Review Article

Novel Drug Delivery Systems for Combating *H. pylori*: A Brief Review

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ABSTRACT

It is well established that *Helicobacter pylori* infection is a primary cause of gastritis. There is an alarming potential for this infection to progress into gastric cancer if left unaddressed. However, the efficacy of conventional treatments is undermined by the growing challenge of antibiotic resistance and the necessity for complex multidrug and high-dose therapeutic regimens. Furthermore, the presence of factors such as biofilm formation, efflux pumps, and gene mutations significantly elevates the risk of treatment failure. In view of these significant challenges, contemporary drug delivery systems represent a vital adjunct in the battle against *H. pylori*. These advanced and sophisticated systems offer significant advantages, including enhanced drug protection, controlled release, and targeted delivery to specific tissues. Nanoparticles, in particular, show promise in combating *H. pylori* infection through a variety of mechanisms, including direct drug delivery into the bacteria and the destruction of bacterial walls, as well as generation of free radicals. This review provides an overview of the current therapeutic landscape, including both existing and evolving treatment options. It delves into the transformative potential of novel drug delivery systems, including micro- and nanoparticles, to play a transformative role in the complex field of *H. pylori* infection treatment. By examining the complex relationship between infection dynamics and cutting-edge delivery technologies, this review seeks to identify avenues for more effective and targeted interventions against this persistent threat. As our understanding of *H. pylori* infection advances, new treatments and enhanced drug delivery methods offer the prospect of a more effective and personalized approach to combating this persistent health problem. This dynamic intersection of microbiology and nanotechnology exemplifies the relentless pursuit of innovative solutions to safeguard against the formidable challenges posed by *H. pylori*. Ultimately, it offers hope for improved patient outcomes and a healthier population.

Keywords: *Helicobacter Pylori* Infection, Antibiotic Resistance, Novel Drug Delivery Systems, Micro- and Nanoparticles

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1. Context

H. pylori is a gram-negative, spirally shaped, microaerophilic, fastidious bacterium that possesses 5–7 flagella. The helical shape of the bacterium enables it to achieve a corkscrew motion, which allows it to quickly reach the stomach epithelium. Bacterial infections can lead to a range of gastrointestinal abnormalities, including peptic ulcers, lymphoma of the stomach, mucosa-associated lymphatic tissue (MALT), and gastric adenocarcinomas. These complications can occur even in the absence of overt symptoms. Nevertheless, the most prevalent pathological condition resulting from bacterial infection is peptic ulcer. The World Health Organization (WHO) has classified *H. pylori* as a category I carcinogen, making it the only bacteria of its kind in this regard. It is postulated that *Helicobacter pylori* has adapted and played a contributory role throughout the process of human evolution (1,2). The pathogenicity of *H. pylori* depends on a number of factors, including those related to the bacterium itself, the host, and the environmental characteristics (Table 1).The production of urease enables *H. pylori* to persist in the stomach. In typical circumstances, urea is present within the stomach lumen, where it can be hydrolyzed by urease to generate ammonia and carbon dioxide gas. The colonization of epithelial cells is facilitated by the interaction of host cell receptors with outer membrane proteins (OMPs) from *Helicobacter pylori*. Initially, a link with the gastric mucosa is formed, protecting the bacteria from stomach displacement caused by peristalsis and gastric emptying via a protein called BabA, encoded by the babA2 gene, which binds to the Lewis-b antigen of blood types. Attaching stomach cells by means of OMPs allows *H. pylori* to inject proteins and toxins, which in turn results in a wide range of host cell changes and, ultimately, inflammation. Considering the established link between CagA and stomach cancer, this bacterial oncoprotein has become the subject of intensive research. Due to its capacity for biofilm formation, *H. pylori* is capable of persisting and resisting a wide variety of antimicrobial agents (2–4). The present review encompasses both the traditional and modern therapeutic options for *H. pylori*, while emphasizing the utilization of novel drug delivery systems to overcome current challenges.

2. Evidence Acquisition

In this systematic literature review, a comprehensive search was conducted using Google Scholar as the primary database. The search spanned from 2011 to 2023, and the keywords employed included "*H. pylori* characteristics", "*H. pylori* treatment options", and" novel drug delivery system".To ensure clarity and accessibility, we limited our inclusion criteria to articles published in the English language. The selected studies encompassed both original research and review articles, with the objective of providing a comprehensive overview of the evolving landscape in novel drug delivery systems for combating *H. pylori* over the specified time frame.

3. Results

3.1. Common Approach

It is recommended that patients with ulcers, cancer, or certain precancerous conditions receive anti-*H. pylori* treatment. Nevertheless, the treatment of asymptomatic patients remains a topic of contention. This infection affects approximately half of the world's population and remains challenging to control, since there is currently no definitive therapeutic approach. The treatment failure rate for *H. pylori* infection remains high, with more than 20% of patients exhibiting no response to therapy. At present, the ideal validated first-line therapeutic options are triple and quadruple regimens. The standard triple therapy represents the initial treatment for *H. pylori* infection and is based on proton pump inhibitors (PPI), clarithromycin (CAM), and either amoxicillin (AMX) or metronidazole (MTZ). The optimal duration of therapy was 2 weeks.A quadruple therapy comprising proton pump inhibitors, tetracycline, metronidazole, and bismuth salt) has been demonstrated to be highly efficacious, even in areas or settings with a high prevalence of antibiotic resistance. It may therefore be considered as an alternative first-line treatment option. Given the rapid emergence of quinolone resistance (2–4),lLevofloxacin-based regimens should be designated as second- or more-line treatment alternatives because of the rapid emergence of quinolone resistance(2–4). It is estimated that Antimicrobial resistance (AMR) will cost approximately $100 trillion worldwide by 2050, with an estimated 10 million deaths annually. The principal factor contributing to the failure of treatment for *H. pylori* infection is elevated resistance to major antibiotics, particularly clarithromycin (CAM), metronidazole (MNZ), and levofloxacin. Infectious diseases must be treated with second-line medications due to the emergence of microbial resistance. The administration of these treatment options via an expensive, time-consuming intravenous route, and they may result in a multitude of severe complications. A sequential approach was employed, PPI and AMX were used for the first five days of treatment, followed by PPI, MTZ, and CLR for the remaining days. This represents an alternativeoption. However, sequential therapy is no longer

Table 1. Various factors associated with *H pylori* infection

***H. pylori* pathogenicity**		
Bacterial factors	**Host factors**	**Environmental factors**
Urease Flagella Adhesins (BabA) Enzymes Exotoxins (vacA)	Polymorphism in inflammatory cytokines Alcohol Smocking Excessive consumption of salted food	Infected family members Health care professionals Contact with animals Unclean food or water

advised due to the difficulty in maintaining compliance. Antimicrobial susceptibility testing represents the most effective method for reducing the reliance on antibiotics in the treatment of *H. pylori* infections. In the coming years, a tailored therapeutic strategy may be possible thanks to the genotypic characterization of *H. pylori* vulnerability to therapeutic interventions (4–7).

3.2. Barriers for Effective Treatment

Two factors contribute to the limited efficacy of *H. pylori* treatment: the short gastrointestinal residence time of conventional dosage forms in the stomach and the adaptability of *H. pylori* to existing therapies. A further challenge associated with the administration of conventional antibiotic is the instability of these drugs in the acidic gastric environment. In contrast, the overuse of antibiotics and the acquisition of mutations carrying resistance genes represent significant contributors to the emergence and dissemination of drug-resistant infections (1). Epithelial cells in the stomach are responsible for the production of mucus. The mucus layer on the membrane serves as a protective barrier for the underlying epithelium. Mucosal membranes, such as the lining of the stomach, form a type of mucus known as loose or sloppy mucus. The primary challenge in treating this infection with antibiotics is that, following the infection, the bacterium resides below the gastric mucus, adhering to the gastric epithelium, which makes it difficult for medications to reach this specific site. The formation of an *H. pylori* biofilm has been observed to result in elevated resistance to CLR, MTZ, and AMX. The plasma concentrations of PPIs and, consequently, the management of *H. pylori* infection are influenced by genetic variation in the activity of cytochrome P450 (CYP) 2C19 (CYP2C19). Moreover, the efficacy of *H. pylori* eradication is contingent upon IL-1β polymorphisms (4,7,8).

3.3. Alternative Regimens

Two factors contribute to restrict the efficacy of treating *H. pylori* infections: the short gastrointestinal residence time of traditional dosage forms in the stomach and the adaptability of *H. pylori* to existing therapies. Another issue encountered with conventional antibiotic administration is the drug vonoprazan, a novel potassium-competitive acid blocker that suppresses potassium binding to H+/K+-ATPase. The prevalence of clarithromycin resistance can be significantly reduced by triple therapy with the potent acid inhibitor vonoprazan. A promising alternative approach is high-dose dual therapy, which involves the administration of aproton pump inhibitor in conjunction with amoxicillin (9). Rifabutin has been demonstrated to be an effective agent in the prevention and slowing of the progression of Mycobacterium avium complex (MAC) disease in patients with human immunodeficiency virus (HIV) infection. Furthermore, it is also employed in conjunction with PPI and AMX to eliminate *H. pylori*, a highly efficacious approach that and is anticipated to facilitate treatment.The FDA has granted approval to a Rifabutin-based combination product(10). Therapeutically used sulfonamide medicines, such as ethoxzolamide (EZA), acetazolamide, and methazolamide, have been observed todemonstrate antimicrobial properties against the gastric pathogen *Helicobacter pylori*. This is despite the fact that these medicines were originally designed to treat illnesses unrelated to bacteria (such as glaucoma). EZA exhibited the greatest activity and was successful in killing clinical isolates resistant to metronidazole, clarithromycin, and/or amoxicillin. This indicates that EZA eradicates *H. pylori* through mechanisms that are distinct from those of these antibiotics(11). Daphnetin, an anti-MDR *H. pylori* compound derived from coumarin, has been demonstrated to exhibit good activity. It has been proposed that changes in membrane structure, enhancement of DNA damage and PS translocation, and reduction in *H. pylori* adhesion to GES-1 cells may be mechanisms by which daphnetin exerts its action against *H. pylori*(12). Intervenolin, a compound with antitumor properties, has been shown to target dihydroorotate dehydrogenase, which is an essential enzyme involved in the biosynthesis of de novo pyrimidines. Intervenolin and its derivatives have been demonstrated to reduce the protein and mRNA concentrations of *H. pylori* urease, which serves to defend *H. pylori* against acidic environments in the stomach (13). Flavodoxins are small, soluble proteins and are primarily found in bacteria. They have not been reported in vertebrates. Flavodoxins are proteins that participate in various metabolic pathways. It has been demonstrated that flavodoxins in certain bacteria are essential proteins, rendering them promising therapeutic targets in the treatment of bacterial infections in acidic environments (14). Conversely, the overuse of antibiotics and the acquisition of mutations carrying resistance genes represent significant factors in the emergence and dissemination of drug-resistant infections (1). Epithelial cells in the stomach are responsible for the production of mucus. The mucus layer on the membrane serves as a protective barrier for t the underlying epithelium. Mucosal membranes, such as the lining of the stomach, form a type of mucus known as loose or sloppy mucus. The primary challenge in treating this infection with antibiotics is that, following the infection, the bacterium resides below the gastric mucus, adhering to the gastric epithelium, which makes it difficult for medications to reach this specific site. The formation of an *H. pylori* biofilm has been observed to result in elevated resistance to CLR, MTZ, and AMX. The plasma concentrations of PPIs and, consequently, the management of *H. pylori* infection are influenced by genetic variation in the activity of cytochrome P450 (CYP) 2C19 (CYP2C19). Furthermore, the efficacy of *H. pylori* eradication is contingent upon IL-1β polymorphisms (4,7,8). Antimicrobial peptides (AMPs) are cationic, highly positively charged, 5-kDa peptides with α-helical structures possess an elevated isoelectric point. Recently, there has been a growing consensus that antimicrobial peptides (AMPs) represent an efficacious alternative to antibiotics for fighting pathogenic microorganisms(15). Probiotic

supplementation has been proposed as a potential strategy to improve eradication rates and mitigate the occurrence of medication-related complications.The current scientific evidence supports the administration of Saccharomyces boulardi or Lactobacillus spp. supplementation as an adjunct to traditional triple therapy, despite the evaluation of various single- or multi-strain substances. Peptide and non-peptide antipathogenic substances produced by probiotics, including Lactobacillus bulgaricus, Lactobacillus reuteri, and Lactococcus lactis, have been demonstrated to impede the growth and adhesion of *H. pylori*(16). Despite its considerable potential to facilitate treatment, it has been shown that plant extract therapy is not a viable monotherapy. The addition of turmeric extract (curcumin) to conventional triple therapy resulted in a notable enhancement in the rate of *H. pylori* eradication and a reduction in DNA oxidative damage. Molecular docking experiments have demonstrated that chlorogenic acid and pyrocatechol contribute to the antibacterial properties of the gel and CSNPs by interacting with the crystal structure of the *H. Pylori* (4HI0) protein(17). The administration of patchouli alcohol (PA), a natural tricyclic sesquiterpene, for a period of two weeks demonstrated an extremely effective protective effect against *H. pylori*-induced gastritis and associated damage. The underlying mechanism may involve antioxidant activity, pro-inflammatory factor inhibition, and regulation of NLRP3 inflammasome function. Furthermore, these findings molecular evidence of a novel antibacterial mechanism of some natural flavonoids against *H. pylori*, thereby supporting the application of HsrA as a novel and efficient therapeutic target in *H. pylori* infection(18). Antimicrobial Photodynamic Therapy (aPDT) is a light-based treatment that can be used to inactivate a variety of bacteria, viruses, fungi, and protozoan parasites. A moderate AC magnetic field in conjunction with Mn0.3Fe2.7O4@SiO2 nanoparticles has been demonstrated to deposit heat locally and inhibit the growth and virulence of *H. pylori* at ultra-low concentrations. In comparison to amoxicillin alone and nanoparticle heating, the dual-functional amoxicillin-Mn0.3Fe2.7O4@SiO2 treatment demonstrated a further seven-fold and five-fold reduction in bacterial survival, respectively. The synergistic effect of heating may enhance antibiotic penetration into bacteria due to the damage caused to the cellular membrane and protective biofilm by heating(19). An anti-adhesion nanomedicine platform was developed by wrapping synthetic polymeric cores with outer bacterial membranes. The nanoparticles, designated "OM-NPs," exhibited analogous behavior to that of the bacteria, attempting to attach to the host and competing with the real bacteria. Infection of host cells by *H. pylori* results in the secretion of extracellular vesicles (EVs), which play a key role in the inflammatory response and contribute to disease progression. Furthermore, *H. pylori* releases vesicles known as outer membrane vesicles (*H. pylori*-OMVs), which contribute to gastric epithelial atrophy and cell transformation(20). It has been established that the neutrophil-activating protein A subunit (NapA) of *H. pylori* serves the functions of an immunomodulator, a protective antigen, and a virulence factor. The potential applications of NapA extend to the development of anti-*H. pylori* vaccines and the management of some allergic conditions and carcinomas.(21).

3.4. Micro and Nanotechnological Drug Delivery Systems

The creation of a physical barrier between the medicine and the harsh gastrointestinal environment, comprising enzymes and acidity, may enhance drug stability through the utilization of micro- and nanotechnological drug delivery systems. Accordingly, micro- and nanostructured drug delivery systems may be developed to facilitate the entry of the drug into the bacterial cell and to prolong the interaction of the antimicrobial agent with the bacteria for a sufficient time to achieve minimal inhibition or bactericidal intensity (Table 2).

3.4.1. Microparticles

During periods of fasting, dosage forms typically remain in the stomach for an hour or less and pass quickly through the small intestine in less than three hours. Gastroretentive dosage forms (GRDFs) are designed to remain in the stomach for an extended duration, thereby increasing the residence time of dosage forms in the stomach, thereby enhancing the bioavailability of the drug. DDSs have been developed with the objective of achieving gastroretention, and they mainly include bioadhesive swelling and floating systems. The mucoadhesive properties of a substance are dependent on the formation of hydrogen bonds, the hydration of polymers, and then the gelation of polymers,. Examples of floating systems include Raft-forming systems, hydrodynamically balanced systems (HBS), hollow microspheres, and gas-generating systems (1). Ruiz-Rico et al demonstrated that essential oil components (EOCs) immobilized on silica microparticles can inhibit the growth of *H. pylori* and elucidate its mechanism of action(22). Malek et al. fabricated chitosan- and pectin-based microparticles containing Zataria multiflora extract in a laboratory setting with the objective of suppressing *Helicobacter pylori* (23). In another study, a bubble-propelled Janus gallium/zinc (Ga/Zn) micromotor with favorable biocompatibility and biodegradability was synthesized for the active targeting of bacteria. These miniature motors demonstrated the capacity to propel themselves in a simulated stomach acid with a pH of 0.5, reaching speeds of up to 383 $\mu m\, s^{-1}$. The movement was powered by bubbles of hydrogen created through a reaction between zinc and acid(24).

3.4.2. Nanoparticles

The use of nanoparticles as antimicrobial delivery vehicles represents a promising avenue for combating resistant pathogens. As shown in Figure 1, due to their small size, nanoparticles interact with bacteria through various mechanisms. These interactions encompass electronic binding, targeted binding ,and simple destabilization, which allows for entry into the *H.pylori*. Once within the bacterial

Table 2. Summary of recent studied micro and nano drug delivery systems

System	Composition	Anti-bacterial agent	Effect on bacteria	Ref
Microparticles	Silica microparticles	essential oil components (EOCs)	Antibacterial activity	**22**
	Chitosan and pectin microparticles	Zataria multiflora extract	Antibacterial activity	**23**
Micromotors	Janus gallium/zinc	Ga^{III} cations	Antibacterial activity	**24**
Liposomes and lipid NPs	Nanostructured lipid carriers (NLCs)	hesperidin (Hesp) and clarithromycin (CLR)	Antibacterial activity	**28**
	Lipid polymer nanoparticles	clarithromycin (CLR)	Anti-biofilm and antibacterial activity	**29**
	Lipid NPs	amoxicillin	Antibacterial activity	**30**
Polymeric NPs	Chitosan/carbon dots	amoxicillin	Antibacterial activity	**31**
	Chitosan/PMLA nanoparticles	-	Anti-biofilm and antibacterial activity	**32**
	Chitosan-alginate nanoparticles	Amoxicillin and docosahexaenoic acid	Antibacterial activity	**33**
	chitosan/poly (acrylic acid) particles	Amoxicillin	Anti-biofilm and antibacterial activity	**34**
	Chitosan-PMLA nanoparticles	-	Anti-biofilm and antibacterial activity	**35**
	Carboxymethyl chitosan and stearic acid	Clarithromycin	Antibacterial activity	**36**
	poly(ε-caprolactone) polymer	silver I [Ag(I)] compounds	Anti-biofilm and antibacterial activity	**37**
	Chitosan/PLGA nanoparticles	Amoxicillin	Antibacterial activity	**38**
	HP55/poly(*n*-butylcyanoacrylate) (PBCA) nanoparticles	-	orally administrated vaccines	**39**
	poly(lactic-*co*-glycolic) acid	JO146	Antibacterial activity	**40**
	PLGA	Curcumin	Antibacterial activity	**41**
Fullerene NPs	FNP	-	Antibacterial activity	**42**
Self-assembled NPs	PEG-Suc polymer	-	orally administrated vaccines	**43**
	Metformin-linoleic acid	ebselen (EB)	Anti-biofilm and antibacterial activity	**44**
Membrane coated NPs	PLGA core	-	anti-adhesion efficacy	**20**
Gold NPs	GNP	-	Antibacterial activity	**45,46**
	Gold coated iron nanoparticles	-	Antibacterial activity	**47**
Silver NPs	AiiA-AgNPs	-	Anti-biofilm activity	**48**
	AgNPs	-	Antibacterial activity	**49, 50, 51**
Zinc oxide NPs	ZnONPs	Amoxicillin	Antibacterial activity	**54**
Copper oxide NPs	CuO NPs	-	Antibacterial activity	**52**
Metal organic frame work	Pd(H)@ZIF-8	-	Antibacterial activity	**53**
Iron oxide NPs	SIONs	-	Antibacterial activity	**55**
Platinum NPs	Platinum nanoparticles/ Reduced graphene oxide (red-GOx)	-	immunosensing	**56**

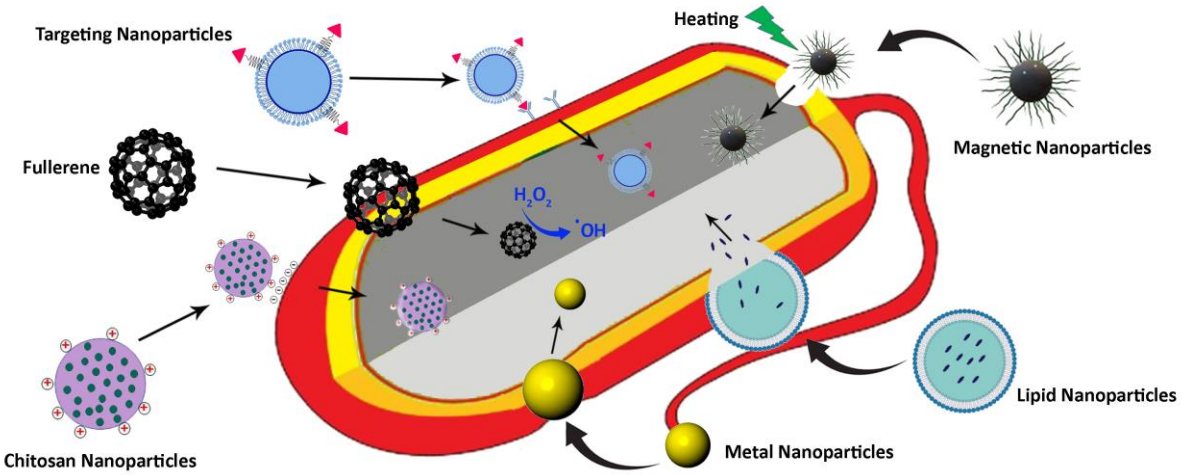

Fig 1. A schematic representation related to various nano-drug delivery systems targeting *helicobacter pylori*

membrane, nanoparticles prompt the formation of free radicals, which in turn cause damage to proteins and DNA. In physiologicaland clinical settings, different NPs, but not microparticles, rapidly form stable complexes with enteric pathogens, including the class I carcinogen *H. pylori*. The use of nanoparticles as carriers enables the regulation of antimicrobial absorption by pathogens, avoiding issues and concerns related to antimicrobial resistance mechanisms, including hyperactive efflux pumps. Furthermore , they can contain a variety of medications in a single formulation, which is advantageous in treating infections caused by *Helicobacter pylori* or HIV that require a medication mixture. (25) They have been applied to antimicrobials with the objective of enhancing both effectiveness and pharmacokinetic parameters, including half-life or bioavailability. This has the potential to enable improved dosage regimens. The dense fiber mesh resulted in a significant reduction in particle movement, with the particles becoming immobilized within the mucus gel layer. Particles with diameters of 40 and 100 nm, designated as multiple penetrating particles (MPPs), demonstrate the capacity and potential to disseminate throughout the mucosa and penetrate the epithelium of the GI tract.In contrast, larger nanoparticles exhibit a propensity to merely disperse over the surface. The mobility of particles within mucus is significantly influenced by several interactions between the particles and the mucus, including ionic contacts, hydrogen bonds, and hydrophobic interactions (26).

3.4.2.1. Organic Nanoparticles

Of the various types of nanoparticles, liposomes are the most commonly used NPs. Formulationshave been developed for use in preclinical research, clinical trials, and even commercial applications such as Ambisome® in the field of antibacterial agents(6). It was demonstrated that liposomes with a diameter of 100 nm exhibited greater mucus layer penetration than larger liposomes. Hence, the mobility of particles within mucus is significantly influenced by their diameter(27). In a study conducted by Sharaf M et al, the efficacy of the co-delivering hesperidin (Hesp) and clarithromycin (CLR) in nanostructured lipid carriers (NLCs) against *H. pylori* was investigated. The prepared NLCs provide sustained and controlled drug release, which can be employed to increase the rate of *H. pylori* eradication(28). P Li et al employed nanoparticles called lipid polymer nanoparticles to eliminate of *H. pylori* biofilms. The researchers concentrated their efforts on a particular mixture comprising 100% rhamnolipids in the outer layer. The formulation demonstrated a notable reduction in biofilm size and viability, disruption of its structure, and removal of the extracellular polymeric substances surrounding it. Subsequently, LPNs were further modified with DSPE-PEG2000 to enhance their hydrophilicity by incorporating chitosan nanoparticles (CS NPs) onto their surfaces, thereby improving their hydrophilicity. To treat *H. pylori* infections, clarithromycin (CLR) has been encapsulated in polymer nanoparticles (LPN). The anti-biofilm activities of LPNs are related to three factors:1) the disrupting effect of RHL on the biofilm matrix, 2) the antibacterial effects of CLR and CS NPs on biofilm bacteria, and 3) the inhibitory effects of CS NPs and RHL on bacterial adhesion and biofilm formation(29). In another study, amoxicillin was encapsulated in lipid nanoparticles with the objective of increasing the retention time at the site of infection (gastric mucosa) while

simultaneously protecting the drug from the harsh conditions of the stomach lumen(30). Chitosan is the most frequently employed polymer to fabricate NPs due to its mucoadhesive, antimicrobial, and simple chemical modification properties, chitosan is the most frequently employed polymer to fabricate NPs. This phenomenon can be attributed to the strong mucoadhesive properties of cationic chitosan, which result from its electrostatic interaction with negatively charged mucin. A synthetic cysteine-conjugated chitosan derivative was employed in designing and preparing Cys-CS/PMLA nanoparticles (31). In the pursuit of alternative therapies and treatments, the reductive amination of chitosan with mannose, followed by ionic gelation, has been shown to produce mannose-functionalized chitosan nanoparticles. Subsequently, the authors employed molecular docking and simulations to examine the role of *H. pylori* lectin (HPLectin), a protein that is involved in bacterial adhesion to host cells, biofilm formation , and cytotoxicity (32). The encapsulation of amoxicillin (AMX) for the purpose of drug delivery against *Helicobacter pylori* infection and aspirin-induced ulcers in rat stomachs was performed using docosahexaenoic acid (DHA)-loaded chitosan/alginate (CA) nanoparticles (NPs), which were developed using the ionotropic gelation method(33). Amoxicillin and superparamagnetic iron oxide nanoparticles were co-loaded into the particles using the nanocarrier. The nanocarrier enables the drug to remain in the stomach for an extended period, resulting in a reduced dosage and a shorter treatment duration (34).A chitosan-PMLA nanoparticle system is currently being developed for the delivery of antimicrobial glycolipids. The simple ionic gelation method yielded stable nanoparticles were obtained that exhibited satisfactory encapsulation. It was determined that Rhamnolipids chitosan nanoparticles (RL-CS-NP) were the most effective in reducing biofilm growth by 99% against *H. pylori* (ATCC 26695) at the minimum inhibitory concentration for *H. pylori* (ATCC 26695) (35).In another study, polymeric nanomicelles were developed. Initially, carboxymethyl chitosan (CMCS) was hydrophobically modified with stearic acid (SA) to create a hydrophobically modified copolymer (CMCS-g-SA). This copolymer was then conjugated with urea to create a new copolymer, U-CMCS-g-SA (36). The CMCS backbones of these nanomicelles afford them an excellent retention time in the stomach of almost 24 hours; meanwhile, the grafted ureido groups confer effective targeting to *H. pylori*. Polymeric nanoparticles (PN1) were developed through the nanoprecipitation of a poly (ε-caprolactone) polymer and poloxamer 407 surfactants. The incorporation of silver complexes within polymeric nanoparticles has been demonstrated to exhibit antibacterial activity against *H. pylori*(37). Our group developed pH-sensitive amoxicillin-loaded AMX-PLGA/UCCs-2 nanoparticles were developed by our group using the ureI-mediated drug delivery system developed by Luo et al. The objective of this study was to target the ureI channel protein expressed by *H. pylori*, utilizing urea-modified UCCs-2 as the targeting moiety. The nanoparticles were produced using UCCs-2 and PLGA with the objective of treating *H. pylori* infection. The nanoparticles were synthesized via a process known as double emulsion solvent evaporation. It has been demonstrated that AMX-PLGA/UCC-2 nanoparticles represent a valuable system for targeted drug delivery through UreI in the treatment of *Helicobacter pylori* (38). Liu H et al developed a prophylactic mouse model for evaluating the efficacy of HP55/poly(n-butyl cyanoacrylate) (PBCA) nanoparticles (NPs) in the delivery of *Helicobacter pylori (H. pylori)* subunit vaccine CCF as a prophylactic vaccine. The nanoparticles were synthesized using interfacial polymerization, and mice that received an injection of HP55/PBCA-CCF NPs exhibited the presence of serum antibodies, mucosal secretory IgA, and anti-inflammatory cytokines. Furthermore, a Th1/Th17 response and increased lymphocytes were also observed in the gastric tissues of mice immunized with HP55/PBCA-CCF NPs, indicating a notable reduction in *H. pylori* colonization (39). Hwang J et al demonstrated that JO146 exhibited antibacterial activity against *Helicobacter pylori* with a minimum bactericidal concentration of 18.8–75.2 µg/mL. A microfluidic technology design of experiments approach was employed to formulate JO146-loaded poly(lactic-co-glycolic) acid nanoparticles and investigate the impact of nanoparticle size on drug delivery. Nanoparticles of JO146-loaded were formulated in in three different sizes (90, 150, and 220 nm) were formulated with a uniform particle size distribution and drug encapsulation efficiency of up to 25%(40). Another research group has studied the anticancer and antibacterial effects of nano-curcumin in the context of gastric cancer and *H. pylori*. Curcumin-loaded PLGA nanoparticles (CUR-NPs) were prepared using the single-emulsion solvent evaporation method(41). As a result of vicinal hydroxyl rearrangement in a pinacol reaction at low pH, fullerene nanoparticles (FNPs) with various chemical structures are formed as carbonyls. A notable elevation in the C═O/C–O ratio was observed at low pH. This increase was found to be positively associated with the peroxidase activity. Due to their peroxidase-like properties, fullerene nanoparticles (FNPs) have been demonstrated to exert excellent effects on the eradication of *H. pylori* in both in in vivo and in vitro models (42). An electrostatically self-assembled nanoparticle comprising an antigen and a cell-penetrating peptide (CPP) was developed and coated with an impermeable polyethylene glycol (PEG) PEG derivative to

prevent mucus infiltration. In addition to their hydrophilic properties, nanoparticles possess slightly negative surface properties, which contribute to their exceptional capacity to penetrate mucus. The development of an oral vaccine that protects against gastrointestinal infections caused by recalcitrant *H. pylori* may be feasible using PEGylated nanoparticles rich in CPP (43). In this study, we constructed fucoidan (FU)-coated nanoparticles encapsulating the urease inhibitor ebselen in combination with antibiotics via simple self-assembly of new biguanide derivatives (metformin-linoleic acid, ML), along with linoleic acid (LA). The negatively charged FU/ML-LA/EB NPs are capable of readily penetrating easily penetrate the gastric mucus layer, enabling their arrival at infection sites and eradication of extracellular polymeric substances (EPS) to destroy the *H. pylori* biofilm structure. The antibiotic-free FU/ML-LA/EB NPs have been demonstrated to enhance bacterial eradication and mitigate oxidative stress, thereby establishing them as a highly efficacious strategy for combating *H. pylori*(44).

3.4.2.2. Inorganic Nanoparticles

A research group has developed a simple and straightforward method for synthesizing gold nanoparticles (GNPs) of varying sizes using a dried fruit extract derivedfrom Tribulus Terrestris. In this study, biogenic gold nanoparticles (GNP) exhibited size-dependent anti-*Helicobacter pylori* activity against multidrug- resistant H. pylori strains. Furthermore, biogenic GNPs exhibit high catalytic activity for the reduction of p-nitroaniline to p-phenylenediamine, a non-toxic byproduct (45).The anti-diabetic, anti-*Helicobacter pylori*, and cytotoxic properties of phyto-synthesized AuNPs based on Pituranthos tortuosus (Desf.) aqueous extracts were investigated. The findings of this study indicate that the photo-synthesized AuNPs exert a pronounced inhibitory effect on multi-drug resistant *H.pylori* strains (46). In a separate study, an environmentally friendly and plant-mediated synthetic approach was employed to synthesize gold-coated iron (Fe@Au) nanoparticles using an extract solution of olive oil, licorice root (Glycyrrhiza glabra), and coconut oil (OLC). The application of microwave irradiation during the production of nanoparticle resulted in a higher reaction rate and an improvement in the quality of the resulting product (47). A recent study investigated work explored the potential role of N-acyl homoserine lactonase-stabilized silver nanoparticles (AiiA-AgNPs) as a treatment for *H. pylori* biofilms. The authors demonstrated that the degradation of quorum sensing (QS) molecules canreduce biofilm formation and urease production as well as alter the hydrophobicity of *H. pylori* cell surfaces(48). In a separate study, the anti-*H. Pylori* activity of A. Bisporus (AB)-AgNPs was examined. The findings of this study indicated that AB-Ag nanoparticles are an effective means of controlling *H. pylori*, and may prove beneficial in the treatment of ulcerative colitis(49). The Tv-AgNPs demonstrated a minimal inhibitory concentration (MIC) of 8.12 μg.mL−1 and 18.14 μg.mL−1 against steC and *H. pylori* respectively. This multipotent property of TV--AgNps was attributed to the shape- and size-specific properties that facilitated easy penetration into bacterial and cancer cells, thereby enabling targeted therapy(50). Another study was conducted with the objective of synthesizing and characterizing silver nanoparticles (AgNPs) derived from the Acacia nilotica leaf extract-mediated compound pyrogallol (py). The authors conducted tests on py-AgNPs to evaluate their potential as antioxidants, anti -microbial agents and their ability to combat biofilm formation against *H. pylori* (51). Copper oxide nanoparticles were successfully synthesized from Cassia fistula and Melia azedarach leaf extracts via a cupric nitrate method. Scanning electron microscopy (SEM) was employed to further study the antibacterial effect of the compounds, whereby disruption of bacterial cell shape and damage to the DNA of the bacteria were observed. The antibacterial activity of the biosynthesized CuO NPs was confirmed against two antibiotic-resistant clinical strains of Klebsiella pneumoniae and *Helicobacter pylori* (52). Attia et al. reported that the combination of amoxicillin and biocompatible oxide nanoparticles (ZnONPs) could reduce the minimum inhibitory concentration (MIC) by four-fold while each of the agents demonstrated moderate anti-*H. pylori* activity(53). In a recent study, spirugenic iron oxide nanoparticles (SIONs) were biosynthesized using a new, simple, expeditious, and benign approach. This was achieved by combining ferric chloride with a Spirulina platensis water extract. Moreover, SIONs have been demonstrated to possess effective antibacterial properties against multidrug-resistant *Helicobacter pylori* (54). The growing challenge of combating antimicrobial resistance underscores the versatility of silica nanoparticles in antimicrobial therapies, including biofilm therapy. The incorporation of metals with silica nanoparticles results in the formation ofefficient antimicrobial co-delivery payloads (19). A pH-responsive metal-organic framework hydrogen-generation nanoparticle (Pd(H)@ZIF-8) was encapsulated in a hydrogel composed of ascorbate palmitate (AP). An outer layer of the AP hydrogel has been demonstrated to possess the capacity for electrostatic targeting and adhesion at the inflammatory site, which is then hydrolyzed by matrix metalloproteinase (MMP) enriched at the site of inflammation. These findings were observed both in vitro and in vivo settings. The Pd(H)@ZIF-8 nanoparticles released by the ZIF-8 nm are decomposed by gastric acid into hydrogen and zinc ions (Zn2+),which have been demonstrated to kill *H. pylori*, alleviate inflammation, and restore damaged gastric mucosa. It was unexpectedly

discovered that this metal–organic framework hydrogen-generation platform (Pd(H)@ZIF-8@AP) also has the effect of avoiding the imbalance of intestinal flora. This provides a more precise, effective, and healthy strategy for the treatment of *H. pylori* infection. (55). An immunosensor based on a platinum nanoparticle/poly (3,4-ethylenedioxythiophene)/reduced graphene oxide (Ptnano/PEDOT/red-GOx)-modified gold electrode (Au-ET) was fabricated for the detection of cytotoxin-associated gene A antibody (CagA antibody). The newly developed diagnostic tool has the potential to facilitate the early detection of gastric infections such as *H. pylori* in clinical laboratories, thereby offering significant assistance in diagnostic procedures.

4. Conclusions

For thousands of years, *H. pylori* has coexisted with humans, demonstrating an ability to adapt and survive in a variety of environments. However, the range of available therapeutic options has also extended over time. To date, a range of treatment options, including mono, dual, and multiple treatments have been investigated for the management of *H. pylori*. In recent decades, the efficacy of commonly used antibiotic cocktails for eradicating *H. pylori* has diminished, while increasing the dosage may worsen the chance of antimicrobial resistance. This underscores necessity for the implementation of intelligent drug delivery systems for *H. pylori* eradication. The use of micro particles and nanoparticles is of particular importance in the context of *H. pylori* exhibits resistance to conventional treatments. These innovative systems have been demonstrated to be efficacious demonstrate efficacy in overcoming *H. pylori* through the use of co-delivery, direct targeting of the bacterial membrane, disruption of bacterial biofilm, or penetration of the bacterial mucus membrane. It has been demonstrated that microparticles can function as miniature engines, actively tracking the bacteria under the mucosal barrier. Furthermore, nanoparticles can serve as bactericidal agents, acting as a Trojan horse in the targeted delivery of new antibiotics. In the future, the combination of compound nanoparticles, which contain both organic and inorganic components, may offer a promising approach to leverage the strengths of each while addressing the limitations of their individual components.

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Authors' Contribution

S.M. contributed to the acquisition of this data, its interpretation and the writing of the article, while M.I. provided critical revision of the manuscript and supervised the project.

Ethics

We hereby affirm that all ethical standards have been adhered to in the preparation of the submitted article.

Conflict of Interest

The authors declare that they have no conflicts of interest.

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Data Availability

The data that support the findings of this study are available on request from the corresponding author.

References

1. Adebisi A, Conway BR. Gastroretentive microparticles for drug delivery applications. Journal of microencapsulation. 2011;28(8):689-708.
2. de Souza MP, de Camargo BA, Sposito L, Fortunato GC, Carvalho GC, Marena GD, Meneguin AB, Bauab TM, Chorilli M. Highlighting the use of micro and nanoparticles based-drug delivery systems for the treatment of *Helicobacter pylori* infections. Critical Reviews in Microbiology. 2021;47(4):435-60.
3. Pop R, Tăbăran AF, Ungur AP, Negoescu A, Cătoi C. *Helicobacter Pylori*-induced gastric infections: from pathogenesis to novel therapeutic approaches using silver nanoparticles. Pharmaceutics. 2022;14(7):1463.
4. Roszczenko-Jasińska P, Wojtyś MI, Jagusztyn-Krynicka EK. *Helicobacter pylori* treatment in the post-antibiotics era—searching for new drug targets. Applied Microbiology and Biotechnology. 2020;104(23):9891-905.
5. Selvarajan V, Obuobi S, Ee PL. Silica nanoparticles—a versatile tool for the treatment of bacterial infections. Frontiers in Chemistry. 2020;8:602.
6. Zazo H, Colino CI, Lanao JM. Current applications of nanoparticles in infectious diseases. Journal of Controlled Release. 2016;224:86-102.
7. Papastergiou V, Georgopoulos SD, Karatapanis S. Treatment of *Helicobacter pylori* infection: Past, present and future. World journal of gastrointestinal pathophysiology. 2014;5(4):392.
8. Netsomboon K, Bernkop-Schnürch A. Mucoadhesive vs. mucopenetrating particulate drug delivery. European Journal of Pharmaceutics and Biopharmaceutics. 2016;98:76-89.
9. Graham DY, Lu H, Shiotani A. Vonoprazan-containing *Helicobacter pylori* triple therapies contribution to

global antimicrobial resistance. Journal of Gastroenterology and Hepatology. 2021;36(5):1159-63.
10. Ribaldone DG, Fagoonee S, Astegiano M, Durazzo M, Morgando A, Sprujevnik T, Giordanino C, Baronio M, De Angelis C, Saracco GM, Pellicano R. Rifabutin-based rescue therapy for *Helicobacter pylori* eradication: a long-term prospective study in a large cohort of difficult-to-treat patients. Journal of Clinical Medicine. 2019;8(2):199.
11. Modak JK, Tikhomirova A, Gorrell RJ, Rahman MM, Kotsanas D, Korman TM, Garcia-Bustos J, Kwok T, Ferrero RL, Supuran CT, Roujeinikova A. Anti-*Helicobacter pylori* activity of ethoxzolamide. Journal of enzyme inhibition and medicinal chemistry. 2019;34(1):1660-7.
12. Wang G, Pang J, Hu X, Nie T, Lu X, Li X, Wang X, Lu Y, Yang X, Jiang J, Li C. Daphnetin: A novel anti-*Helicobacter pylori* agent. International journal of molecular sciences. 2019;20(4):850.
13. Ohishi T, Masuda T, Abe H, Hayashi C, Adachi H, Ohba SI, Igarashi M, Watanabe T, Mimuro H, Amalia E, Inaoka DK. Monotherapy with a novel intervenolin derivative, AS-1934, is an effective treatment for *Helicobacter pylori* infection. *Helicobacter*. 2018;23(2):e12470.
14. Salillas S, Sancho J. Flavodoxins as novel therapeutic targets against *Helicobacter pylori* and other gastric pathogens. International Journal of Molecular Sciences. 2020;21(5):1881.
15. Choudhury A, Ortiz P, Kearney CM. In vitro inhibition of *H. pylori* in a preferential manner using bioengineered L. lactis releasing guided antimicrobial peptides. bioRxiv. 2021.
16. Ji J, Yang H. Using probiotics as supplementation for *Helicobacter pylori* antibiotic therapy. International journal of molecular sciences. 2020;21(3):1136.
17. Judaki A, Rahmani A, Feizi J, Asadollahi K, Hafezi Ahmadi MR. Curcumin in combination with triple therapy regimes ameliorates oxidative stress and histopathologic changes in chronic gastritis-associated *Helicobacter pylori* infection. Arquivos de gastroenterologia. 2017;54:177-82.
18. Zhong Y, Tang L, Deng Q, Jing L, Zhang J, Zhang Y, Yu F, Ou Y, Guo S, Huang B, Cao H. Unraveling the novel effect of patchouli alcohol against the antibiotic resistance of *Helicobacter pylori*. Frontiers in Microbiology. 2021;12:674560.
19. Wu T, Wang L, Gong M, Lin Y, Xu Y, Ye L, Yu X, Liu J, Liu J, He S, Zeng H. Synergistic effects of nanoparticle heating and amoxicillin on *H. pylori* inhibition. Journal of Magnetism and Magnetic Materials. 2019;485:95-104.
20. Zhang Y, Chen Y, Lo C, Zhuang J, Angsantikul P, Zhang Q, Wei X, Zhou Z, Obonyo M, Fang RH, Gao W. Inhibition of pathogen adhesion by bacterial outer membrane-coated nanoparticles. Angewandte Chemie International Edition. 2019;58(33):11404-8.
21. Sutton P, Boag JM. Status of vaccine research and development for *Helicobacter pylori*. Vaccine. 2019;37(50):7295-9.
22. Ruiz-Rico M, Moreno Y, Barat JM. In vitro antimicrobial activity of immobilised essential oil components against *Helicobacter pylori*. World Journal of Microbiology and Biotechnology. 2020;36(1):1-9.
23. Malek S, Pirouzifard MK, Yadegar A, Bonab SM, Jannat B, Moslemi M. Synthesis, Characterization, and Evaluation of Anti-*Helicobacter* Activity of Chitosan and Pectin Microparticles Containing Zataria multiflora Extract In Vitro. Applied Food Biotechnology. 2022;9(4):321-31.
24. Lin Z, Gao C, Wang D, He Q. Bubble-propelled Janus gallium/zinc micromotors for the active treatment of bacterial infections. Angewandte Chemie International Edition. 2021;60(16):8750-4.
25. Westmeier D, Posselt G, Hahlbrock A, Bartfeld S, Vallet C, Abfalter C, Docter D, Knauer SK, Wessler S, Stauber RH. Nanoparticle binding attenuates the pathobiology of gastric cancer-associated *Helicobacter pylori*. Nanoscale. 2018;10(3):1453-63.
26. Maisel K, Ensign L, Reddy M, Cone R, Hanes J. Effect of surface chemistry on nanoparticle interaction with gastrointestinal mucus and distribution in the gastrointestinal tract following oral and rectal administration in the mouse. Journal of Controlled Release. 2015;197:48-57.
27. Takeuchi H, Yamamoto H, Kawashima Y. Mucoadhesive nanoparticulate systems for peptide drug delivery. Advanced drug delivery reviews. 2001;47(1):39-54.
28. Sharaf M, Arif M, Khan S, Abdalla M, Shabana S, Chi Z, Liu C. Co-delivery of hesperidin and clarithromycin in a nanostructured lipid carrier for the eradication of *Helicobacter pylori* in vitro. Bioorganic Chemistry. 2021;112:104896.
29. Li P, Chen X, Shen Y, Li H, Zou Y, Yuan G, Hu P, Hu H. Mucus penetration enhanced lipid polymer nanoparticles improve the eradication rate of *Helicobacter pylori* biofilm. Journal of Controlled Release. 2019;300:52-63.
30. Lopes-de-Campos D, Pinto RM, Lima SA, Santos T, Sarmento B, Nunes C, Reis S. Delivering amoxicillin at the infection site–a rational design through lipid nanoparticles. International Journal of Nanomedicine. 2019;14:2781-95.
31. Arif M, Sharaf M, Samreen, Dong Q, Wang L, Chi Z, Liu CG. Bacteria-targeting chitosan/carbon dots nanocomposite with membrane disruptive properties improve eradication rate of *Helicobacter pylori*. Journal of Biomaterials Science, Polymer Edition. 2021;32(18):2423-47.
32. Arif M, Ahmad R, Sharaf M, Muhammad J, Abdalla M, Eltayb WA, Liu CG. Antibacterial and antibiofilm activity of mannose-modified chitosan/PMLA nanoparticles against multidrug-resistant *Helicobacter*

pylori. International Journal of Biological Macromolecules. 2022;223:418-32.
33. Khoshnood S, Negahdari B, Kaviar VH, Sadeghifard N, Abdullah MA, El-Shazly M, Haddadi MH. Amoxicillin-docosahexaenoic acid encapsulated chitosan-alginate nanoparticles as a delivery system with enhanced biocidal activities against *Helicobacter pylori* and improved ulcer healing. Frontiers in Microbiology. 2023;14:1083330.
34. Yang SJ, Huang CH, Yang JC, Wang CH, Shieh MJ. Residence time-extended nanoparticles by magnetic field improve the eradication efficiency of *Helicobacter pylori*. ACS Applied Materials & Interfaces. 2020;12(49):54316-27.
35. Arif M, Sharaf M, Samreen, Khan S, Chi Z, Liu CG. Chitosan-based nanoparticles as delivery-carrier for promising antimicrobial glycolipid biosurfactant to improve the eradication rate of *Helicobacter pylori* biofilm. Journal of Biomaterials Science, Polymer Edition. 2021;32(6):813-32.
36. Cong Y, Geng J, Wang H, Su J, Arif M, Dong Q, Chi Z, Liu C. Ureido-modified carboxymethyl chitosan-graft-stearic acid polymeric nano-micelles as a targeted delivering carrier of clarithromycin for *Helicobacter pylori*: Preparation and in vitro evaluation. International journal of biological macromolecules. 2019;129:686-92.
37. Almeida Furquim de Camargo B, Soares Silva DE, Noronha da Silva A, Campos DL, Machado Ribeiro TR, Mieli MJ, Borges Teixeira Zanatta M, Bento da Silva P, Pavan FR, Gallina Moreira C, Resende FA. New silver (I) coordination compound loaded into polymeric nanoparticles as a strategy to improve in vitro anti-*Helicobacter pylori* activity. Molecular Pharmaceutics. 2020;17(7):2287-98.
38. Luo M, Jia YY, Jing ZW, Li C, Zhou SY, Mei QB, Zhang BL. Construction and optimization of pH-sensitive nanoparticle delivery system containing PLGA and UCCs-2 for targeted treatment of *Helicobacter pylori*. Colloids and Surfaces B: Biointerfaces. 2018;164:11-9.
39. Liu H, Liu W, Tan Z, Zeng Z, Yang H, Luo S, Wang L, Xi T, Xing Y. Promoting immune efficacy of the oral *Helicobacter pylori* vaccine by HP55/PBCA nanoparticles against the gastrointestinal environment. Molecular Pharmaceutics. 2018;15(8):3177-86.
40. Hwang J, Mros S, Gamble AB, Tyndall JD, McDowell A. Improving antibacterial activity of a HtrA protease inhibitor JO146 against *Helicobacter pylori*: a novel approach using microfluidics-engineered PLGA nanoparticles. Pharmaceutics. 2022;14(2):348.
41. Alam J, Dilnawaz F, Sahoo SK, Singh DV, Mukhopadhyay AK, Hussain T, Pati S. Curcumin encapsulated into biocompatible co-polymer PLGA nanoparticle enhanced anti-gastric cancer and anti-*Helicobacter Pylori* effect. Asian Pacific journal of cancer prevention: APJCP. 2022;23(1):61.
42. Zhang J, Chen Z, Kong J, Liang Y, Chen K, Chang Y, Yuan H, Wang Y, Liang H, Li J, Mao M. Fullerenol nanoparticles eradicate *Helicobacter pylori* via pH-responsive peroxidase activity. ACS applied materials & interfaces. 2020;12(26):29013-29023.
43. Zhang Y, Li H, Wang Q, Hao X, Li H, Sun H, Han L, Zhang Z, Zou Q, Sun X. Rationally designed self-assembling nanoparticles to overcome mucus and epithelium transport barriers for oral vaccines against *Helicobacter pylori*. Advanced Functional Materials. 2018;28(33):1802675.
44. Zou Y, Chen X, Sun Y, Li P, Xu M, Fang P, Zhang S, Yuan G, Deng X, Hu H. Antibiotics-free nanoparticles eradicate *Helicobacter pylori* biofilms and intracellular bacteria. Journal of Controlled Release. 2022;348:370-85.
45. Gopinath V, Priyadarshini S, MubarakAli D, Loke MF, Thajuddin N, Alharbi NS, Yadavalli T, Alagiri M, Vadivelu J. Anti-*Helicobacter pylori*, cytotoxicity and catalytic activity of biosynthesized gold nanoparticles: multifaceted application. Arabian journal of chemistry. 2019;12(1):33-40.
46. Abd El-Moaty HI, Soliman NA, Hamad RS, Ismail EH, Sabry DY, Khalil MM. Comparative therapeutic effects of Pituranthos tortuosus aqueous extract and phyto-synthesized gold nanoparticles on *Helicobacter pylori*, diabetic and cancer proliferation. South African Journal of Botany. 2021;139:167-74.
47. Al-Radadi NS. Microwave assisted green synthesis of Fe@ Au core–shell NPs magnetic to enhance olive oil efficiency on eradication of *helicobacter pylori* (life preserver). Arabian Journal of Chemistry. 2022;15(5):103685.
48. Gopalakrishnan V, Masanam E, Ramkumar VS, Baskaraligam V, Selvaraj G. Influence of N-acylhomoserine lactonase silver nanoparticles on the quorum sensing system of *Helicobacter pylori*: A potential strategy to combat biofilm formation. Journal of basic microbiology. 2020;60(3):207-15.
49. Al-Bahrani RM, Radif HM, Albaayit SF. Evaluation of potent silver nanoparticles production from *Agaricus bisporus* against *Helicobacter pylori*. Pakistan Journal of Agricultural Sciences. 2020;57(4):1197–1201.
50. Saravanakumar K, Chelliah R, MubarakAli D, Oh DH, Kathiresan K, Wang MH. Unveiling the potentials of biocompatible silver nanoparticles on human lung carcinoma A549 cells and *Helicobacter pylori*. Scientific reports. 2019;9(1):5787.
51. Sampath G, Shyu DJ, Rameshkumar N, Krishnan M, Sivasankar P, Kayalvizhi N. Synthesis and characterization of pyrogallol capped silver nanoparticles and evaluation of their in vitro anti-bacterial, anti-cancer profile against AGS cells. Journal of Cluster Science. 2021;32:549-57.
52. Naseer M, Ramadan R, Xing J, Samak NA. Facile green synthesis of copper oxide nanoparticles for the eradication of multidrug resistant Klebsiella pneumonia

and *Helicobacter pylori* biofilms. International Biodeterioration & Biodegradation. 2021;159:105201.
53. Attia HG, Albarqi HA, Said IG, Alqahtani O, Raey MA. Synergistic effect between amoxicillin and zinc oxide nanoparticles reduced by oak gall extract against *Helicobacter pylori*. Molecules. 2022;27(14):4559.
54. Sharaf S, Abbas HS, Ismaeil TA. Characterization of spirugenic iron oxide nanoparticles and their antibacterial activity against multidrug-resistant *Helicobacter pylori*. Egyptian Journal of Phycology. 2019;20(1):1-28.
55. Zhang W, Zhou Y, Fan Y, Cao R, Xu Y, Weng Z, Ye J, He C, Zhu Y, Wang X. Metal–organic-framework-based hydrogen-release platform for multieffective *Helicobacter pylori* targeting therapy and intestinal flora protective capabilities. Advanced Materials. 2022;34(2):2105738.
56. Gupta S, Tiwari A, Jain U, Chauhan N. Synergistic effect of 2D material coated Pt nanoparticles with PEDOT polymer on electrode surface interface for a sensitive label free *Helicobacter pylori* CagA (Ag-Ab) immunosensing. Materials Science and Engineering: C. 2019;103:109733.