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Effects of Nanoparticles on Gastrointestinal Disorders and Therapy

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Abstract

Gastrointestinal (GI) diseases are the diseases that affect any part of the gastrointestinal tract including acute, chronic, recurrent or functional disorders. There are a numbers of factors affecting the biology of GI tract. Nanoparticles are one of them in causing diseases. As there are many conventional therapeutic strategies for the treatment of GI diseases but these are not very efficient. Nanotechnology is the emerging and rapidly evolving field of the current era with new hopes in the field of nano-medicine for the detection, prevention and the treatment of diseases. Chemotherapeutic drug delivery in the field of nanotechnology has gained much attention and focus recently. Nano materials have wider range of potential applications for the detection and treatment of diseases while toxicological effects cannot be neglected and safe and non-toxic nano drugs should be considered for the treatment of pathological and physiological gastrointestinal diseases to reduce the existing conventional treatments. The parameters such as shape, size, surface chemistry and geometry of nanoparticles are important to consider in the designing of nano carrier. The review aims at integrating toxicological effects of nano materials and their safe and effective role in the treatment of GI disorders. Although there are disorders caused by nanoparticles but counteracting as well in a safe and targeted delivery of the conventional drugs into the GI system.

Keywords: Drug delivery; Gastrointestinal diseases; Gut microbiota; Nanoparticles; Toxicity of nanoparticles

Abbreviations

GI diseases: Gastro-Intestinal Diseases; NPs: Nanoparticles; ROS: Reactive Oxygen species; CeO_2: Cerium Oxide; TiO_2: Titanium Oxide; IL-1beta1: Interleukin-1-beta; TGF-beta1: Transforming Growth Factor Beta1; TEM: Transmission Electron Microscope; GES-1: Human Gastric Epithelial Cells; Caco-2: Colorectal Adenocarcinoma Cells; SiO_2: Silicon Dioxide; HT29: Colon Carcinoma Cells; MAPK: Mitogen Activated Protein Kinase; ERK 1: Extra Cellular Regulated Kinase 1; Nrf2: Nuclear Respiratory Pathway; IBD: Inflammatory Bowel Disease; ECM: Extracellular Matrix; MAP-9: Matrix Metalloproteinase-9; NAS-2: Nitric Oxide Synthase Type-2; COX-2: Cyclooxygenase 2.

Introduction

Gastrointestinal (GI) diseases are the diseases affecting the gastrointestinal tract, from the esophagus to the rectum, and the accessory digestive organs such as liver, gall bladder and pancreas. GI diseases include acute, chronic, recurrent or functional disorders while covering a broad range of diseases, including the most common acute and chronic inflammatory bowel disease [1]. There are different ways of drug incorporation and drug delivery systems such as transdermal, parenteral, trans-mucosal and oral. Oral drug delivery system is considered to be the widely accepted system for drug delivery due to cost effectiveness and easy administration [2]. It is the most important route for the uptake of particles and molecules in gastrointestinal. Oral drug delivery systems are considered complex barrier-exchange systems for taking up the molecules and their absorption in the gut. Variable absorption patterns of the drugs in the GI tract is making oral drug delivery system challenging due to low solubility, low apparent permeability and poor bioavailability by indicating the limiting factor for oral chemotherapy [3,4]. To overcome this limitation scientific community has been focusing on nano-technological based new and more effective drug carrier systems that could be helpful to overcome the challenging factors of conventional drug delivery systems. Nanotechnology enables the scientists to figure out the barriers of conventional approaches and now it is possible to deliver the hydrophobic drugs; specific targeting of drugs to particular regions of GI tract; transcytosis of drugs across the intestinal barriers and intracellular delivery of drugs [5].

Nano sized engineered particles (nanoparticles; NPs) in the size range of 1-100 nm (Figure 1) have a broad spectrum of applications in electronics, chemistry, environmental protection and medicine. In the field of biomedicines the use of nanoparticles has been growing exponentially [6]. To increase the treatment efficacy and to reduce the side effects, nano based drug delivery systems are being applied for the therapeutic applications from years. The nano based delivery systems includes polymeric, solid lipid, hydrogels, gold, silver nano systems etc [7]. A range of metal nanoparticles are currently used in the medical and food industry such as iron, cobalt, copper, zinc and silica [8]. These types of nanoparticles are physiologically important due to their different synthesis route because of their different physical and chemical properties. Although there are many advantages of the nano based drug carrier systems but toxicity parameters cannot be over looked as there are various toxicological routes associated with the

exposure of nanoparticles in the human being and environment while toxicological effects on human beings are still ambiguous [9]. Apart from this there are many types of safe nano-based drug delivery systems that are being used as therapeutic agents in the GI diseases. These systems have promising and effectual approach in the field of nano-medicine.

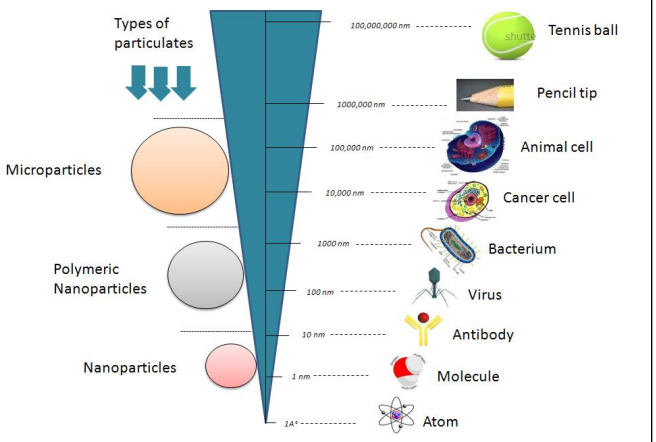

Figure 1: Scale representing the size between particles and main living units.

Nanoparticles Exposure to Gastrointestinal Tract

Human beings and other living organisms are being exposed to nanoparticles through their evolutionary phases. Due to the large population and huge diversity of nanoparticles it is hard to define how nanoparticles are being introduced into living body systems.

But in general, exogenous and endogenous are the two main sources of NPs incorporation into gastrointestinal tract. Endogenous NPs sources based on calcium and phosphate secretion of intestine while NPs from food, water, cosmetics, pharmaceuticals [10] or very small amount of inhaled NPs in gastrointestinal tract was found [11] are called as exogenous sources. Man-made titanium dioxide, silicates or aluminosilicates have been widely used as exogenous inorganic particles for the food (whitening and brightening), in sauces and dressings. These type of nanoparticles are found in the gut are of around 100 nm in size and spherical in shape showed resistivity to degradation. Endogenous particles that are naturally occurring are soluble in the gut such as calcium and phosphorous and re-circulate as ionic forms in the gut environment [10].

Skin, lungs and gastrointestinal tract are the potential routes of nanoparticles exposure [12-14]. Dietary micro and nanoparticles are the normal way of getting into the GI tract. Nano-technological approaches have increased the intake of these nanoparticles into the GI tract [15] in an intentional way to get the personalized medicines [16]. Nanoparticles can be entered into the GI tract by various ways. They can be ingested by food, water, drugs and cosmetics and can be inhaled and ultimately become the part of GI tract after clearance from the respiratory system [17]. Smaller particle size can easily diffuse in the GI secretions and becomes the part of the blood stream and translocate to other parts [18].

Parameters affecting nanoparticles in gastrointestinal tract

Various parameters such as shape, size, dose, surface characteristics, and translocation are known to play very distinguishing role in the nanoparticles toxicity. These parameters are not still fully understood in vivo. Therefore it is significant to have proper knowledge of nano-materials interaction with the biological system prior to synthesize. These parameters can influence delivery efficiency and distribution of drugs (Figure 2). In designing of nanoparticles few key points should be considered such as appropriate surface charge, specific ligands, be in the circulatory system. Nanoparticles can escape from the clearance mechanism and opsonisation, resistant to drugs and other related parameters. Therapeutic applications of nanoparticles are dependent on these parameters when interacting with the biological system.

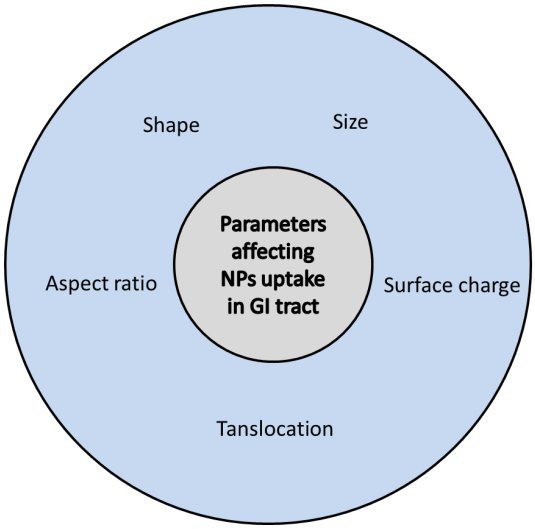

Figure 2: Parameters affecting nanoparticles uptake in GI tract.

Shape

Shape is an important and critical parameter in nano based systems for the drug delivery and for behaving itself as drugs. Different shaped nanoparticles have different surface area, thickness and degradation rates [19]. Spherical nanoparticles have advantage over non-spherical nanoparticles [20]. It has been reported in *in vivo* experiments that blood circulation is also dependent on the shape and length-width ratio of nanoparticles [21]. Cristina et al. have demonstrated that nickel (Ni) nanoparticles of different shapes and diameter can cause the toxicity to zebrafish embryos. 60 nm aggregated particles results in higher toxicity (LD10 and LD50) just because of shape and aggregation as the synthesis method and composition is similar [22].

Size

Nanoparticle size plays a major role when interacting with the biological system [23]. Size is inversely proportional to the surface area and volume as with the decrease of particle size, ratio between surface area and its volume increases rapidly and can influence the particle interaction with the biological system. Nanoparticles can be more reactive as compare to micro and macro particles [24]. Distribution of nanoparticles is also size dependent [25]. Nanoparticles can easily

cause the toxicity due to their nanoscale dimensions as they can readily enter into the biological system. Deposition of nanoparticles into the renal tissues and redistribution from the deposition site is also reported [26]. Small sized nanoparticles can easily escape from the phagocytosis while it should be large enough to escape from translocation in tissues and organs. Nanoparticles with different sizes and doses have different effects on cellular metabolism and it is in correlation with the intestinal bioavailability of nanoparticles [27]. Nano sized particles of less than 20 nm can be easily taken up by the small intestinal epithelial cells and further translocate to other organs by lymphatic system and capillaries in a short duration of time [17] while 1000 nm sized-nanoparticles or bigger than this size seldom crossing intestinal barrier. Nanoparticles vary in chemical composition with reference to disease subjects as after analyzing the colon mucosa from microscopic and energy dispersive spectroscopy a number of NPs are found like carbon, ceramic filo silicates, gypsum, sulphur, calcium, silicon, stainless steel, silver, and zirconium [28] and the size range is from 50 nm to 100 μm. This is the indication that NPs size smaller then this range can cross and penetrate the gastrointestinal barrier as most of the particles are found at the inter junction of healthy and cancerous tissues [29]. There is a need of key information on the toxicity, distribution, metabolism, and excretion of nanoparticles to understand the mechanism of toxicity [24].

Surface charge

Surface charge is an important factor among the design parameters of nanoparticles for therapeutic applications. According to particle kinetics positively charged particles can easily attach to the negatively charged mucus layer and negatively charged nanoparticles can diffuse easily across this layer. Keeping in view the cytotoxic effects of nanoparticles; charge density and charge polarity are among the major factors. Charged particles are cytotoxic as compared to the neutral charge nanoparticles [30] but it depends on the nature and the type of nanoparticles also. From few studies it has been revealed that uptake of charged iron oxide nanoparticles and polystyrene nanoparticles are superior to their uncharged counterparts [31]. Some researchers also reported that positively charged nanoparticles are more cytotoxic then negatively charged ones [32,33] but from few reports it is justified that positively charged nanoparticles such as super paramagnetic iron oxide , gold and silver particles are taken up at an elevated level as compare to negatively charged particles [34,35].

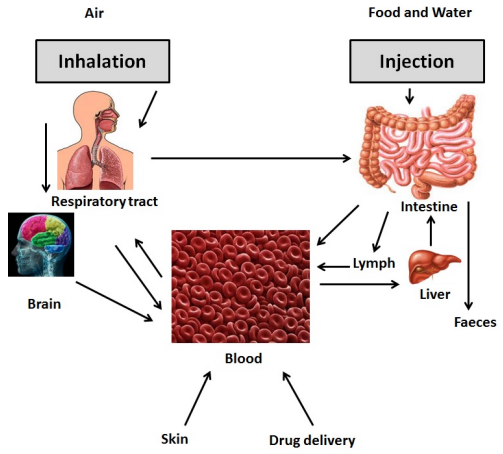

Figure 3: Illustration of possible routes of nanoparticles uptake, allocation and excretion in humans.

Translocation

Various physicochemical properties of nanoparticles allow site-specific targeting of different regions of the gastro-intestinal tract. Nanoparticles translocation to stomach and small intestine [36] has been documented. The rate of ingested nanoparticles elimination has been cited in many studies for example, 98% excrement removal of nanoparticles has been documented within 48 hours and remaining via urine (Figure 3) [37].

Aspect ratio

Aspect ratio of nanoparticles is also one of the causes of the NPs toxicity. Lin et al. have suggested the toxicological effects for long aspect ratio of cerium oxide nanoparticles *in vivo* in the mouse lung and GI tract of zebrafish larvae. It has been concluded after their comparative study that nano rods having high aspect ratio IL-1beta and TGF-beta1 production in the bronchoalveolar lavage fluid at 21 days but did not induce pulmonary fibrosis while at longer duration (44 days). 4 mg/kg of the high aspect ratio nanorods, production of more collagen has been observed with growth inhibition, reduction in body weight and delayed process of vertebral calcification have been seen in the oral exposure model of zebrafish larvae. From histological and transmission electron microscopic studies these nano-rods are the main causing factor of injury in the epithelial lining of the G1 tract. Blunted microvilli demonstrated the disruption in digestive function and the lung toxicity relevant to inhalation is contributing to the potential environmental hazards as well [38]. Oral exposure of TiO_2 NPs cause variable age dependent adverse health effects. In a comparative toxicity study of TiO_2 NPs on different aged groups rats has revealed that young rats are found with liver edema, heart injuries and non-allergic mast activation in stomach tissues as compare to the adult ones [39] .

Methodological Considerations in Nanoparticles Synthesis

Recently researchers have great emphasis on methodological issues in the synthesis of nanoparticles and nanoparticle-cell interactions.

They are focusing on the applications of nano materials in the gastrointestinal tract and have reported many nano based systems to overcome the conventional system of therapy. But there is a considerable need to investigate more specific and reliable nano system for the gastrointestinal diseases and therapy [40]. Many types nanoparticles can easily get aggregated and show agglomeration with the changing environment. Light scattering techniques should be used for this event. Other technical issues such as a) excessive obscuration, b) concentrations of particles, c) masking of small particles by larger fewer particles and d) presence of particle like structures in the medium is of consideration.

In cell cultures techniques, the published data was not most of the time well characterized as experiments are showing the false nanoparticles uptake even after not having the good microscopy techniques. This is in relevance with the *in-vivo* systems that is not very easy to determine as nanoparticles can aggregate or remain disperse in the gut lumen. There should be careful approach in the sample preparation for the microscopy. Oral delivery of Nano medicines are making them more technical to elucidate. There should be a detailed tracking system for the nanoparticles [41-43].

Nanoparticle interaction with the soluble molecules is another important technical point and it has been recently documented for the 'corona' (protein coated nanoparticle surfaces). This is happening from the last many years in the aqueous environment for these types of interactions [44]. In gastrointestinal tract there is a variable pH indices, for example stomach is more acidic as compare to the small bowel lumen. Gastrointestinal enzymes help the ingested particles for surface adsorption and then re-adsorbed by the small intestinal entities and the adsorptive phenomenon was reported on the basis of chemical composition of the nano entities and of the ionic environment. Ashwood et al. have investigated the phenomenon in which calcium ions present in the gut luminal fluids helps the bacterial lipo-polysaccharide to bind with the titanium dioxide nanoparticles. Calcium irons present in the cell cultures medium can change the particle size and reactivity by conjugating with other entities forming the particles of great challenge. Chemical assays have been used from decades in the laboratories and the interactions of the nanoparticles with the chemical composition of the assays are of main concern [45]. Cells have numerous defense mechanisms that is another point to be focused that what should be the concentration of the nanoparticles with the drug that is best to consider (lower doses may not have high side effects due to the cell self defense mechanisms). To do this a lot of optimization steps must be taken in both *in-vitro* and in-vivo systems. In *in-vivo* experiments should have careful handling required for stress of animals, abnormal transit time and abnormal perfusion. Radio labelled particles or the other particles that is not found endogenously, tissue analysis is the best way to check the compartmentalization of nanoparticles with the given time frame [46,47].

But measuring kinetic profiles is still a challenge due to the re-circulation of the nano materials such a s mono nuclear cells migrate below from the gut epithelial layer to mesenteric lymph nodes and then circulate back to the intestinal mucosa [48]. To examine the fate of nanoparticles imaging techniques are widely used. Labeled nanoparticles can easily be identified by the laser microscopes or electron microscope [49]. Nanoparticles interactions with the cell cultures such a s colonic carcinoma cell lines and CaCo-2 (differentially dividing features) and with the gut requires careful consideration of nanoparticles behavior and physiology of gut in response to *in vivo* experiments [50,51].

Toxic Effects and Disorders Caused by Nanoparticles

Toxicity of any type of nanoparticles to an organism is determined by the individual's genetic complement, which provides the biochemical toolbox to adapt and fight with toxic substances. Oxidative stress, alteration of calcium homeostasis, gene expression, pro-inflammatory responses and cellular signaling are the main events that cause NPs toxicity [6]. *In vivo* toxicity diagnostics is of main concern as of major part in laboratory diagnostics rather than just relying on *in vitro*/cyto-toxicological approaches [52]. It has been documented that orally administered copper nanoparticles by oral gavage caused acute toxicity in kidney, spleen and liver of experimental mice group *in vivo* [53].

Cellular toxicity

The increasing use of nano-medicine as a current technology to treat various diseases has raised concerns about their toxicity in living beings. Synthetic preparation of nano-medicines have been used tremendously in a wide range of applications (in medicine and surgery) and living beings are being exposed to them at an elevated levels [54,55].

Nanoparticles cause cellular toxicity at particular concentration used. According to Yang and co-workers silica nanoparticles have tested at cellular level in cell lines that originates from the gastrointestinal tract. The cell uptake, cellular reactive oxygen species (ROS) level, cell cycle and apoptosis were determined for toxicity studies in human gastric epithelial cell GES-1 and colorectal adenocarcinoma cell Caco-2. It has been concluded that 24 hours exposure time and 100 micrograms of concentration is safe for both cell lines as silica NPs do not pass through Caco-2 cell monolayer after 4 hours. These NPs have low capability to cross the gastrointestinal tract *in vivo* while long term effect should be considered [8].

Particle size and incubation time of nanoparticles affect the toxicity of the cells. It has been reported that SiO_2 nanoparticles stimulate the proliferation of human colon carcinoma cells (HT29) that is concentration, size of nanoparticles and incubation time dependent and cause interference with MAPK/ERK1/2 and Nrf2/ARE signaling pathways [56].

Dose dependent cellular toxicity of TiO_2 nanoparticles was demonstrated by Botelho et al. in human gastric epithelial cell line as these NPs induce tumor like phenotypes as a result of increased proliferation and decreased apoptosis [13].

Cellular toxicity is also depended on the types of nanoparticles and their surface modifications. CeO_2 have radical scavenging and UV-filtering properties in the biomedical field but the safety and toxicity of these nanoparticles is of main concern. Cell uptake, ROS level and cytotoxicity of 2-5 nm particles coated with different polymers have been determined in the BGC-803 (gastric cancer cell lines). The cytotoxicity is dependent on the functional groups present on these CeO_2 NPs [57]. Aspect ratio of nanoparticles is also causing toxicological effects as CeO_2 nano-rods, greater than or equals to 22 is the cause of potential cell toxicity in the human myeloid cell line, THP-1 induced lysosomal damage and progressive effects on IL-1beta production [38].

Genotoxic effects are also related to the use of nanoparticles either direct or indirect way. Nano-composite of cobalt-chromium of size 29.5 ± 6.3 nm in diameter potentially damage the human fibroblast cells in an intact cellular manner rather than crossing the barrier due

to the transmission of purine nucleotides and intercellular signaling mechanism. DNA damage occurred with the significant cell death when exposed to nanoparticles in an indirect way [58].

Gastrointestinal disorders

Considerable potential health risks are documented on human health and environment due to nanoparticle. Nanoparticles are extensively used in biomedical fields showing complex and unexpected interactions with the biological systems particularly with oral route drug administration [59]. A number of diseases are caused due to widespread usage of nanoparticles. As far as GI tract is considered, nanoparticles are major cause of the Crohn's disease, ulcerative colitis and cancer in the gastrointestinal tract. Uptake and translocation of larger particles may cause inflammation [29]. In diabetic patients there is a higher rate of particle absorption in the gastrointestinal tract [17]. Crohn's disease is caused by higher uptake of NPs (100 nm-1 μm) from diet while genetic and environmental factors are also playing a role in the occurrence of this disease. It is prevalent in developed as well as under developed countries and about 1 among the population of 1000 people including native and immigrants. Crohn's disease signs appear by the lymphoid aggregation containing the exogenous nanoparticles in macrophages [60]. From microscopic studies it has been suggested that macrophages located in lymphoid tissue uptake nanoparticles with different size and various morphologies [61]. There are some controversies about the nanoparticles are the cause of Crohn's disease, it may be due to abnormal response to dietary nanoparticles intake and are responsible in inflammation in Crohn's disease [10]. A genetic variation due to the intake of nanoparticles develops Crohn's disease [62].

Gut microbiome alteration

Gut microbiome alteration can cause enteric disorders in humans and animals [63] as the gut microbiota is playing a key role to maintain the GI homeostasis [64]. Altered microbiota can cause serious health risks including cancer risks also (colorectal cancer as an example) [65]. Nanoparticles can modulate the overall homeostasis of the gastrointestinal tract by altering the gut microbiota and gut-associated immune response. GI tract is an area for complex symbiotic interactions between host cells and residing microbiome [66] consisting of intense population of bacteria of phyla Bacteroidetes and Firmicutes in human and mouse gut. More than half population of GI microbiome is non-cultivable that provide the new room for the scientific research in non-cultivable based sequence techniques of gut microbiome (Figure 4).

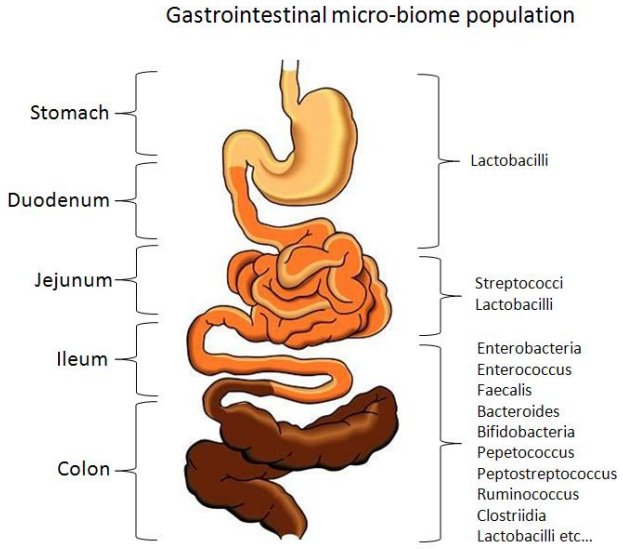

Figure 4: Micro-biome population in different organs of GI tract.

Cecum and colon is considered the organs with highest microbial activity and from the overall calculation it is assumed that in an adult human there is approx. 1 kg of gut microbiome upto more than 5000 species (Figure 5) [39,52,53,67-69]. Among them bacteria is in major population that are commensals and playing key roles in the normal digestion and immunological functions; such as bile acid conjugation, colonic enterocyte regulation (by producing fatty acid butyrate), vitamins B 12 production and detoxification of ingested drugs in GI tract [70]. It has been reported that oral delivery of silver nanoparticles in the food additives can changes the intestinal-microbiota population and intestinal-mucosal gene expression in a size and dose dependent manner. DNA based studies revealed that exposure to 10 nm AgNPs and low-dose silver acetate caused a decrease in populations of Firmicutes phyla and a decrease in Lactobacillus genus has occurred [71]. Water dispersible silver nanoparticles (Ag-NPs) are found to be a reason of ultra-structural changes in the organs (liver and spleen) as by passing through the epithelim of the small intestine and confirming the health risks [72]. There is a close association between altered gut microbiota and several diseases like IBD, obesity, colitis, colon cancer [64].

A better understanding of gut microbiome is helpful in intestinal health and is a better way to prevent the GI disease and will lead to the preventive and therapeutic strategies to cure the GI diseases.

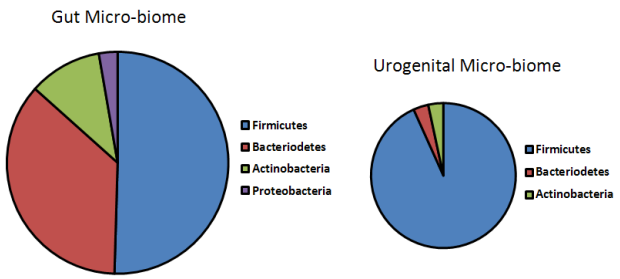

Figure 5: Selected major population of micro-biome in gut (more than 1000 species) and urogenital tract (~150 species) [69].

Nanoparticles Associated with the Treatment of GI Diseases

The field of nano-medicine is becoming the future of medicine by the use of number of synthetic nanoparticle. These nanoparticles are being used as vectors for the chemotherapeutic drugs with lower side effects and higher specificity. Nanoparticles have a broad range of applications due to many physiochemical characteristics. Particle size and surface characteristics of NPs can be modulated for both passive and active drug targeting, sustained and controlled drug release to increase the drug efficacy and to reduce the side effects, high drug loading capacity, site specific targeting and most important is administration of the drugs and NPs system via different routes including oral, nasal, parenteral, intra-ocular [73]. Different nanoparticles have been investigated to check the toxicity such as silicon carbide nanoparticles (SiC) were found as a safe delivery agent in an *in vivo* rat model. These nanoparticles were excreted in the feces and very less amount was retrieved from the urine giving the indication that these orally delivered nanoparticles can cross the intestinal barrier without any organ damage even at higher doses of these nanoparticles [74]. There are different types of GI diseases and disorders caused by nanoparticles and their treatment is necessary for the normal body functioning.

Inflammatory bowel disease

The chronic inflammation of the gut is due to Crohn's disease and ulcerative colitis; the two main forms of inflammatory bowel disease. They have no cure and require surgical intervention and treatment includes anti-inflammatory drugs particularly in liquid formulations [60] and these drugs are associated with an increased risk of gastrointestinal damage even in small continuous doses. Nanoparticles based drug carrier systems have been used for the specific site targeting with higher drug concentration and less toxic effects as nanoparticles have the ability to accumulate in the inflamed region [75].

One of the examples of intestinal inflammation is orally delivered indomethacin (IND) drug. To overcome this problem Yoshitomi et al; have developed core-shell miceller nanoparticles loaded with indomethacin (IND@RNP(O)) for oral drug delivery. These nanoparticles have nitroxide radicals that scavenge the ROS, efficiently accumulated in the intestine while improved uptake of indomethacin have been observed without causing intestinal inflammation and adverse effects in the small intestine [76].

Gastric cancer

Gastric cancer is a complicated and multifaceted process. There are many processes involved such as ROS (reactive oxygen species) production, ECM (extra cellular matrix) degradation and mitochondrial damage. Scientists have investigated nano based approach to for the treatment of gastric ulcer by encapsulating drugs into nanoparticles. Quercetin loaded polymeric nanoparticles significantly reduce the oxidative stress in an ethanol induced gastric ulcer in mice by down-regulating MMP-9 and NOS-2 with highly bioavailability [77].

Gastric cancer can be treated by inhibiting the expression of cyclooxygenase-2 (COX-2) and it has been discovered that ursolic acid could induce apoptosis in the cancer cell lines but the hydrophobic nature of this drug limits its clinical application. To address this issue the scientist have designed ursolic acid nanoparticles (UA-NPs), NPs of amphilic methoxy poly(ethylene glycol)-polycaprolactone (mPEG-PCL) block copolymers used as drug carriers and the drug was efficiently transported into SGC7901 cells by effectively penetration into the membrane and significantly increased cell death and inhibition of COX-2 and caspase-3 activity as well [78]. Effects of titanium dioxide nanoparticles with an average size of 75 nm have been tested in the mouse model with gastric ulcer and found statistical increase in the white blood cells and red blood cells even at prolonged nanoparticles treatment without any effect on the coagulation index factor [79].

Paclitaxel (Ptx) has been used in the treatment of gastric cancer. There are few side effects affiliated with the use of paclitaxel and to overcome this problem paclitaxel loaded biodegradable nanoparticles have been synthesized with tetrandrine to increase the stability of paclitaxel loaded nanoparticles. Oxidation therapy by these nanoparticles can be by the ROS production from tetrandrine while paclitaxel could synergistically deplete the cellular antioxidants in the cells and increase cytotoxicity. The co-administration of these two drugs provides an efficient therapeutic strategy for the gastric cancer [80].

Gastrointestinal irritation

Gastrointestinal irritation caused by many drugs. One of them is triptolide is being used in many biological applications [81] behaving as anti-inflammatory, immunosuppressive, anti-fertility, anti-cytogenesis and anti-cancerous drug [82] irrespective to poor solubility and highly toxicity. It is responsible in causing adverse effects of gastrointestinal tract such as nausea, anorexia, vomiting, diarrhea, and gastrointestinal ulcer and bleeding [83]. Triptolide-loaded solid lipid nanoparticles (TP-SLN) of particle size 179.8 ± 5.7 nm have reduced gastric irritation in rats of oral administration and the drug was released in a sustained released pattern in vitro and stable in gastric fluids without significant size change even at 3 h of incubation [84].

Nanoparticles with peptidic ligands can be used for specific targeting in the gastrointestinal (GI) tract due to having small size, high surface area and high selectivity for the functional groups modification. Nanotechnology is trying to overcome the problem of oral delivery of proteins drugs having poor membrane permeability, high molecular weight, and enzymatic degradation of protein drugs

[9]. Tsai et al. have synthesized the hyaluronan-cisplatin conjugate nanoparticles (HCNPs) as a specific drug delivery carrier for colon targeting by entrapping them in Eudragit S100-coated pectinate/alginate microbeads (PAMs) that are helpful to alleviate the nephrotoxicity *in vivo* caused by cisplatin [85]. As for as the therapeutic effects are concerned micro and nanoparticles have a great contribution in disease treatment. CD98 siRNA/polyethyleneimine (PEI)-loaded NPs have beneficial effects to decrease the colitis by releasing CD98-specific siRNA to colonic cells and down regulation of CD 98 in the intestinal epithelial and in macrophage cell in the treated mice [86].

Colorectal cancer

Colorectal cancer is among the frequently diagnosed cancers affecting around a million of people per year in the world [87]. Recurrent colon cancer is not easy to cure by conventional chemotherapeutic approaches [88]. There is a need for the development of effective therapies to prevent the colorectal cancer. Many delivery systems including nanoparticle delivery systems have been used recently to deliver the drugs in a target delivery. One of the example is CS-TPP/IL-21 nanoparticles (chitosan encapsulated IL-12 incorporated by tri-polyphosphate as a cross linking agent). Cytokine delivery system by these nanoparticles significantly reduce the colorectal liver metastasis due to the IL-21 as compare to the CS-TPP treated mouse by exploiting liver immunity [89].

Methotrexate loaded and folic acid conjugated guar gum nanoparticles (MTX-FA-GGNP) directly release the methotrexate in the colonic fluid while protecting the pre-release of drug in the upper gastrointestinal tract. From in vivo studies it has been revealed that folic acid conjugated NPs can address the colorectal cancer by over expressing the folate receptors on the cancerous cells [90]. Retinoic acid has been used in the treatment of various tumors due to its anti-proliferative, anti-migration and anti-invasive efficacy but there are some factors that limit its efficacy and to overcome this limitation; deoxycholic acid conjugates nanoparticles (DexDA) with the incorporation of retionic acid has been used in vitro and in vivo studies to investigate the anti-cancer activity. These nanoparticles showed similar anti cancerous activity *in vitro* and higher anti-metastatic activity in vivo in a CT26 pulmonary metastatic animal model [91].

Solid lipid nanoparticles have been used as a delivery system for the anti-cancer drugs and acting as anti-inflammatory agents. As cited cholesteryl butyrate solid lipid nanoparticles (cholbut SLN) offer a delivery system for anti-cancer drug butyrate by inhibiting the adhesion of cancer cells (polymorphic nuclear cells) to the endothelium derived from various human cancer cell lines by down modulating the ERK and p38 phosphorylation [92].

Gastric toxicity

Ibuprofen (IBU) cause gastric toxicity revealed by growing number of studies while in case of oral delivery and incorporating this drug into biodegradable polymer; Poly (DL-lactic acid) (PLA) reduced the gastric toxicity by systematic circulation of drug [93]. As it is a non-steroidal anti-inflammatory drug is responsible to inhibit the promotion and proliferation of various tumors. Anti-proliferative effects of ibuprofen have been tested on MKN-45 human gastric cell line by ibuprofen-loaded PLGA NPs with greater efficiency and at low doses of ibuprofen [94]. Colloidal nanoparticles as nano-carrier agents are the well suited drug delivery systems to overcome the dose limited adverse effects of the unselective drug availability particularly in the treatment of inflammation of bowel disease and in gastric ulcer [95]. Poly (amido amine) (PAMAM) dendrimers conjugated to SN38 has improved oral bioavailability of persuasive anti-cancer drugs with minimal GI toxicity [96].

Esophageal cancer

Esophageal cancer related deaths are at seventh level world worldwide can be treated by photothermal ablation therapy using chitosan-coated gold/gold sulfide (CS-GGS) nanoparticles. Biocompatible gold nanoparticles (GNPs) with chitosan surface modification are used in cell's response to X-ray irradiation applications in tumor radiation therapy by increasing the radiation therapeutic sensitivity to cells [97]. Combining gold nanoparticles with near infrared-absorbing light is a feasible approach to destroy the malignant tissue while leaving healthy tissue unharmed by providing an optimal endo-luminal therapeutic option for esophageal cancer [98]. CeO_2 NPs have radical scavenging and UV-filtering properties in the biomedical applications [57].

Colon cancer

Colon is the representative targeted organ in GI diseases and a large number of drugs are used to cure and to target the colon. The current strategy is the use of different natured drugs loaded nanoparticles including small modalities like siRNA and tripeptide to larger molecules like proteins for example nano-lactoferin; an iron binding protein has also been used in the diagnostic, imaging, cancer and in infectious diseases [99]. These modalities can be used in an unaccompanied or co administered way to treat the diseases associated with GI tract in a cost effective way.

PLGA nano system is considered as best drug delivery system that is associated with different drug delivery systems. Meloxicam is a non-steroidal anti-inflammatory drug that is an enolic acid type effective in the inhibition of COX-2 enzymes as these are the cancer causing enzymes. Sengel-Turk et al. have prepared the meloxicam loaded PLGA nano particles by combining and modifying the salting out and emulsion evaporation technique. PLGA (50:50 of 5-15 kDa or 40-75 kDa) and meloxicam (1:3) were mixed in an organic phase in the presence of acetone and dichloromethane. Aqueous phase transfer was done in the varying weights of PVA and then emulsification was done with the ultra-sonication. Continuous stirring and addition of aqueous PVA completely evaporates the di-choloromethane and pure form of modalities was acquired after ultracentrifugation and washing with ultra-pure water. As prepared spherical shaped, negatively charged meloxicam loaded PLGA nanoparticles is effective for the colon cancer. These nanoparticles are efficiently taken up by the HT-29 cells (COX-2 expressing human colon adenocarcinoma cell line) and markedly increase the cytotoxicity at 800 micro-molar concentrations. These nanoparticles have considerable cytotoxic effects and effective drug delivery system of meloxicam for the treatment of colon cancer [100].

Hydrogel based anti-inflammatory drugs loaded nanoparticles are used to target the digestive tract including colon. This strategy is based on electrostatic interactions of positive and negative polysaccharides effective in the reduction of colon inflammation even at lower doses and efficient delivery of drugs to the colon. Laroui et al. have designed the hydrogel based nanoparticles *in situ* by double cross linking process mediated by Ca^{2+} and SO_4^{2-} of chitosan and alginate. These

nanoparticles can specifically target the colon after the oral administration (by double gavage) into the mouse gastrointestinal tract with a reduced rate of nanoparticles degradation in the aggressive environmental conditions of gastrointestinal tract [101].

Colitis induced by dextran sulfate sodium (DSS) can be treated by using fruit derived grape exosome-like nanoparticles (GELNs). The findings of Ju et al. have revealed that these edible exosomes like nanoparticles can efficiently take up by the mouse intestinal stem cells and helps to promote the $Lgr5^{hi}$ stems cells of intestine by mediating the intestinal tissues remodeling and protection [102].

In the intestinal tract mixture of complex compounds including enzymes, food, bacteria, etc., can sometimes reduce the toxicity of the ingested nanoparticles [17].

Conclusions

This review has summarized the advantages and disadvantages of nano based systems in the treatment of major gastrointestinal diseases. In the field of medicine, nanotechnology is the rapidly growing area of investigation. Nano-medicine is a promising therapeutic representative in the gastrointestinal tract. Their physio- chemical properties such as high surface to volume ratio, less cytotoxic to healthy tissues, ease in hydrophobic drug delivery, stability and biodegradability are important to be considered. Different types of nanoparticles have prospective uses in the field of gastroenterology as they overcome the conventional system of treatment in many gastrointestinal diseases due to their less toxic, target specific, efficient, reliable and practicable approach and they can be used in the diagnosis and personalized therapies. Keeping in view the advantages of nano materials, disadvantages of the nano based systems cannot be overlooked in the applications of modern health care practices. So, there is an imperative need of careful approach and consideration in the selection of less toxic nano-based drugs in the disease therapy. Risk assessment of these nanoparticles is of great concern to avoid unnecessary hazardous effects because most of the nanoparticles possess toxicity and drug resistance in the biological systems after incorporation. A safe approach and detail study in the selection of nano based system is of main concern particularly in the *in-vivo* systems as these systems are based on close clinical diagnosis and these studies play key role in the future of nano-medicines.

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Conflict of Interest

There is no any conflict of interests regarding the publication of this article.

References

1. Bellmann S, Carlander D, Fasano A, Momcilovic D, Scimeca JA, et al. (2015) Mammalian gastrointestinal tract parameters modulating the integrity, surface properties, and absorption of food-relevant nanomaterials. Wiley Interdiscip Rev Nanomed Nanobiotechnol 7: 609-622.
2. Misra R, Sahoo SK (2010) Intracellular trafficking of nuclear localization signal conjugated nanoparticles for cancer therapy. Eur J Pharm Sci 39: 152-163.
3. Agüeros M, Ruiz-Gatón L, Vauthier C, Bouchemal K, Espuelas S, et al. (2009) Combined hydroxypropyl-beta-cyclodextrin and poly(anhydride) nanoparticles improve the oral permeability of paclitaxel. Eur J Pharm Sci 38: 405-413.
4. Devalapally H, Chakilam A, Amiji MM (2007) Role of nanotechnology in pharmaceutical product development. J Pharm Sci 96: 2547-2565.
5. Ugazio E, Cavalli R, Gasco MR (2002) Incorporation of cyclosporin A in solid lipid nanoparticles (SLN). Int J Pharm 241: 341-344.
6. Roy R, Kumar S, Tripathi A, Das M, Dwivedi PD (2014) Interactive threats of nanoparticles to the biological system. Immunol Lett 158: 79-87.
7. Sengupta J, Ghosh S, Datta P, Gomes A, Gomes A (2014) Physiologically important metal nanoparticles and their toxicity. J Nanosci Nanotechnol 14: 990-1006.
8. Yang YX, Song ZM, Cheng B, Xiang K, Chen XX, et al. (2014) Evaluation of the toxicity of food additive silica nanoparticles on gastrointestinal cells. J Appl Toxicol 34: 424-435.
9. Yun Y, Cho YW, Park K (2013) Nanoparticles for oral delivery: targeted nanoparticles with peptidic ligands for oral protein delivery. Adv Drug Deliv Rev 65: 822-832.
10. Lomer MC, Hutchinson C, Volkert S, Greenfield SM, Catterall A, et al. (2004) Dietary sources of inorganic microparticles and their intake in healthy subjects and patients with Crohn's disease. Br J Nutr 92: 947-955.
11. Takenaka S, Karg E, Roth C, Schulz H, Ziesenis A, et al. (2001) Pulmonary and systemic distribution of inhaled ultrafine silver particles in rats. Environ Health Perspect 109 Suppl 4: 547-551.
12. Shukla RK, Sharma V, Pandey AK, Singh S, Sultana S, et al. (2011) ROS-mediated genotoxicity induced by titanium dioxide nanoparticles in human epidermal cells. Toxicol In Vitro 25: 231-241.
13. Botelho MC, Costa C, Silva S, Costa S, Dhawan A, et al. (2014) Effects of titanium dioxide nanoparticles in human gastric epithelial cells in vitro. Biomed Pharmacother 68: 59-64.
14. Magdolenova Z, Bilanicova D, Pojana G, Fjellsba LM, Hudecova A, et al. (2012) Impact of agglomeration and different dispersions of titanium dioxide nanoparticles on the human related in vitro cytotoxicity and genotoxicity. J Environ Monit 14: 455-464.
15. Powell JJ, Faria N, Thomas-McKay E, Pele LC (2010) Origin and fate of dietary nanoparticles and microparticles in the gastrointestinal tract. J Autoimmun 34: J226-233.
16. Medina C, Santos-Martinez MJ, Radomski A, Corrigan OI, Radomski MW (2007) Nanoparticles: pharmacological and toxicological significance. Br J Pharmacol 150: 552-558.
17. Hoet PH, Brüske-Hohlfeld I, Salata OV (2004) Nanoparticles - known and unknown health risks. J Nanobiotechnology 2: 12.
18. Jani P, Halbert GW, Langridge J, Florence AT (1990) Nanoparticle uptake by the rat gastrointestinal mucosa: quantitation and particle size dependency. J Pharm Pharmacol 42: 821-826.
19. Panyam J, Dali MM, Sahoo SK, Ma W, Chakravarthi S, et al. (2003) Polymer degradation and in vitro release of a model protein from poly (D,L-lactide-co-glycolide) nano-and microparticles. Journal of Controlled Release 92: 173-187.
20. Moghimi SM, Hunter AC, Murray JC (2001) Long-circulating and target-specific nanoparticles: theory to practice. Pharmacol Rev 53: 283-318.
21. Geng Y, Dalhaimer P, Cai S, Tsai R, Tewari M, et al. (2007) Shape effects of filaments versus spherical particles in flow and drug delivery. Nat Nanotechnol 2: 249-255.
22. Ispas C, Andreescu D, Patel A, Goia D V, Andreescu S, et al. (2009) Toxicity and developmental defects of different sizes and shape nickel nanoparticles in zebrafish. Environmental science & technology 43: 6349-6356.
23. Foster KA, Yazdanian M, Audus KL (2001) Microparticulate uptake mechanisms of in-vitro cell culture models of the respiratory epithelium. J Pharm Pharmacol 53: 57-66.

24. Hagens WI, Oomen AG, de Jong WH, Cassee FR, Sips AJ (2007) What do we (need to) know about the kinetic properties of nanoparticles in the body? Regul Toxicol Pharmacol 49: 217-229.
25. De Jong WH, Hagens WI, Krystek P, Burger MC, Sips AJ, et al. (2008) Particle size-dependent organ distribution of gold nanoparticles after intravenous administration. Biomaterials 29: 1912-1919.
26. Meng H, Chen Z, Xing G, Yuan H, Chen C, et al. (2007) Ultrahigh reactivity provokes nanotoxicity: explanation of oral toxicity of nano-copper particles. Toxicol Lett 175: 102-110.
27. Wang Y, Yan X, Fu L (2013) Effect of selenium nanoparticles with different sizes in primary cultured intestinal epithelial cells of crucian carp, Carassius auratus gibelio. Int J Nanomedicine 8: 4007-4013.
28. Gatti AM (2004) Biocompatibility of micro- and nano-particles in the colon. Part II. Biomaterials 25: 385-392.
29. Ballestri M, Baraldi A, Gatti AM, Furci L, Bagni A, et al. (2001) Liver and kidney foreign bodies granulomatosis in a patient with malocclusion, bruxism, and worn dental prostheses. Gastroenterology 121: 1234-1238.
30. Siegel IA, Gordon HP (1985) Surfactant-induced increases of permeability of rat oral mucosa to non-electrolytes in vivo. Arch Oral Biol 30: 43-47.
31. Misra R, Upadhyay M, Mohanty S (2013) Nanoparticles as Carriers for Chemotherapeutic Drugs: A Review. J Nanopharmaceutics and Drug Delivery 1: 103-137.
32. Schaeublin NM, Braydich-Stolle LK, Schrand AM, Miller JM, Hutchison J, et al. (2011) Surface charge of gold nanoparticles mediates mechanism of toxicity. Nanoscale 3: 410-420.
33. Baek M, Kim IS, Yu J, Chung HE, Choy JH, et al. (2011) Effect of different forms of anionic nanoclays on cytotoxicity. J Nanosci Nanotechnol 11: 1803-1806.
34. Thorek DL, Tsourkas A (2008) Size, charge and concentration dependent uptake of iron oxide particles by non-phagocytic cells. Biomaterials 29: 3583-3590.
35. Cho J, Caruso F (2005) Investigation of the interactions between ligand-stabilized gold nanoparticles and polyelectrolyte multilayer films. Chem Mater 17: 4547-4553.
36. Rae CS, Khor IW, Wang Q, Destito G, Gonzalez MJ, et al. (2005) Systemic trafficking of plant virus nanoparticles in mice via the oral route. Virology 343: 224-235.
37. Oberdorster G, Oberdörster E, Oberdorster J (2005) Nanotoxicology: an emerging discipline evolving from studies of ultrafine particles. Environ Health Perspect 113: 823-839.
38. Lin S, Wang X, Ji Z, Chang CH, Gonzalez MJ, et al. (2014) Aspect Ratio Plays a Role in the Hazard Potential of CeO2 Nanoparticles in Mouse Lung and Zebrafish Gastrointestinal Tract. ACS Nano 8: 4450-4464.
39. Wang Y, Chen Z, Ba T, Pu J, Chen T, et al. (2013) Susceptibility of young and adult rats to the oral toxicity of titanium dioxide nanoparticles. Small 9: 1742-1752.
40. Dobrovolskaia MA, Germolec DR, Weaver JL (2009) Evaluation of nanoparticle immunotoxicity. Nat Nanotechnol 4: 411-414.
41. Stone V, Johnston H, Schins RP (2009) Development of in vitro systems for nanotoxicology: methodological considerations. Crit Rev Toxicol 39: 613-626.
42. Bihari P, Vippola M, Schultes S, Praetner M, Khandoga AG, et al. (2008) Optimized dispersion of nanoparticles for biological in vitro and in vivo studies. Part Fibre Toxicol 5: 14.
43. Allouni ZE, Cimpan MR, Høl PJ, Skodvin T, Gjerdet NR (2009) Agglomeration and sedimentation of TiO2 nanoparticles in cell culture medium. Colloids Surf B Biointerfaces 68: 83-87.
44. Lundqvist M, Stigler J, Elia G, Lynch I, Cedervall T, et al. (2008) Nanoparticle size and surface properties determine the protein corona with possible implications for biological impacts. Proc Natl Acad Sci U S A 105: 14265-14270.
45. Ashwood P, Thompson RP, Powell JJ (2007) Fine particles that adsorb lipopolysaccharide via bridging calcium cations may mimic bacterial pathogenicity towards cells. Exp Biol Med (Maywood) 232: 107-117.
46. Powell JJ, Ainley CC, Evans R, Thompson RP (1994) Intestinal perfusion of dietary levels of aluminium: association with the mucosa. Gut 35: 1053-1057.
47. Moller W, Felten K, Meyer G, Meyer P, Seitz J, et al. (2009) Corrections in dose assessment of 99mTc radiolabeled aerosol particles targeted to central human airways using planar gamma camera imaging. J Aerosol Med Pulm Drug Deliv 22: 45-54.
48. Jani PU, Nomura T, Yamashita F, Takakura Y, Florence AT, et al. (1996) Biliary excretion of polystyrene microspheres with covalently linked FITC fluorescence after oral and parenteral administration to male Wistar rats. J Drug Target 4: 87-93.
49. Cho M, Cho WS, Choi M, Kim SJ, Han BS, et al. (2009) The impact of size on tissue distribution and elimination by single intravenous injection of silica nanoparticles. Toxicol Lett 189: 177-183.
50. Gaumet M, Gurny R, Delie F (2009) Localization and quantification of biodegradable particles in an intestinal cell model: the influence of particle size. Eur J Pharm Sci 36: 465-473.
51. Cartiera MS, Johnson KM, Rajendran V, Caplan MJ, Saltzman WM (2009) The uptake and intracellular fate of PLGA nanoparticles in epithelial cells. Biomaterials 30: 2790-2798.
52. Jain KK (2007) Applications of nanobiotechnology in clinical diagnostics. Clin Chem 53: 2002-2009.
53. Chen Z, Meng H, Xing G, Chen C, Zhao Y, et al. (2006) Acute toxicological effects of copper nanoparticles in vivo. Toxicol Lett 163: 109-120.
54. Tiede K, Boxall AB, Tear SP, Lewis J, David H, et al. (2008) Detection and characterization of engineered nanoparticles in food and the environment. Food Addit Contam Part A Chem Anal Control Expo Risk Assess 25: 795-821.
55. Asiyanbola B, Soboyejo W (2008) For the surgeon: an introduction to nanotechnology. J Surg Educ 65: 155-161.
56. Gehrke H, Frühmesser A, Pelka J, Esselen M, Hecht LL, et al. (2013) In vitro toxicity of amorphous silica nanoparticles in human colon carcinoma cells. Nanotoxicology 7: 274-293.
57. Li C, Zhao W, Liu B, Xu G, Liu L, et al. (2014) Cytotoxicity of ultrafine monodispersed nanoceria on human gastric cancer cells. J Biomed Nanotechnol 10: 1231-1241.
58. Bhabra G, Sood A, Fisher B, Cartwright L, Saunders M, et al. (2009) Nanoparticles can cause DNA damage across a cellular barrier. Nat Nanotechnol 4: 876-883.
59. Sergent JA, Paget V, Chevillard S (2012) Toxicity and genotoxicity of nano-SiO2 on human epithelial intestinal HT-29 cell line. Ann Occup Hyg 56: 622-630.
60. Lomer MC, Hutchinson C, Volkert S, Greenfield SM, Catterall A, et al. (2004) Dietary sources of inorganic microparticles and their intake in healthy subjects and patients with Crohn's disease. Br J Nutr 92: 947-955.
61. Powell JJ, Ainley CC, Harvey RS, Mason IM, Kendall MD, et al. (1996) Characterisation of inorganic microparticles in pigment cells of human gut associated lymphoid tissue. Gut 38: 390-395.
62. Oberdorster E (2004) Manufactured nanomaterials (fullerenes, C60) induce oxidative stress in the brain of juvenile largemouth bass. Environ Health Perspect 112: 1058-1062.
63. Zoetendal EG, Collier CT, Koike S, Mackie RI, Gaskins HR (2004) Molecular ecological analysis of the gastrointestinal microbiota: a review. J Nutr 134: 465-472.
64. Young VB (2012) The intestinal microbiota in health and disease. Curr Opin Gastroenterol 28: 63-69.
65. Canani RB, Costanzo MD, Leone L, Pedata M, Meli R, et al. (2011) Potential beneficial effects of butyrate in intestinal and extraintestinal diseases. World J Gastroenterol 17: 1519-1528.
66. Bergin IL, Witzmann FA (2013) Nanoparticle toxicity by the gastrointestinal route: evidence and knowledge gaps. Int J Biomed Nanosci Nanotechnol 3.
67. Manson JM, Rauch M, Gilmore MS (2008) The commensal microbiology of the gastrointestinal tract. Adv Exp Med Biol 635: 15-28.

68. Kim Y, Suh HS, Cha HJ, Kim SH, Jeong KS, et al. (2009) A case of generalized argyria after ingestion of colloidal silver solution. Am J Ind Med 52: 246-250.
69. D'Argenio V, Salvatore F (2015) The role of the gut microbiome in the healthy adult status. Clin Chim Acta 451: 97-102.
70. Atarashi K, Honda K (2011) Microbiota in autoimmunity and tolerance. Curr Opin Immunol 23: 761-768.
71. Williams K, Milner J, Boudreau MD, Gokulan K, Cerniglia CE, et al. (2015) Effects of subchronic exposure of silver nanoparticles on intestinal microbiota and gut-associated immune responses in the ileum of Sprague-Dawley rats. Nanotoxicology 9: 279-289.
72. Platonova TA, Pridvorova SM, Zherdev AV, Vasilevskaya LS, Arianova EA, et al. (2013) Identification of silver nanoparticles in the small intestinal mucosa, liver, and spleen of rats by transmission electron microscopy. Bull Exp Biol Med 155: 236-241.
73. Mohanraj V, Chen Y (2007) Nanoparticles-a review. Tropical Journal of Pharmaceutical Research 5: 561-573.
74. Lozano O, Laloy J, Alpan L, Mejia J, Rolin S, et al. (2012) Effects of SiC nanoparticles orally administered in a rat model: biodistribution, toxicity and elemental composition changes in feces and organs. Toxicol Appl Pharmacol 264: 232-245.
75. Wachsmann P, Lamprecht A (2012) Polymeric nanoparticles for the selective therapy of inflammatory bowel disease. Methods Enzymol 508: 377-397.
76. Yoshitomi T, Sha S, Vong LB, Chonpathompikunlert P, Matsui H, et al. (2014) Indomethacin-loaded redox nanoparticles improve oral bioavailability of indomethacin and suppress its small intestinal inflammation. Ther Deliv 5: 29-38.
77. Chakraborty S, Stalin S, Das N, Choudhury ST, Ghosh S, et al. (2012) The use of nano-quercetin to arrest mitochondrial damage and MMP-9 upregulation during prevention of gastric inflammation induced by ethanol in rat. Biomaterials 33: 2991-3001.
78. Zhang H, Li X, Ding J, Xu H, Dai X, et al. (2013) Delivery of ursolic acid (UA) in polymeric nanoparticles effectively promotes the apoptosis of gastric cancer cells through enhanced inhibition of cyclooxygenase 2 (COX-2). Int J Pharm 441: 261-268.
79. Wang Y, Ba T, Chen ZJ, Pu J, Cui XX, et al. (2012) [Effect of titanium dioxide nanoparticles on hemogram in rats with gastric ulcer]. Zhonghua Yu Fang Yi Xue Za Zhi 46: 740-744.
80. Li X, Lu X, Xu H, Zhu Z, Yin H, et al. (2012) Paclitaxel/tetrandrine coloaded nanoparticles effectively promote the apoptosis of gastric cancer cells based on "oxidation therapy". Mol Pharm 9: 222-229.
81. Zhou ZL, Yang YX, Ding J, Li YC, Miao ZH (2012) Triptolide: structural modifications, structure-activity relationships, bioactivities, clinical development and mechanisms. Nat Prod Rep 29: 457-475.
82. Li J, Jin J, Li M, Guan C, Wang W, et al. (2012) Role of Nrf2 in protection against triptolide-induced toxicity in rat kidney cells. Toxicol Lett 213: 194-202.
83. Liu L, Jiang Z, Liu J, Huang X, Wang T, et al. (2010) Sex differences in subacute toxicity and hepatic microsomal metabolism of triptolide in rats. Toxicology 271: 57-63.
84. Zhang C, Gu C, Peng F, Liu W, Wan J, et al. (2013) Preparation and optimization of triptolide-loaded solid lipid nanoparticles for oral delivery with reduced gastric irritation. Molecules 18: 13340-13356.
85. Tsai SW, Yu DS, Tsao SW, Hsu FY (2013) Hyaluronan-cisplatin conjugate nanoparticles embedded in Eudragit S100-coated pectin/alginate microbeads for colon drug delivery. Int J Nanomedicine 8: 2399-2407.
86. Laroui H, Geem D, Xiao B, Viennois E, Rakhya P, et al. (2014) Targeting intestinal inflammation with CD98 siRNA/PEI-loaded nanoparticles. Mol Ther 22: 69-80.
87. Parkin DM, Bray F, Ferlay J, Pisani P (2005) Global cancer statistics, 2002. CA Cancer J Clin 55: 74-108.
88. Berrino F, De Angelis R, Sant M, Rosso S, Bielska-Lasota M, et al. (2007) Survival for eight major cancers and all cancers combined for European adults diagnosed in 1995-99: results of the EUROCARE-4 study. Lancet Oncol 8: 773-783.
89. Xu Q, Guo L, Gu X, Zhang B, Hu X, et al. (2012) Prevention of colorectal cancer liver metastasis by exploiting liver immunity via chitosan-TPP/nanoparticles formulated with IL-12. Biomaterials 33: 3909-3918.
90. Sharma M, Malik R, Verma A, Dwivedi P, Banoth GS, et al. (2013) Folic acid conjugated guar gum nanoparticles for targeting methotrexate to colon cancer. J Biomed Nanotechnol 9: 96-106.
91. Jeong YI, Chung KD, Kim da H, Kim YH, Lee YS, et al. (2013) All-trans retinoic acid-incorporated nanoparticles of deoxycholic acid-conjugated dextran for treatment of CT26 colorectal carcinoma cells. Int J Nanomedicine 8: 485-493.
92. Minelli R, Serpe L, Pettazzoni P, Minero V, Barrera G, et al. (2012) Cholesteryl butyrate solid lipid nanoparticles inhibit the adhesion and migration of colon cancer cells. Br J Pharmacol 166: 587-601.
93. Reis C, Candeias S, Fernandes C, Martinho N, Aniceto N (2013) Ibuprofen nanoparticles for oral delivery: Proof of Concept. J Nanomedine Biotherapeutic Discov 4: 2.
94. Bonelli P, Tuccillo FM, Federico A, Napolitano M, Borrelli A, et al. (2012) Ibuprofen delivered by poly (lactic-co-glycolic acid) (PLGA) nanoparticles to human gastric cancer cells exerts antiproliferative activity at very low concentrations. Int J Nanomedicine 7: 5683-5691.
95. Moulari B, Beduneau A, Pellequer Y, Lamprecht A (2013) Nanoparticle targeting to inflamed tissues of the gastrointestinal tract. Curr Drug Deliv 10: 9-17.
96. Goldberg DS, Vijayalakshmi N, Swaan PW, Ghandehari H (2011) G3.5 PAMAM dendrimers enhance transepithelial transport of SN38 while minimizing gastrointestinal toxicity. J Control Release 150: 318-325.
97. Zhang C, Huang P, Bao L, He M, Luo T, et al. (2011) Enhancement of gastric cell radiation sensitivity by chitosan-modified gold nanoparticles. J Nanosci Nanotechnol 11: 9528-9535.
98. Li Y, Gobin AM, Dryden GW, Kang X, Xiao D, et al. (2013) Infrared light-absorbing gold/gold sulfide nanoparticles induce cell death in esophageal adenocarcinoma. Int J Nanomedicine 8: 2153-2161.
99. Kanwar JR, Samarasinghe RM, Sehgal RK, Rupinder K (2012) Nano-lactoferrin in diagnostic, imaging and targeted delivery for cancer and infectious diseases. J Cancer Sci & Therapy 4: 31-42.
100. Sengel-Turk CT, Hascicek C, Dogan AL, Esendagli G, Guc D, et al. (2012) Preparation and in vitro evaluation of meloxicam-loaded PLGA nanoparticles on HT-29 human colon adenocarcinoma cells. Drug Dev Ind Pharm 38: 1107-1116.
101. Laroui H, Sitaraman SV, Merlin D (2012) Gastrointestinal delivery of anti-inflammatory nanoparticles. Methods Enzymol 509: 101-125.
102. Ju S, Mu J, Dokland T, Zhuang X, Wang Q, et al. (2013) Grape exosome-like nanoparticles induce intestinal stem cells and protect mice from DSS-induced colitis. Mol Ther 21: 1345-1357.