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REVIEW

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The role of *Shigella* spp. in propagating bacillary dysentery in humans and the prominence of nanotechnology in disease prevention

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Abstract

Background Shigellosis, also known as bacillary dysentery, is an acute infection of the intestine. The symptoms can vary from mild watery diarrhoea to severe inflammatory bacillary dysentery, which is characterized by fever, intense abdominal cramps, and the presence of blood and mucus in the stools. While the disease typically resolves on its own, it can become life-threatening in immunocompromised individuals or in the absence of adequate medical care.

Main body of the abstract *Shigella* is the primary cause of bacillary dysentery worldwide. It is comprised of four distinct species—*S. dysenteriae, S. flexneri*, *S. boydii,* and *S. sonnei*—each with unique genomic characteristics and disease-causing abilities. *Shigella* spp. have developed resistance to multiple drugs and have also adapted well to the gut environment over time. They have become well-suited to infecting the human gut epithelial cells and causing dysentery. Consequently, numerous studies have investigated the potential application of nanotechnology in the treatment of shigellosis by leveraging its capability for drug delivery and targeted therapy, thereby improving effectiveness while reducing side effects.

Short conclusion It is crucial to maintain ongoing surveillance and develop new strategies to effectively manage this issue. In this review, we shed light on the present comprehension of distinct *Shigella* spp. and their potential contribution to the pathogenesis of shigellosis, along with their interaction with the gut microbiota. We also provide insight into how nanotechnology may be a major factor in preventing shigellosis in the future.

Keywords Bacillary dysentery, Shigellosis, *Shigella dysenteriae*, *Shigella flexneri*, *Shigella boydii*, *Shigella sonnei*, T3SS, Gut microbiome, Nanotechnology

Background

The most prevalent kind of dysentery is shigellosis, often known as bacillary dysentery. Due to their shared genetic and phenotypic traits, the genus *Shigella*, which is a contemporary member of the *Escherichia* tribe, is responsible for this enterobacterial illness [1]. Globally, it is estimated that *Shigella* is responsible for 80–165 million instances of illness and 600,000 fatalities each year, with the majority occurring in children residing in resource poor nations. Of all shigellosis cases worldwide, around 20–119 million illnesses and 6900–30,000 deaths are linked to foodborne transmission [2, 3]. The WHO has identified South Asia and sub-Saharan Africa as the regions with the highest burden [4], albeit regions of heightened activity are also present in Central America, South America, the Ganges–Brahmaputra Delta, and New Guinea island [5]. *Shigella* spp. is a genus of bacteria

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that are gram-negative, nonmotile, non-spore-forming, non-lactose fermenting, bacillus-shaped, facultatively anaerobic, and genetically highly correlated with *Escherichia coli*. There are four species in the genus *Shigella* (*S. dysenteriae, S. boydii, S. sonnei*, and *S. flexneri*), each with numerous serotypes [6]. *Shigella boydii* is most prevalent in the Indian subcontinent. The two most widespread species worldwide are *S. sonnei* and *S. flexneri.* In overcrowded areas with insufficient sanitation and personal cleanliness, the illness is more prevalent [1]. Shigellosis can also arise as an asymptomatic infection to moderate diarrhoea*. S. dysenteriae* type I represents the most severe and potentially fatal strain of dysentery. Shigellosis brought on by *S. dysenteriae* type I might occasionally trigger one or more problems [7]. The pathogenesis of shigellosis involves *Shigella spp.* bacterium. *Shigella* is typically transmitted via. the faecal–oral route, contaminated food or water sources, and poor hygiene. After being ingested by the host, Shigella starts to invade the intestinal lining, particularly the colon, resulting in inflammation and intestinal mucosal disruption. This results in symptoms like fever, abdominal cramps, watery diarrhoea, and bloody stools [8]. Further insights on how each *Shigella* spp. involves in propagating shigellosis in humans are discussed under the sub-heading causative microbe's section.

Common therapy

The first medication, sulphonamides, was introduced in the early 1940s, but their potency had decreased by the late 1940's. To alleviate this issue, chloramphenicol was recommended followed by tetracycline as a therapy for the management of dysentery. Later research revealed that neither of these medications is efficient. Following that, ampicillin and cotrimoxazole were subsequently made available for purchase. Different antibiotics, including ofloxacin, nalidixic, norfloxacin, and ciprofloxacin, were introduced to the Indian market later in the 1980s for the management of bacillary dysentery and proved to be incredibly effective. Later, more medications like cefotaxime and amikacin entered the market. In 1990, ciprofloxacin was shown to be significantly more effective than drugs like chloramphenicol, ampicillin, and nalidixic acid. Following that, it was reported repeatedly that *S. flexneri* exhibits 45.6% resistance to ciprofloxacin and 74.1% resistance to nalidixic acid. *S. flexneri* was discovered to be resistant to fluoroquinolones in 2004; as a result, this medication was no longer favoured for therapy. Following this, the WHO suggested azithromycin, ceftriaxone, and pivmecillinam as substitute medications for treating *shigellae* that were resistant to fluoroquinolone antibiotics. In recent years, *Shigella* has grown resistant to these recommended medications. It is alarming that *Shigella* has developed such extensive resistance to almost all currently used medication classes [9–11].

Management of shigellosis

The prevention and control of shigellosis require the implementation of several strategies. Prevention of bloody diarrhoea caused by *Shigella* relies primarily on measures that prevent the spread of the bacteria within the community, including person-to-person transmission. These measures include ensuring a safe water supply, providing proper sanitation facilities, and practising good personal hygiene and food safety, with a strong emphasis on handwashing. It is crucial to wash hands before eating, before feeding children, after using the toilet, and after handling children's waste. Symptomatic individuals are recommended to avoid sexual contact to reduce transmission. These measures would aid in controlling the disease, but progress is slow in impoverished communities where the disease is most prevalent. Consequently, many individuals believe that the development of a vaccine is the only hope for effectively managing shigellosis [12]. However, creating a vaccine for shigellosis is challenging due to the heterogeneous distribution of *Shigella* species and serotypes [13]. Nevertheless, progress has been made in developing safe and cost-effective multivalent vaccines. To effectively manage cases of shigellosis, standardized reporting and surveillance practices should be implemented across jurisdictions, taking into account the public health significance of PCR-positive results [8].

Antibiotic treatment is advised for non-resistant shigellosis cases that are moderate to severe. Non-drug-resistant *Shigella* patients can anticipate clinical improvement within 48 h of antibiotic therapy, leading to reduced chances of severe complications and death, shorter symptom duration, elimination of the bacteria from the stool, and a lower likelihood of transmission to others [13, 14]. Previously, antibiotics such as tetracycline, ampicillin, and cotrimoxazole were highly effective. However, newer fluoroquinolones such as norfloxacin, ciprofloxacin, ofloxacin, azithromycin, and ceftriaxone have proven to be effective as well. Concurrent administration of oral rehydration salt is necessary to prevent or correct dehydration [15]. Overall, the management and prevention of shigellosis depend on an all-encompassing strategy that incorporates effective treatment methods with preventative measures.

Main text

Causative microbes

The genus *Shigella* can be classified into four distinct species, namely *S. dysenteriae* (serogroup A, which comprises 12 different serotypes); *S. flexneri* (serogroup B,

which consists of 6 distinct serotypes); *S. boydii* (serogroup C, which encompasses 18 serotypes); and *S. sonnei* (serogroup D, which consists of a solitary serotype). The physiological makeup of serogroups A, B, and C is extremely similar, although ornithine decarboxylase and positive β-D-galactosidase biochemical responses can distinguish *S. sonnei* from the other serogroups [16]. Figure 1 shows the general mechanism by which *Shigella* spp. cause pathogenicity in the host. The following discussion pertains to the four primary categories of *Shigella*.

Shigella dysenteriae

In 1896, during a major dysentery outbreak in Japan, more than 90,000 cases were reported with a fatality rate close to 30%. Kiyoshi Shiga was the first to isolate *Shigella dysenteriae*, also known as *S. dysenteriae* type 1. The next half-century saw the clarification of *Shigella* spp. microbiology and epidemiology, as well as a thorough investigation of the processes by which the microbe causes illness [17]. One of the main causes of shigellosis or bacillary dysentery is thought to be *S. dysenteriae* type 1 [18]. There is only one known reservoir for *Shigella* spp., and that is humans. The bacteria are spread through direct human contact as well as contaminated food and water. In men who have sex with men, there has been evidence of sexual transmission [19]. Lower-middle-class and low-income nations are significantly more likely to have *S. dysenteriae* infections and intoxications, particularly in children. The loss of intestinal proteins resulting from these diseases might induce chronic diarrhoea and malnourishment [20, 21]. Furthermore, the significance of Shiga toxin [22] in the pathogenesis of dysentery remains unclear, despite the fact that *S. dysenteriae* type 1 produces this toxin. However, dysentery caused by *S. dysenteriae* type 1 is generally more severe than that caused by mutants of *S. dysenteriae* type 1 or other *Shigellae* that produce little or no Shiga toxin, suggesting that while Shiga toxin is not essential for the pathogenesis of dysentery, it does contribute to the severity of the disease [23]. Shiga toxin produced by *S. dysenteriae* type 1 predominantly induces haemolytic uraemic syndrome (HUS) in patients, with the secreted toxin resulting in over 2,800,000 acute diseases and approximately 3900 HUS cases each year, while 2–7% of *S. dysenteriae* infections in humans lead to HUS [24]. Moreover, *Shigella dysenteriae* type 1 strains are notorious for acquiring resistance against a myriad of antibiotics, rendering

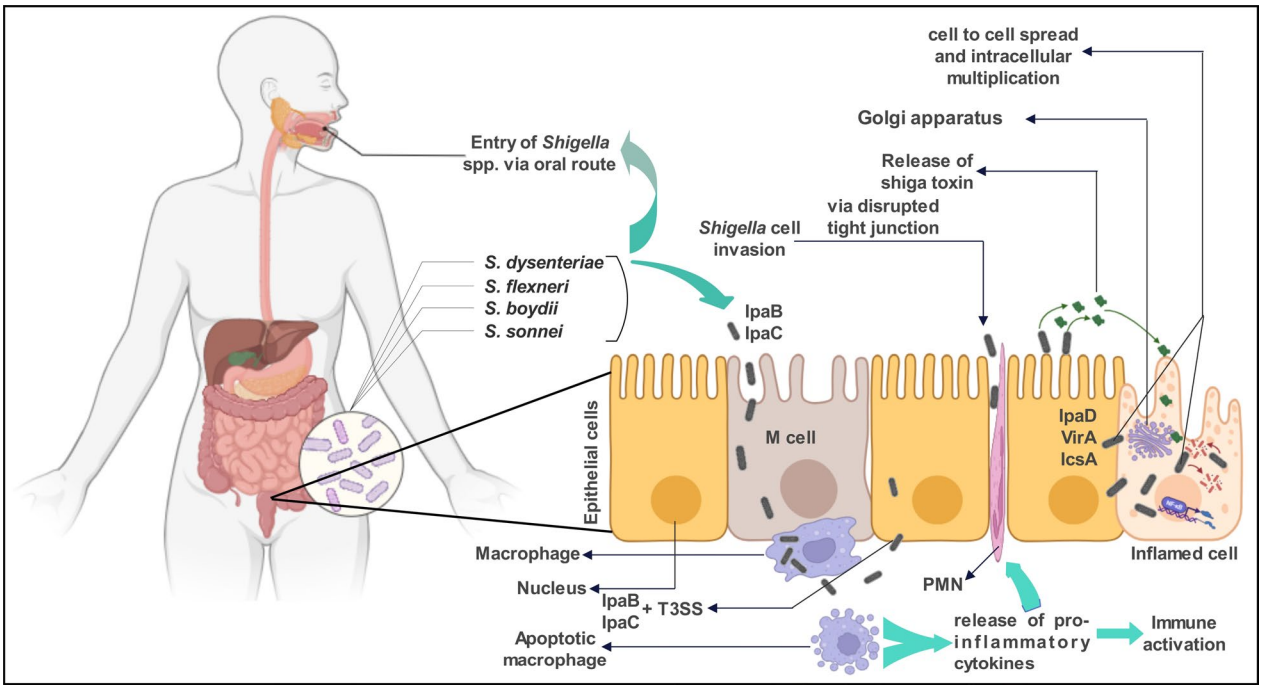

Fig. 1 Shigella utilizes transcytosis to breach the epithelial cell barrier and interact with macrophage. Proteins (IpaB and IpaC) can be directly injected into host cells in a manner akin to using a syringe owing to the protein secretion mediated by the T3SS. By evoking an apoptotic-like cell death that attracts PMN (polymorphonuclear leukocytes) into the infected tissue and releases pro-inflammatory cytokines that draw neutrophils and trigger innate defences, the bacterium avoids being broken down by the macrophages. Moreover, Shigella effectively penetrates the lamina propria to access the main replicative niche and the cytoplasm of epithelial cells on the basolateral side of the colonic epithelium, from whence it spreads infection from cell to cell. The figure was created using BioRender (trial version) and Wondershare EdrawMax (free version)

previously effective drugs ineffective, as they frequently exhibit resistance to inexpensive and ordinary antibiotics while remaining susceptible to more extravagant or intravenous medications across their distribution [7]. Resistance to antimicrobial agents used to treat shigellosis is growing, leaving only two widely available drugs for outpatient treatment: ciprofloxacin and azithromycin. The increasing resistance to these drugs may lead to a time when there are no effective treatment options for shigellosis [25]. Treatment with the right antibiotics shortens the length of diarrhoea, alleviates symptoms, and expedites healing [7]. The global occurrence of *S. dysenteriae* type 1 infections has decreased since 2000, but the reasons for this are unknown. *S. dysenteriae* type 1 has previously become rare for many years before resurfacing in fatal epidemics, a pattern that could potentially happen again. Infections with *S. dysenteriae* types other than type 1 are even less frequent [25].

Shigella flexneri

Gram-negative, rod-shaped bacteria make up the genus *Shigell*a, which includes the species of bacterium known as *Shigella flexneri (S. flexneri)* [26]. *S. flexneri* is a significant cause of global bacterial diarrhoea, especially in developing nations. It causes a considerable amount of illness, particularly in children under 5 years old [27]. Research in non-human primates has shown that *S. flexneri* is a pathogen that lives inside colon epithelial cells [28]. It has specialized structures known as Type III secretion systems (T3SS), which function as complex molecular machinery enabling the direct injection of proteins into host cells resembling a syringe-like action [29]. Injected proteins alter the host cell's processes, enabling bacterial invasion, replication, and dissemination within the colon lining [30], causing damage to the intestinal mucosa through the production of Shiga toxins, also known as verotoxin, resulting in inflammation and haemorrhage [31]. This invasion results in the characteristic shigellosis symptoms [32]. The mechanisms implicated entail the initial interaction of *S. flexneri* with intestinal epithelial cells of the host, wherein the bacteria can attach to the cell surface using different adhesins and outer membrane proteins, ultimately culminating in the assembly of the T3SS of *S. flexneri* [33]. The bacteria employ a translocator protein known as IpaB, or Invasion plasmid antigen B [34], which creates pores in the membrane of the host cell. This protein is a crucial element of the T3SS. IpaB functions as a conduit through which effector proteins are transported into the cytoplasm of the host cell. Additionally, it collaborates with another translocator protein called IpaC, or Invasion plasmid antigen C. These translocators are secreted by the *S. flexneri* T3SS apparatus via the needle, forming a complex called IpaB/IpaC translocon [35, 36], which penetrates the host cell membrane and opens a channel to facilitate the transfer of effector proteins from the bacterium into the cytoplasm of the host cell. This process is vital for modifying signalling pathways in host cells, rearranging actin, and creating a space within the cell for *S. flexneri* [37]. The essential translocator proteins associated with the T3SS of *S. flexneri* are IpaB and IpaC [37]. Nevertheless, additional effector proteins, such as IpaD [38], VirA [39], and IcsA [40], might also contribute to the effective invasion of the host cell, either through direct or indirect means. Furthermore, *S. flexneri* causes a severe inflammatory response in the gut mucosa [32]. The infiltration of epithelial cells and subsequent annihilation emancipates pro-inflammatory cytokines, like interleukin-1 (IL-1), interleukin-6 (IL-6), and tumour necrosis factor-alpha (TNF-alpha). These cytokines beckon immune cells, encompassing neutrophils and macrophages, to the location of infection, thus engendering additional detriment to tissues and inflammation [41]. The clinical symptoms of bacillary dysentery caused by *S. flexneri,* such as severe diarrhoea with abdominal pain, bloody and mucus-filled diarrhoea, fever, and inflammation of the intestinal lining, are a result of the combined action of these mechanisms [27].

Shigella boydii

Shigella boydii (S. boydii) is a gram-negative bacterium that is typically nonmotile and does not produce spores [42]. However, there are some shreds of evidence suggesting the presence of flagella, which are about 10 microns long and 12–14 nm in diameter, primarily located at one end of the cell, although their motility is not essential for intestinal infection [43]. The electrophoretic examination of flagellins demonstrated that the movement of *S. boydii* C3 flagellin is quicker than that of *S. flexneri* flagellin despite the fact that the estimated molecular mass of C3 flagellin (58 kD) is higher than that of *S. flexneri* flagellin (56.6 kD) [44]. The flagella genes in *S. dysenteriae, S. flexneri, S. boydii,* and *S. sonnei* exhibit variation, contributing to the genetic diversity within these species [43].

18 serotypes of *S. boydii* belonging to serogroup C have been documented [16]; however, Akter et al. [45] identified around 20 serotypes, with *S. boydii* type 1 being the second most commonly observed serotype among the various serotypes of *S. boydii* in Bangladesh. Within 12–48 h after consuming food tainted with these germs, shigellosis develops. Initial symptoms include fever, pains, weariness, and appetite loss. These symptoms may be accompanied by watery diarrhoea, which can potentially progress into the presence of bloody stools or dysentery. Certain severe cases can lead to the development of a fatal HUS caused by the production of Shiga

toxin [46], while the severity of the disease varies for different strains of *Shigella* bacteria (low in *S.sonnei* and *S. boydii,* moderate to severe in *S. flexneri*, and severe in *S. dysenteriae*) [47]. In the GEMS study, a more detailed analysis revealed that the majority of the isolates were comprised of *S. flexneri* accounting for 65.9%, with *S. sonnei* coming in second with 23.7%, while the percentages for *S. dysenteriae* and *S. boydii* were 5.0% and 5.4% [48]. In affluent nations, *S. boydii* is comparatively uncommon and is usually connected to people who have visited endemic regions [49]. Furthermore, examination of the whole genome sequencing (WGS) information also demonstrated a strong phylogenetic connection between *S. boydii* serotypes 1 and 20, suggesting that serotype 20 emerged recently from serotype 1. Travel reports from patients to Egypt, Afghanistan, India, and Sierra Leone indicate that this new serotype is widely distributed regionally, even if the PHE (Public Health England) archives' travel data for isolates *S. boydii* 20 were not fully completed [50]. *S. boydii* outbreaks are more prevalent in Central and South America compared to other regions [51], and there is limited research available on certain serotypes of *S. boydii* [45].

Shigella sonnei

Shigella sonnei (*S. sonnei)*, a Gram-negative facultative intracellular pathogen, was named 'Sonne's bacillus' after Carl Olaf Sonne, who identified it as the cause of bacillary dysentery [52]. Watery diarrhoea is the main clinical manifestation in most *S. sonnei*-infected patients. There is just one serotype of *S. sonnei* [53], and it can be distinguished from other serogroups by specific biochemical reactions with β-D-galactosidase and ornithine decarboxylase [16]. *S. sonnei,* originating from Europe, has now spread globally and [54] has emerged as the dominant subgroup in Asian countries [55]. The prevalence of *S. sonnei* is more common in industrialized nations compared to developing countries and results in less severe illness than *S. dysenteriae* and *S. flexneri* [56]. The spread of *S. sonnei* across borders is often associated with international travel and cross-border food trade [57]. The persistence of *S. sonnei* is facilitated by water and food contamination, fomites, unsanitary conditions, and ecological factors, leading to the emergence of severe outbreaks [27]. The rapid increase in *S. sonnei* has been attributed to potential factors such as passive immunization caused by *Plesiomonas shigelloides* and the favourable environment provided by the widespread amoeba species *Acanthamoeba castellanii* [58]. Food, water, insects, fauna, birds, and amoeba are among the common reservoirs and modes of transmission that *S. sonnei* shares with other *Shigella* species [59]. *S. sonnei* uses a T3SS to inject effector proteins into host macrophages and epithelial cells after they enter the gastrointestinal system. This is an essential step for tissue invasion and immune response evasion. Like *S. flexneri, S. sonnei* utilizes IcsA, an adhesin regulated by the T3SS, to adhere to epithelial cells. However, *S. sonnei* possesses an additional adhesin called multivalent adhesion molecule (MAM SS01327), which also aids in adhesion. These two adhesins work together, along with IcsA, to efficiently attach *S. sonnei* to host cells [54]. Moreover, *S. sonnei* has the Type VI Secretion System (T6SS) [60] which helps in host colonization. *S. sonnei's* possession of T6SS gives it an advantage over *S. flexneri*, which lacks this system. This advantage could be the reason for *S. sonnei's* dominance in causing Shigellosis [61]. Colicinogenic plasmids in *S. sonnei* might also contribute to its dominance [62]. *S. sonnei* has the group 4 capsule (G4C) which accounts for 8.8% of extracellular capsules. Identical in structure to the O-Antigen (OAg) affixed to the lipid A-core of lipoprotein-associated liposomes (LPS), these capsules, sometimes referred to as OAg capsules, are composed of high molecular weight surface polysaccharides. The bacteria are shielded by the G4C from serum-mediated destruction [63, 64].

Entry of *Shigella* in the gut and its interaction with the gut microbiome

The human microbiota is made up of trillions of symbiotic microbial cells in each person, mainly in the gut. The human microbiome consists of the genes in these cells [65]. The gut microbiota has important roles in nutrient metabolism, drugs and xenobiotic metabolism, maintaining the integrity of the gut barrier, influencing the immune system, and protecting against pathogens [66]. *Shigella* has developed the ability to adapt to various environmental conditions (temperature, pH, oxygen or osmolarity) as a result of coevolution, which is facilitated by the expression of specific transcriptional regulators [67]. *Shigella* species, in contrast to many other bacteria, are highly successful in invasive systems, which allow bacteria to penetrate and grow within the epithelia of the human gut and ultimately cause severe inflammatory colitis, known as shigellosis [68]. *Shigella* enters the intestinal mucosa after ingestion, causing a severe inflammatory response that causes tissue damage [32].

Shigella secretes neuraminidases and mucinases in the colon to cross the mucus layer and reach the epithelial surface [69], where the *iphH* gene (encoded by chromosomal DNA and/or recombinant plasmids) allows bacterial cell-to-cell movement and dissemination, while the *ial* gene which is encoded by plasmids (invasion-associated loci) enables penetration of intestinal epithelial tissues [70, 71]. Oxygen sensing plays a crucial role in infection by priming *Shigella* at the epithelial surface.

Although strict anaerobes are mainly found in the colon, where oxygen levels are low, at the epithelial surface, oxygen concentrations increase as oxygen diffuses from the oxygenated epithelium. Oxygen diffusion may be restricted by the thick mucus layer, but at the epithelial surface oxygen levels remain highest. *Shigella* senses increasing oxygen content at the epithelial surface to trigger their T3SS and improve invasion, avoiding needless activation of their T3SS while physically distant from their cellular target, even if the transcription of their T3SS is hindered under anaerobic circumstances [72]. T3SS is regarded to be a crucial element for bacterial entrance. It is made up of many proteins, one of which is an oligomer with a needle-like form that is anchored in the protein complex that joins the inner and outer bacterial membranes. An oligomer consisting of the invasion plasmid antigens *ipaB, ipaC,* and *ipaD* makes up the needle's tip [73–75]. Conversely, the T3SS regulatory cascade consists of three transcription activators, VirB (ParB family), VirF (AraC-family), and MxiE (AraC family), as well as a repressor called H-NS (histone-like nucleoid structure protein) [76]. Following close bacterial contact with host cells, the T3SS introduces effector proteins into the cells, causing the bacteria to transfer their products into the target cells' cytosol and cause cell invasion, tissue damage, and immune evasion [77, 78], which resembles phagocytosis. Subsequently, *Shigella* utilizes actin-based motility and effectors to invade neighbouring cells through a process called "cell-to-cell spread", which shares some similarities with the initial entry [76], and this invasion and spread within the colonic epithelium is the main cause of the severe inflammatory response associated with the infection [79].

Unknown is the precise way in which *Shigella* interacts with inherent host elements like the microbiota. Ndungo et al. [80] proposed that *Shigella* infection could potentially affect the development of the microbial community in infancy, while changes in the gastrointestinal microbiome could make individuals more susceptible to infections. Following *Shigella's* invasion and replication within host cells, the innate immune system promptly detects DAMPs or PAMPs, transmits warning signals to the immune system as a whole, and eventually starts an inflammatory response [81]. Suryavanshi et al. [82] emphasized the crucial role of the gut microbiome in maintaining health and preventing infection through the production of antimicrobial compounds such as bacteriocins, organic acids like acetic acid and lactic acid, and hydrogen peroxide. Conversely, Oyewale et al. [83] have asserted alterations in the intestinal microbial community have significant implications for human health and disease pathogenesis, which can be attributed to lifestyle and the presence of underlying diseases. When the gut is dysbiotic, disease-causing and pathogenic bacteria proliferate and the protecting bacteria disappear [84]. Additionally, Table 1 provides information on how *Shigella* might exploit dysbiosis circumstances**.** In the presence of bile salts, *Shigella* may develop biofilms, which alter the makeup of the gut microbiota, according to certain studies. Chenodeoxycholate, the prime bile salt, stimulates the synthesis of exopolysaccharides, which in turn encourages the formation of biofilms, facilitating their colonization and propagation [85, 86]. Yang et al. [87] have also mentioned that an oral *Shigella* infection had a quick and noticeable impact on the gut microbiota, primarily leading to an early stage of infection with an increase in *Prevotella* and *Shigella/Escherichia* and a decrease in probiotics like *Faecalitalea* and *Lactobacillus reuteri*. On the other hand, a number of strains of *Escherichia coli*, *Lactobacillus, Bifidobacteria*, and a recent generation of probiotics, such as *Bacteroides thetaiotaomicron* and *Akkermansia muciniphila,* can support intestinal epithelial homeostasis and increase health [88]. Kutshik et al. [89] study demonstrated the potential of probiotics in treating Shigellosis in rats, aligning with the current research that highlights the curative properties of lactic acid bacteria (LAB) against this life-threatening diarrhoea. Lima et al. [90] also mentioned the use of biotherapeutic agents, ideally

Table 1 The table illustrates how *Shigella* uses the disturbed intestinal environment as a means of proliferation

Conditions	Benefits for *Shigella* during Dysbiosis	References
Weakened immune system	A decrease in the variety of microorganisms and the simultaneous absence of helpful bacteria contribute to the significant involvement of *Shigella* in its early rivalry with the microbiota of the host	[91–93]
Intestinal barrier changes	Increase the ability of *Shigella* to enter and multiply inside the colonic epithelium, causing a severe inflammatory reaction in the intestines and the loss of epithelium cells	[94, 95]
Variations in nutrient availability	A number of microbiomes that are important for preserving health and preventing infection by generating antimicrobial compounds like bacteriocins are diminished during dysbiosis, which creates a condition where *Shigella* has to contend for nutrients found in the gut	[82, 96, 97]
Variations in pH and bacterial metabolic activities	Since coevolution, *Shigella* is more able to adapt to its environment and proliferate since a set of transcriptional regulators are expressed under such situations	[75, 98]

probiotics, as an alternate therapeutic option for the treatment of infectious gastroenteritis and as a means of preventing antibiotic-induced diarrhoea. It is important to remember, though, that further research in this area is required to determine how probiotics hinder *Shigella* and boost immunity in the process.

Potential role of nanotechnology in countering the disease

Nanotechnology offers a promising alternative to the conventional treatment methods that usually rely on antibiotics as the main approach for dealing with shigellosis. The excessive use of antibiotics over time can result in the development of antibiotic resistance, making nanomedicine an attractive option. Nanomedicine can be tailored to target infected cells specifically, thereby enhancing treatment effectiveness and reducing potential side effects. Moreover, the unique mechanism of action of nanomedicine may provide a solution to combat *Shigella* strains that have developed resistance to conventional antibiotics [99, 100]. The potential of nanotechnology in combating shigellosis is being investigated through the utilization of nanoparticles to improve drug delivery, develop targeted antimicrobial agents, and enhance diagnostic techniques, as illustrated in Fig. 2 and extensively discussed below.

Nanomaterials as antibacterial agents

Antimicrobial resistance poses a significant threat to human health at present, which necessitates the use of drugs that are more noxious, costlier, and with low efficiency [99]. To counter antibiotic resistance, nanoparticles have emerged as promising tools that can directly or indirectly combat deadly bacterial infections. Nanomaterials provide a means of accessing novel antibacterial modalities that bacteria do not possess in their natural defence arsenal. The therapeutic impact of nanomaterials largely stems from their confinement at the nanoscale, which allows for multivalent interactions and a high surface-to-volume ratio. Nano-sized metals, organic nanoparticles (NPs), metal oxides, and nanocomposites exhibit potent antibacterial properties and offer strategic advantages for controlling superficial infections and infectious diseases in a safe manner [101]. Silver (Ag) is well recognized among metallic NPs for being the most potent over bacteria and other pathogens. It is also well-suited for usage in medical applications due to its excellent biocompatibility [102]. It has been established as a superior antibacterial agent with the ability to fight bacteria that cause illnesses in vitro as well as in vivo. AgNPs can combat both Gram-positive and Gram-negative bacteria, such as those that are resistant to several drugs [103]. A plethora of research has been conducted

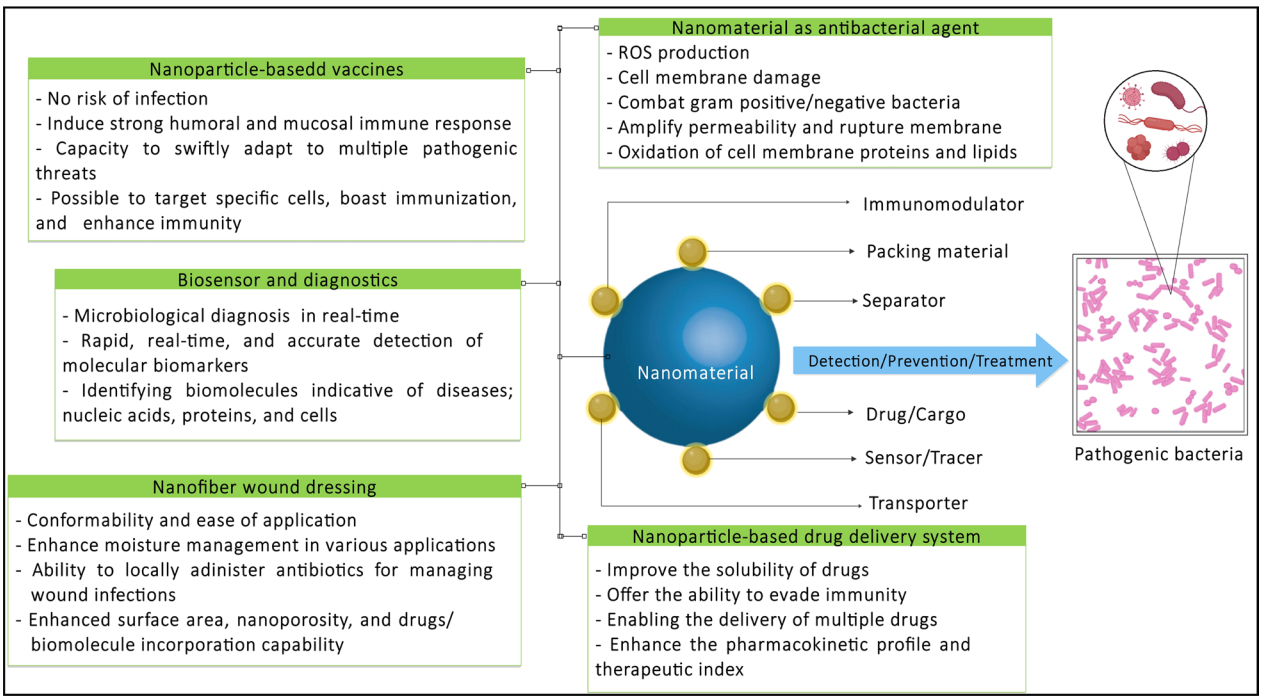

Fig. 2 This figure demonstrates the diverse functions of nanotechnology in combatting bacterial diseases, emphasizing important mechanisms like targeted drug delivery, nanoscale diagnostics, and antimicrobial nanomaterials. The figure was created using BioRender (trial version) and Wondershare EdrawMax (free version)

to assess and gauge the antibacterial potential of silver and its related compounds. The results have shown that Ag-particles induce protein malfunction, oxidative stress, DNA and membrane damage and ultimately cause harm to microbial cells [104]. Nevertheless, the precise mechanism by which they impede the proliferation of bacteria or exhibit bactericidal action remains unclear. In order to explain how AgNPs work against bacteria, scientific evidence currently endorses three main processes that have been noted either together or independently [103]. These mechanisms encompass the following:

(1) Because AgNPs can pass through outer membranes and accumulate in the inner membranes, where their adherence to the cell causes destabilization and destruction, the particles act at the membrane level, increasing membrane permeability and causing cellular content to leak out and ultimately cause the cell to succumb [102, 105].
(2) Nanoparticles not only possess the ability to breach the cell membrane, altering its structure and permeability, but they can also enter the cell, where it has been suggested that due to their properties, AgNPs are thought to interact with phosphorus and sulphur groups within intracellular components like proteins and DNA, thereby affecting their structure and functions. Similarly, they may also disrupt the respiratory chain in the inner membrane by reacting with thiol groups in enzymes, resulting in reactive free radicals and oxygen species, causing damage to intracellular machinery, and initiating the apoptotic process [106–109].
(3) The discharge of silver ions resulting from NPs, which, owing to their size and charge, can interact with biological components, thereby affecting membranes, metabolic pathways, and even genetic material [107, 110].

For instance—Gurunathan et al. [111] have previously documented the efficacy of antibiotics, AgNPs, and combinations thereof in fighting pathogenic bacteria such as *Staphylococcus aureus, Shigella flexneri, Pseudomonas aeruginosa*, and *Streptococcus pneumoniae*. In comparison with antibiotics or AgNPs alone, the results indicate that the combination of both antibiotics and AgNPs demonstrated notable anti-biofilm and antibacterial properties at the lowest concentration of both substances. Wang et al. [112] recently published a study that unveiled an innovative type of nanomaterial called Bacitracin-AgNCs (Bacitracin-Ag Nanoclusters) that exhibited strong antibacterial efficacy against *S. flexneri* and exhibited the ability to impede bacterial growth even at low concentrations. The mechanism of action involved rupturing the membrane and causing observable morphological alterations and intracellular nucleotide leakage prior to cell proliferation was obstructed.

Nanoparticle-based vaccines

NPs have emerged as a viable option for targeted delivery of vaccines to immune cells, resulting in enhanced vaccine effectiveness through controlled release, facile antigen absorption, and stimulation of both humoral and cellular immune responses [113]. These NPs can be composed of lipids, inorganic materials such as metals and nonmetals, various polymers, and even virus-like particles, all of which have been extensively investigated in research studies. The properties of the NPs have made it possible to target certain antigen-presenting cells to enhance immunization techniques and provide immunity [114]. In a study conducted by Gilavand et al. [115], recombinant MxiH antigen and purified antigen-loaded into chitosan NPs (CS-MxiH) demonstrated several advantages in terms of vaccine efficacy against *Shigella* infection. Similarly, the authors deduced that vaccine-based CS-NPs had a substantial immunogenic potential to boost humoral and mucosal immunity based on the elevated levels of IgA and IgG in mice subjected to intranasal injection of CS-MxiH. Despite extensive research and development, no effective or secure vaccine against *Shigella* has received clinical approval. Adjuvants are necessary to produce adequate immunogenicity in conserved recombinant subunit vaccines, notwithstanding the possibility of cross-protection, which may present safety concerns [116]. Koley et al. [117] discovered next-generation outer membrane vesicles (OMVs)-based antigens derived from *Shigella* during their research. By disrupting the tolA gene in the Tol-Pal system of the *Shigella* membrane, the release rate of OMVs was increased by ~ 80%. They revealed that among the 50 circulating *Shigella* subtypes in mice models, there are four serotype-subtype cross-protection. Consequently, OMVs-based immunogens hold promise as affordable non-living, next-generation candidate vaccination for human shigellosis. Baruah et al. [118] designed biomimetic nanovaccines (NVs) based on a 50:50 poly (lactic-co-glycolide)/PLGA blend. These NVs included stabilized antigens or immunostimulants of *S. dysenteriae* 1 origin that were surface-modified by basic chemical methods. By administering a large dose of heterologous *S. flexneri* 2a to immunized groups and keeping an eye out for noticeable symptoms such as weight loss, diarrhoea, and survival rates, the cross-protective effectiveness of these NVs was assessed. When challenged with heterologous *Shigella*, the immunized groups exhibited ~ 70–80% survival rates, providing protection against weight loss and diarrhoea. Therefore, passive defence in neonates suggests that the immunization

of parents might protect newborns, who are the most susceptible group in the event of a *Shigella* infection. Furthermore, on 23 April 2019, the Indian Council of Medical Research (ICMR) granted a licence for the *Shigella* vaccine technology to MSD Wellcome Trust Hilleman Laboratories Pvt Ltd for expanded development and commercialization. The Biotech Consortium India Limited (BCIL), New Delhi, facilitated the License Agreement with NICED on behalf of ICMR and Hilleman Labs [119]. The ICMR-NICED-developed *Shigella* vaccine is anticipated to have enormous potential and to help children residing in low- and middle-income environments.

Nanoparticle-based drug delivery system

The efficacy of conventional antibiotic therapeutics for shigellosis has been progressively diminished due to the emergence of multidrug-resistant (MDR) strains [120]. In response to this issue, nanoparticle delivery systems have recently emerged as a potential strategy to counteract antibacterial resistance as well as the difficulties in administering antibacterial agents. These challenges include low bioavailability, drug-related toxicities, regular drug dosing schedules, and sub-therapeutic drug buildup in bacterial reservoirs [121]. NP delivery systems offer several advantages, such as enhancing drug solubility, providing immune evasion capabilities, controlling drug release, targeting specific sites, and enabling the delivery of multiple drugs simultaneously. These unique advantages contribute to improving the pharmacokinetic profile and therapeutic index of drug payloads when compared to free drug equivalents. Consequently, several applications focusing on local antimicrobial therapy are seeing a rise in the usage of therapeutic NP, particularly polymeric NP, liposomes, inorganic NP, and dendrimers to increase therapeutic efficacy [122, 123]. According to Mukherjee et al. [124], tetracycline-embedded calcium-phosphate NPs (Tet-CPNPs) can treat mice's fatal shigellosis, a diarrheal illness brought on by *Shigella* infection. Tet-CPNP therapy significantly decreased the excretion of mushy stool, weight loss, shortened colon length, and bacterial colonization in the GI tract of mice afflicted with shigellosis, according to their results. Additionally, investigations including immuno- and histological analysis showed that Tet-CPNP administration restored almost normal characteristics to the intestinal tissue of the *Shigella*-induced mouse model, as well as altered the inflammatory cytokines level of IL-1β, TNF-α, and IFN-γ. In contrast, bulk tetracycline had no effect on shigellosis. NPs serve as carriers (such as solid lipid NPs, liposomes, polymers, etc.), encapsulating antibiotics to extend their half-life [125], and discharge their load in a regulated way, enabling controlled release at the infection site [126]. In addition to reducing the likelihood of side effects and the development of antibiotic resistance since the medication is exposed to fewer non-target bacteria, these nanoparticle-based techniques often improve the physiochemical features of engaged antibiotics, boosting their kinetic rates of absorption and distribution [127, 128].

Biosensors and diagnostics

The field of nanotechnology has made significant contributions to the advancement of biosensors through extensive research on nanomaterials and nanostructures. Various nanomaterials such as carbon nanotubes, graphene quantum dots (GQDs), metal nanoclusters, polymer nanocomposites, metal oxide NPs, plasmonic nanomaterials, and nanogels have been investigated [129]. This research has led to the development of biosensors with immense potential for microbiological diagnosis in real-time. By integrating nanotechnology, biosensors enable rapid, real-time, and accurate detection of molecular biomarkers in actual samples [130]. Typically, biosensors are capable of identifying biomolecules such as nucleic acids, proteins, and cells that are indicative of diseases. This capability is attributed to the three major components of biosensors: the reading device, the physiologically sensitive element, and the detection element [131]. Elahi et al. [132] conducted a study that unveiled an early method of detecting infectious *Shigella*. The researchers successfully designed a DNA-probe gold NPs (AuNPs)-fluorescence system by immobilizing two DNA probes (sensing element) on the surface of AuNPs. Furthermore, they synthesized iron NPs (Magnetic NPs) that were subsequently altered using Sulfosuccinimidyl 4-Nmaleimidomethyl cyclohexane-1-carboxylate (SMCC). Another system was created by immobilizing a third DNA probe on MNPs to separate the target DNA. The results demonstrated an increase in fluorescence intensity corresponding to an increased concentration of target DNA. Ali et al. [133] devised a DNA biosensor without the need for labels to track *S. flexneri.* This was achieved by immobilizing the detection probe onto a surface consisting of polyglutamic acid (PGA) and polymelamine (P-Mel), and using a disuccinimidyl suberate (DSS) functionalized flexible indium tin oxide (ITO) electrode. Signal indication for *S. flexneri* detection is anthraquinone-2-sulfonic acid monohydrate sodium salt (AQMS). The biosensor demonstrated outstanding recovery rates in detecting *S. flexneri* within spiked food samples. Various biosensing methods for pathogenic bacteria detection have proven successful and are now under consideration by health authorities and research institutions. This is primarily due to their rapid response, high performance capability, reliable results, and enhanced sensitivity compared to conventional detection methods [129].

Nanofiber wound dressing

The investigation of nanofiber (NF)-based membranes for scaffolds and wound dressings has experienced a rise in recent years due to their notable characteristics such as increased surface area, nano-porosity, and the ability to incorporate drugs or biomolecules [134]. Their size ranges from 50 to 1000 nm and possess low density, high porosity, tiny pore sizes, and substantial surface area. Various methods for nanofiber formulation include thermally induced phase separation, molecular assembly, and electrospinning. Different types of polymers utilized in the production of nanofibers consist of biodegradable hydrophilic polymers, hydrophobic polymers, and amphiphilic polymers [135], all of which are designed to emulate the porous topography of the natural extracellular matrix (ECM) making them advantageous for tissue regeneration [136]. There are two primary categories of nanofibers employed in wound healing to combat *Shigella:*

(1) NF dressings can be intended to possess a large surface area and the capability to locally administer antibiotics and antibacterial agents to manage infection within the wound milieu [137, 138]. Electrospun NF is considered for pH-mediated and targeted drug delivery to minimize undesirable adverse effects and toxicity in normal tissues [139]. NF prepared through electrospinning are designed for rapid wetting by saliva and will dissolve or disintegrate in the patient's mouth, thereby releasing drugs into the buccal mucosa for immediate absorption without the need to drink or chew. This can be accomplished by employing water-soluble polymers and a significant surface area exposed to the dissolution medium. For controlled release, the drug delivery system must dissolve or disintegrate within a specific time frame. Controlled-release methods, whether oral or transcutaneous, enable the administration of pharmaceutical drugs once or twice daily, enhancing patient compliance and reducing the toxic plasma peak concentrations associated with repeated immediate-release formulations [140].
(2) Due to their distinctive features, NF can be employed to enhance wound healing. Additionally, their spatial structure mimics the ECM [141], a connective network composed of fibrous glycoproteins that coordinate in vivo to furnish the mechanical stability, physical scaffolding, and biochemical cues requisite for tissue morphogenesis and homeostasis [142]. These scaffolds, resembling the ECM, support repair and regeneration, hasten wound healing, and aid in the rapid restoration of functional gastrointestinal tissue [143, 144]. Effective applications typically involve sponges, foams, hydrogels, and nanofibrous networks with highly porous structures as scaffolds [145].

To enhance the treatment of *Shigella,* the nanofibers can be altered to include probiotics and other active agents, resulting in improved stability of NPs within the host body, aiding in the treatment and prevention, while ensuring that the probiotics stay in the GI tract [87, 138, 146, 147].

The utilization of appropriate nanomaterials and the mitigation of potential adverse effects comprise the essence of nanotechnology. It is vital to acknowledge that the assessment of risks is imperative before authorizing new nano-based products for clinical and commercial utilization, to minimize any potential threats to human health and the environment [148]. Some of the potential drawbacks of nanotechnology in treating shigellosis are given in Table 2. The evaluation of toxicity plays a pivotal role in guaranteeing the safety of nanomedicines and safeguarding public health. Although nanomedicines hold promise in enhancing targeted cellular bioavailability and potency and reducing toxicity, regulatory bodies must comprehend the underlying scientific principles and regulate these products accordingly. Presently, there is a scarcity of testing methodologies available for the assessment of nanotoxicology in clinical translation. Conforming to standard preclinical and clinical protocols is necessary to support the development and approval of nanomedicines, encompassing the evaluation of efficacy, toxicity, and biophysical characteristics. These assessments are pivotal in ensuring the successful introduction of a diverse array of nanodrugs into the market [149–151].

Conclusions

Although there is not a vaccination that protects against *Shigella* at the moment, there are many vaccines that utilize bacterial components or attenuated bacteria, either killed or live, for immunization purposes. Currently, these vaccinations are going through several stages of clinical testing. It is essential to acknowledge that therapeutic interventions aimed at certain microbe components or activities may encounter obstacles due to resistance-causing mutations and selection. Considering this, we ventured into how nanotechnology may be used to create a treatment that effectively combats shigellosis. Nanomaterials might be employed as antibacterial agents, and biosensors could be utilized to deliver vaccinations to immune cells specifically and provide real-time microbiological diagnostics. Nanofiber-based membranes may also be used as wound dressings and

Table 2 Potential disadvantages of using nanotechnology in treating shigellosis

Sl	Drawbacks	Description	References
1	Toxicity	Studies show that certain NP's can accumulate in the body and damage organs and tissues, underscoring the need to comprehend their effects on human health and the environment for safe usage. NPs are a relatively new subject in medicine, and little is known about their long-term toxicity	[152]
2	High costs	NP availability and affordability may be constrained by the high cost of their development and production	[152]
3	Unintended interactions	Apart from application-specific particle functionalization, nanomaterials themselves can interact with biological systems. Ancillary effects are the distinct biological consequences that have been shown to be induced by this nanoparticle bio-interface	[153]
4	Regulatory challenges	Strict regulatory permission is required before using nanomedicine on humans, which might impede the development and adoption of novel treatments	[152]
5	Scalability	The problem for this issue is twofold. Firstly, the properties of the materials alter when scaling up, thereby losing the precise control observed at the nanoscale. And secondly, pharmaceutical industries are hesitant put larger money in large-scale nanomaterial production without assured significant profits	[154]
6	Immune response reactions	Because of the way cells are arranged in a self-coordinated manner, the immune system is naturally able to distinguish between foreign and self-substances. Consequently, when NPs enter the body, the immune system may misinterpret them for foreign entity, triggering undesirable immunological response that includes tissue damage, inflammation, and lessened therapeutic capability	[155]
7	Unclear long-term effects	Prolonged exposure to nanoparticles can harm the respiratory system, causing conditions like inflammation, fibrosis, oxidative stress, and lung cancer. These effects depend on the particles' physiochemical properties and the exposure level	[156]

scaffolds. The utilization of these tools is crucial in combating the rising prevalence of antimicrobial-resistant *Shigella* strains. However, it is important to note that nanomedicine, like any medical intervention, must undergo rigorous control and thorough evaluation before it can be used to treat patients to the fullest extent; toxicity assessment and multistage clinical studies must be conducted. The overall aim of this is to provide insight to readers and researchers with an understanding of the role of different *Shigella* spp. in causing shigellosis in humans, as well as the potential of nanotechnology in addressing this issue.

Abbreviations

S. dysenteriae	*Shigella dysenteriae*
S. flexneri	*Shigella flexneri*
S. boydii	*Shigella boydii*
S. sonnei	*Shigella sonnei*
HUS	Haemolytic uraemic syndrome
T3SS	Type III secretion systems
IpaC	Invasion plasmid antigen C
IpaB	Invasion plasmid antigen B
ipaD	Invasion plasmid antigen D
IL-1	Interleukin-1
IL-6	Interleukin-6
IFN-γ	Interferon-gamma
TNF-alpha	Tumour necrosis factor-alpha
GEMS	Global Enteric Multicenter Study
PHE	Public Health England
MAM	Multivalent adhesion molecule
T6SS	Type VI Secretion System
G4C	Group 4 capsule
OAg	O-Antigen
LPS	Lipoprotein-associated liposomes
PMN	Polymorphonuclear leukocytes
H-NS	Histone-like nucleoid structure protein
DAMPs	Damage-associated molecular patterns
PAMPs	Pathogen-associated molecular patterns
LAB	Lactic acid bacteria
NPs	Nanoparticles
Ag	Silver
Bacitracin-AgNCs	Bacitracin-Ag Nanoclusters
CS-Nps	Chitosan nanoparticles
IgA	Immunoglobulin A
IgG	Immunoglobulin B
OMVs	Outer membrane vesicles
NVs	Nanovaccines
ICMR	Indian Council of Medical Research
BCIL	Biotech Consortium India Limited
NICED	National Institute of Cholera and Enteric Diseases
MDR	Multidrug-resistant
Tet-CPNPs	Tetracycline-embedded calcium-phosphate nanoparticles
GQDs	Graphene quantum dots
AuNPs	Gold nanoparticles
MNPs	Magnetic nanoparticles
NF	Nanofiber
ECM	Extracellular matrix

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Author contributions
Dr. H.K Sharma conceptualized the idea, synthesized the review technique, and reviewed the manuscript. El Bethel Lalthavel Hmar and Sujata Paul contributed to the content significantly and edited the paper. All authors read and approved the final manuscript.

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