Table S1. Relevant *in vitro* and *in vivo* studies on anti-*H. pylori* effectiveness of AMPs in the past five years

AMP	Description	Study design	Outcome	Reference
Cathelicidin	Synthetic mouse cathelicidin CRAMP, human cathelicidin LL-37 and shortened LL-37	Antimicrobial and anti-biofilm assays were performed *in vitro* with strains *H. pylori* SS1 and 10783, where the resident biofilm was measured by crystal violet assay or BacLight Live / Dead. Anti-*H. pylori* activity tested *in vivo* using 129/SVJ wild-type (Cnlp+/+) and cathelicidin-knockout (Cnlp−/−) mice	In the *in vitro* assays *a*ll three forms of cathelicidin significantly inhibited *H. pylori* SS1 growth at the micromolar range of concentrations. In contrast, CRAMP, LL-37, and sLL-37 markedly inhibited *H. pylori* 10783 growth. In the *in vivo* tests*,* human cathelicidin LL-37 decreased and disrupted the biofilm formation in a dose-dependent manner in the stomachs of mice.	[1]
PGLa-AM1	Recombinant peptide glycine-leucine-amide AM1 (rPGLa-AM1)	Anti-*H. pylori* activity analysed *in vitro* (bactericidal dynamics method, agar dilution method for MIC determination) and *in vivo* with the mouse adaptive SS1 *H. pylori* strain and an *H. pylori*-infected mouse model.	Strong anti-*H. pylori* activity and therapeutic effect of rPGLa-AM1 exerted both *in vitro* (rPGLa-AM1 killing of *H. pylori* within 15 min at 32 μg/mL or 30 min at 16 μg/mL) and *in vivo* (100 % removal efficiency to *H. pylori* colonization achieved at a dose of 40 mg/kg body weight).	[2]
Bicarinalin	Synthetic analogue of venom peptide bicarinalin, isolated from the ant *Tetramorium bicarinatum*;	*In vitro* assay with 44 *H. pylori* clinical strains isolated from stomach ulcer biopsies of Peruvian patients and *H. pylori* ATCC 43504 strain. MIC determination by broth microdilution assay.	Bicarilin had a cytotoxic effect on *H. pylori* clinical isolates (MIC_{50} = 0.99 μmol/L) and in the reference strain (MIC_{50} = 3.9 μmol/L).	[3]
Distinct member of the defensin family	Human neutrophil peptide 1 (HNP1)	MIC determination by agar dilution method in the *in vitro* tests and HPN1 anti-*H. pylori* activity tested *in vivo*, using an infected mouse model.	HNP1 exerted strong effect against antibiotic-resistant *H. pylori* activity (MIC = 8 μg/mL*) in vitro*.	[4]

			In *in vivo* assays HNP1 significantly reduced colonization of antibiotic-resistant *H. pylori* in the stomach of mice.	
BSF AMPs	Peptides Isolated From Black Soldier Fly (*Diptera: Stratiomyidae*)	*In vitro* assay with strain *H. pylori* ATCC 43504. Anti-*H. pylori* activity was evaluated by inhibition zone assay.	Inhibition halos of the isolated peptides compared to the metronidazole halo in the gel diffusion test, where a 21 mm inhibition zone with metronidazole (5 µg) indicates susceptibility.	[5]
Cathelicidin-like antimicrobial peptide	Cbf-K16 is a variant of BF-30, which was found in the venom of the snake *Bungarus fasciatus*	MIC determination against *H. pylori* SS1, 26695 and 11637, and anti-*H. pylori* activity analysed by paper disk, spectrophotometer at 600 nm and microscope, in *in vitro* tests. Anti-*H. pylori* activity tested *in vivo* using an infected C57BL/6 male mice.	In the *in vitro t*he MIC and MBC of Cbf-K16 against the tested *H. pylori* were 16 and 32 µg/ml, respectively, and its killing kinetics was time-dependent, reflecting the thorough elimination of drug-resistant bacteria within 24 h. This peptide also protected *H. pylori*-infected gastric epithelial cells (GES-1) from death by reducing the cell supernatant and intracellular bacterial counts by 1.9 and 2.9-$\log_{10}$ units, respectively. Antimicrobial activity in the mouse gastritis model was observed, with decreasing bacterial counts by 3.9-$\log_{10}$	[6]

ATCC - American Type Culture Collection; MBC – Minimum Bactericidal Concentration; MIC – Minimum Inhibitory Concentration

Table S2. Relevant *in vitro* studies on the application of PDT to treat *H. pylori* infections in the past five years

Light delivery mode	Study design	Outcome	Reference
Wireless ingestible capsule prototype with 625 nm red or 405 nm blue LED, battery, and dedicated electronic boards	*In vitro* study with *H. pylori* ATCC 49503 strain. Following 30 min of light irradiation, a suspension was removed and cultured. Surviving CFU were counted and survival fractions were determined relative to unilluminated bacterial suspensions.	With an irradiation time of 30 min, the death efficiency of *H. pylori* was up to 96 %.	[7]
405 nm (range 402−407 nm) blue light LED delivered to samples placed from 10 cm. The irradiances were 300 μW/cm^2, 500 μW/cm^2 and 600 μW/cm^2. The luminous energy at 1 h was approximately 1.08 J/cm^2 , 1.08 J/cm^2 and 2.16 J/cm^2 respectively.	*In vitro* study with 10 *H. pylori* clinical isolates antibiotic-resistant and with an *H. pylori* sensitive strain. The effect of blue LED on the viability of *H. pylori* at each time point was performed by counting the colonies with/without irradiation. The morphology and length of bacteria were examined and measured under SEM. *H. pylori* reductase activity assay and ROS detection were carried out.	Blue LED with irradiance of 300 μW/cm^2 killed resistant-*H. pylori* in 6h; irradiance of 500 μW/cm^2 took 2 h to achieve statistically significant killing; irradiance of 600 μW/cm^2 took 1 h to achieve statistically significant killing; For an LED irradiation under 500 μW/cm^2, the surviving fraction of metronidazole-resistant strain was 1 % after 4 h; for the triple-antibiotic resistant strain was <10 % after 5 h; for the reference strain 26695 was <10 % after 4 h and <1 % after 5 h *H. pylori* exposed to blue LED irradiation of 600 μW/cm^2. *H. pylori* cells exhibited a short rod-shaped morphology after irradiation.	[8]

		The decrease in cell activity and significant increase in ROS indicator fluorescence was observed only in samples exposed to blue LED for up to 2 h.	
Red LED with a wavelength of 660 nm. Applied energy fluencies of 10 J/cm^2 (at 2 min 40 s) and 15 J/cm^2 (at 4 min).	*In vitro* study where *H. pylori* strain JCM No.12093 was smeared on a medium with basic methylene blue (MB) (after addition of $NaHCO_3$) and irradiated using a red LED with a wavelength of 660 nm. After 4 days of culture, the effect was determined according to the bacterial growth area.	The basic effect of MB appeared between a pH of 8.6 and 9.0. The $NaHCO_3$ concentration was between 4% and 6%. The basic effect at 15 J/cm^2 was greater than that at 10 J/cm^2.	[9]
400 nm light source	*In vitro* study with 3 *H. pylori* strains (ATCC 700392, 43504 and 49503) grown on solid medium either with, or without, doxycycline at subinhibitory concentrations, and irradiated for 10, 20 and 30 minutes with a 400 nm-peaked light source. The phototoxicity tests on AGS cells were evaluated by MTT assay.	PDT and doxycycline combination showed an antibacterial synergistic effect with no significant toxicities.	[10]
Blue LED irradiation for 1-6 minutes	*In vitro* study of the effect of blue LED irradiation for 1-6 minutes on the viability (evaluated by counting the number of CFU) and virulence factors	Blue LED for 1-6 minutes significantly decreased the viability of *H. pylori* and decreased urease activity, and swarming motility. Blue LED irradiation for 6	[11]

	of *H. pylori* (urease production, motility, adhesion and biofilm formation).	minutes caused greater than 50 % disruption of preformed mature biofilms of *H. pylori*, relative to controls.	
Irradiation procedure performed with endoscopic light in a dark room and with *H. pylori* culture plates placed 10 cm from the light source. The amount of endoscopic light energy was 7.5 mJ/cm^2.	*In vitro* PDT study with *H. pylori* ATCC 700392, using endoscopic light as light source, methylene blue (MB) as a photosensitizer and comparing bactericidal effects of low molecular weight (LMW) and high molecular weight (HMW) chitosan, combined with PDT. Bacterial removal rate and membrane damage evaluated by ethidium bromide monoazide PCR method (EMA q-PCR). Measurement of 8-oxo-2'-dexoyguanosine by ELISA for oxidative stress.	At a chitosan concentration of ≤ 0.05 %, the killing effect did not differ between the two molecular weights, and 100 % bacterial removal rate was observed at a light energy ≥ 6.23 mJ/cm^2 powers under 0.02 % MB. After 15 min irradiation, LMW chitosan with high concentration of MB (0.004 %) showed highest killing effects, consistent with the results of EMA q-PCR but not with the level of 8-OHdG. Bactericidal effects of LMW chitosan plus PDT using 0.002 and 0.004 % MB for 15 min irradiation were significantly higher than those using HMW chitosan plus PDT.	[12]
Irradiation for 5 minutes with blue LED source with a light power of 10 mW cm^{-2} at a wavelength of 470 nm.	*In vitro* study of the effect of curcumin with and without irradiation with blue LEDs on the viability of *H. pylori* ATCC 700392 (evaluated by counting the number of CFU) and on virulence factors of *H. pylori* (urease production, motility, adhesion and biofilm formation).	The combination of curcumin and blue LEDs caused significant reductions in viability, urease production, motility, haemagglutination activity, as well as increased disruption of mature preformed biofilms of *H. pylori* , in comparison to curcumin alone ($P < 0.0001$), at sublethal concentrations of curcumin.	[13]

LED-based device irradiating visible light with LEDs NVSU233A-U405 (Violet, 405 nm, FWHM ≈ 12 nm, 8 LEDs per board), NSSC146AT (Blue, 460 nm, FWHM ≈ 18 nm, 40 LEDs per board), NCSE119BT-V1 (Bluish-Green, 500 nm, FWHM ≈ 30 nm, 8 LEDs per board) and NCSR219BT-V1-E (Red, 630 nm, FWHM ≈ 16 nm, 8 LEDs per board).	*In vitro study with H. pylori* strain ATCC 43504 and virulent strain (*cag*A+ and *vac*A+) ATCC 700824 (J99). Bacterial suspensions were placed in a Petri dish and irradiated according to the absorption spectrum of *H. pylori* endogenous porphyrins. Illumination efficacy was assessed in comparison with the dark control by plating serial dilutions of each sample on Brucella agar plates with 10 % FBS. After incubation at 37 °C in microaerophilic atmosphere, surviving bacterial cells (CFU/ml) were counted.	Exposure to visible light induced bacterial photokilling most effectively at 405 nm and 460 nm. Sub-lethal light dose at 405 nm caused morphological changes on bacterial surface indicating the cell wall as one of the main targets of photodamage. Besides porphyrins, PPIX and CPI and III, the endogenous photosensitizers responsible for bacterial photokilling also include flavin-type molecules such as riboflavin.	[14]

ATCC - American Type Culture Collection; CFU - Colony-Forming Unit; KCTC - Korean Collection for Type Cultures; LED - Light Emitting Diode; PDT – photodynamic therapy; ROS - Reactive Oxygen Species

Table S3. Relevant *in vitro* and *in vivo* studies on anti-*H. pylori* effectiveness of micro- or nanoparticles in the past five years

Micro/nanoparticles	Study design	Outcome	Reference
Floating mucoadhesive alginate beads containing amoxicillin trihydrate with a size range of 1.39 ± 0.07 mm to 1.66 ± 0.03 mm	In the *in vitro* study the *H. pylori* ATCC 26695 growth inhibition was performed by OD checked at several time points. The *in-vivo* study was carried out by administering beads to six healthy New Zealand breed white rabbits and monitoring them through an X-ray imaging method.	*In vitro*, the optimized batch showed 100 % *H. pylori* growth inhibition in 15 h. In rabbit stomach was confirmed the gastric retention of optimized formulation demonstrated its efficacy as stomach-specific delivery of the drug.	[15]
Biomimetic hydroxyapatite nanocrystals coated with lactoferrin (LF-Coated HA) combined with cell free supernatant from probiotic *Lactobacillus paracasei* (LFHP)	*In vitro* and *in vivo* evaluation of antibacterial and antinflammatory properties, humoral antibody induction, histopathological analysis and absence of side effects.	*In vitro*, LFHP treatment showed a higher antibacterial activity against *H. pylori* compared to antibiotic pool (AP) therapy. *In vivo*, LFHP therapy demonstrated higher antibacterial, anti-inflammatory and immune response activities and absence of hematological alterations, compared with AP therapy.	[16]
Chitosan-coated amoxicillin trihydrate-loaded *Caesalpinia pulcherrima* galactomannan (CPG)-alginate beads (CCA-CPG-A)	*In vitro* studies of mucoadhesion, drug release, floating and *H. pylori* growth inhibition performed with a clinical isolated strain. *In vivo* studies in Wistar rats for gastric mucoadhesion, *H. pylori* growth inhibition using PCR amplification of isolated DNA, rapid urease test.	*In vitro–in vivo* growth inhibition study showed complete eradication of *H. pylori*. *In vivo* mucoadhesion study showed more than 85 % mucoadhesion of beads even after 7th hour.	[17]

HP55/PLGA nanoparticles (~200 nm)	HP55/PLGA NP was developed as an oral delivery system of *H. pylori* recombinant antigen CCF. Study about the immunogenicity and prophylactic vaccination of the vaccine was performed in SPF BALB/c mice, which were immunized by intraperitoneal injection or oral administration. Two weeks after the final immunization, mice were infected with *H. pylori* SS1 and, after 1 month, the mice were sacrificed to evaluate *H. pylori* infection.	HP55/PLGA NPs controlled the release of antigen CCF in the acidic environment (pH $\leqslant$ 5.5). Immunized mice with HP55/PLGA-CCF nanoparticles induced high levels of urease-specific antibodies and memory T cell responses. A month after *H. pylori* challenge, 43 % of mice were completely protected.	[18]
AGS membrane-coated nanoparticles (AGS-NPs)	*In vitro* determination of bactericidal activity of clarithromycin (CLR)-loaded AGS-NPs against *H. pylori* through bacterial enumeration after incubation with the NPs. *In vivo* determination of anti-*H. pylori* efficacy of CLR-loaded AGS-NPs orally administered in C57BL/6 male mice infected with *H. pylori.* Acute toxicity AGS-NPs evaluated *in vivo*, by orally administration of AGS-NPs to uninfected C57BL/6 male mice.	AGS-NPs loaded with CLR demonstrated an enhanced bactericidal effect *in vitro* due to preferential binding of AGS-NPs with *H. pylori*. *In vivo*, CLR-loaded AGS-NPs showed superior anti-*H. pylori* efficacy when compared to free CLR or a non-targeted NP formulation. Toxicity tests showed no adverse effects from the AGS-NPs.	[19]
Ureido-conjugated amoxicillin-UCCs-2/TPP nanoparticle	*In vivo* assay with six-week old Balb/C male mice. After treatment the stomachs were cut and the *H. pylori* bacterial colony counting was performed.	Control: 163 ± 25 CFU/stomach; Amoxicillin-loaded UCCs-2/TPP nanoparticles: 21 ± 9 CFU/stomach, 8 ± 1 CFU/stomach for 15 mg/kg and 30 mg/kg of amoxicillin, respectively.	[20]
HP55/poly(n-butylcyanoacrylate)	Oral administration in a prophylactic mice model (male BALB/c mice). The cytotoxicity of	NPs protected the CCF antigen from the acidic pH in simulated gastric fluid (SGF, pH	[21]

(PBCA) NPs carrying *H. pylori* subunit vaccine CCF.	HP55/PBCA-CCF NPs was evaluated in RAW 264.7 and GES-1 cells by MTT assay. Vaccine immunogenicity and the response of humoral immunity was evaluated through checking elevation of the levels of antigen-specific antibodies in the serum.	1.2) and from the proteolysis in simulated intestinal fluid (SIF, pH 7.4). No significant cytotoxicity of HP55/PBCA-CCF NPs was found at concentrations from 10 to 100 μg/mL after 24 h both in RAW 264.7 and GES-1 cells. Vaccination of mice with HP55/PBCA-CCF NPs triggered a local and systemic humoral immune response and elicited a Th1/Th17 response.	
Amoxicillin-loaded urea-modified (AMX-PLGA/UCCs-2) NPs and Amoxicillin-loaded unmodified (AMX-PLGA/Cs) NPs with 190 and 360 nm to pH 1.2 and 7.4, respectively.	*In vitro* study: growth inhibition of *H. pylori* ATCC 26695 was determined using OD_{590} measurements. Male mice (Balb/c strain) with 4 weeks were used for the *in vivo* study. The viable bacterial count of each stomach was calculated by counting the number of colonies.	*In vitro*, with an AMX concentration of 2 μg/mL AMX-PLGA/Cs NPs and AMX-PLGA/UCCs-2 NPs showed significant antibacterial activity during all co-incubation periods; compared with the AMX solution, both NPs exhibited better bacterial growth inhibition effect after 6 h; to 12 and 24 h, AMX-PLGA/UCCs-2 NPs showed more antibacterial effect than AMX and AMX-PLGA/Cs nanoparticles *In vivo*, with an AMX concentration of 15 mg/Kg the mice treated once a day for 7 days with AMX-PLGA/Cs NPs and AMX-PLGA/UCCs-2 NPs all had lower bacterial load than AMX-treated mice.	[22]
Gold nanostars conjugated with acid-sensitive *cis*-aconitic	*In vitro* evaluation of the photothermal antibacterial effect of GNS@Ab. Gold nanostar-based theranostic agents were	Photoacoustic imaging confirmed that prepared GNS@Ab targeted actively *H. pylori* in the stomach. GNS@Ab nanoprobes	[23]

anhydride modified anti-*H. pylori* polyclonal antibodies (GNS@Ab)	employed for photothermally eradicating *H. pylori in vivo* in SPF BALB/c mice, and 40 *H. pylori* strains with antibiotic resistance isolated from clinical patients. GNS@Ab influence on gut microbiome was investigated by sequencing.	killed *H. pylori in vivo* under NIR laser irradiation and all GNS@Ab nanoprobes were excreted out of gut within 7 days after oral administration. Gastric local lesion caused by *H. pylori* restored to normal status within 1 month. GNS@Ab nanoprobes within therapeutic doses did not damage intestinal bacteria imbalance. Forty clinical specimens of *H. pylori* with antibiotic resistance were treated and killed with GNS@Ab nanoprobes.	
Chitosan-DNA nanoparticles (mean diameter of 117.7 nm)	*CagW* gene DNA vaccine was encapsulated in chitosan NPs (pcDNA3.1 (+)-cagW-CS-NPs). The stability and *in vitro* expression of chitosan NPs were studied by DNase I digestion and transfection, and the immune responses elicited in specific pathogen-free (SPF) mice by the pcDNA3.1 (+)-cagW-CS-NPs were evaluated. The protective potential pcDNA3.1 (+)-cagW-CS-NPs was evaluated by challenging with *H. pylori* (ATCC: 43504).	Chitosan encapsulation protected the DNA plasmid from DNase I digestion, and the cagW gene could express in HDF cells and maintain good bioactivity at the same time. In *in vivo* assays, mice immunized with pcDNA3.1 (+)-cagW-NPs showed better immune responses and prolonged release of the plasmid DNA, in comparison to the mice immunized with the control plasmid.	[24]
Amoxicillin (AMX) minitab tablets (AMX-MTs) with mean diameter of 4.0± 0.0 mm and average thickness between 3.4 and 4.5 mm, and AMX	*In vitro* study of the release profiles of AMX-MTs and AMX-LPNs and antimicrobial activity assessment using *H. Pylori* ATCC 700392/26695 for the agar plate diffusion method assays. MIC determined by the microdilution broth test.	*In vitro*, MT-6 and LPN-11 showed a significantly higher antibacterial activity, with a significantly wider zone of inhibition (33.2 ± 2.5 and 34.1 ± 1.3, respectively), compared to control (28.5 ± 1.8). The MIC of both optimized tablet formula (MT-6) and	[25]

lipid polymer nanoparticles (AMX-LPNs) with size ranging between 235±34 nm and 390 ± 28 nm.	*In vivo* study of the antimicrobial activity and oral pharmacokinetics of the optimum MT and LPN formulations in comparison to market tablet using 24 male Wistar rats.	LPNs formula (LPN-11) was around two-fold lower than the control against *H. pylori*. *In vivo*, relative bioavailability of the AMX was 1.85 and 1.8 after the oral use of LPN11 and MT-6, respectively, compared to the market tablet.	
Chitosan microspheres (ChMics) of different size (XL, ∼120 µm and XS, ∼40 µm) and degree of acetylation (6% and 16%)	*In vitro* evaluation of ChMics ability to adhere *H. pylori* SS1 and clinical isolate J99 by incubation of ChMics with FITC-labelled *H. pylori* strains and visualization of ChMics and adherent FITC-labelled *H. pylori* by CLSM. ChMics cytotoxicity evaluated towards human gastric adenocarcinoma cell line (AGS, ATCC® CRL-1739™) using elution/extract and direct contact assays. *In vivo* studies: evaluation of ChMics penetration into gastric mucus of C57BL/6 mice and study of ChMics efficiency in *H. pylori*-infected C57BL/6 mice. At the end of the treatment plan, animals were sacrificed and *H. pylori* infection levels in mice stomach tissue were quantified by colony forming assay. PCR and histological analysis were performed.	*In vitro*, ChMics adhered both *H. pylori* strains without cytotoxicity towards human gastric cells. *Ex vivo* studies showed that smaller (XS) microspheres penetrate further within the gastric foveolae. *In vivo* assays showed 88 % reduction of infection when *H. pylori*-infected mice (C57BL/6) were treated with more mucoadhesive XL6 and XS6 ChMics.	[26]
Chitosan/poly (acrylic acid) particles co-loaded with	*In vitro* studies of drug release, mucoadhesion and mucopenetration evaluation, preventive antibiofilm assay, cytotoxicity (with NIH/	SPIO/AMO@PAA/CHI NPs are biocompatible and retain the biofilm inhibition and the bactericidal effect of amoxicillin against *H.*	[27]

superparamagnetic iron oxide nanoparticles and amoxicillin (SPIO/AMO@PAA/CHI)	3T3 and AGS cell lines) and bacterial growth inhibition assay (with *H. pylori* strains127-4, 125-54, and 125-57). *In vivo* study of the eradication efficacy of *H. pylori* by SPIO/AMO@PAA/ CHI NPs and determination of residual SPIO/AMO@PAA/CHI NPs in the stomach of BALB/c mice.	*pylori*. SPIO/AMO@PAA/CHI NPs adhered to the gastric mucus layer, due to the mucoadhesive property of chitosan, and passed rapidly through the mucus layer after exposure to a magnetic field. The NPs prolonged the amoxicillin residence time in the stomach, reducing the required drug dose and treatment time.	
Fullerenol nanoparticles (FNPs)	*In vitro*, the survival of treated *H. pylori* cells with different concentrations of FNP A (50,100, and 200 µg/mL) was detected in acidic medium (pH 2.20). *In vivo*, a model of *H. pylori* infection in C57BL/6 mouse was generated. *H. pylori*-specific serum Ig levels in the infected mice were detected by ELISA. Biofilms were cultured in pH 2.20 to simulate *H. pylori* colonies in the stomach, treated with different concentrations of FNP A (50, 100, and 200 µg/mL) for 40 min and observed by SEM.	FNPs exerted strong effect on *H. pylori* eradication *in vitro* and *in vivo* due to peroxidase-like activity. FNP treatment of *H. pylori* biofilm resulted in collapse of the bacteria due to break down of polysaccharides by FNPs in cell wall components.	[28]

CFU - Colony-Forming Unit; CLSM - confocal laser scanning microscopy; FESEM - Field Emission Scanning Electron Microscopy; ELISA - enzyme-linked immunosorbent assay; MBC - Minimum bactericidal concentration; MIC - Minimum Inhibitory Concentration; PCR - - Polymerase chain reaction; ROS - Reactive Oxygen Species; TEM - Transmission Electron Microscopy

Table S4. List of *H. pylori* vaccines tested in animal models, over the past six years

Vaccine	Vaccine component(s)	Adjuvant	Administration route(s)	Protective response(s)	Animal model	Reference
Epitope vaccine CTB-Lpp20	*H. pylori* Lpp20 epitopes	CTB	Intraperitoneal	Antibody Production (IgG, IgA, and sIgA) and Th1-biased response	BALB/c mice	[29]
Multi-epitope vaccine CTB-UE displayed on the surface of non-genetically modified *L. lactis* particles (CUE -GEM)	Tandem copies of the B cell epitopes and Th cell epitopes from the *H. pylori* urease A and B sub-units	CTB	Oral	Urease-specific antibody and pro-inflammatory cytokine response; CD4+Th cell-mediated and humoral immunity, regulation of gastric pro-inflammatory cytokine profile (IFN-γ and IL-17).	BALB/c mice	[30]
Fusion protein vaccine	Recombinant *L. lactis* strain expressing a fusion protein of Omp22 and HpaA from *H. pylori*	FA	Oral	Induction of significant systematic humoral immune response	BALB/c mice	[31]
Recombinant *L. lactis* strain expressing *H. pylori* Lpp20	*H. pylori* Lpp20 protein	FA	Oral	Elevated levels of serum Lpp20-specific IgG antibodies	SPF BALB/c mice	[32]
Multivalent epitope-based vaccine (CWAE)	*H. pylori* urease, NAP, HSP60	HA	Oral	Significant reduction of the number of *H. pylori* colonies in the stomach of Mongolian gerbils. Elicited higher levels of mixed $CD4^+$ T cell (Th cell) response, IgG, and secretory	Mongolian gerbils	[33]

				IgA (sIgA) antibodies against *H. pylori*.		
Multivalent epitope-based vaccine (CFAdE)	*H. pylori* adhesins urease, Lpp20, HpaA, CagL	PA	Oral	Induction of high levels of specific antibodies against urease, Lpp20, HpaA and CagL. *H. pylori* colonization was decreased. Protection correlated with IgG and sIgA antibody and antigen-specific CD4+ T cells.	Mongolian gerbils	[34]
Systemic whole cell inactivated vaccine	Heat inactivated *H. pylori* WC	Aluminum phosphate	Systemic (intramuscular, subcutaneous)	High IgG titer levels and long term protective immunity.	Swiss albino mice	[35]
CCF-encapsulated acid-resistant HP55/PLGA NPs	*H. pylori* recombinant antigen CCF	AH	Oral	Th1/Th17-bias immune response. Increased levels of antigen-specific antibodies, switched IgG2a/IgG1 ratio and proinflammatory cytokines detected.	BALB/c mice	[18]
Inactivated *V. cholerae*-HpaA-CFA/I	Formaldehyde-inactivated recombinant *V. cholera* expressing HpaA alone or together with CFA/I	CT	Oral	Induction of high serum anti-HpaA responses.	C57/Bl6 mice	[36]
CotC-CTB-UreB-expressing *B. subtilis* spores	*H. pylori* urease B (UreB) and *B. subtilis* spore coat protein CotC as a fusion protein	CTB	Oral	Increased levels of UreB-specific IgG in serum and UreB-specific IgA in faeces, elevated levels of IL-10 and IFN-γ in splenocytes.	BALB/c mice	[37]

Recombinant vaccine	Brucella OMPs-CagA	CpG	Subcutaneous	Decrease of bacterial colonization in gastric, splenetic and blood tissues. Increased levels of IgG, promotion of Th1 immune response.	BALB/c mice	[38]
Vaccines composed of *H. pylori* FliD and the adjuvants CpG, Addavax, or CTB	rFLiD	CpG, Addavax, or CTB	Subcutaneous	Induction of antigen-specific immune responses of Th1/Th17 type, particularly with CpG-adjuvanted FLiD	C57BL/6 mice	[39]
whole cell vaccine (WCV)	Formalin-inactivated *H. pylori* WCV	mmCT	Oral	Reduction in colonization of *H. pylori* in the stomach of mice, increase in serum IgG and intestinal-mucosal IgA anti-*H. pylori* antibody responses and strong T cell and IFNγ and IL-17A cytokine responses.	C57BL/6 mice	[40]
HP55/PBCA-CCF NPs oral subunit vaccine	subunit vaccine CCF	AH	Oral	Production of serum antigen-specific antibodies, mucosal secretory IgA, and proinflammatory cytokines. Th1/Th17 response and augmented lymphocytes.	BALB/c mice	[21]
Multivalent epitope-based vaccine (CTB-HUUC)	CTB-HUUC	CTB	Oral	Promotion of *H. pylori*-specific lymphocyte responses and mixed CD4+ T cell immune response, indicated by IFN-γ, IL-4, and IL-17 production in mice. Both oral prophy-lactic and	BALB/c mice	[41]

				therapeutic vaccinations reduced gastric urease activity and *H. pylori* infection and protected stomachs in mice.		
Engineered *L. lactis* strain expressing NapA	*H. pylori* NapA subunit	-	Oral	Induction of both polarized Th17 and Th1 responses.	BALB/c mice	[42]
Epitope-based vaccine	Immunodominant epitope peptides derived from HpaA	CpG	Subcutaneous, intranasal	Protection of mice against *H. pylori* infection and stimulation of strong Th1 responses.	BALB/c mice	[43]
Oral vaccine	Engineered *L. lactis* strain expressing HpaA	FA	Oral	Enhanced serum IgG level	BALB/c mice	[44]
Outer-membrane vesicles (OMVs) vaccine	*H. pylori* OMVs	CT	Oral	Strong humoral and significant mucosal immune response, induction of T helper 2 (Th2)-biased immune responses.	C57BL/6 mice	[45]
α-GalCer-adjuvanted *H. pylori* vaccine	Whole-cell inactivated *H. pylori* antigen	α-GalCer	Oral	Strong intestinal and systemic Th1 responses and significant antigen-specific mucosal and systemic antibody responses.	C57BL/6, IL-17RA$^{-/-}$ and IL-1RI$^{-/-}$ mice	[46]
Oral vaccine	*L. lactis* strain expressing *H. pylori* Lpp20	*L. lactis*	Oral	Elevated serum IgG levels and lowered urease activity	BALB/cmice	[47]
Oral vaccine	Recombinant *L. lactis* expressing *H. pylori* CagL (*L. lactis*-pAMJ2008-CagL)	-	Oral	Stimulation of CagL-specific antibodies: IgA, IgG, cytokine IL-17 and IFN-γ. Specific anti-CagL IgA	BALB/c mice	[48]

				response detected in the feces of immunized mice.		
Parenteral vaccine	Recombinant *H. pylori* UreA, UreB, and NAP	cGAMP	Parenteral (intranasal, intramuscular, subcutaneous)	Gastric mucosal *H. pylori* colonization significantly reduced. Antigen-specific serum IgG and mucosal IgA responses. Induction of antigen-specific Th1 and Th17 responses.	BALB/c mice	[49]
Live attenuated measles virus vaccine	Live attenuated measles virus expressing *H. pylori* HspA (MV-HspA)	FA	Intraperitoneal	Induction of humoral immune response	BALB/c mice	[50]
Multivalent, subunit vaccine	NAP, UreA and UreB	dmLT	Oral	Reduction of gastric bacterial colonization; increased serum antigen-specific IgG and mucosal IgA responses. Induction of Th1/Th17 immune responses	SPF BALB/c mice	[51]
Multi-component vaccine	*H. pylori* LPS and recombinant CagA (rCagA)	CpG	Systemic (intramuscular)	Induction of robust Th1-biased immune responses	BALB/c mice	[52]
Outer membrane proteins (OMPs) and whole cell vaccine (WCV)	OMP and WCV	Purified *H. pylori* outer membrane vesicles (OMVs)	Gavage	Enhancement of systematic and gastric mucosal immunity, and humoral immunity. Induction of Th1 immune response. Eradication of *H. pylori* enhanced.	C57BL/6 mice	[53]
Semisynthetic CRM197−1	Totally synthesized tri-D-*glycero*-D-*manno*-heptose antigen **1** from *H. pylori* LPS	FA	Subcutaneous	Very robust T-cell-dependent antigen-specific immune response, with very	C57BL/6J mice	[54]

glycoconjugate vaccine				high titers of IgG1 and IgG2b protective antibody isotypes.		
Trivalent subunit *H. pylori* vaccine	Recombinant *H. pylori* antigens (NAP/UreA/UreB)	dmLT	Oral	Significant reduction of *H. pylori* gastric colonization 6 weeks after challenge, associated with the induction of antigen-specific Th17 and local mucosal IgA immune responses.	BALB/c mice	[55]
Saccharomyces cerevisiae-based oral vaccine	EBY100/pYD1-UreB and EBY100/pYD1-VacA	*S. cerevisae*	Oral	Significant production of IgG and secretory IgA responses and reduced *H. pylori* loads.	BALB/c mice	[56]

AH - Aluminum hydroxide; CagA - cytotoxin-associated gene A; CTB - Cholera toxin B; dmLT - double-mutant heat-labile toxin; FA - Freund's adjuvant; HSP60 - heat shock protein 60; HpaA - *H. pylori* adhesin A; HspA - heat shock protein A; LPS - lipopolysaccharide; mmCT - multiple mutant cholera toxin; NapA - neutrophil-activating protein A subunit; OMPs - outer membrane proteins; NAP - neutrophil-activating protein; PA - Polysaccharide adjuvant; VacA - vacuolating cytotoxin A; WC- whole cells

Table S5. Relevant *in vivo* studies on anti-*H. pylori* effectiveness of natural products in the past six years

Natural product	Extract/ compound	Study design	Outcome	Reference
Conifer Green Needle Complex (CGNC)	CGNC contains chlorophyll derivatives, carotenoids, vitamins A, E, and K, phytosterols, polyprenols, squalene, resin acids (approximately 20 %), essential oils and natural antibiotics (phytoncides)	Study with adult patients (26 treated, 24 no treatment) with precancerous gastric lesions. Patients received 600 mg per day of CGNC before food for six months. During gastroscopy and immediately after obtaining biopsy samples with one piece of tissue from the antral section, a rapid urease test for detecting *H. pylori* was carried out.	After six months of CGNC therapy, *H. pylori* infection could no longer be observed in 57.1 % of infected patients compared with 15.4 % infected patients in the control, untreated group. Moreover, partial regression of dyspeptic symptoms, reduction in endoscopic signs of gastritis, an increase of pepsinogen–pepsin in gastric juice, and total regression or reduction in the degree of intestinal metaplasia and lymphoplasmacytic infiltration were observed.	[57]
Medicinal herb and spice	Methanol extract of *Eryngium foetidum*	*In vivo*, swiss mice were inoculated with *0.2 mL of* 10^8 *CFU/mL of H. pylori* and divided into 5 groups; the control group received the vehicle and the four others received 125, 250, and 500 mg/kg of methanol extract of *Eryngium foetidum* and ciprofloxacin (500 mg/kg) for 7 days, respectively. *H. pylori* colonization and number of colonies in gastric biopsies culture were assessed on days 1 and 7 after treatment.	The number of *H. pylori* infected animals was 17 % (plant-extract) and 0 % (ciprofloxacin) compared to 100 % for the infected untreated group. Plant-extract (381.9 ± 239.5 CFU) and ciprofloxacin (248 ± 153.2 CFU) significantly reduced bacterial load in gastric mucosa compared to untreated, inoculated mice (14350 ± 690 CFU)	[58]

Medicinal herb	*Tinospora sagittata* (Oliv.) *Gagnep. var. craveniana* (S.Y. Hu) *Lo* (TSG)	*In vivo*, two groups of 48 mice were inoculated intragastrically with 0.3 mL of *H. pylori* SCYA201401 (1×10^8 CFU/mL) and 0.3 mL of *H. pylori* SS1 (1×10^8 CFU/mL), respectively on three alternate days. Animals were fasted 24 h before and 2 h after each inoculation. After 24 days, 8 mice from each experimental group were sacrificed. The eradication ratios were determined by use of rapid urease tests and bacterial culture.	*In vivo*, the eradication ratios in the TSG and palmatine groups of mice were 80 and 50 % compared with 70 % in the triple-therapy group.	[59]
Medicinal herb	Geniposide and genipin found in *Gardenia jasminoides*	*In vivo,* 60 male C57BL/6 mice were used for tests. All of the mice, apart from those in the control group, were infected with 1×10^9 CFU of *H. pylori* 26695 every other day for a total of 3 doses using stomach tubes. All test samples (geniposide and genipin) were dissolved in water and administered orally every day at a volume of 0.2 mL per mouse. Stomach and blood samples were collected from all of the groups the day after the last treatment was administered.	Geniposide and genipin reduced *H. pylori* infections *in vivo*, interfering with the growth and virulence of *H. pylori*, as well as mitigating gastric inflammation caused by a *H. pylori* infection.	[60]
Medicinal herb	Bryophyllum pinnatum	Sixty mice were inoculated orally through a feeding tube four times at 2-day intervals with 0.2 mL of an *H. pylori* α2 suspension containing 10^8 CFU/mL. The presence of *H. pylori* on the mice stomachs was confirmed by urease,	Treatment of infected animal with plant-extract significantly increases the percentage of negativity from 67 to 83 %, respectively, at 125 and 500 mg/kg doses. Bryophyllum pinnatum extract (85.91 ± 52.91 CFU) and standard (25.74 ± 16.15 CFU) also	[61]

		catalase, and oxidase testing, and Gram staining.	reduced significantly ($p < 0.05$) bacterial load of gastric mucosa as compared to untreated infected mice (11883 ± 1831 CFU).	
Medicinal herb	Wasabi (Wasabia japonica Matsum)	Male Mongolian gerbils were infected with *H. pylori* and then, wasabi leaf extract (30 mg / kg body weight) and allyl isothiocyanate (AIT) (3.0 mg / kg body weight) were orally administered. The CFU of *H. pylori*, gastric mucosal erosion, and petechial hemorrhage scores in the stomachs of the animals in each group were analysed.	The CFU in the stomachs of the *H. pylori*-infected groups by treatment with wasabi leaf extract (1.9 ± 1.8) or AIT (2.3 ± 1.8) showed a decreasing tendency compared with the positive control group (3.4 ± 1.4). The treatment decreased the score of gastric mucosal erosion in the *H. pylori*-infected animals.	[62]
Medicinal herb	*Goshuyuto*	2 man and 1 woman received goshuyuto 7.5 g/day and rabeprazole 20 mg/day for 28 days after the failure of each secondary eradication therapy. All cases received a post-treatment UBT.	The eradication of *H. pylori* was achieved after treatment with goshuyuto plus rabeprazole, in the three studied individuals.	[63]
Medicinal herb	Burdock complex (BC) constitutes of *burdock (Arctium lappa), angelica (Angelica sinensis), gromwell (Lithospermum erythrorhizon),* and *sesame*	In the clinical trial, *H. pylori* positive individuals (n = 36) were enrolled and requested to ingest BC (n = 19) or placebo (n = 17) for 8 weeks. Antioxidant capacity, total phenol, UBT, inflammatory markers were analysed in the first, 4th, 8th and 10th weeks. Furthermore, an endoscopic examination was performed at the initial consultation and at the 10th week.	Individuals infected with *H. pylori* treated with BC for 8 weeks significantly decreased ($P < 0.05$) the UBT value, had inflammatory markers with improved antioxidant activity and phenolic levels compared to placebo. In addition, the consumption of BC healed the ulcer wound considerably	[64]

	(Sesamum indicum) oil			
Vitamins and garlic	vitamin (C, E, and selenium) and garlic (extract and oil)	3365 adult patients (2258 *H. pylori* positive, 1107 *H. pylori* negative). Incidence of gastric cancer was ascertained from gastroscopies.	*H. pylori* treatment for two weeks and vitamin or garlic supplementation for seven years were associated with a statistically significant reduced risk of death due to gastric cancer for more than 22 years. *H. pylori* treatment and vitamin supplementation were also associated with a statistically significantly reduced incidence of gastric cancer.	[65]
Plant	Essential oil and ethanolic extract obtained from *Casearia sylvestris Swartz* leaves.	*In vivo* action was investigated by employing male Wistar rats experimentally infected with *H. pylori* ATCC 43504. Stomach fragments were used to determine activity against *H. pylori*	*In vivo* tests showed that ethanolic extract eradicated *H. pylori* from the gastric lesions and decreased the ulcerative lesion size.	[66]
Edible fungi	Hericium erinaceus extracts	*In vivo* tests were performed with C57BL mice. Colonization tests were carried out in homogenized stomachs 3 weeks after the inoculation of *H. pylori* in the animals;	Mice receiving the H. erinaceus extract had a mean *H. pylori*, about 1 log lower than the control (no extract) animals.	[67]
Medicinal herb	-	A meta-analysis of 8 trials with 919 participants	Compared with using the drug therapy only, the combination of Chinese herbal medicines with the drug therapy more effectively eliminates *H. pylori* and alleviates adverse reactions	[68]
Ginger (*Zingiber officinale*)	1-g ginger powder tablets	Clinical trial: 15 patients with *H. pylori* positive functional dyspepsia received 3 g/day ginger powder as three 1-g tablets	Significant *H. pylori* eradication rate of 53.3 % (P = 0.019) and improvement of	[69]

		for 4-weeks. Dyspepsia symptoms were asked before and after the intervention and *H. pylori* eradication was assessed by a non-invasive stool antigen test.	dyspeptic symptoms after ginger supplementation.	
Cinnamon	Cinnamon extract capsule	Clinical trial with 98 healthy and *H. pylori*-infected patients: the cinnamon group received multidrug treatment and a cinnamon extract capsule and control group received multi-drug treatment and a 40 mg starch capsule, for 3 months. Cinnamon extract efficacy was analysed by the UBT.	Significant reduction of clinical symptoms and higher *H. pylori* eradication rate in cinnamon group (73.47 % in cinnamon group compared to 53.06 % in the control group).	[70]
Cloves, basil, cinnamon leaves, and copaiba balsam.	β-caryophyllen, a natural bicyclic sesquiterpene	A total of 160 mice were divided into eight groups (n = 10 each) and were administered different treatments for 2 and 4 weeks. *H. pylori* SS1 eradication was assessed using a Campylobacter-like organism (CLO) test and *H. pylori* qPCR of the gastric mucosa. The levels of inflammation of gastric mucosa were assessed using histology and immunostaining.	The CLO test and *H. pylori* PCR in the gastric mucosa after treatment showed that the treatment rate increased as the dose of β-caryophyllen increased. β-caryophyllen -treated mice had significantly reduced levels of *H. pylori*-induced inflammation compared to that in *H. pylori*-infected but untreated mice.	[71]

ATCC - American Type Culture Collection; CFU – Colony-Forming Unit; UBT – Urease Breath Test

Table S6. Phages of *H. pylori* isolated and characterized in laboratory

Phage identification	Phage host strain	Isolation/detection method	Family	Head/Tail size (nm)	Accession number	Reference
-	SchReck 290	Spontaneously production	Undetermined	Head: 70 ± 5x60±4 Tail: 120	Not-sequenced	[72]
HP1	IMMi 290/89	Spontaneously production	*Syphoviridae*	Head: 55-60 Tail: 170 x 9.5	Not-sequenced	[73]
-	Clinical isolate	Isolated from human faeces	Undetermined	Head: 100 No tail	Not-sequenced	[74]
PhiHp33	B45	UV and low pH induction	*Syphoviridae*	Head: 62.5 ±7.3 Tail: 92.4±2.97x5-6	NC_016568.1	[75, 76]
1961P	NCTC 11637*	Spontaneously production	*Podoviridae*	Head: 71.1 ± 2.9 Tail: 23.0 ± 1.0 x 13.3	NC_019512.1	[77]
KHP30	Clinical isolate	Spontaneously production	*Corticoviridae*/*Tectiviridae*	Head: 68.8 ± 2.3 No tail	NC_019928.1	[78, 79]
KHP40	Clinical isolate	Spontaneously production	*Podoviridae*	Undetermined	NC_019931.1	[78]
ΦHPE1	Clinical isolate	Isolated from Zagazig wastewater	*Podoviridae*	Head: 62 Tail: 12 × 6	Not-sequenced	[80]
ΦHPE2	Clinical isolate	Isolated from Zagazig wastewater	*Siphoviridae*	Head: 92.5 Tail: 180 x 15	Not-sequenced	[80]
Hp φ	Clinical isolate	Isolated from human gastric biopsies	Undetermined	Undetermined	Not-sequenced	[81]

* Propagation and indicator host

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