REVIEW ARTICLE

Copper-Driven Phyto-Nanotechnology in Gastroretentive Drug Delivery: A Precision Strategy for H. Pylori Eradication

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ABSTRACT

The infection Helicobacter pylori is one of the most common causes of chronic gastritis, peptic ulcer disease, mucosa-associated lymphoid tissue lymphoma, and gastric adenocarcinoma. Thus, this remains a priority global health burden. Conventional antibiotic-based eradication regimens have surely improved clinical outcomes, but their effectiveness is increasingly compromised because of rising antibiotic resistance, poor drug stability in the acidic gastric milieu, limited mucus penetration, and inadequate local drug residence time. Next-generation gastroretentive drug delivery systems (GRDDS), such as stimuli-responsive hydrogels and mucoin-binding ligands, have been found to be better drug delivery platforms compared to the earlier floating tablets. The earlier floating tablets were based on the buoyancy concept only, whereas the advanced drug delivery platforms are able to deliver the drug directly to the H. pylori niche by bypassing the gastric emptying cycle, which is only 30-120 minutes.

The following review explores the therapeutic potentials of copper nanoparticles and bioactive phytochemicals incorporated within gastroretentive drug delivery systems as a novel and synergistic strategy for the eradication of Helicobacter pylori. CuNPs have a distinct multifunctional antibacterial activity that distinguishes them from other metallic nanoparticles, including silver and bismuth. In addition to non-specific oxidative stress, CuNPs have been found to have specific immunomodulation via ALPK1 and urease inhibition. This offers a cost-effective and chemically diverse alternative to precious metal nanoparticles. Phytochemicals, including curcumin, catechins, allicin, quercetin, and resveratrol, contribute anti-H. pylori, anti-inflammatory, and mucosal protective effects with reduced potential for resistance development.

The integration of these agents into mucoadhesive, floating, or pH-responsive GRDDS enables site-specific delivery, improved stability, sustained release, and extended interaction time with gastric mucosa. This review discusses new mechanistic paradigms, formulation strategies, synergistic interactions, and translational challenges and underlines the importance of rational design and standardized safety testing for nanoparticles. CuNP- and phytochemical-based GRDDS collectively hold promise for a new generation of therapy for the treatment of H. pylori infections beyond that which is possible with the current armamentarium.

Key words: Helicobacter pylori, copper nanoparticles, gastroretentive drug delivery system, phytochemicals, biofilm disruption.

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INTRODUCTION

H. pylori is a gram-negative, spiral-shaped, microaerophilic, and fastidious bacterium that has 5 to 7 flagella. Its spiral shape helps it to move in a corkscrew manner, easily penetrating the stomach mucosa. Infection with H. pylori can cause a variety of conditions related to gastrointestinal diseases like peptic ulcers, lymphoma of the stomach, mucosa-associated lymphoid tissue lymphoma (MALT), and gastric adenocarcinoma. Such infections may occur even when the symptoms are not evident. However, the most common pathological state arising from bacterial infections is peptic ulcer. The World Health Organization (WHO) has labelled H. pylori as a class I carcinogen, which is the single bacteria from this class. It is hypothesized that Helicobacter pylori has adapted and also contributed during the process of human evolution[1,2]

Virulence factors in H. pylori are mediated by various factors, which include bacterial attributes, host-related factors, and environmental factor (Table 1). The urease enzyme enables the bacteria to thrive in the acidic environment of the stomach by splitting urea in the stomach lumen to form ammonia and carbon dioxide. The bacteria also colonize the gastric epithelium through the interaction between the host cell receptors and the Helicobacter pylori outer membrane proteins (OMPs). First, H. pylori make initial contact with gastric mucosa, providing a protective mechanism against being dislodged from colonization due to peristaltic and gastric emptying actions. Initial host-cell contact is facilitated through the BabA protein, which is encoded by the gene babA2 and has a specific affinity for the Lewis b antigen found in host cells. Binding stomach cells through OMPs allows H. pylori to introduce proteins and toxins, consequently inducing numerous changes in their own host cells, finally resulting in inflammation. Given the confirmed association between CagA and stomach cancers, research has recently focused intensely on the bacterial oncogene CagA. The property of biofilm formation by these bacteria gives H. pylori the ability to withstand a vast array of antibiotics[3,4].

According to the epidemiological studies, a huge number of the global population are infected with H. pylori. A global meta-analysis showed that more than 4.4 billion are infected with H. pylori, but with highly variable prevalence in differing geographic and socioeconomic conditions worldwide. The prevalence of H. pylori worldwide is generally higher in low- to middle-income countries, especially in environments with poor sanitation/hygiene conditions, increasing with age in a positive dose-response relationship with household overcrowding [5,6].

The eradication regimen for H. pylori consists of a combination of strong acid-relieving medications and antimicrobials[7.] The primary regimen of eradication encompasses a Proton Pump Inhibitor-based triple regimen (PPI-TT), comprising antimicrobials such as clarithromycin, amoxicillin, and metronidazole, or, in environments with a greater prevalence of resistance, levofloxacin. However, antibiotic resistance is identified as the main factor accounting for the failure of PPI-TT treatment[8,9,10].The current clinical data shows that resistance rates for clarithromycin and metronidazole have climbed to alarming rates of 15-30% and 30-40%, respectively. This has resulted in eradication rates falling below the vital 70% mark [11]. This is a key research gap in that while current treatments are based on single-target approaches that are more likely to be affected by resistance, there is a need for multi-target approaches. Our proposed approach may improve eradication rates by using synergistic bactericidal pathways that avoid these specific resistance pathways. The rising incidence of drug-resistant strains makes the treatment of H. pylori infection increasingly difficult[12]. The World Health Organization has designated clarithromycin-resistant H. pylori infection as a high-threat type of community-acquired infection[13].

A large meta-analysis, including data from 65 countries, reported that primary resistance of H. pylori to key antibiotics such as clarithromycin, metronidazole, and levofloxacin now exceeds 15% in most World Health Organization regions, above which threshold standard empiric therapies are no longer recommended. In many areas, but particularly in Asia and parts of Africa, resistance levels far exceed these limits, making conventional treatment significantly less reliable. These resistance patterns have a direct negative impact on treatment outcomes, with resistance to clarithromycin strongly associated with therapy failure[14,15].

Treatment failure not only leads to chronic infection but also increases the complication of serious outcomes, such as gastric mucosal atrophy and cancer. Considering the fact that the eradication of H. pylori infection has proven to decrease the incidence of gastric cancer by a large margin, it is an important task to enhance the success rate of eradication methods to prevent cancer world-wide[15].

Nevertheless, to overcome these issues, gastroretentive drug delivery systems (GRDDS) have been introduced as an attractive approach that enables the extended retention of drugs in the gastric environment to facilitate the sustained localized delivery of antibacterial agents at the site where they are required. When combined with the development in nanotechnology in the form of metal nanoparticles that possess inherent antimicrobial activity and bioactive phytochemicals that possess activity against H. pylori, these high-tech platforms may have the potential to improve eradication rates while addressing associated concerns regarding drug resistance and systemic side effects[15,16,17].

Among various nanomaterials, copper nanoparticles have attracted attention due to their strong antimicrobial activity, multiple mechanisms of bacterial killing, and economic feasibility[18,19].Concurrently, phytochemicals such as flavonoids, polyphenols, and alkaloids have demonstrated significant anti-*H. pylori* activity and gastric mucosal protection. The integration of CuNPs and phytochemicals within gastroretentive systems represents a novel and multifaceted approach to *H. pylori* eradication. A combination of CuNPs and phytochemicals in

gastroretentive systems has been a modern and multi-attribute approach toward H. pylori eradication [20,21].

2. Why Gastroretentive Drug Delivery Matters for Helicobacter pylori

The successful eradication of Helicobacter pylori infection still remains a challenge despite extensive research over the past several decades and the existence of quite a few antibiotic therapies. The most important and, to a certain extent, overlooked reason for the difficulty associated with the treatment of such infections is the special environment offered by the stomach and the very specific niche represented by Helicobacter pylori bacteria. Unlike most other pathogens that infect the digestive system, Helicobacter pylori does not live inside the stomach cavity but rather near the stomach epithelium, within the mucus layer.

2.1. Gastric Physiology and Its Relevance to *H. Pylori* Colonization

The stomach is a dynamic organ having complex variables in terms of pH, secretion of mucin, and gastric motility. The pH in the stomach changes from extremely acidic (pH 1-2) when the stomach is empty to slightly acidic or neutral when food is consumed. The pH can affect the stability and release rate of drugs. There are several antimicrobials whose stability/solubility decreases in an acidic pH environment due to which the efficacy decreases before it can reach the site of action[22,23,24].

The stomach mucosal surface is protected with a viscoelastic mucous layer that consists mainly of mucin glycoproteins. H. pylori cross this mucous layer due to its flagellar motility and binds to host epithelial cells, thereby creating its own niche microenvironment that provides protection to the organism against the corrosive effects of gastric acid and mechanical removal[25,26,27]. Moreover, H. pylori have urease, an enzyme that catalyses the hydrolysis of urea into ammonia and carbon dioxide, thereby neutralizing the action of gastric acid. Such a niche provides an insurmountable barrier for systemically administered antibiotics since high drug concentrations need to be sustained within the mucous layer for an extended period of time for effective killing of the organism (table.1) (figure.1[28-31].

Another major impediment to the effective eradication of H. pylori is the development of biofilms that can result in up to 1000-fold resistance to antibiotics compared to planktonic cells[32,33]. Conventional oral dosage forms are less effective because of the short gastric residence time of the drug formulations, which is often insufficient to achieve high-intensity localized drug concentrations to overcome the biofilm resistance. The longer gastric residence time of over 8-12 h is ensured with GRDDS formulations to allow CuNPs to physically disrupt the biofilm structure and inactivate the protected bacteria within H. pylori biofilms[12].

Table.1 Interaction Between Gastric Acid Physiology and *Helicobacter pylori* Survival Mechanisms

Aspects	Normal gastric physiology	H. pylori Adaptive Mechanism	Ref.
Gastric lumen acidity(pH ~1–3)	Strong acidic barrier to microbes and helps digestion	Produces urease to hydrolyse urea into ammonia and CO_2, neutralizes local acidity and protecting the bacteria from acid toxicity	34
pH gradient in mucus	Acidic at lumen side, near pH-6 closer to epithelial surface due to bicarbonate and mucus buffering	Neutralizes local pH via urease activity, enabling swimming toward less acidic regions and colonization near the epithelium	35
Mucus viscoelasticity	Gel at low pH, impeding bacterial motility	Urease mediated pH increase converts gel to more fluid state, facilitating motility and mucus penetration	34
Motility requirement in mucus	Flagellar motility needed to navigate through mucin mesh	Spiral shape and flagella allow corkscrew movement; bacteria follow pH gradients towards protective niches	36
Colonization niche	Neutral pH near epithelium preferred for growth	Bacteria localize deep in mucus where V is elevated by urease and adhesion to epithelial cells occurs	34
Growth pH range	Optimal growth at neutral pH (~6-7)	Survival and motility in pH <3 require urease, growth best at ~5-7 with pH modulation	37

Note: Table 1. Physiological aspects of gastric acid and corresponding adaptive mechanisms employed by *Helicobacter pylori* for survival, motility, and colonization within the gastric mucosa.

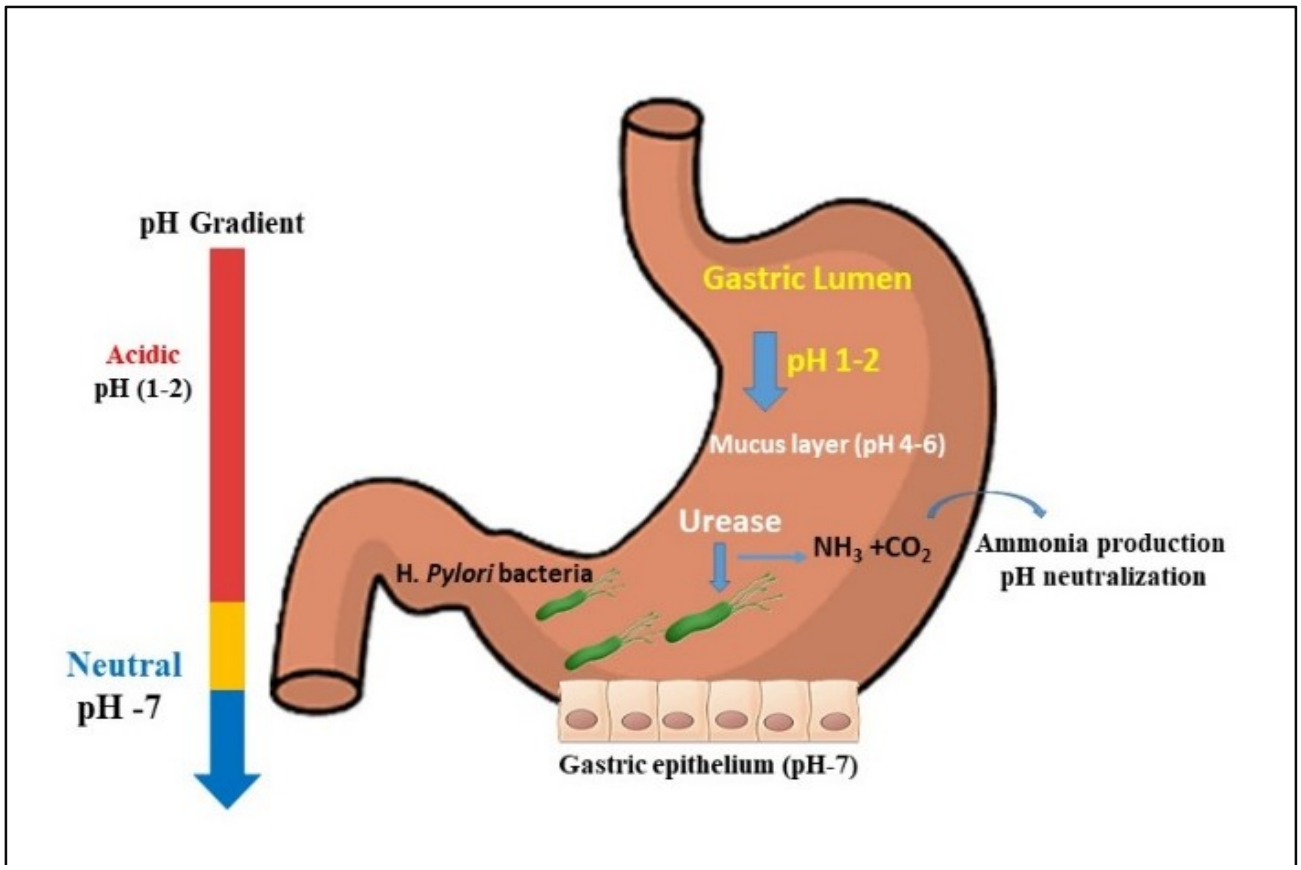

Figure 1. Gastric Physiology and *H. pylori* colonization

Figure 1. The figure represents the stomach physiology, mucus layer, and localization of *H. pylori* beneath the gastric mucus.pH gradients across the gastric lumen, mucus layer, and epithelial surface displaying the protected microenvironment for *H. pylori* survival.

2.2. Limitations of Conventional Oral Drug Delivery for *H. pylori*

Conventional solid oral dosage formulations like tablets and capsules are known to empty the gastric content very quickly, especially after an overnight fasting state. The gastric residence time of the commonly taken solid dosage formulations will be between 30 minutes to 2 hours[38]. This will drastically reduce the contact time of the drug with H. pylori bacteria, which are lodged within the gastric mucus epithelial interface. This will result in the failure of the antibiotics even after showing in vitro effectiveness.

Moreover, the concentrations of drugs produced by conventionally formulated dosage forms go through fluctuations with a burst release followed by a rapid decrease. Moreover, these pharmacokinetic characteristics hamper the elimination of H. pylori species, as it is necessary to maintain concentrations of drugs above the MIC to resist bacterial defences[39].

2.3. Concept and Rationale of Gastroretentive Drug Delivery Systems

Gastroretentive drug delivery systems (GRDDS) have been designed to help drugs spend more time in the stomach, thus increasing local concentrations of drugs. GRDDS have been shown to resist gastric emptying due to properties such as buoyancy, muco-adhesion, or density gain or due to a combination of these properties[40-42]. Since these systems help drugs spend more time in the stomach, they help drugs be released locally where H. pylori resides.

Gastroretention is beneficial for H. pylori infections in many ways. First, the prolonged stay of the bacteria in the stomach enables it to be attacked by medications continuously, thus assuring total eradication. Secondly, the use of gastroretention leads to less absorption of a drug, hence fewer side effects for the patient. Thirdly, gastroretention involves the controlled release of a high peak concentration of medication, which shields it from resistance development due to fluctuating levels[43-46].

3. Gastroretentive Drug Delivery Systems (GRDDS): Mechanisms, Types, Design Considerations and Emerging Hybrid Approaches

Gastroretentive drug delivery systems, or GRDDS, are novel oral dosage forms designed to extend drug residence times in the gastrointestinal tract and so improve treatment efficacy for compounds showing specific gastrointestinal absorption, poor stability under gastrointestinal conditions,

or requiring specific targeting of gastric pathogens. Traditional oral dosage forms tend to demonstrate unpredictable gastric emptying and to have low residence times, so that inadequate drug concentration is presented to the specific site of action. GRDDS could potentially compensate for natural bodily constraints by controlling formulation properties like density, size, adhesion, or response to the stomach environment. This literature review aims to address all these topics related to gastroretentive drug delivery systems and to contribute to knowledge expansion in this area by providing an overview of recent and relevant literature surrounding novel oral drug targeting and its continued development[40,47,49].

The stomach represents a very dynamic physiological environment that exhibits different pH gradient concentrations, gastric motility cycles, enzymatic secretion, and mucus turnover. This has been observed to significantly affect drug solubilization, drug stability, and absorption processes (table.1) [4]. In conditions like Helicobacter pylori infection, whereby organisms colonize in the mucus layer lining the gastric epithelium, it becomes imperative to optimize drug concentration within this particular location through GRDDS designs intended to improve therapeutic responses at a reduced frequency of systemic administration (Figure.2)[48,50,51]

Table 2. Physiological factors of the stomach influencing GRDDS performance

Sl. no	Factor	Impact on GRDDS
1	Gastric pH	Affects drug stability and release
2	Gastric emptying	Determines retention time
3	Mucus thickness	Influence mucoadhesion
4	Motility pattern	Affects system displacement

3.1. Mechanisms governing Gastroretention

Floating (Buoyant) Mechanism

Floating drug delivery systems are designed to have a density lower than that of gastric fluid so as to withstand gastric emptying. The drug delivery systems are designed to float on top of the gastric fluid. They stay on top of the gastric fluid and slowly release drug while having extensive contact with gastric mucosae[52,53,54]. The drug delivery systems can either be effervescent or non-effervescent.

Effervescent systems produce carbon dioxide upon contact with gastric acid in the presence of gas-releasing substances like sodium bicarbonate or calcium carbonate. The resultant trapped gases reduce system density to promote flotation[55]. Non-effervescent systems have swellable polymers like hydroxypropyl methylcellulose (HPMC) that have trapped air within their swelled mass. Also, floating systems can be very effective for locally acting gastric chemicals, although they can be affected by gastric motility and fed or fasted conditions. In another study, floating and sustained-release systems containing morphine were prepared and made to float by adding ammonium chloride (table.2)[56].

Mucoadhesive Mechanism

Mucoadhesive GRDDS employ polymers which have the ability to bind to the mucus lining of the stomach by hydrogen bonds, van der Waals interactions, electrostatic interactions, or entanglements. Chitosan, Carbopol, polyacrylic acid, or sodium alginate polymers have been widely utilized owing to their muco-adhesive properties[57]. Being mucoadhesive, Mucoadhesive systems resist being cleared from the stomach. They ensure a high localization of drugs in close proximity to the gastroepithelial surface. Mucoadhesion has a high degree of importance for H. pylori eradication, since H. pylori exists below the mucus layer instead of being present in the stomach lumen. Mucoadhesive properties increase penetration of drugs into the mucus and bacterial eradication efficiency (table.2) [58].

Mechanism of Swelling and Expansion

Swelling or expandable systems are designed to increase rapidly in size when in contact with gastric fluids. The expanded system is larger than the pyloric opening, thus preventing early gastric emptying[59,60,61]. These systems usually employ hydrophilic polymers capable of absorbing large volumes of water and forming gel-like structures. Recent innovations in the field include stimuli-responsive swelling systems-ones that expand selectively depending

on the changes in pH. Such systems remain compact in the acidic lumen of the stomach but are subjected to rapid expansion near the mucus layer, where pH is comparatively higher, ensuring site-specific retention and release (table.2)[62].

High-Density and Magnetic Retention Systems

High-density GRDDS are prepared using densities higher than that of gastric content, and hence they sink and stay in the lower parts of the stomach. Such systems use materials like barium sulphate and zinc oxide to have sufficient density[16,63,64]. In magnetic systems, the magnet is included in the formulation and an external magnetic field is needed to help retain them in the stomach for gastric retention of pellets. Even though this is effective in theory, for its application in practice, there can be patient compliance issues and complexity (table.2) [65].

Table 3. Types of GRDDS and their Retention Mechanisms

Type	Mechanism	Polymers	Advantages	Limitations
Floating	Buoyancy	HPMC, EC	Simple Design	Affected by motility
Mucoadhesive	Mucus adhesion	Chitosan, Carbopol	Localized Action	Mucus turnover
Swelling	Size expansion	HPMC, SCMC	Strong Retention	Risk of obstruction
High density	Sedimentation	$BaSO_4$	Simple concept	Limited application

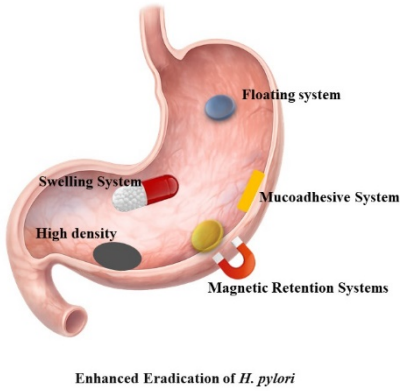

Figure.3mechanism of GRDDS in H. pylori eradication

4. Copper Nanoparticles in *Helicobacter pylori* Infection in the Gastrointestinal Tract: Mechanisms, Targeted Delivery, and Novel Insights

Despite several decades of antibiotic therapy, H. pylori remain a global health challenge due to the increase in antibiotic resistance, poor gastric retention of conventional drugs, and the difficulty in achieving bactericidal concentrations in a sustained manner at the mucus–epithelium interface, where this bacterium resides. This has begun to stimulate other antimicrobial strategies; metal-based nanoparticles (NPs) represent one such auspicious candidate. Among them, CuNPs have been rendered particularly attractive due to their intrinsic antimicrobial properties, moderate cost compared to noble metals, and potential for functional engineering[66-69].

In this section, the special aspects of CuNP interaction with H. pylori will be discussed, exploring beyond the typical mechanism and also including interactions mediated towards the mucus, the modulation of the microenvironment within the stomach, immune response, overcoming resistance, and combining these for a broader format of delivery systems such as GRDDS.

4.1. Mechanistic Insights: Extending beyond Traditional Antibacterial Properties

Although other metallic nanoparticles, like silver (AgNPs) and bismuth, have been studied for antimicrobial activities, CuNPs provide therapeutic and economic advantages for the eradication of H. pylori infection. Unlike AgNPs, which act by inducing oxidative stress, CuNPs show high binding specificity to the enzymes of the bacteria, thereby inhibiting the essential urease enzyme for the survival of H. pylori at low pH levels. Also, copper is an economical substitute for noble metals and functions as a specific signaling molecule to initiate innate immunity

via the ALPK1 pathway, which is not usually activated by bismuth-based therapies [70,71].

4. 1.1. Membrane Disruption and Ionic Stress

Copper nanoparticles cause significant changes to the structure of the bacterial cell envelope through physical interaction as well as the release of metallic ions. Unlike conventional antibiotics, which target specific molecules, Cu^{2+} ions as well as CuNPs interact with negatively charged compounds such as lipopolysaccharides and membrane proteins of bacteria resulting in:

Membrane fluidity and/or

Loss of Integrity & Permeability

Leakage of cytoplasmic contents

Loss of proton motive force

Such effects are most toxic to H. pylori because this organism has the ability to resist the effects of the acid stress by preserving the membrane and proton gradients (table.3) [72-74].

4.1.2. Reactive Oxygen Species (ROS) and Oxidative Stress

CuNPs catalyse Fenton-like reactions in the presence of hydrogen peroxide and form ROS such as hydroxyl radicals, superoxide anions, and singlet oxygen molecules. Unlike conventional bactericidal antibiotics, which target specific entities, the ROS cause widespread damage to macromolecules such as proteins, lipids, and nucleic acids, thus making it hard for microorganisms to develop resistance against them (table.3)[75,76].

Disruption

Copper ions have a strong affinity for the sulfur groups of cysteine residues, which are plentiful within many bacterial proteins. This gives rise to:

Inactivation of Essential Enzymes

Impaired energy metabolism (NADH dehydrogenase)

Destruction of urease activity

Urease is an important virulence factor that helps H. pylori neutralize the acidic environment, and this process is inhibited by CuNPs, which reduces H. pylori's survival ability within the acidic environment of the stomach (table.3)[77,78,79].

4.1.4. Genotoxicity and DNA Damage

The Cu^{2+} ions are able to bind to the nucleotide bases, which may cause strand breaks and cross-links of DNA. The interaction is proposed to be achieved through ionic binding and ROS-induced damage, which inhibits replication and transcription (table.3)[80,81,82].

Table.4 Antibacterial Mechanisms of Copper Nanoparticles Relevant to H. pylori Eradication

Mechanism	Target site	Effect on H. pylori	Therapeutic activity
Membrane disruption	Outer membrane	Leakage of cellular contents	Rapid bactericidal action
ROS generation	Cytoplasm	Oxidative stress, protein and lipid damage	Low resistance risk
Urease inhibition	Enzymatic action	Loss of acid neutralization	Reduced gastric survival
DNA damage	Nucleic acid	Replication arrest	Prevents proliferation
Biofilm disruption	Biofilm matrix	Increased susceptibility	Overcome persistence

Note: The table.4 describes the major mechanisms involved in making copper nanoparticles effective anti-H. pylori agents through the machinations of disrupting the bacterial cell membranes, inducing oxidative stress, inhibiting enzymes, causing DNA damage, and disrupting bacterial biofilms.

4.2. New Mechanistic Paradigms

To ensure that this section is original and distinct among reviews, we bring forward three novel and specific mechanisms in relation to H. pylori (table.4):

4. 2.1. Mucus-Targeted Antibacterial Action

H. pylori is known to dwell deeply within the mucus layer of the stomach, which serves as a physical and biochemical barrier to many medications. Common antibiotics lack sufficient mucus penetration, leading to poor concentrations of drugs.17 Recent evidence has shown that the surface charges and functionalization of nanoparticles impact mucus penetration as follows:

A neutral to slightly positive surface charge facilitates diffusion in negatively charged mucin meshwork.

PEGylation or mucolytic surface coating: Increase penetration depth.

Furthermore, ligand functionalization (such as mucoin-binding peptide functionalization) can actively target the mucus layer.

Therefore, designed CuNPs can better enter the H. pylori microenvironment than the conventional drug and improve bacterial sensitivity[83-86].

4. 2.2. Immunomodulatory Effects of Copper

Apart from the direct antibacterial activity, CuNPs also affect the host immune systems by:

Activation of macrophage and dendritic cells by redox signalling pathways

Increased secretion of pro-inflammatory cytokines with potential roles in bacterial clearance

Modulation of gastric epithelial innate immunity

Such immunomodulatory properties are not observed in conventional antibiotics and might work toward the greater efficacy of nanoparticles *in vivo.* Besides direct antimicrobial activities, copper and copper nanomaterials have been demonstrated to have modulatory effects on host innate immunity responses. Recent research indicates that copper is able to work as a signalling molecule involved in innate immunity by triggering alpha-kinase 1 (ALPK1), which is a pattern recognition receptor found intracellularly. The intracellular content of copper increases the sensitivity of ALPK1 to bacteria, which increases the production of pro-inflammatory cytokines and the number of phagocytic cells involved in innate immunity responses against bacteria, hence triggering host immunity responses[87].

Experimental studies conducted on animals have also demonstrated the induction of an inflammatory reaction, which manifests as an influx of neutrophils, thereby signifying the triggering of an immune response upon exposure to copper nanoparticles[88].

Moreover, the immunoregulatory role of copper-coordinated nanoparticles has been evidenced in macrophage cultures, in which cytokine expression patterns were affected by the morphology of nanoparticles, pointing out the potential role of CuNP design in regulating macrophage-mediated immunity. As indicated by the above-cited findings, it appears that copper nanoparticles are capable not only of directly killing bacteria but also can interact with the host immune system through the promotion of proinflammatory responses, which, in turn, could contribute to its potential application in treating H. pylori infection, provided it is optimally designed in a formulation (figure.3)[89,90].

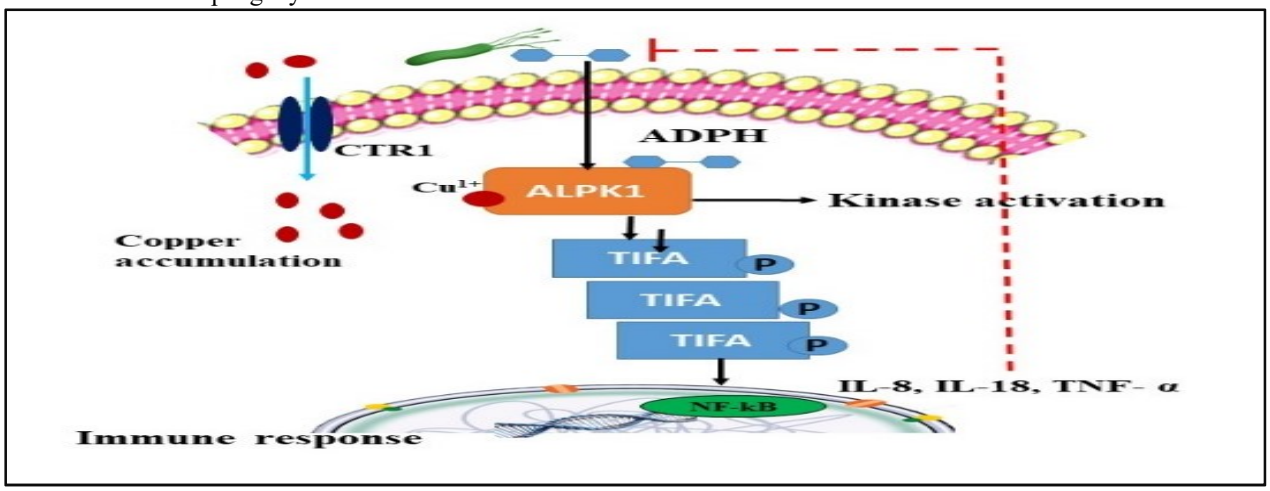

Figure.3 An illustration of immunomodulatory mechanisms of copper nanoparticles in H. pylori infection

Note: Schematic representation of the proposed immunomodulatory and antibacterial mechanisms of copper nanoparticles against Helicobacter pylori infection. Copper nanoparticles, upon gastroretentive delivery, release Cu^{2+} ions in the gastric microenvironment. Copper ions can trigger innate immune signalling pathways, including ALPK1-mediated NF-κB activation in gastric epithelial cells and macrophages, which can further enhance pro-inflammatory cytokine production and recruitment of phagocytic immune cells. Paralleling these actions, copper nanoparticles can directly exert their bactericidal effects on H. pylori, ultimately promoting synergistic bacterial clearance through combined antimicrobial and host immune mechanisms.

4.2.3. Disruption of Biofilm-Like Communities

Helicobacter pylori can form biofilm-like colonies on the gastric mucosa, which greatly increase H. pylori survival rates by reducing antibiotic diffusion and inhibiting clearance by the immune system. Biofilm H. pylori shows higher resistance to antimicrobial agents than is observed in planktonic H. pylori, leading to treatment resistance and persistent infection. Biofilm components, specifically the extracellular matrices, physically shield and select cells with resistance, thus making H. pylori biofilms a target in H. pylori therapy[33].

Copper nanoparticles (CuNPs) have also exhibited pronounced antibiofilm activity against various bacterial pathogens in a way that is different from conventional antibiotics. These involve penetration and disruption of the biofilm matrix, blocking critical biofilm-modulating signalling pathways, and localized ROS production in biofilms, causing biofilm matrix instability and bacterial damage. It is clear that these biofilm-modulating strategies pose a major benefit compared with conventional antimicrobial agents, which are ineffective in destroying bacteria within structured biofilms, making CuNPs a potential tool in resolving biofilm-related persistence in H. pylori infection [82.]

4.3. Integration with GRDDS for Enhanced Local Delivery

Copper nanoparticles (CuNPs) combined with Gastroretentive drug delivery systems (GRDDS) have the potential to greatly facilitate the localized therapy of gastric infections by prolonging the stay of the medication within the stomach. GRDDS have the capability of remaining within the gastric environment for an extended period, making use of mechanisms like muco-adhesion, floating, and hydrogel formation to overcome the evacuating motions of the stomach. By doing this, GRDDS allow the therapeutic agents encapsulated in the system to have continuous interactions with the infected mucosa of the stomach, thus greatly increasing the local concentration of the medication at the site of colonization caused by the bacterium Helicobacter pylori when compared to existing fast-clearing dosage forms that only travel quickly through the stomach. Muco-adhesive and floating GRDDS have been quantitatively shown to have an extended residence profile within the stomach, thereby reiterating the validity of these systems to be utilized as local antibacterial agents[91].

Recent progress in the field of GRDDS has included the use of pH-responsive or hydrogel matrices, which may offer controlled, pH-sensitive release of metal ions, including Cu^{2+}, in the acidic pH of the gastric cavity or in the microenvironment close to the surface of the mucous lining of the gastrointestinal tract. Therefore, pH-responsive superporous and responsive hydrogels, designed to have pH-responsive swelling or release of the drug, may be developed, where the drug delivery may be targeted to the specific site of the body, in this case, the stomach, to stay for a longer period of time by swelling in the body along with pH-responsive release of the drug. pH-responsive or mucoadhesive drug delivery may be employed to deliver CuNPs to the targeted site, where it will release the CuNPs, ensuring a longer exposure to H. pylori while avoiding systemic exposure and the consequent toxic effects[92].

4.4. Synergism with Phytochemicals and Antibiotics

Copper nanoparticles (CuNPs) or Nano formulations in combination with phytochemicals and traditional antibiotics have demonstrated promising synergistic effects on H. pylori and other bacterial pathogens. Curcumin, a natural dietary polyphenol, demonstrates natural anti-H. pylori activity in terms of inhibiting the growth, biofilm formation, and adhesion of bacteria to the epithelial cells, and these effects are further improved by the use of Nano formulations. Curcumin Nano emulsions have also demonstrated the potential to synergize the effects of traditional antibiotics, azithromycin, and have improved the eradication capabilities against H. pylori[93].

Similarly, metal nanoparticles, including CuNPs, often exhibit synergistic antibacterial action in combination with traditional antibiotics, enhancing their efficacy through various mechanisms such as enhanced cellular uptake, disruption of membranes, and elevation of intracellular oxidative stress. While specific investigations into the synergy of CuNP-antibiotic interactions in H. pylori infections are still developing, related bacterial systems have demonstrated that combinations involving metal nanoparticles can greatly reduce the quantities of required antibiotics and enhance bactericidal potentials, thus signifying the potential for such combinatorial approaches in overcoming resistive trends and improving clinical outcomes[94].

Table.5 Comparison of Copper Nanoparticles and Conventional Antibiotics in *H. Pylori* Therapy

Parameter	Copper Nanoparticles (CuNPs)	Conventional Antibiotics
Mode of antibacterial action	Multi target action including membrane disruption, ROS generation and metabolic interferences	Predominantly single target mechanisms
Mucus layer penetration	Enhanced penetration via surface charge modulation and functionalization	Limited penetration through gastric mucus
Resistance development	Low probability due to multi-site bacterial damage	High prevalence due to target specific mechanisms
Activity in acidic gastric pH	Stable and active under acidic conditions	Often reduced stability and activity
Biofilm disruption capability	High antibiofilm efficacy through matrix penetration and ROS generation	Limited efficacy against structured biofilms
Immunomodulatory effects	Activates innate immune responses and cytokine signaling	Minimal immunomodulatory activity
Compatibility with GRDDS	Excellent compatibility with mucoadhesive and pH responsive systems	Variable compatibiity
Potential for synergistic therapy	Demonstrates synergy with phytochemicals and antibiotics	Limited synergy, resistance concerns

Table 5. Mechanistic and functional comparison of copper nanoparticles and conventional antibiotics in the management of *Helicobacter pylori* infection, based on evidence discussed in Sections 4.2–4.4.

4.5. Challenges, Clinical Translation, and Regulatory Aspects

Although the preclinical data are promising, the translation of copper nanoparticle (CuNP)-based therapies to the clinic has a few notable hurdles that will need to be addressed before these nanoparticles can be broadly applied clinically. Reproducibility and scalability in the formulation and scale-up of nanoparticle preparations are a large concern because it would be difficult to work with consistent physiochemical properties on an industrial scale, especially when dealing with more complicated nanoparticles, in which small changes have already been shown to influence biodistribution, efficacy, and toxicities. Furthermore, standardized studies on the safety evaluation of these nanoparticles in human gastric tissue and the long-term biocompatibility and toxicities are yet to be done, and most work has been restricted to *in vitro* and animal studies to date, thereby emphasizing the need for thorough preclinical and phase I studies to be carried out[95]. From the regulatory viewpoint, metal nanoparticles such as CuNPs are considered outside the existing categories of small molecules and biologics, making it uncertain how they should be approved, as there is a significant need for safety and efficacy information. The existing regulations by bodies such as the Food and Drug Administration (FDA) in the United States and the European Medicines Agency (EMA) do not as yet fully cover nanomedicines regarding protocols such as nanomedicines characterization, biocompatibility studies, and long-term risk assessment, making it even more challenging regarding clinical translation. The lack of well-established regulations regarding nanomedicines, apart from the challenges and needs described, illustrates the importance of collective actions by researchers and developers, as well as those involved in the regulations, including authorities such as the FDA and EMA, in establishing frameworks that can ensure safe and successful clinical translation[96].

5. Phytochemicals in Gastroretentive Drug Delivery Systems and Copper Nanoparticles for Eradication of Helicobacter pylori

Infection with Helicobacter pylori remains a leading global health problem causing gastritis, peptic ulcers, and gastric cancer. Conventional antibiotic treatments often fail due to poor retention in the stomach, increasing antibiotic resistance, and inadequate local drug concentrations at the mucosa, where H. pylori reside. These limitations accelerated the interest in alternative strategies for antimicrobials, including phytoactive compounds or bioactive plant-derived molecules, and nanotechnology-based delivery systems such as GRDDS impregnated with metal nanoparticles like copper. The latter offers an extended residence time in the stomach for sustained local delivery of both copper nanoparticles and phytochemicals at the site of infection (figure.4) [97].

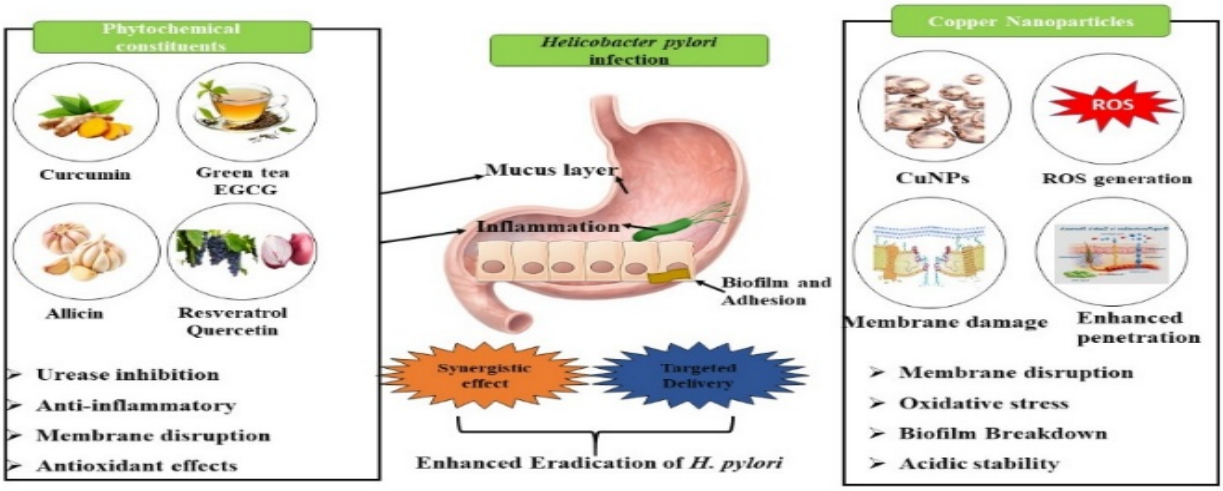

Figure.4 Phytochemicals and nanoparticles in H. pylori treatment

Note: Figure .4 represents the number of phytochemicals obtained from edible and medicinal plants had shown promising anti- H. pylori activity through various mechanisms such as bacterial growth inhibition, suppression of urease activity, disruption of membrane integrity, and anti-inflammatory activity, among others. These natural agents may hold great promise in the gastro-retentive drug delivery system, especially in combination with some antimicrobial nanotherapeutics, such as copper nanoparticles.

5.1. Anti-H. pylori Activities of Phytochemicals

Phytoactive compounds represent a broad range of plant secondary compounds, including flavonoids, polyphenols, terpenoids, alkaloids, and compounds containing sulfur, many of which have been found to have antibacterial and anti-inflammatory properties that would be useful for H. pylori eradication. There have been several *in vitro* and animal experiments showing that they have several modes of action, including growth inhibition, adhesion to epithelial cell inhibition, and reduction of virulence factors [98]. For instance, flavonoids like quercetin, kaempferol, and epigallocatechin gallate (EGCG), have demonstrated the ability to inhibit the growth of H. pylori, down-regulate the expression of virulence genes, and impair the integrity of the bacterial cell membrane [99].

Epigallocatechin gallate (EGCG), a prominent polyphenol in green tea, inhibits bacterial adhesion, as well as pro-inflammatory pathways like NF-κB, which protects the gastric mucosa in gastric epithelial cells. Likewise, the active component of ginger, gingerol, has been shown to impair the growth of H. pylori bacteria and to reduce the expression of inflammatory genes in host cells. Other phytochemicals, like curcumin, allicin from garlic, and Ellagic acid, have also been demonstrated to be inhibitors of the important H. pylori viability factor, urease, as well as inhibitors of the bacterial binding to the gastric mucosa. Such multi-targeting properties make phytochemicals interesting additives or alternatives to antibiotics, especially when resistance makes antibiotics less effective (Table.5)[98].

Table.6Phytochemicals with Anti-*Helicobacter pylori* Activities and Their Mechanisms

Phytochemical	Natural source	Reported anti-*H. pylori* mechanism(s)	Key evidence	Ref
Curcumin	*Curcuma longa* (turmeric)	Inhibits bacterial growth, suppresses NF-κB–mediated inflammation, reduces adhesion to gastric epithelial cells	In vitro and animal studies demonstrate growth inhibition and anti-inflammatory effects	[100]
Epigallocatechin gallate (EGCG)	Green tea (*Camellia sinensis*)	Disrupts bacterial cell membrane, inhibits urease activity, reduces bacterial colonization	In vitro inhibition of *H. pylori* growth and urease	[101]
Quercetin	Fruits and vegetables (onion, apple)	Antioxidant and anti-inflammatory activity; suppresses urease and bacterial growth	Enzyme inhibition and antibacterial studies	[102]
Resveratrol	Grapes, berries	Inhibits bacterial proliferation, attenuates inflammatory cytokine production	In vitro antibacterial and anti-inflammatory studies	[103]
Allicin	Garlic (*Allium sativum*)	Direct bactericidal activity through thiol-reactive mechanisms	Strong in vitro antibacterial activity	[104]
Berberine	*Berberis* species	Disrupts bacterial membrane integrity, inhibits growth and adhesion	In vitro and animal infection models	[105]
Catechins (mixture)	Green tea	Inhibit bacterial growth, suppress virulence factors, reduce colonization	In vitro and epidemiological studies	[101]
Licorice flavonoids	*Glycyrrhiza glabra*	Inhibits bacterial adhesion and growth, gastroprotective effects	In vitro studies and clinical observations	[106]

Note: Table 6. Representative phytochemicals exhibiting anti-*Helicobacter pylori* activity, their natural sources, and reported antibacterial or anti-inflammatory mechanisms.

5.2. Limitations of Free Phytochemical Delivery and Advantages of GRDDS

Despite promising antibacterial activity, phytochemicals often present significant pharmacokinetic challenges, including poor water solubility, chemical instability in the acidic gastric environment, and rapid systemic metabolism. These limitations reduce their therapeutic efficacy against H. pylori residing within the mucus layer adjacent to epithelial cells. These limitations are addressed by GRDDS, which prolong gastric residence time and consequently provide localized and controlled release of bioactives in the stomach. Common platforms for GRDDS include floating systems that remain buoyant on the gastric contents, mucoadhesive formulations that attach themselves to the gastric mucosa, and expandable systems that resist gastric emptying.

Entrapping phytochemicals into GRDDS increases their gastric localization and provides them at effective concentrations for longer periods at the mucosal interface. Such sustained release may increase the interactions with

H. pylori and improve eradication chances over that from free phytochemical administration [97] For example, chitosan-based mucoadhesive microspheres are being developed to prevent the gastric degrad ation of labile phytochemicals such as andrographolide, a diterpenoid lactone, while prolonging gastric retention and promoting sustained release. Such systems have been reported to deliver the bioactive compound directly to the mucosal surface, acting against bacterial colonization and inflammation [107-109].

5.3. Role of Copper Nanoparticles and Phytochemicals in GRDDS

Copper nanoparticles (CuNPs) display remarkable antimicrobial properties due to their capacity to interact with the bacterial membrane, produce ROS, and release toxic copper ions, inhibiting the energetics of the bacterial cells. Nanotechnology has found great success in the targeted therapy of H. pylori, leading to improved efficacy of the medication due to its stability and penetration properties within the stomach environment[110].When combined with phytochemicals in GRDDS, CuNPs can provide the following synergistic advantages:

Complementary mechanisms: Although CuNPs display bactericidal effects due to cell membrane damage, production of ROS, and ion release, phytochemicals act through virusence modulation of bacterial virulence factors and signalling pathways. This could be a complementary mechanism to avoid bacterial resistance[110].
Biofilm inhibition: Some phytochemicals are known to be inhibitors of biofilm formation. Also, the eventual use of metal nanoparticles can physically invade the biofilms. Both effects could be complementary in the removal of bacteria when the use of antibiotics fails[110].

Localized delivery and retention: GRDDS delivery platforms facilitate the sustained co-delivery of CuNPs and phytoactive components in the stomach, thus maximizing localized bacterial exposure and reducing systemic side effects[110]. These synergistic interactions make CuNP-phytochemical pairs, administered through GRDDS, a promising new generation strategy to efficiently remove H. pylori infections, even those causing resistance against antibiotics.

5.4. Experimental Evidence and Nanoplatform Designs

Despite a lack of studies directly examining a combination of copper nanoparticles (CuNPs) and phytochemicals within GRDDS for H. pylori eradication, a considerable body of experimental evidence from other nanoplatform studies gives a strong rationale for this area of investigation. Current reviews discussing nanoparticle-based delivery of drugs for H. pylori treatment particularly highlight how nanocarriers of a polymeric, liposomal, or mimetic origin can be designed to better target gastric mucosa, overcome mucus barriers, and deliver drugs in a controlled manner within an acidic environment, thereby increasing eradication efficacy and overcoming systemic toxicity issues of drugs against H. pylori[111].

Polymeric nanoparticle systems, especially chitosan, and other mucoadhesive polymers, have shown improved binding efficacy to the gastric epithelial layer and an enhanced residence time within the stomach. These factors assume prime importance within the case of H. pylori, which adheres to the mucus layer lining the neighboring epithelial cells. Targeted delivery systems of nanoparticles have demonstrated the capability to bind to the cell surface or employ the host-pathogen binding concept, thereby allowing an improved accumulation of the antimicrobial agents at the infection site. Such targeting strategies improve local drug concentration and therapeutic outcomes compared with free drug administration[112].
Furthermore, nanoscaled emulsion-based delivery platforms have also been investigated for gastric and mucosal uses, ensuring sustained releases, stabilized bioactive agents, and facilitated cellular uptake in the mucosa. In H. pylori infections, it has been demonstrated that nanoemulsion-based platforms could increase the residence time of the antigen/drug in the body, which opens an avenue for using them in delivering antibacterial drugs or phytochemicals in the stomach. These data confirm that lipid-based nanocarriers could be good candidates for co-delivery in GRDDS[113].
More sophisticated designs of Nano platforms, including biomimetic nanoparticles and surface-functionalized nanoparticles, have also improved the targeted therapeutic possibilities of H. pylori. Surface-functionalized nanoparticles prepared by coating nanoparticles with the membranes of gastric epithelial cells or by functionalizing nanoparticles with specific ligands have been shown to have a targeting preference for H. pylori colonization sites and improved mucus diffusion and bactericidal activity against H. pylori *in vitro* and *in vivo* studies. These Nanoplatforms represent the interest of nanotechnology to counteract obstacles like mucus diffusion and rapid gastric emptying[114].
Taken together, these experimental results reveal that phytochemical and CuNP-based GRDDS have sound scientific rationale and potential. Relying upon combined attributes of prolonged gastric residence and multiple antibacterial modalities, phytochemical/CuNP-loaded GRDDS could potentially provide better efficacy in eliminating bacterial load of H. pylori infections. Specifically, those in which prior therapies are attenuated owing to instabilities in chemical structure and properties of pharmaceutical agents, reduced residence in stomach, and emergence of resistant strains[115].

Conclusion and Future Prospective

The widespread prevalence of Helicobacter pylori infections worldwide and rising resistance to conventional methods of treatment emphasize the pressing need for novel approaches aimed at effectively tackling infections. This review marks an attempt to address the potential offered by phytochemicals and copper nanoparticles in their conjugation with Gastroretentive drug delivery as a holistic treatment system aimed at countering the complexities of Helicobacter pylori infections. For example, while conventional antibiotics target single

pathogens, the multi-tiered mechanism of action of CuNPs stands out due to their immune-modulating properties.

The key role played by GRDDS includes optimization for increased gastric residence time, improved mucosa contact, and achievement of localized drug release in acidic environments. The integration of Nano-engineering technology, phototherapy, and Gastroretentive drug design introduces novel mechanisms for overcoming antibiotic resistance, physicochemical instability, and bioavailability limitations inherent in present treatment strategies. However, in spite of such an encouraging preclinical scenario, there is much to be overcome before clinical translation can be envisaged, including the preparation of reproducible large-scale nanoparticles, standardized safety/toxicity tests in gastric tissues, and a clearer regulatory framework regarding metal-based Nano medicines.

Future studies should be directed toward well-designed *in vivo* investigations, optimization of formulation parameters, and personalized treatment approaches, with early-phase clinical trials. In a word, CuNP and phytochemical-loaded GRDDS represent a promising and innovative therapeutic platform for H. pylori eradication that might redefine future therapeutic paradigms, provided robust translational and clinical investigations are available to support this.

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