



## Bioactive peptides as alternative treatment for *Helicobacter pylori* infection

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Submission Date: April 10<sup>th</sup> 2024; Acceptance Date: May 20<sup>th</sup> 2024; Publication Date: May 23<sup>rd</sup>, 2024

Please cite this article as: Franca-Oliveira G., Hernández-Ledesma B., Martínez-Rodríguez A. J. Bioactive peptides as alternative treatment for *Helicobacter pylori* infection. *Bioactive Compounds in Health and Disease* 2024; 7(5): 245-264.

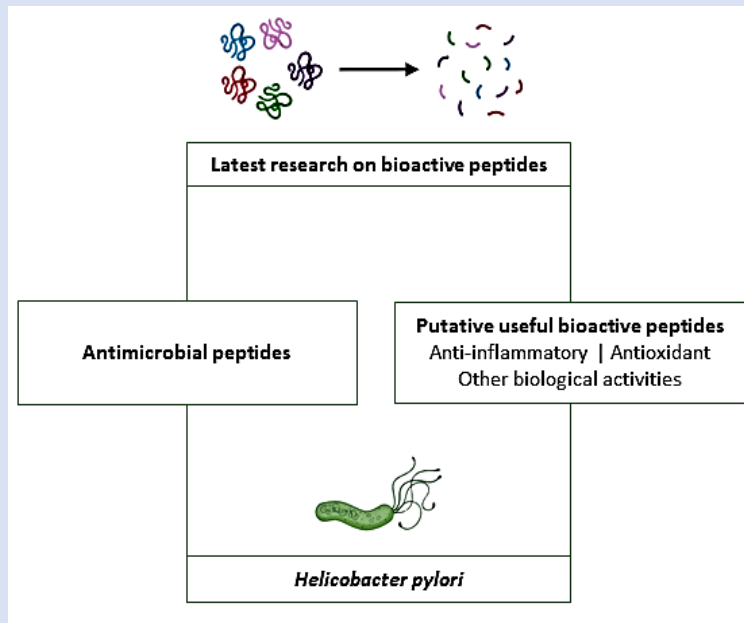
DOI: <https://www.doi.org/10.31989/bchd.v7i5.1348>

### ABSTRACT

The infection and chronic inflammatory response generated by *Helicobacter pylori* is a global health concern. This pathogen is characterized as a major risk factor in the development of gastric cancer and other diseases. Conventional eradication therapies are based on antibiotic regimens and as a consequence there is an increase in antimicrobial resistance of the pathogen strains, besides other potential side effects for the host. Therefore, it is necessary to explore new alternatives. This review delves into the realm of antimicrobial peptides, exploring their efficacy against *H. pylori* sourced from diverse origins. Furthermore, it sheds light on food-derived peptides exhibiting remarkable biological activity. These peptides exhibit promising effects on biomarkers associated with *H. pylori* infection, demonstrating anti-inflammatory and antioxidant properties validated through rigorous testing in both cell and animal models. Regarding the anti-inflammatory activity, the peptide VPY derived from soybean and the peptides derived from animal sources such as meat ( $\beta$ -Ala-His), egg (DEDTQAMPFR, DEDTQAMPF, MLGATSL, MSYSAGF, CR, FL, HC, LL, MK) and milk (IPAV) have reported a reduction of the cytokine IL-8, biomarker directly related to *H. pylori* infection. For the antioxidant activity, peptides derived from milk (EAMAPK, AVPYPQ) and from *Spirulina maxima* (LDAVNR, MMLDF) have reduced ROS levels and could have a positive effect on the control of *H. pylori* infection. Food-derived bioactive peptides with an anti-adhesive effect were also discussed. They derive from vegetable sources (corn, pea and wheat) and are capable of interacting with the host cells, interfering the adherence of *H. pylori*. Food-derived bioactive peptides have potential to avoid and/or mitigate

undesired outcomes of infectious diseases due to the possibility of its application in nutraceuticals and food products, resulting in a preventive approach.

**Keywords:** *Helicobacter pylori*, antibiotic resistance, bioactive peptides, antimicrobial peptides



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## INTRODUCTION

*Helicobacter pylori* (*H. pylori*) is a gram-negative, helical-shaped bacterium with flagella, which confer motility enabling it to penetrate the protective mucosal layer and colonize the gastric epithelium [1-5]. It is estimated that half of the world population is infected by *H. pylori*, but the global prevalence varies significantly between countries and regions [6,7]. This pathogen boasts a myriad of virulence factors, including enzymes, effector proteins, adhesins, and other biomolecules. These elements bestow distinct characteristics upon the pathogen and play a crucial role in shaping the intensity and nature of the immune response [8,9]. These virulence factors vary between strains, contributing to the variation in clinical manifestations [10,11]. The

immune system of the host will be activated starting inflammatory processes and pathways to fight against the pathogen, such as the release of cytokines and oxidative stress, which can also create conditions conducive to damaging host cells [12-14].

The infection with *H. pylori* provokes a chronic inflammatory response and it is the strongest risk factor for the development of gastric cancer [15-17]. *H. pylori* has been classified by the International Agency for Research on Cancer as a class I carcinogen and currently correlated with 80% of malignancies associated to infectious diseases worldwide [18-20]. For this reason, eradication treatment has been indicated, even in cases that patients are asymptomatic, through the application of a test-and-treat strategy tailored to each specific case.

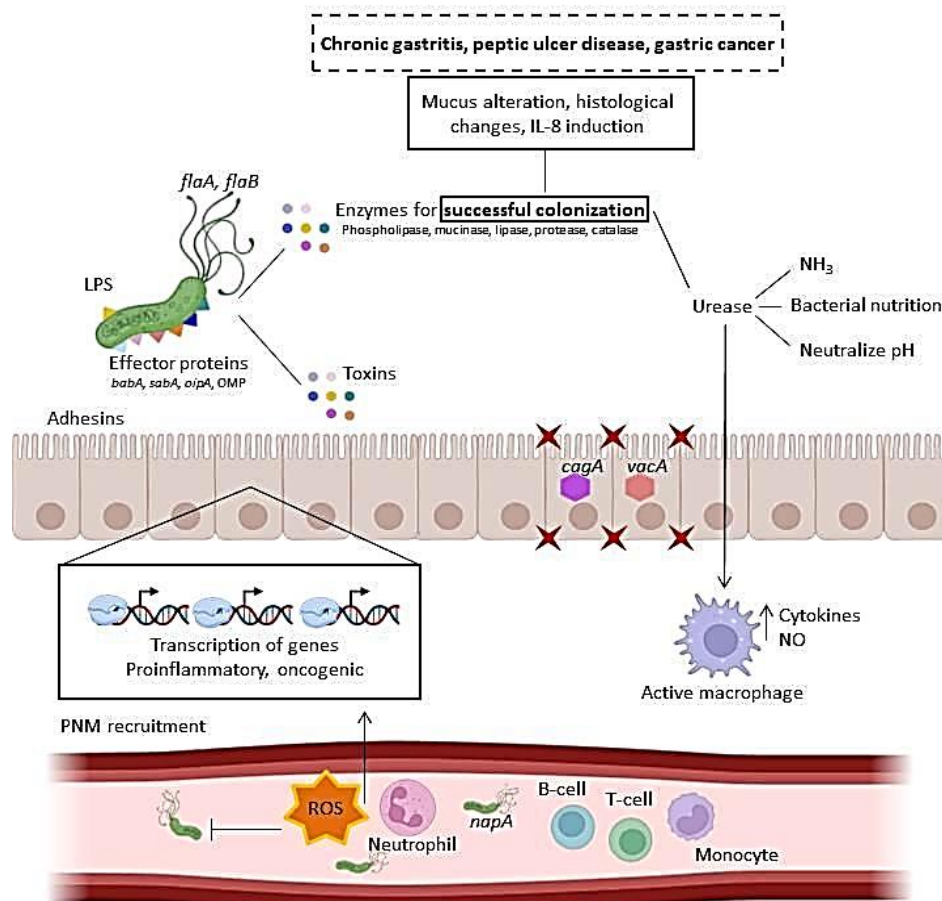
The treatment for the eradication of *H. pylori* is conducted with classic antibiotic therapy combined with strong acid suppressants to potentiate the treatment and manage side-effects. The first-line treatment is selected based on regional or antibiotic resistance considerations, although the therapeutical approach would change based on the response to the treatment [21-23].

Antimicrobial resistance (AMR) is a challenge in the treatment of infectious diseases. The escalating resistance of *H. pylori* to antibiotics underscores the imperative need to explore alternative methods for eradicating this pathogen [24-28]. The main studied alternatives are vaccine technologies, probiotics, nanoparticles and natural products derived from plants [29]. In this regard, there is a growing interest in the use of bioactive compounds from food components as alternative options to antibiotics. Bioactive compounds are food components that can exert health benefits, preventing diseases and/or mitigating symptoms [30,31]. Among them, antimicrobial peptides (AMPs) are a promising option to be used in the treatment of antibiotic-resistant bacteria. In contrast to many antibiotics, AMPs with antibacterial activity typically have a broader range of possible targets, having several putative mechanisms of action, which makes challenging for bacteria to develop resistance [31-33]. Some AMPs have been tested against a variety of pathogens and also against *H. pylori*, showing promising results [31, 32]. Besides AMPs, other peptides that do not present antibacterial activity can also be useful in the treatment of *H. pylori* infection, helping to regulate the immune response of the host provoked by the pathogen. The peptides showing anti-inflammatory and antioxidant activity can modulate inflammatory and oxidative stress biomarkers, being potentially beneficial to prevent and/or treat patients against infectious diseases.

The present work aims to summarize the current state of AMPs with activity against *H. pylori*. These AMPs serve as potential alternatives or adjuncts to conventional treatments against this pathogen. The focus initially lies on AMPs sourced from various origins. Later, attention shifts to food-derived peptides with biological activity. These peptides have demonstrated promising effects on antioxidant and anti-inflammatory biomarkers associated with the progression of pathologies linked to *H. pylori* infection.

***H. Pylori* as a human pathogen:** *H. pylori* is considered a successful human pathogen due to the variety of its virulence factors and mechanisms of adaptation which are crucial for the colonization of the human stomach [8]. Infection with *H. pylori* may or may not produce symptoms, but always results in a gastritis phenotype from which its pathological progression depends [21]. The survival of this microorganism in the stomach and the progression of symptoms depends on several variables such as environmental factors, host factors and virulence factors [34]. To infect the host, the pathogen colonizes gastric epithelial cells with the mechanical assistance of flagellar motility, which adjusts according to the acidity of the gastric environment and acts as a sensor for optimal invasion spots within the mucosal layer.

This colonization process is synchronized with the secretion of a variety of enzymes by the pathogen, which induce pH changes, alter mucus composition, and release effector proteins to facilitate adhesion and invasion of host cells, resulting in damage and successful colonization (Figure 1) [21, 35]. The *H. pylori* virulence factors and their mechanisms of action have been reviewed and explained extensively in the above-mentioned studies.



**Figure 1.** Main virulence factors and mechanisms for the successful colonization of the host by *Helicobacter pylori*. Adapted from Sharndama and Mba et al. [35].

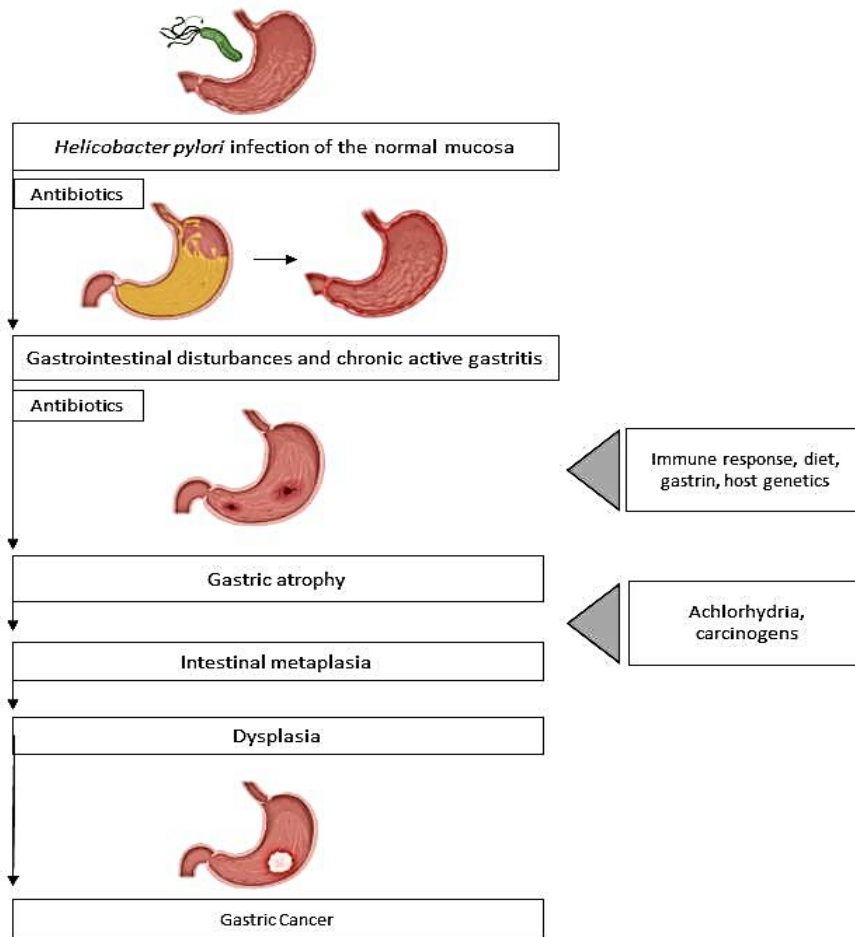
The major virulence factors described in literature closely related to the infection and progression of the disease are the lipopolysaccharide (LPS), adhesins and outer membrane proteins (OMPs) and toxins *cagA* and *vacA*. LPS, present in the outer membrane of the bacteria with the function of a protective barrier, plays an essential role in the genesis of the infection, being recognized by the toll-like receptor 4 (TLR4) and activating other receptors and pathways to induce immune responses such as interleukin-8 (IL-8) release and nuclear factor (NF)-κB activation, amongst other pro-inflammatory and pre-carcinogenic responses [6]. The adhesins and outer membrane proteins (OMPs) primarily facilitate the adherence of *H. pylori* to gastric cells, initiating the inflammatory response by recognizing specific host cell types for the translocation of bacterial effector proteins [36-38]. The progression of the

infection has also been associated with the presence of the *cag* Pathogenicity Island (*CagPAI*), a set of 27 genes that are unique to the strains that are positive for the cytotoxin-associated gene A (*cagA*-positive), from which 17 genes are related to the activity of the Type IV Secretion System (T4SS) that allows the translocation of effector proteins inside the targeted cell inducing morphological changes and affecting cell proliferation [34, 39-42]. The gene *cagA* encodes an effector protein that is also known as an oncoprotein, therefore patients infected with *cagA*-positive strains are more prone to the development of peptic ulcers and to the progression to gastric cancer [21,43,44]. Additionally, vacuolating cytotoxin A (*VacA*) is another virulence factor that appears to interact functionally with *cagA*, enhancing its accumulation within gastric epithelial cells. However, the mechanisms underlying this interaction are not fully

understood [45]. Associated with the mentioned virulence factors, precisely with *cagA*, is the enzymatic activity of superoxide dismutase (SOD), catalase and glutathione peroxidase, that are more active in *cagA*-positive strains, resulting in a protection from reactive oxygen species (ROS), which can lead to the damage of the cells of the host due to ROS overproduction. In addition, the oxidative stress generated by ROS production promotes *H. pylori* biofilm formation, therefore increasing the pathogen potential for multidrug resistance [13, 46, 47].

As previously noted, the majority of patients infected with *H. pylori* exhibit histologic gastritis, and the phenotype of this gastritis will influence the progression of symptoms [48-50]. Most of the patients have a mild gastritis phenotype that in general is asymptomatic and do not affect the acid secretion, 10 to 15% presents the

duodenal ulcer phenotype that affects the secretory function with a higher production of gastrin and acid secretion, with disturbances in the inhibitory control of acid secretion leading to dyspeptic symptoms and/or duodenal ulcer, and less than 1% present the gastric cancer phenotype that culminates in a strong reduction or absence of acid secretion, leading to severe atrophic gastritis, intestinal metaplasia and gastric cancer [21, 34, 51-53]. In Figure 2, a cascade model for the progression of *H. pylori* infection from gastritis to gastric cancer is exposed. The progression of the disease may not necessarily involve all the stages represented, as it varies according to environmental factors (such as smoking, alcohol consumption, use of non-steroidal anti-inflammatory drugs (NSAIDs), and proton pump inhibitors), virulence factors, and host factors (including genetics and individual immune response) [34, 54-56].



**Figure 2.** Cascade model proposed by Correa et al. showing the putative progression of *H. pylori* infection from chronic gastritis to gastric cancer [34, 57].

A variety of mechanisms of resistance according to the treatment and strain genetic mutations have been determined and described in literature [58, 59]. The increasing resistance of this pathogen to conventional therapies due to adaptive changes of bacterial strains is currently of relevant concern. Therefore, the search for new therapeutic strategies against *H. pylori* infection is highly significant [60-64]. Nevertheless, there is controversy about the need for *H. pylori* eradication treatment when patients do not manifest any relevant symptoms due to the fact that it has been observed that in some cases the eradication of *H. pylori* is associated with the rise of other pathologies such as metabolic syndrome, gastroesophageal reflux disease (GERD) and its consequences, including esophageal and gastric cardia glandular malignancies [65-67]. In children, eradication is not recommended and other guidelines must be followed in order to manage the infection [68-71]. Besides that, *H. pylori* infection and treatments with virulence factors from this pathogen have been reported as an immunomodulatory with potential to mitigate symptoms for diseases such as inflammatory bowel disease and allergic airway diseases [72,73]. Furthermore, the pathogen dynamics with the microbiota of the gastrointestinal tract is highly complex, and eradication not only affects the gastrointestinal tract itself, but also its absence has been associated with dysbiosis and the emergence of a variety of systemic disorders, weight gain or loss, and susceptibility to allergic diseases such as asthma [43, 74-79]. In contrast, research over the years has demonstrated that eradicating *H. pylori* prior to the onset of precancerous histological changes can prevent the development of gastric cancer and dysbiosis can be managed with the integration to the antibiotic treatment of probiotics and other alternatives for microbiota modulation [80-82]. This forms the basis for the screen-and-treat approach to

*H. pylori* infection and optimization strategies such as family-based. [21, 76, 83].

According to the latest guidelines from the World Gastroenterology Organization, achieving successful eradication of the pathogen requires consideration of several factors. The recommended principles to select a therapy are based in treatment trials data combined with resistance assessments and other measurements that could be useful, being evaluated according to regions [76]. The transmission of the infection is not well determined, but it occurs in the early childhood and since the infection is often asymptomatic, it is a challenge to diagnose and treat it [84, 85]. The most common antibiotic therapy is conducted using a proton pump inhibitor with amoxicillin and clarithromycin.

AMPs and other peptides with biological activity can be among the compounds that, even without eradicating *H. pylori*, can contribute to modulate its virulence and restore the equilibrium in the gastric ecosystem. Considering the characteristics and the mechanism of action of the AMPs that commonly target the bacterial cell membrane through multiple mechanisms and pathways, the efficacy of the treatment is increased and the development of resistance becomes unlikely to occur [24, 31, 86-89].

#### **Antimicrobial Peptides as alternatives to conventional**

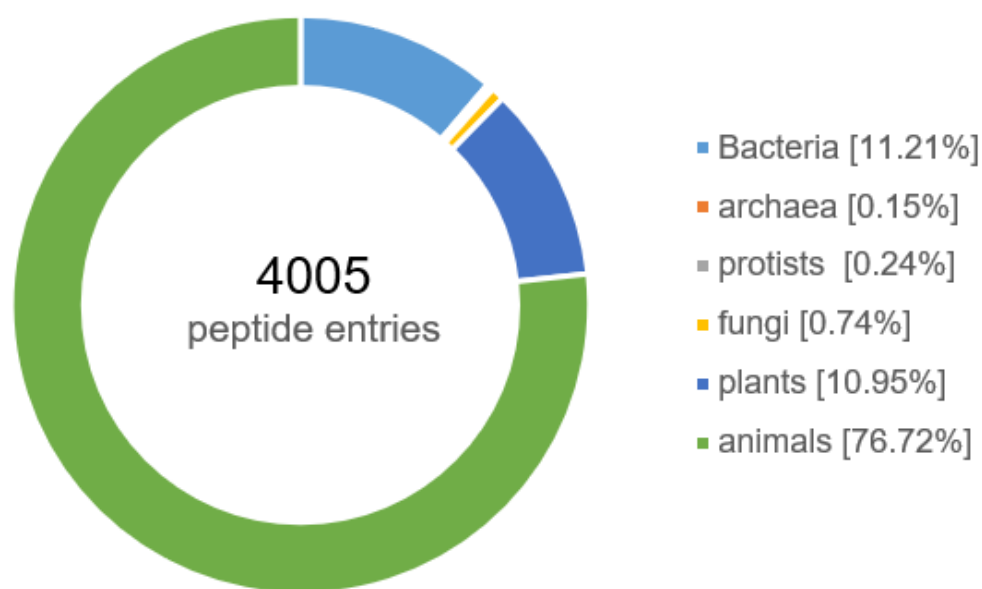
**therapies:** The use of antimicrobials dates from ancient civilizations with treatments based on natural sources such as plants, honey and animal excrements. The antibiotics were a groundbreaking discovery and the development of these substances reduced significantly the mortality by infectious diseases [90-94], which makes it the conventional therapy for communicable diseases in medicine until the present day. However, the development and widespread use of antibiotics have directly influenced changes in targeted microorganisms, resulting in antibiotic resistance as a consequence of

evolutionary changes in bacteria [95-98]. As one of the primary concerns in healthcare, global antibiotic resistance has led to heightened interest in discovering new antimicrobial agents and is recognized as a significant global threat to modern medicine [99-102]. The last new class of antibiotics was discovered in the 1980s and with the course of time antimicrobial resistance has been addressed as an urgent problem. In 2015, the World Health Organization declared it as a global emergency making a priority to find new alternatives to be used against health-threatening microorganisms, developing a global action plan [103].

AMPs are sequences that generally have less than 100 amino acids. These peptides were identified in the late 1990s associated with the innate immune system of insects and plants, being subsequently identified in all life domains due to the interest in its discovery and the

potential use against pathogens [31, 104, 105]. There are currently 4005 peptides entries on the Antimicrobial Peptides Database (APD) [106]. From them, 3437 are AMPs that can exert also other bioactive effects concurrently, such as antioxidant and anti-inflammatory. In Figure 3 the distribution of AMPs according to their deriving life kingdom is graphically represented.

These peptides can be naturally produced by organisms as a mechanism of defense against pathogens and other threats in biological endogenous processes, but like other bioactive peptides, can also be obtained through fermentation, digestion, extraction, and hydrolysis [107-109]. Peptides with biological activity can also be synthesized based on a predicted biological function of the sequence and its characteristics, taking the structure of natural peptides as a model but not directly derived from them [110-112].



**Figure 3.** Distribution of peptides entries (4005) in the Antimicrobial Peptides Database according to life kingdom of origin [106].

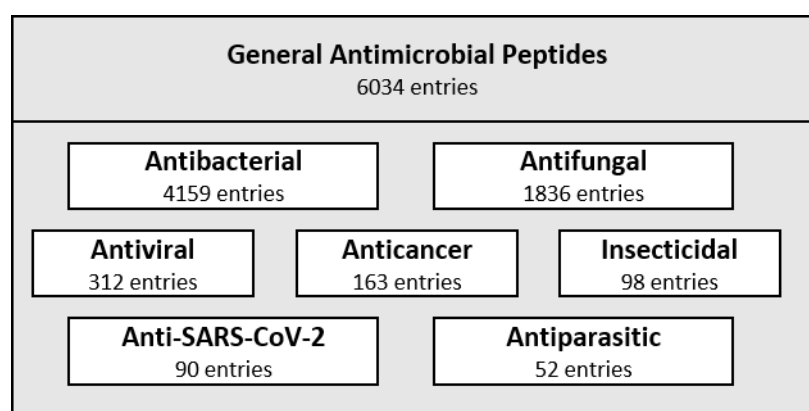
The Data Repository of Antimicrobial Peptides (DRAMP) [113] is another database for such peptides, containing over 6000 entries of general AMPs, including both natural and synthesized ones. These peptides are

classified according to their attributed target for biological activity, as shown in Figure 4. As described above, AMPs can perform various functions and thus can be utilized for different purposes. Out of 4159 entries in

the DRAMP database, 2562 have demonstrated effects specifically against gram-negative bacteria. Although the majority have not yet been elucidated regarding their binding target and/or mechanism of action, there is a recurring tendency suggesting that the putative action of these peptides could mainly be related to the cell membrane and LPS-binding.

**Bioactive Peptides as antibacterial tools against *Helicobacter Pylori*:** AMPs peptides that have proven effective against *H. pylori* come from both natural and synthetic sources based on natural structures. They are the following: a) Pexiganan or MSI-78; b) Tilapia piscidin (3 and 4); c) Epinecidin-1; d) Cathelicidins (human

cathelicidin LL-37 and mouse cathelicidin CRAMP); e) Defensins (Human neutrophil peptide 1 and SolyC); f) Bicarinalin; g) Odorrainin-HP; h) PGLa-AM1; i) Bacteriocins (Nisin A, Lacticin a164, Lacticin BH5, Lacticin jw3, Lacticin NK24, Pediocin PO2, Leucocin k and others without specified sequence) [32]. These peptides share some common characteristics according to the conducted analysis: all of them are cationic and positively charged at pH 7.4, mainly presenting  $\alpha$ -helical structure and ranging between 1.99 to 4.4 kDa of molecular weight. These peptides are mostly associated with secreting processes and the immune cells' activities.



**Figure 4.** Number of peptides entries in the Data Repository of Antimicrobial Peptides (DRAMP) according to biological function [113].

Recently, new peptide sequences with similar characteristics have been identified, demonstrating anti-*H. pylori* effects. One such peptide is HF-18, derived from the intestine of Hagfish. HF-18 has exhibited potent antibacterial activity against strains of *H. pylori* that are resistant to clarithromycin and amoxicillin [114]. In research involving black soldier flies, the production of antimicrobial peptides (AMPs) was induced in larvae challenged with *Escherichia coli*. Four sequences derived from these AMPs were subsequently tested against *H. pylori*, demonstrating a potent effect comparable to that observed with metronidazole [115]. Additionally, another study utilizing Attacin A, a peptide derived from

the cecropia moth, revealed a reduction in the histological changes caused by *H. pylori* infection in rats [116]. The guided production of AMPs is also an interesting mechanism used to obtain antibacterial peptides. In a study conducted using an engineered *Lactococcus lactis* strain co-cultured with *H. pylori* in order to obtain guided-AMPs (gAMPs), these peptides were tested in mice infected with *H. pylori*. They were found to effectively eliminate the pathogen, although a rebound effect was observed in other gastric species [117]. The majority of the AMPs that have enough evidence to be used clinically are antibacterial peptides but a clinical trial has only been conducted for MSI-78



(Pexiganan). It is an analog of the Magainin-2, a peptide derived from the African clawed frog. The trials were conducted for its application in the treatment of impetigo and diabetic foot ulcers, and it failed to be approved [113, 118]. In order to potentiate the effects of MSI-78, studies tested the nanoencapsulation of the peptide and also surface grafting onto nanoparticles, showing high potential in gastric infection management [119]. From food-derived peptides, SolyC is the only one with known effect against *H. pylori*. This peptide was synthesized based on a tomato defensin and have shown antibacterial and anti-inflammatory effects against *H. pylori* and a variety of pathogens [120]. Other compounds from food sources, such as polyphenols, and carotenoids, have shown bactericidal effects against *H. pylori*, but not other peptides [106, 121].

**Other bioactive peptides are putative useful in *Helicobacter Pylori* prevention/treatment:** In addition to antibacterial peptides, there are other bioactive peptides that could be of potential interest in the treatment of *H. pylori* infection. These mainly include anti-inflammatory

and antioxidant peptides. The immune response to *H. pylori* is a combination of events that can be both protective and detrimental to the host. In fact, much of the pathological evidence related to *H. pylori* infection is considered to arise from the action of the host immune system rather than from the bacterial infection itself [34]. In the process of colonization of gastric cells, *H. pylori* produces a severe inflammatory response mediated by neutrophils and macrophages, which contribute to the generation of ROS in the epithelial tissue [47]. For this reason, modulation of the inflammatory and oxidative response in the gastric cells has been shown to be particularly effective, avoiding tissue damage and the progression of pathologies associated with *H. pylori* infection [121]. Table 1 summarizes the putative beneficial food-derived peptides against *H. pylori* based on their anti-inflammatory and antioxidant activity results observed in immune cells, as well as in vitro and/or in vivo models of gastrointestinal inflammation. These peptides exhibit effects on biomarkers associated with *H. pylori* infection signaling pathways.

**Table 1.** Putative useful food protein-derived peptides against *H. pylori* infection

Source	Process	Sequence	Cell/Animal Model	Bioactivity	Reference
Fish protein	Enzymatic hydrolysis	Not specified	Human and rat intestinal epithelial cells	Anti-inflammatory, increase of proliferation	[122]
			Mouse colitis	Improvement of healing	[123]
Salmon protein	Enzymatic hydrolysis	PAY	LPS-induced RAW264.7 cells	Inhibition of inflammation Reduction of NO, PGE2, TFN- $\alpha$ , IL-6, IL-1 $\beta$ , iNOS, and COX-2 production/expression	[124]
<i>Ruditapes philippinarum</i>	Enzymatic hydrolysis	QCQQAVQSAV	LPS-induced RAW264.7 cells	Inhibition of inflammation Inhibition of NO production	[125]
Meat products	Commercial	$\beta$ -Ala-His (carnosine)	H <sub>2</sub> O <sub>2</sub> -induced Caco-2 cells	Inhibition of inflammation via MAPK and PepT1 pathways Inhibition of IL-8 and p38 and ERK activation	[126]
Velvet antler protein from red deer	Hydrolysis	VH, LAN, IA, AL	LPS-induced RAW264.7 cells	Inhibition of inflammation Inhibition of NO production	[127]

Source	Process	Sequence	Cell/Animal Model	Bioactivity	Reference
Egg white protein	Enzymatic hydrolysis	DEDTQAMPFR, DEDTQAMPF, MLGATSL, MSYSAGF	TNF- $\alpha$ -induced Caco-2 cells	Inhibition of inflammation via MAPK pathway Inhibition of TNF- $\alpha$ , IL-8, IL-6, IL-1 $\beta$ , IL-12, JNK, I $\kappa$ B, and p38 expression Increase of IL-10 expression	[128]
Egg ovotransferrin	Synthesized based on simulated peptide-cut	CR, FL, HC, LL, MK	TNF- $\alpha$ -induced Caco-2 cells	Inhibition of intestinal inflammation Reduction of IL-8 secretion and TNF- $\alpha$ , IL-8, IL-6, IL-1 $\beta$ , and IL-12 expressions Increase of IL-10 expression	[129]
Casein	<i>In vitro</i> gastrointestinal digestion	EAMAPK, AVPYPQ	H <sub>2</sub> O <sub>2</sub> -induced IEC-6 cells	Antioxidant Reduction of ROS levels Increase of SOD and Nrf2 activities	[130]
	Bacterial fermentation	Not specified	Mouse colitis	Anti-inflammatory	[131]
	Enzymatic hydrolysis	Not specified	Macrophages	Downregulation of COX-2 NF- $\kappa$ B inhibition	[132]
Whey protein	Enzymatic hydrolysis	Not specified	Intestinal Epithelial cells	Reduction of IL-8	[133]
		IPAV	TNF- $\alpha$ -induced Caco-2 cells	Inhibition of intestinal inflammation via PepT1 Reduction of IL-8 and inhibition of NF- $\kappa$ B, ERK1/2, JNK1/2, Syk, and p38 expression	[134]
Soybean protein	Enzymatic hydrolysis	Lunasin	Macrophages	Reduction of cytokines NF- $\kappa$ B inhibition	[135]
		VPY	Mouse colitis	Reduction in cytokines, oxidative stress, and improved histology	[136]
	Synthetic	FLV	TNF- $\alpha$ -induced 3T3-L1 co-cultured with RAW264.7	Inhibition of inflammation Inhibition of TNF- $\alpha$ , IL-6, and MCP-1 production and JNK, IKK, and I $\kappa$ B $\alpha$ expression	[137]
Defatted soybean meal protein	Ion-exchange chromatography (IEC) and size exclusion chromatography (SEC)	Lunasin	LPS-induced RAW264.7 cells	Inhibition of inflammation Inhibition of NO and PGE2 production and COX-2 and iNOS expressions	[138]
Germinated soybean protein	Enzymatic hydrolysis	QQQQQGGGSQSQ, QEPQESQ, QQQQQGGGSQSQSQK, PETMQQQQQQ	LPS-induced RAW264.7 cells	Inhibition of inflammation Inhibition of NO and PGD2 production	[139]
Soy hydrolysate	-	VPY	Caco-2 cells THP-1 macrophages colitis DSS-induced mice	Treat IBD via PepT1 Inhibition of IL-8 and TNF- $\alpha$ secretions	[136]
Amaranth protein	Enzymatic hydrolysis	GPR	LPS-induced Human THP-1 and RAW264.7 cells	Inhibition of inflammation via NF- $\kappa$ B pathway Inhibition of TNF- $\alpha$ secretion	[140]

Source	Process	Sequence	Cell/Animal Model	Bioactivity	Reference
		SSEDIKE	Caco-2 cells	Inhibition of inflammation Reduction of CCL20 and NF-κB expressions	[141]
Germinated amaranth flour	Gastrointestinal digestion	Putative	RAW264.7 cells	Anti-inflammatory	[142]
Wheat gluten	Hydrolysis and fractionation	Pro-glutamyl leucine	Mouse colitis	Improvement of mucosal histology	[143]
	Synthesized by conventional solution method	pyroGlu-Leu	LPS-induced RAW264.7 cells	Inhibition of inflammation via NF-κB and MAPK pathways Inhibition of NO production, TNF-α, IL-6, and IκBα degradation, and JNK, ERK, and p38 phosphorylation	[144]
<i>Spirulina maxima</i>	Enzymatic hydrolysis	LDAVNR, MMLDF	RBL-2H3 mast cells and histamine-stimulated EA.hy926 endothelial cells	Inhibition of inflammation Reduction of histamine release, IL-8 production, and ROS production	[145]

CCL20: Chemokine ligand 20; COX-2: Cyclooxygenase-2; ERK: Extracellular signal-regulated kinase; IBD: Inflammatory bowel disease; IKK: Inhibitor of NF-kappaB kinase; IκB: IκappaB kinase; IL-1β: interleukin-1beta; IκBα: nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha; IL-6: interleukin-6; IL-8: interleukin-8; IL-10: Interleukin-10; IL-12: Interleukin-12; iNOS: inducible nitric oxide synthase; JNK: Jun N-terminal kinase; MAPK: Mitogen-activated protein kinase; MCP-1: Monocyte chemoattractant protein-1; NO: Nitric oxide; NF-κB: Nuclear factor kappa-light-enhancer of activated B cells; Nrf2: Nuclear factor erythroid 2-related factor 2; PepT1: Proton coupled oligopeptide transporter 1; PGD2: Prostaglandin D2;

PGE2: Prostaglandin E2; p38: MAPK signal transduction mediator; ROS: Reactive oxygen species; SOD: Superoxide dismutase; Syk: Syk non-receptor tyrosine kinase; TFN-α: Tumor necrosis factor Alpha.

In addition to their anti-inflammatory and antioxidant effects, there is growing interest in food-derived peptides that can bind to adhesins. These peptides have the potential to directly interfere with bacterial adherence to host cells, thereby either preventing infection or reducing its pathological effects [146]. In Table 2, food-derived peptides with anti-adhesive and other effects against *H. pylori* in infected cell models and mice are listed

**Table 2.** Anti-adhesive food-derived bioactive peptides obtained through enzymatic hydrolysis process effective against *H. pylori*

Source	Model	Effective dosage	Bioactivity	Reference
Corn protein	Infected GES-1 cells Infected mice	4 mg/mL 400–600 mg/kg-bw	Anti-adhesive Anti-inflammatory Inhibition of histological changes	[147]
Corn gluten meal	Infected GES-1 cells	4 mg/mL	Anti-adhesive Antioxidant Anti-inflammatory	[148]
Pea protein	Infected AGS cells	100-500μg/mL	Anti-adhesive	[149, 150]
Defatted Wheat germ protein	Infected GES-1 cells	10 mg/mL	Anti-adhesive	[151]

## CONCLUSIONS

The rise in resistance to commonly used antibiotics in conventional treatments *against H. pylori* has triggered an increasing interest in the search for alternative options. Among them, AMPs may be of special interest, mainly because many peptides may have a dual function and act as antibacterial and antioxidant, thus contributing to modulate the inflammatory process associated with *H. pylori* infection. Moreover, certain AMPs have the potential to interfere with *H. pylori* colonization of epithelial cells, thereby impeding the pathogen's evasion strategies against the immune system. At present, the available analytical and bioinformatics tools should contribute to the identification, characterization and production of new peptides useful in the future for the treatment of human infection by *H. pylori*.

**Abbreviations:** AMPs: antimicrobial peptides; AMR: Antimicrobial resistance; APD: Antimicrobial Peptides Database; *CagA*: cytotoxin-associated gene A; *CagA*-positive: positive for the cytotoxin-associated gene A; *CagPAI*: cytotoxin-associated genes pathogenicity Island; CCL20: Chemokine ligand 20; COX-2: Cyclooxygenase-2; DRAMP: Data Repository of Antimicrobial Peptides; ERK: Extracellular signal-regulated kinase; gAMPs: guided-AMPs; GERD: gastroesophageal reflux disease; *H. pylori*: *Helicobacter pylori*; HF-18: intestinal peptide from Hagfish; IBD: Inflammatory bowel disease; IKK: Inhibitor of NF-kappaB kinase; IL-10: Interleukin-10; IL-12: Interleukin-12; IL-1 $\beta$ : interleukin-1beta; IL-6: interleukin-6; IL-8: interleukin 8; iNOS: inducible nitric oxide synthase; I $\kappa$ B: I $\kappa$ B kinase; I $\kappa$ B $\alpha$ : nuclear factor of kappa light polypeptide gene enhancer in B-cells inhibitor alpha; JNK: Jun N-terminal kinase; LPS: Lipopolysaccharide; MAPK: Mitogen-activated protein kinase; MCP-1: Monocyte chemoattractant protein-1; NF- $\kappa$ B: Nuclear factor kappa-light-enhancer of activated

B cells; NO: Nitric oxide; Nrf2: Nuclear factor erythroid 2-related factor 2; NSAIDs: non-steroidal anti-inflammatory drugs; OMPs: Outer membrane proteins; p38: MAPK signal transduction mediator; PepT1: Proton coupled oligopeptide transporter 1; PGD2: Prostaglandin D2; PGE2: Prostaglandin E2; ROS: reactive oxygen species; SOD: superoxide dismutase; Syk: Syk non-receptor tyrosine kinase; T4SS: Type IV Secretion System; TFN- $\alpha$ : Tumor necrosis factor Alpha; TLR4: toll-like receptor 4; *VacA*: vacuolating cytotoxin A.

**Competing interest:** The author has no financial interests or conflicts of interest.

**Authors' contribution:** The author wrote the entire review article.

**Acknowledgments:** There was no external funding supporting this publication. G. Franca-Oliveira gratefully acknowledges the Ministry of Science, Innovation, and Universities (Spain) for her predoctoral fellowship FPU20/06555.

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