.* **2022**, *613*, 121389. [CrossRef] [PubMed]
92. Manconi, M.; Rezvani, M.; Manca, M.L.; Escribano-Ferrer, E.; Fais, S.; Orrù, G.; Lammers, T.; Asunis, F.; Muntoni, A.; Spiga, D.; et al. Bridging biotechnology and nanomedicine to produce biogreen whey-nanovesicles for intestinal health promotion. *Int. J. Pharm.* **2023**, *633*, 122631. [CrossRef]
93. Vafaei, S.Y.; Abdolghaffari, A.H.; Mahjub, R.; Eslami, S.M.; Esmaeili, M.; Abdollahi, M.; Atyabi, F.; Dinarvand, R. Budesonide-Loaded Hyaluronic Acid Nanoparticles for Targeted Delivery to the Inflamed Intestinal Mucosa in a Rodent Model of Colitis. *BioMed Res. Int.* **2022**, *2022*, 7776092. [CrossRef] [PubMed]
94. Wang, J.-L.; Gan, Y.-J.; Iqbal, S.; Jiang, W.; Yuan, Y.-Y.; Wang, J. Delivery of tacrolimus with cationic lipid-assisted nanoparticles for ulcerative colitis therapy. *Biomater. Sci.* **2018**, *6*, 1916–1922. [CrossRef] [PubMed]
95. Huang, J.; Dai, M.; He, M.; Bu, W.; Cao, L.; Jing, J.; Cao, R.; Zhang, H.; Men, K. Treatment of Ulcerative Colitis by Cationic Liposome Delivered NLRP3 siRNA. *Int. J. Nanomed.* **2023**, *18*, 4647–4662. [CrossRef]
96. Li, Z.; Zhang, X.; Liu, C.; Peng, Q.; Wu, Y.; Wen, Y.; Zheng, R.; Yan, Q.; Ma, J. Macrophage-Biomimetic Nanoparticles Ameliorate Ulcerative Colitis through Reducing Inflammatory Factors Expression. *J. Innate Immun.* **2022**, *14*, 380–392. [CrossRef] [PubMed]
97. Zhang, S.; Fu, J.; Dogan, B.; Scherl, E.J.; Simpson, K.W. 5-Aminosalicylic acid downregulates the growth and virulence of Escherichia coli associated with IBD and colorectal cancer, and upregulates host anti-inflammatory activity. *J. Antibiot.* **2018**, *71*, 950–961. [CrossRef] [PubMed]
98. Yuri, T.; Kono, Y.; Fujita, T. Transport characteristics of 5-aminosalicylic acid into colonic epithelium: Involvement of sodium-coupled monocarboxylate transporter SMCT1-mediated transport system. *Biochem. Biophys. Res. Commun.* **2020**, *524*, 561–566. [CrossRef] [PubMed]
99. Tang, H.; Xiang, D.; Wang, F.; Mao, J.; Tan, X.; Wang, Y. 5-ASA-loaded SiO_2 nanoparticles-a novel drug delivery system targeting therapy on ulcerative colitis in mice. *Mol. Med. Rep.* **2017**, *15*, 1117–1122. [CrossRef] [PubMed]
100. Li, J.; Chen, H.; Wang, B.; Cai, C.; Yang, X.; Chai, Z.; Feng, W. ZnO nanoparticles act as supportive therapy in DSS-induced ulcerative colitis in mice by maintaining gut homeostasis and activating Nrf2 signaling. *Sci. Rep.* **2017**, *7*, 43126. [CrossRef] [PubMed]
101. Wang, Z.-H.; Liu, J.-M.; Li, C.-Y.; Wang, D.; Lv, H.; Lv, S.-W.; Zhao, N.; Ma, H.; Wang, S. Bacterial Biofilm Bioinspired Persistent Luminescence Nanoparticles with Gut-Oriented Drug Delivery for Colorectal Cancer Imaging and Chemotherapy. *ACS Appl. Mater. Interfaces* **2019**, *11*, 36409–36419. [CrossRef] [PubMed]
102. Smith, T.; Affram, K.; Nottingham, E.L.; Han, B.; Amissah, F.; Krishnan, S.; Trevino, J.; Agyare, E. Application of smart solid lipid nanoparticles to enhance the efficacy of 5-fluorouracil in the treatment of colorectal cancer. *Sci. Rep.* **2020**, *10*, 16989. [CrossRef] [PubMed]
103. Cho, S.; Yoon, Y.-R. Understanding the pharmacokinetics of prodrug and metabolite. *Transl. Clin. Pharmacol.* **2018**, *26*, 1–5. [CrossRef] [PubMed]
104. Li, S.; Xie, A.; Li, H.; Zou, X.; Zhang, Q. A self-assembled, ROS-responsive Janus-prodrug for targeted therapy of inflammatory bowel disease. *J. Control. Release* **2019**, *316*, 66–78. [CrossRef]
105. Tan, C.; Fan, H.; Ding, J.; Han, C.; Guan, Y.; Zhu, F.; Wu, H.; Liu, Y.; Zhang, W.; Hou, X.; et al. ROS-responsive nanoparticles for oral delivery of luteolin and targeted therapy of ulcerative colitis by regulating pathological microenvironment. *Mater. Today Bio* **2022**, *14*, 100246. [CrossRef]
106. Ostadhossein, F.; Moitra, P.; Altun, E.; Dutta, D.; Sar, D.; Tripathi, I.; Hsiao, S.-H.; Kravchuk, V.; Nie, S.; Pan, D. Function-adaptive clustered nanoparticles reverse *Streptococcus mutans* dental biofilm and maintain microbiota balance. *Commun. Biol.* **2021**, *4*, 846. [CrossRef] [PubMed]
107. Enwereuzo, O.O.; Akakuru, O.C.; Uwaoma, R.C.; Elemike, E.E.; Akakuru, O.U. Self-assembled membrane-polymer nanoparticles of top-notch tissue tolerance for the treatment of gastroesophageal reflux disease. *J. Nanostruct. Chem.* **2021**, *11*, 707–719. [CrossRef]
108. Deng, L.; Zhu, X.; Yu, Z.; Li, Y.; Qin, L.; Liu, Z.; Feng, L.; Guo, R.; Zheng, Y. Novel T7-Modified pH-Responsive Targeted Nanosystem for Co-Delivery of Docetaxel and Curcumin in the Treatment of Esophageal Cancer. *Int. J. Nanomed.* **2020**, *15*, 7745–7762. [CrossRef] [PubMed]
109. Wu, Y.; Song, Z.; Deng, G.; Jiang, K.; Wang, H.; Zhang, X.; Han, H. Gastric Acid Powered Nanomotors Release Antibiotics for *In Vivo* Treatment of *Helicobacter pylori* Infection. *Small* **2021**, *17*, 2006877. [CrossRef]
110. Zhang, W.; Zhou, Y.; Fan, Y.; Cao, R.; Xu, Y.; Weng, Z.; Ye, J.; He, C.; Zhu, Y.; Wang, X. Metal–Organic-Framework-Based Hydrogen-Release Platform for Multieffective *Helicobacter Pylori* Targeting Therapy and Intestinal Flora Protective Capabilities. *Adv. Mater.* **2022**, *34*, 2105738. [CrossRef] [PubMed]
111. Wang, J.; Yao, M.; Zou, J.; Ding, W.; Sun, M.; Zhuge, Y.; Gao, F. pH-Sensitive Nanoparticles for Colonic Delivery Anti-miR-301a in Mouse Models of Inflammatory Bowel Diseases. *Nanomaterials* **2023**, *13*, 2797. [CrossRef] [PubMed]
112. Mahami, S.; Salehi, M.; Mehrabi, M.; Vahedi, H.; Hassani, M.S.; Bitaraf, F.S.; Omri, A. pH-sensitive HPMCP-chitosan nanoparticles containing 5-aminosalicylic acid and berberine for oral colon delivery in a rat model of ulcerative colitis. *Int. J. Biol. Macromol.* **2023**, *244*, 125332. [CrossRef] [PubMed]

113. Tian, B.; Liu, S.; Wu, S.; Lu, W.; Wang, D.; Jin, L.; Hu, B.; Li, K.; Wang, Z.; Quan, Z.A. pH-responsive poly (acrylic acid)-gated mesoporous silica and its application in oral colon targeted drug delivery for doxorubicin. *Colloids Surf. B Biointerfaces.* **2017**, *154*, 287–296. [CrossRef] [PubMed]
114. Medina, T.P.; Gerle, M.; Humbert, J.; Chu, H.; Köpnick, A.-L.; Barkmann, R.; Garamus, V.M.; Sanz, B.; Purcz, N.; Will, O.; et al. Lipid-Iron Nanoparticle with a Cell Stress Release Mechanism Combined with a Local Alternating Magnetic Field Enables Site-Activated Drug Release. *Cancers* **2020**, *12*, 3767. [CrossRef] [PubMed]
115. Choi, H.S.; Jo, Y.K.; Ahn, G.; Joo, K.I.; Kim, D.; Cha, H.J. Magnetically Guidable Proteinaceous Adhesive Microbots for Targeted Locoregional Therapeutics Delivery in the Highly Dynamic Environment of the Esophagus. *Adv. Funct. Mater.* **2021**, *31*, 2104602. [CrossRef]
116. Jiang, Z.; Xiao, W.; Fu, Q. Stimuli responsive nanosonosensitizers for sonodynamic therapy. *J. Control. Release* **2023**, *361*, 547–567. [CrossRef] [PubMed]
117. Liu, T.; Chai, S.; Li, M.; Chen, X.; Xie, Y.; Zhao, Z.; Xie, J.; Yu, Y.; Gao, F.; Zhu, F.; et al. A nanoparticle-based sonodynamic therapy reduces Helicobacter pylori infection in mouse without disrupting gut microbiota. *Nat. Commun.* **2024**, *15*, 844. [CrossRef] [PubMed]
118. Zhang, R.-Y.; Cheng, K.; Xuan, Y.; Yang, X.-Q.; An, J.; Hu, Y.-G.; Liu, B.; Zhao, Y.-D. A pH/ultrasonic dual-response step-targeting enterosoluble granule for combined sonodynamic-chemotherapy guided via gastrointestinal tract imaging in orthotopic colorectal cancer. *Nanoscale* **2021**, *13*, 4278–4294. [CrossRef] [PubMed]
119. Ren, Y.; Yan, Y.; Qi, H. Photothermal conversion and transfer in photothermal therapy: From macroscale to nanoscale. *Adv. Colloid Interface Sci.* **2022**, *308*, 102753. [CrossRef]
120. Correia, J.H.; Rodrigues, J.A.; Pimenta, S.; Dong, T.; Yang, Z. Photodynamic Therapy Review: Principles, Photosensitizers, Applications, and Future Directions. *Pharmaceutics* **2021**, *13*, 1332. [CrossRef]
121. Wang, H.; Wang, D.; Huangfu, H.; Lv, H.; Qin, Q.; Ren, S.; Zhang, Y.; Wang, L.; Zhou, Y. Branched AuAg nanoparticles coated by metal–phenolic networks for treating bacteria-induced periodontitis via photothermal antibacterial and immunotherapy. *Mater. Des.* **2022**, *224*, 111401. [CrossRef]
122. Moawad, M.; Youssef, A.M.; Elsherbeni, S.A.E.; Fahmy, A.M.; El-Ghannam, G. Silver Nanoparticles Enhanced Doxorubicin treatment for Improving their Efficacy against Esophageal Cancer Cells. *Egypt. J. Chem.* **2024**, *67*, 505–512. [CrossRef]
123. Zhi, X.; Liu, Y.; Lin, L.; Yang, M.; Zhang, L.; Zhang, L.; Liu, Y.; Alfranca, G.; Ma, L.; Zhang, Q.; et al. Oral pH sensitive GNS@ab nanoprobes for targeted therapy of Helicobacter pylori without disturbance gut microbiome. *Nanomed. Nanotechnol. Biol. Med.* **2019**, *20*, 102019. [CrossRef] [PubMed]
124. Xiao, J.; Cheng, L.; Fang, T.; Zhang, Y.; Zhou, J.; Cheng, R.; Tang, W.; Zhong, X.; Lu, Y.; Deng, L.; et al. Nanoparticle-Embedded Electrospun Fiber–Covered Stent to Assist Intraluminal Photodynamic Treatment of Oesophageal Cancer. *Small* **2019**, *15*, e1904979. [CrossRef] [PubMed]
125. Yang, X.; Xue, X.; Luo, Y.; Lin, T.-Y.; Zhang, H.; Lac, D.; Xiao, K.; He, Y.; Jia, B.; Lam, K.S.; et al. Sub-100 nm, long tumor retention SN-38-loaded photonic micelles for tri-modal cancer therapy. *J. Control. Release* **2017**, *261*, 297–306. [CrossRef] [PubMed]
126. Hao, Y.; Chen, Y.; He, X.; Yu, Y.; Han, R.; Li, Y.; Yang, C.; Hu, D.; Qian, Z. Polymeric Nanoparticles with ROS-Responsive Prodrug and Platinum Nanozyme for Enhanced Chemophotodynamic Therapy of Colon Cancer. *Adv. Sci.* **2020**, *7*, 2001853. [CrossRef] [PubMed]
127. Shi, S.; Zhang, L.; Zhu, M.; Wan, G.; Li, C.; Zhang, J.; Wang, Y.; Wang, Y. Reactive Oxygen Species-Responsive Nanoparticles Based on PEGlated Prodrug for Targeted Treatment of Oral Tongue Squamous Cell Carcinoma by Combining Photodynamic Therapy and Chemotherapy. *ACS Appl. Mater. Interfaces* **2018**, *10*, 29260–29272. [CrossRef] [PubMed]
128. Alipour, M.; Habibivand, E.; Sekhavati, S.; Aghazadeh, Z.; Ranjkesh, M.; Ramezani, S.; Aghazadeh, M.; Ghorbani, M. Evaluation of therapeutic effects of nanofibrous mat containing mycophenolate mofetil on oral lichen planus: *In vitro* and clinical trial study. *Biomater. Investig. Dent.* **2023**, *10*, 2283177. [CrossRef] [PubMed]
129. Azizi, A.; Dadras, O.G.; Jafari, M.; Ghadim, N.M.; Lawaf, S.; Sadri, D. Efficacy of 0.1% triamcinolone with nanoliposomal carrier formulation in orabase for oral lichen planus patients: A clinical trial. *Eur. J. Integr. Med.* **2016**, *8*, 275–280. [CrossRef]
130. Kadam, P.; Mahale, S.; Sonar, P.; Chaudhari, D.; Shimpi, S.; Kathurwar, A. Efficacy of silver nanoparticles in chronic periodontitis patients: A clinico-microbiological study. *Iberoam. J. Med.* **2020**, *2*, 142–147. [CrossRef]
131. Dong, Z.; Lin, Y.; Xu, S.; Chang, L.; Zhao, X.; Mei, X.; Gao, X. NIR-triggered tea polyphenol-modified gold nanoparticles-loaded hydrogel treats periodontitis by inhibiting bacteria and inducing bone regeneration. *Mater. Des.* **2023**, *225*, 111487. [CrossRef]
132. De Freitas, L.M.; Calixto, G.M.F.; Chorilli, M.; Giusti, J.S.M.; Bagnato, V.S.; Soukos, N.S.; Amiji, M.M.; Fontana, C.R. Polymeric Nanoparticle-Based Photodynamic Therapy for Chronic Periodontitis *In Vivo*. *Int. J. Mol. Sci.* **2016**, *17*, 769. [CrossRef] [PubMed]
133. Zorraquín-Peña, I.; Cueva, C.; de Llano, D.G.; Bartolomé, B.; Moreno-Arribas, M.V. Glutathione-Stabilized Silver Nanoparticles: Antibacterial Activity against Periodontal Bacteria, and Cytotoxicity and Inflammatory Response in Oral Cells. *Biomedicines* **2020**, *8*, 375. [CrossRef] [PubMed]
134. Zuo, J.; Huo, M.; Wang, L.; Li, J.; Chen, Y.; Xiong, P. Photonic hyperthermal and sonodynamic nanotherapy targeting oral squamous cell carcinoma. *J. Mater. Chem. B* **2020**, *8*, 9084–9093. [CrossRef] [PubMed]
135. Farhadnejad, H.; Mortazavi, S.A.; Jamshidfar, S.; Rakhshani, A.; Motasadizadeh, H.; Fatahi, Y.; Mahdieh, A.; Darbasizadeh, B. Montmorillonite-Famotidine/Chitosan Bio-nanocomposite Hydrogels as a Mucoadhesive/Gastroretentive Drug Delivery System. *Iran. J. Pharm. Res.* **2022**, *21*, e127035. [CrossRef] [PubMed]

136. Lee, S.; Hwang, G.; Kim, T.H.; Kwon, S.J.; Kim, J.U.; Koh, K.; Park, B.; Hong, H.; Yu, K.J.; Chae, H.; et al. On-Demand Drug Release from Gold Nanoturf for a Thermo- and Chemotherapeutic Esophageal Stent. *ACS Nano* **2018**, *12*, 6756–6766. [CrossRef] [PubMed]
137. Fu, Q.; Wang, J.; Liu, H. Chemo-immune synergetic therapy of esophageal carcinoma: Trastuzumab modified, cisplatin and fluorouracil co-delivered lipid–polymer hybrid nanoparticles. *Drug Deliv.* **2020**, *27*, 1535–1543. [CrossRef] [PubMed]
138. Yang, S.-J.; Huang, C.-H.; Yang, J.-C.; Wang, C.-H.; Shieh, M.-J. Residence Time-Extended Nanoparticles by Magnetic Field Improve the Eradication Efficiency of *Helicobacter pylori*. *ACS Appl. Mater. Interfaces* **2020**, *12*, 54316–54327. [CrossRef] [PubMed]
139. Jian, Y.; Zhao, M.; Cao, J.; Fan, T.; Bu, W.; Yang, Y.; Li, W.; Zhang, W.; Qiao, Y.; Wang, J.; et al. A Gastric Cancer Peptide GXI-Modified Nano-Lipid Carriers Encapsulating Paclitaxel: Design and Evaluation of Anti-Tumor Activity. *Drug Des. Dev. Ther.* **2020**, *14*, 2355–2370. [CrossRef] [PubMed]
140. Zhang, Y.; Tan, J.; Zhou, L.; Shan, X.; Liu, J.; Ma, Y. Synthesis and Application of AS1411-Functionalized Gold Nanoparticles for Targeted Therapy of Gastric Cancer. *ACS Omega* **2020**, *5*, 31227–31233. [CrossRef] [PubMed]
141. Zhang, M.; Wang, X.; Han, M.K.; Collins, J.F.; Merlin, D. Oral administration of ginger-derived nanolipids loaded with siRNA as a novel approach for efficient siRNA drug delivery to treat ulcerative colitis. *Nanomedicine* **2017**, *12*, 1927–1943. [CrossRef]
142. Zeeshan, M.; Ali, H.; Khan, S.; Mukhtar, M.; Khan, M.I.; Arshad, M. Glycyrrhizic acid-loaded pH-sensitive Poly-(Lactic-Co-Glycolic Acid) Nanoparticles for the Amelioration of Inflammatory Bowel Disease. *Nanomedicine* **2019**, *14*, 1945–1969. [CrossRef] [PubMed]
143. Zhang, X.; Zhao, M.; Cao, N.; Qin, W.; Zhao, M.; Wu, J.; Lin, D. Construction of a tumor microenvironment pH-responsive cleavable PEGylated hyaluronic acid nano-drug delivery system for colorectal cancer treatment. *Biomater. Sci.* **2020**, *8*, 1885–1896. [CrossRef] [PubMed]
144. Iranpour, S.; Bahrami, A.R.; Nekooei, S.; Saljooghi, A.S.; Matin, M.M. Improving anti-cancer drug delivery performance of magnetic mesoporous silica nanocarriers for more efficient colorectal cancer therapy. *J. Nanobiotechnol.* **2021**, *19*, 314. [CrossRef] [PubMed]
145. Li, Y.; Lu, H.; Liang, S.; Xu, S. Dual Stable Nanomedicines Prepared by Cisplatin-Crosslinked Camptothecin Prodrug Micelles for Effective Drug Delivery. *ACS Appl. Mater. Interfaces* **2019**, *11*, 20649–20659. [CrossRef] [PubMed]
146. Krasteva, N.; Georgieva, M. Promising Therapeutic Strategies for Colorectal Cancer Treatment Based on Nanomaterials. *Pharmaceutics* **2022**, *14*, 1213. [CrossRef] [PubMed]
147. Lama, S.; Merlin-Zhang, O.; Yang, C. *In Vitro* and *In Vivo* Models for Evaluating the Oral Toxicity of Nanomedicines. *Nanomaterials* **2020**, *10*, 2177. [CrossRef] [PubMed]
148. Ghebretatios, M.; Schaly, S.; Prakash, S. Nanoparticles in the Food Industry and Their Impact on Human Gut Microbiome and Diseases. *Int. J. Mol. Sci.* **2021**, *22*, 1942. [CrossRef] [PubMed]
149. Hashem, M.M.; Abo-El-Sooud, K.; Abd-Elhakim, Y.M.; Badr, Y.A.-H.; El-Metwally, A.E.; Bahy-El-Dien, A. The long-term oral exposure to titanium dioxide impaired immune functions and triggered cytotoxic and genotoxic impacts in rats. *J. Trace Elements Med. Biol.* **2020**, *60*, 126473. [CrossRef]
150. Yao, Y.; Zhang, T.; Tang, M. The DNA damage potential of quantum dots: Toxicity, mechanism and challenge. *Environ. Pollut.* **2023**, *317*, 120676. [CrossRef] [PubMed]
151. Lee, Y.; Jeong, M.; Park, J.; Jung, H.; Lee, H. Immunogenicity of lipid nanoparticles and its impact on the efficacy of mRNA vaccines and therapeutics. *Exp. Mol. Med.* **2023**, *55*, 2085–2096. [CrossRef] [PubMed]
152. Liu, N.; Tang, M. Toxic effects and involved molecular pathways of nanoparticles on cells and subcellular organelles. *J. Appl. Toxicol.* **2020**, *40*, 16–36. [CrossRef] [PubMed]
153. Nasnodkar, S.; Cinar, B.; Ness, S. Artificial Intelligence in Toxicology and Pharmacology. *J. Eng. Res. Rep.* **2023**, *25*, 192–206. [CrossRef]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.