Microb Health Dis 2024; 6: e1038

REVIEW: TRENDS IN NANOTHERAPEUTICS TO MANAGE *HELICOBACTER PYLORI*

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Abstract – Antibiotics have been extensively used in the eradication of *Helicobacter pylori*, but their effectiveness is hindered by the bacterium's ability to acquire resistance. Further, the drug's short residence time and low bioavailability in the gastric environment (low pH, presence of digestive enzymes, and difficulty in crossing the mucus layer) also challenge the treatment. Nanotherapeutics to protect and increase antimicrobials residence time in gastric settings and new bactericidal strategies based on localized formation of reactive oxygen species (ROS), after intrinsic (acidic pH) or extrinsic (light source or ultrasound device) stimulus have been developed for gastric infection management. Here the most promising nanotherapeutics published from June 2023 to June 2024, retrieved on PubMed and Scopus using the search keywords "Nanotherapeutics", "Nanoparticles", "Bioengineered", "Biomaterials", plus "*Helicobacter pylori*", are briefly highlighted.

Keywords: *Helicobacter pylori*, Bioengineering, Nanoparticles, Nanotherapeutics, Sonodynamic therapy, Photodynamic therapy.

INTRODUCTION

Helicobacter pylori is one the most common infections worldwide, eliciting a chronic inflammation status that triggers the development of several gastric ailments, including gastric cancer[1]. Currently, the gold therapeutic standard for *H. pylori* infection is the quadruple therapy (2 antibiotics + bismuth subcitrate potassium + proton pump inhibitor)[2], but the menace of antibiotic resistance allied with their low gastric bioavailability and dysbiosis boosted the search for alternatives[3]. Several strategies have been attempted to potentiate antibiotic effectiveness, either by replacing the conventional proton pump inhibitors with new acid suppressors (e.g., vonoprazan)[4,5] or by using probiotics as adjuvants to minimize the antibiotic's disruption of the gut microbiota[6]. Other strategies focused on the replacement of antibiotics with alternative antibacterial compounds, such as antimicrobial peptides or phytocompounds[7]. Still, these approaches are also hampered by the harsh gastric environment, demonstrating lower performance than the standard antibiotic-based therapy. In addition, efforts have been made to develop vaccines against *H. pylori*, but until now, no effective vaccine has been available[8]. Thus, the interest in the use of nanosystems to carry and protect antibiotics and/or alternative antimicrobials has risen in recent years[3]. Nanoparticles (<1000 nm; NP) have been developed

using different gastric retentive biomaterials, such as chitosan (CS), an FDA-approved polymer for oral administration, to act as drug delivery systems[3]. Strategies based on the production of reactive oxygen species (ROS) have also been proposed for *H. pylori* management with the advantage of minimizing the development of bacterial resistance[9,10].

METHODS

In this review, the terms "Nanotherapeutics", "Nanoparticles", "Bioengineered", "Biomaterials", plus "*Helicobacter pylori*" were searched on PubMed and Scopus. Here, the latest and most promising nanotherapeutics, namely with similar/better performance than antibiotics or without disruption of gut microbiota and/or reduction of inflammatory markers, are briefly described.

ANTIBIOTICS

Amoxicillin (AMX) was encapsulated onto CS-NP (AMX-CS-NP: ≈ 160 nm) to increase its bioavailability[11]. *In vitro*, AMX encapsulation decreased the minimal inhibitory concentration that inhibits 50% (MIC_{50}) of *H. pylori* ATCC®43504 strain ≈6 times compared to free AMX (13.4 ng/mL *vs.* 76.2 ng/mL). In addition, AMX encapsulation reduced the probability of developing antibiotic resistance[11]. Inulin, a prebiotic beneficial for gut bacteria with anti-inflammatory action[12], was given in parallel with AMX-CS-NP, protecting the gut microbiota (*Lactobacillus casei*)[11]. Clarithromycin (CLR), bismuth (Bi), and zinc peroxide (ZnO_2-NP) were encapsulated in liposomes (CLR-Bi-ZnO_2-LP; size: ≈140 nm)[13]. Bi has an anti-inflammatory effect, being currently used in *H. pylori* quadruple therapy, and ZnO_2-NP inhibits urease, both possessing antibacterial activity[13]. In *in vivo* studies (model: C57BL/6 mice infected with *H. pylori* standard and multi-drug-resistant strain 7132), CLR-Bi-ZnO_2-LP reduced the *H. pylori* burden in >5 log colony forming units (CFU)/g, while quadruple therapy only reduced 2 log. Additionally, CLR-Bi-ZnO_2-LP did not impact gut microbiota; urease activity significantly diminished (< 20%), and expression of inflammatory factors (IL-6, TNF-α, and IL-1β) decreased to basal levels (non-infected mice). Yet, CLR-Bi-ZnO_2-LP did not achieve *H. pylori* eradication[13].

BIOACTIVES

Antimicrobial Peptides (AMP)

AMP are low molecular weight cationic peptides with broad antimicrobial activity and a low tendency to induce bacterial resistance[14]. However, in solution, AMP may undergo proteolysis/aggregation, and high concentrations *in vivo* are often toxic[14,15]. To protect AMP from proteases and aggregation, the AMP MSI78A was grafted onto CS-NP (MSI78A-NP; ≈115 nm)[16]. MSI78A-NP (10^{11} NP/mL; ≈ 96 mg/mL MSI78A) were more effective than MSI78A in solution, being bactericidal after 30 min against *H. pylori* 26695 and after 24 h for *H. pylori* J99 (ATCC®700824) strains. MSI78A-NP led to bacterial membrane destabilization, formation of extracellular vesicles, and release of cytoplasmatic content. MSI78A-NP were cytocompatible[16], but to date, no pre-clinical validation was reported.

Resveratrol (RESV)

RESV is a flavonoid polyphenol with anti-inflammatory and antimicrobial effects against different *H. pylori* strains by compromising its membrane[17,18]. To overcome its low water solubility and bioavailability (<1%)[19], RESV was encapsulated onto CS-NP (RESV-CS-NP) (≈ 150 nm). RESV encapsulation reduced its MIC/Minimum Bactericidal Concentration (MBC) more than 30 times [3.9 µg/mL *vs.* 125 µg/mL (free RESV)], increased its antibiofilm performance, and decreased its cytotoxicity[20].

Berberine (BBR)

BBR, a benzylisoquinoline alkaloid active against *H. pylori*[21], was encapsulated in nanomicelles of mannosylerythritol (MEL-B; an antimicrobial glycolipid surfactant; BBR-MEL-B-NM; ≈70 nm)[22]. BBR-MEL-B-NM were bactericidal against *H. pylori* 26695 strain, both in planktonic form and in biofilms. *In vivo* studies (model: C57BL/6N mice infected with *H. pylori* SS1) showed that the *H. pylori* burden was reduced in 2 log CFU/g after 7 days of oral gavage, while free BBR and triple therapy (omeprazole, AMX, CLR; OAC), reduced only 1 log CFU/g. Additionally, BBR-MEL-B-NM was anti-inflammatory, diminishing the pro-inflammatory factors IL-1β and TNF-α to basal levels[22].

Docosahexaenoic Acid (DHA)

DHA, an omega-3 polyunsaturated fatty acid, is active against *H. pylori*[23], but its free formulation is not soluble in water and is easily oxidized[24]. DHA loaded into nanostructured lipid carriers (DHA-NLC; ≈300 nm), were bactericidal against several *H. pylori* strains growing in planktonic[24,25] and in biofilms[25,26]. In addition, the development of bacteria resistance to DHA-NLC was not reported[25,26]. I*n vivo* assays (model: C57BL/6 male mice infected with *H. pylori* SS1), showed that DHA-NLC [2 mg/mL (50 µM DHA)], given either by oral gavage or *ad libitum* for 14 days, decreased the *H. pylori* burden in 95% (2 log decrease), eradicated infection in 50% of animals and had no impact on the gut microbiome. In opposite, free DHA (50 µM) only reduced 1 log and achieved eradication in 27% of the animals[25].

METAL NP

Metallic NP have intrinsic antimicrobial properties, mainly due to the production of ROS, which promotes oxidative stress and bacteria membrane disruption[9,27].

Copper (Cu)

HKUST-1, a Cu-based metal-organic framework (MOF)-NP, was encapsulated into LP coated with CS (CS-LP-HKUST-1-NP; ≈ 274 nm). LP had rhamnolipid (RHL), a glycolipid that disrupts the biofilm extracellular polymeric substances (EPS)[28,29]. CS-LP-HKUST-1-NP with RHL were bactericidal against *H. pylori* in planktonic state and organized in biofilm. To improve delivery in *H. pylori* inflammatory sites, CS-LP-HKUST-1-NP were embedded in an inflammatory targeted degradable ascorbyl palmitate hydrogel[30] (AP-CS-LP-HKUST-1)[29]. In *in vivo* assays (model: C57BL/6 mice infected with *H. pylori* PMSS1), AP-CS-LP-HKUST-1-NP reduced bacterial burden in >3 log CFU/mL. Besides, this system was safe for the gut microbiota, decreased the expression of pro-inflammatory factors MPO, IL-1β, and IL-6 to basal levels, and promoted the expression of anti-inflammatory factor IL-10[29].

Bismuth (Bi)

Bi-based MOF coated with selenized chitosan (Bi-MOF-CS-Se-NP) was bactericidal at acidic pH (pH=2) against different *H. pylori* strains[31]. In *in vivo* (model: C57BL/6 mice infected with *H. pylori* PMSS1), Bi-MOF-CS-Se-NP reduced the *H. pylori* burden from $3x10^3$ CFU/mg to less than 50 CFU/mg of stomach, decreased the pro-inflammatory factors IL-1β, IL-6, IL-18 and TNF-α and increased the anti-inflammatory IL-10[31]. Bi-MOF-CS-Se-NP used as adjuvant to the OA therapy (OMZ and AMX) achieved eradication, surpassing the performance of OCA therapy but the gut microbiota was significantly altered[31].

Silver (Ag)

Ag-NP (bactericidal against *H. pylori*[32,33]) and epiberberine (EPI, urease inhibitor[34]) were encapsulated in LP with RHL (EPI-AgNP-RHL-LP)[35]. Its MIC against *H. pylori* ATCC® 43504 was equivalent

to AMX (1.56 µg/mL) with further *H. pylori* urease inhibition[35]. In *in vivo* (model: BALB/c mice infected by *H. pylori* ATCC® 43504), after 5 days of oral gavage with EPI-AgNP-RHL-LP, animals were close to full *H. pylori* eradication and had pro-inflammatory factors IL-6 and TNF-α reduced to basal levels, surpassing the OCA therapy (3 log reduction)[35].

PHOTODYNAMIC AND SONODYNAMIC THERAPY

Photodynamic and sonodynamic therapy have been studied for the treatment of *H. pylori* infection by the encapsulation of photo/sonosensitizers into NP that will generate ROS after an external stimulus, such as a light source or ultrasonication, respectively[36-38].

Photodynamic Therapy (PDT)

A new polymer (3PC), composed of the photosensitizer Chlorin e6 [Ce6; FDA approved for clinical PDT and that generates ROS when irradiated by blue (λ=405 nm) or red (λ=670 nm) lasers[39]], conjugated with a 3'-sialyllactose (specifically binds to *H. pylori* outer membrane proteins) and polyethyleneimine (cationic polymer to increase gastric residence time) was developed[40]. *In vivo* (model: C57BL/6 mice infected with *H. pylori* SS1) 3PC reduced 98% of the bacterial burden after a single oral dose followed by 200 seconds of irradiation with a red laser tip fixed to the feeding needle catheter. OCA therapy achieved similar efficacy (98% reduction) but required 3 days of daily administration[40]. However, Ce6-mediated PDT performance may be limited by the hypoxia present in *H. pylori* environments. Therefore, acid-responsive LP, containing ZnO_2 and Ce6 (ZnO_2-Ce6-LP), were developed[41]. In acidic conditions, ZnO_2 has acid neutralizing capacity, creating bactericidal Zn^{2+} and H_2O_2. Photoirradiation (λ=460 nm; blue laser) induces the photolysis of H_2O_2, generating active •OH that overcomes the O_2 limitation[41]. *In vivo* (model: C57BL/6 mice infected with *H. pylori* ATCC®43504 and antibiotic-resistant clinical isolates), a single ZnO_2-Ce6-LP oral dose ≈2 h prior to laser irradiation (4 min) reduced the bacterial burden 5 times more than traditional OCA triple therapy (1.5 log CFU/mL *vs.* 7.4 log CFU/mL). In addition, treatment was safe and specific to *H. pylori*[41].

Sonodynamic Therapy (SDT)

SDT antibacterial effect is due to oxidative stress and ultrasonic cavitation induced by an external ultrasound device combined with sonodynamic nanotherapeutics[42]. However, hypoxia in *H. pylori* environment is also a concern for SDT. Therefore, sonodynamic NP was developed by using 2,2´-azobis[2-(2-imidazolin-2-yl)propane] dihydrochloride (AIPH) with dopamine-coated PtCu3 (acoustic sensitizer with efficient ROS generation) that were encapsulated in fucoidan for targeting the surface proteins of *H. pylori*. AIPH can generate oxygen-independent alkyl radicals (R•) and N_2 under ultrasound stimulus[43]. While R• promotes radical polymerization and oxidative stress reactions, N_2 enhances the ultrasonic cavitation effect. In *in vivo* assays (model: C57BL/6 female mice infected with *H. pylori* BNCC339501), the bacterial load was reduced in ≈ 1 log CFU/g after 7 days of oral gavage followed by ultrasound therapy (2 min) but had lower performance than the OAC therapy (reduced ≈ 2 log CFU/g)[43]. Nevertheless, it did not affect the gut microbiota and alleviate the inflammatory response by decreasing the levels of IL-1ß and increasing IL-10 expression[43].

CONCLUSIONS

While some nanotherapeutics strategies still rely on the use of antibiotics, those based on bioactives (such as DHA and BRB) or metallic NP have promising results in pre-clinical settings against *H. pylori* infection. Moreover, they positively modulate the inflammatory response, which is crucial to resolve infection. PDT and SDT-based nanotherapeutics are the latest advances with highly promising results. Although PDT is an invasive treatment, since photoirradiation requires endoscopy, this could be overcome by using light-emitting capsules for oral administration that are already

in development. All these strategies were safe and innocuous to the gut microbiota and less prone to induce bacterial resistance. Yet, antibiotics also benefit from a bioengineered approach, as their bioavailability is greatly enhanced and may shield them from the development of resistance. Despite encouraging data, the recrudescence of infection after completing treatment and further *in vivo* bioaccumulation testing should be done to further establish these nanotherapeutics as new agents for *H. pylori* infection management.

Conflict of Interest

The authors declare that they have no conflict of interest to declare.

Funding

Project NanoPyl®: nanoparticles to control *Helicobacter pylori* (CI-0115-2022), Caixa Research Validate, Fundación La Caixa. Fundação para a Ciência e Tecnologia for Rute Chitas (SFRH/BD/151081/2021) PhD grant and Paula Parreira (CEECIND/01210/2018) Junior Researcher contract.

Authors' Contributions

All authors conceptualized the manuscript, wrote the original draft, revised and edited the manuscript. All authors read and approved the final manuscript.

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Ethics Statement

Not applicable due to the type of study.

AI Statement

The authors did not use any type of artificial intelligence during the drafting/conducting of the research.

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