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An Insight into Molecular Drug Targets of Helicobacter Pylori and Potential Therapies

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Abstract

Helicobacter pylori are a gram-negative spiral-shaped bacterium, belonging to the class Epsilonproteobacteria that colonizes the gastric epithelium of humans leading to a common infection that affects nearly 50% of the total population across the globe. They are the common bacteria that evade the gastric tract of humans causing numerous pathologies such as chronic gastritis, peptic ulcers, gastric mucosa-associated lymphoid tissue (MALT) lymphoma and gastric cancer. Usually, treatment of H.pylori is carried out using two or three antibiotics combined with a proton pump inhibitor. Recently, there is an increase in antibiotic resistance throughout the world and henceforth, there is an immediate need in identifying effective treatments. Identifying specific targets in H.pylori that are responsible for host-pathogen interactions, virulence factors etc., and developing specific drugs against them is one of the potential solutions. In doing so, it is important to understand in depth the structure and functions of the targets to develop drugs that are specific to them. This would lead to the effective eradication of the infection. In this review, we have identified 10 potential targets which are Urease, FlgE2, HtrA, Chorismate synthase, Peptide deformylase, VacA, Adhesin BabA, Csd4, Flavodoxins, â-Clamp bound to DNA Ligase peptide. In future, effective drugs can be developed against these targets. Also, insights about the phytochemicals that are effective against H. pylori are mentioned in this review. Potential drugs combined with these phytochemicals can effectively eradicate the infection.

Keywords: *Helicobacter pylori, antibiotic resistance, drug targets, phytochemicals*

1.0 Prevalence

Helicobacter pylori are a gram-negative spiral-shaped bacterium that belongs to the class, Epsilonproteobacteria. It specifically colonizes the gastric epithelium of humans, which leads to a commonly affected infection that nearly affects 50% of the total population in the world[46]. They are the common bacteria that evade the gastric tract of humans causing numerous pathologies such as chronic gastritis, peptic ulcers, gastric mucosa-associated lymphoid tissue (MALT) lymphoma and gastric cancer (Lee et al., 2013). The frequency with which H. pylori infection occurs is largely versatile across countries throughout the globe. For example, the appearance of infection is highly observed in the Latin American countries having percentages that vary from 75 to 83% when compared to the low appearance in the case of Japan and the US has 39.6% and 17.1% respectively[34,60]. The commonness with which the H. pylori infection occurs can be highly associated with social and economic factors. 80% of the senior adults in the developing countries are infected while 20-50% prevalence is observed in the industrialized countries[60]. Gastric H.pylori is considered to be the most successful human pathogen wherein the bacteria infect at a very young age and remains latent for several decades and after which it gets converted to an infection that persists for its whole life. The extent to which the infection is visible from

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person to a person solely depends on the complex interaction among the host, the environment, and factors that affect a specific population of bacteria[73].

2.0 Microbiology

Helicobacter genus belongs to the subdivision called å of the Proteobacteria; order Campylobacterales, family Helicobacteraceae (Kusters et al., 2006). Helicobacter species are organisms that are microaerophilic in nature and are catalase and oxidase positive. Also, most of the species are urease positive except a few. The Helicobacter species are generally classified into two types, gastric and non-gastric species. There is a high level of organ specificity that is observed between these two types[25]. The gastric Helicobacter species are highly adaptive in nature as they colonize the gastric mucosal surface of humans which possess highly acidic conditions[25,10,70].

2.1 Morphological Characteristics of H. Pylori

H. pylori are gram-negative bacteria that have an approximate length of 2 to 4 µm and a width of 0.5 to 1 µm. Generally, they exist as spirally-shaped but, they might also appear as rod, as well as coccoid shapes when cultured in vitro or while treating them with any antibiotics[25,29,78]. The bacteria possess around 2 to 6 unipolar, sheathed flagella which have an approximate length of 3 µm that possess a remarkable bulb at one end[25]. The function of the flagella is to offer motility and allow accelerated motion so that it can move through any viscous solution like the mucus layer that overlays the gastric epithelial cells[25]. H.pylori lacks fimbrial adhesins when compared to other pathogens of the gastrointestinal tract.

2.2 Cell wall structure

The cell envelope of H. pylori has an inner cytoplasmic membrane, a periplasm with peptidoglycan and an outer membrane. The composition of the outer membrane is made up of Lipopolysaccharides and Phospholipids. The phospholipids consist of cholesterol glucosides that are very rarely found in any bacteria. LPS has a lipid A, a core oligosaccharide and an O side chain[25]. The cell wall of H. pylori is considerably similar to that of gram-negative bacteria. The Peptidoglycan is a component of the cell wall that provides shape to the bacteria and ensures the cell content is protected from external environmental factors. Alternative monomers of N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM) crosslink using short peptides that attach to NAM and form a meshwork[28].

2.3 Genome

H. pylori consist of 1.65 million base pairs and these encode for almost 1500 proteins and have a G+C content in the range of 35 to 40%[25,2,60,67]. Duplicates of 6S, 23S, and 5S rRNA genes are present in the genome of the bacteria. Some of the strains carry cryptic plasmids that do not possess any antibiotic resistance or virulence genes[25,20]. Analysis of multiple genomes has led to the establishment of 32 outer membrane proteins (also called Hop proteins) that consists of adhesins and many other genes that can be turned on or off with slipped-strand mispairing-mediated mutagenesis. These phase variable genes encode for enzymes that alter the structure of antigen present on the bacterial surface, restrain the entering of extrinsic genetic material and impact the movement of bacteria[60]. H. pylori are heterogeneous in nature and lack clonality and because of this, each strain has unique features even though the differences existing between them will be relatively low[25,27]. This feature also leads to the constant transformation of the H. pylori genome in a host, wherein extrinsic genetic material from different strains are up taken over a chronic establishment in a constant or temporary mixed infections[25,18]. There are almost 20 homologs that are related to DNA restriction and modification systems and these include type I, II, and III respectively[67,2]. The plasticity zone in the genome consists of 46-48% of sequences that are unique to a strain and the genes present in this region are similar to restriction or modification enzymes[2].

3.0 H. Pylori Infection: A General Overview

On gaining entry into the human stomach, H. pylori makes use of its urease to neutralize the acidic environment at an early stage of the infection. H. pylori utilizes flagella to enter the host gastric epithelium cells after which a particular interaction takes place between the adhesins of bacteria and the cell receptors of the host and this leads to effective colonization and a perpetual infection. Lastly, various effector proteins/toxins are released by H. pylori including cytotoxin-associated gene A (CagA), and vacuolating cytotoxin A (VacA), causing host tissue damage. The gastric epithelium layer acts as an important interface between the H.pylori and the host cells; they secrete chemokines that activate the innate immunity which activates the neutrophils and leads to various conditions like gastritis and ulcers[12] (Figure 1).

4.0 Currently used Treatments and Antibiotics Resistance Against H. Pylori

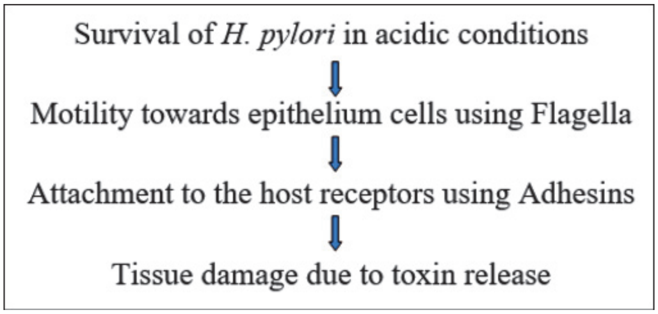

Figure 1: Critical steps for Colonization and pathogenesis in H. pylori

Typically, the treatment of H. pylori has been carried out using either two to three antibiotics along with a proton pump inhibitor (PPI)[57]. The first line of therapy involves Clarithromycin triple therapy that consists of a proton pump inhibitor along with the antibiotics, clarithromycin and amoxicillin or either metronidazole or tinidazole for a period of 14 days if the resistance against clarithromycin is lower than 15%. The use of macrolide antibiotics before the use of antibiotics containing clarithromycin causes the failure to eliminate the H. pylori infection. Therefore it is not advisable to prescribe a clarithromycin triple therapy if, the patient has been formerly administered the macrolides[56,46]. Levofloxacin is a broad-spectrum quinolone that is prescribed instead of Clarithromycin to avoid resistance. Levofloxacin triple therapy is not preferred as a first-line therapy choice as there is an increase in the resistance throughout the world. This therapy is preferable in regions, where people are prone to the low resistance of levofloxacin and high resistance of Clarithromycin and metronidazole resistance or the inaccessibility of bismuth[46,43].

The quadruple therapy without bismuth includes a Proton pump inhibitor along with three antibiotics, clarithromycin, amoxicillin and metronidazole or tinidazole where these antibiotics are administered in a sequential pattern or all three antibiotics are given at the same time concomitantly. The quadruple therapy with bismuth includes a Proton Pump inhibitor along with bismuth salt and antibiotics such as tetracycline and metronidazole for a period of 14 days. Initially, it was prescribed as second-line therapy. Bismuth quadruple therapy is not affected by resistance to Clarithromycin and has several advantages over treatment options in high resistance regions. In regions with high resistance to Clarithromycin and previous antibiotics usage, Bismuth quadruple therapy and concomitant therapy are prescribed as first-line therapy whereas in low resistance regions a 14-day Clarithromycin therapy could be used instead[56,76]. The failure of first-line therapy leads to second-line therapy which does not include the antibiotics prescribed initially. Either Bismuth quadruple therapy or levofloxacin triple therapy could be prescribed as the proceeding treatment method. On the failure of Bismuth quadruple therapy, Levofloxacin triple therapy involving Proton pump inhibitor along with levofloxacin and amoxicillin is considerably used[56,76,8].

On lack of success of second-line therapy, the alternative treatment is decided considering the phenotypic susceptibility testing or genotypic resistance determination. An evidence-based recommendation involves a third-line therapy that includes medications that were not prescribed to the patient in either first or second-line therapies[56,35]. An effectual choice for a third-line therapy would be to either use bismuth-based levofloxacin quadruple therapy or rifabutin-consisting triple therapy consisting of Proton pump inhibitor along with rifabutin and amoxicillin. To completely eradicate the H. pylori infection, the Doctor must enquire about the previous history of the prescribed antibiotics and avoid the usage of the same therapy and recommend a higher dose of Proton pump inhibitor[56,76].

5.0 Failure of Antibiotics: Discovering Potential Drug Targets

Failure of currently available therapies is attributed to increasing antibiotic resistance worldwide, and there is an immediate need in identifying potential treatments. Identifying specific targets in H. pylori that are responsible for host-pathogen interactions, virulence factors etc., and developing specific drugs against them is one of the potential solutions. In doing so, it is important to understand the depth of structure and functions of the targets to develop drugs that are specific to them. This would lead to the effective eradication of the infection[46]. In this review, we have compiled the H.pylori proteins that can act as potential targets (Figure 2 and Table 1) and also given an insight into the phytochemicals that are effective against them.

5.1 Urease

There is an immense quantity of urease that is produced by H. pylori (almost about 10-15% of the whole protein by total weight) that are required in existence and pathogenicity. The urea is hydrolyzed into ammonia which negates the acidic conditions of the stomach and creates an inert

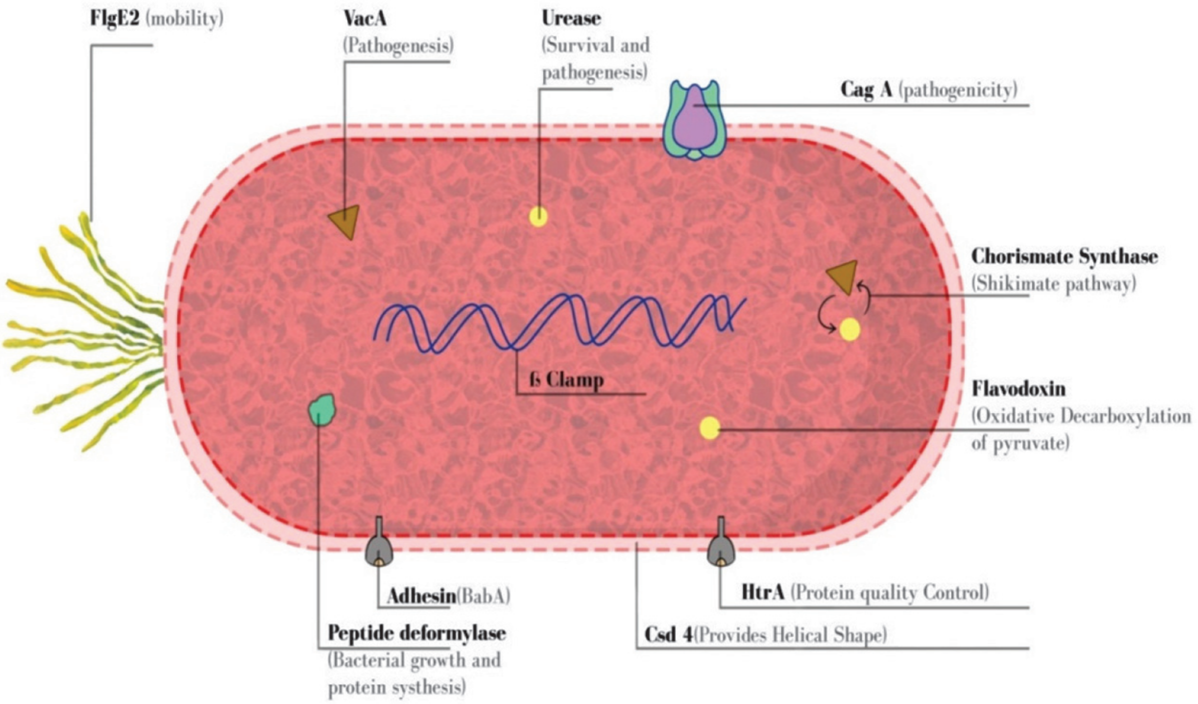

Figure 2: Pictorial representation of the potential drug targets in H. pylori

environment that encircles the bacteria in the gastric lumen. Generally, urease is present in the cytoplasm but on the impulsive breakdown of the bacterial cells, the enzyme adsorbs on the residual exterior bacteria. Both the enzymes are equally working, but the participation of the enzymes in both the place against the resistance towards acid in H. pylori has not been determined yet. The urease present in the cytoplasm is intended to shield the bacteria from acid. It is believed to increase the pH in the periplasm and membrane potential when combined with UreI which is a proton-gated channel. The urease present on the external surface is believed to be required for the existence of the organism that is vulnerable to acid. Urease consists of 238 amino acid residues and has a total molecular weight of 88.43kDa which possesses two subunits having a molecular weight of 61.7kDa (α-subunit) and 26.5kDa (β-subunit) respectively (Figure 3). The revelation of the urease structure has identified that the enzyme is complex in nature and has a diameter of 13nm

Table 1: Potential drug targets and their functions in H. pylori

	Target	Function	References
1.	Urease	Acclimation to low pH	(Ha et al., 2001)
2.	FlgE2	Hook Assembly	(Loconte et al., 2017)
3.	High-Temperature resistance A	Chaperone and proteolysis(intercellular adhesion cleavage)	(Zhang at al., 2019)
4.	Chorismate synthase	Shikimate pathway	(Ahn et al., 2004)
5.	Peptide Deformylase	Protein synthesis	(Dawood et al., 2016)
6.	Vacuolating cytotoxin A	Vacuolation of a cell, cell death and suppression of cell cycle, progress and immune response of the host.	(Zhang et al, 2019)
7.	BabA adhesin	Adherence to host cells	(Hage et al., 2015)
8.	Csd4	The helical shape of the bacterium	(Chan et al., 2014)
9.	Flavodoxins	Oxidative decarboxylation of pyruvate	Salillas and Sancho, 2020)
10.	β-Clamp bound to DNA Ligase peptide	β-Clamp	(Pandey et al, 2016)

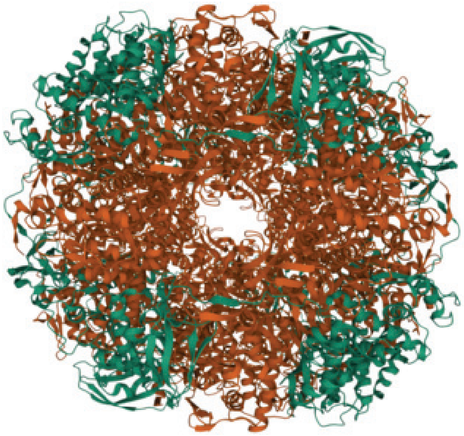

Figure 3: PDB Structure of Urease from H. pylori (DOI: 10.2210/pdb1E9Z/pdb)

having a threefold symmetry (Ha et al., 2001). Urease in H. pylori has been studied thoroughly and several drugs are targeted against it, including omeprazole, lansoprazole and rabeprazole (Juarez I et al., 2009).

5.2 FlgE2

H. pylori have a cluster of five to seven flagella which is at the polar end. This allows the bacterium to transport from the lumen of the stomach to the epithelium and promotes the survival of the bacterium in stressful conditions of the host such as an acidic environment prevailing in the stomach[68,15,50]. One flagellum consists of 30 distinct proteins which encode for the expression and 15 more that allow in the assembling process[68]. The flagellum is an intricate rotator nanomachine that consists of two important parts, the hook basal body and the extracellular filament. The hook basal body is differentiated into three portions, a base, a rod with ring structures and a hook. It is a flexible joint present on the surface of the bacterium and consists of 120 duplicates of the FlgE protein[68,45,30,65]. The basal hook acts as a connection between the filament and the export system. The genes, hp0870 and hp0908 encode for the FlgE protein in H. pylori and these proteins are assigned as FlgE1 and FlgE2 respectively. Even though there are no findings available to date, it is believed that FlgE2 helps in the assembling of the hook (Loconte et al., 2017) (Parkhill J et al., 2000). The HpFlgE2 consists of 605 amino acids and has a molecular weight of 66kDa and has an antibacterial recognition site along with H-antigens that are present at the protruding domains (Figure 4). This factor makes the protein act as a possible vaccine target for a supposed immunological therapy (Loconte et al., 2017) (Rossez Y et al., 2015).

5.3 HtrA

Recently, a new virulence factor was identified called High-temperature requirement A in H. pylori which can penetrate the gastric epithelium by breaking the proteins present in the epithelial tight junction (occluding and claudin-8) and adherens junction (E-cadherin)[64,77]. HtrAconsists of 465 amino acids and has a molecular weight of 53.15kDa (Figure 5). The HtrA proteases consist of an N-terminal signal peptide, a trypsin-like serine protease core domain, a C-terminal PDZ postsynaptic density protein (PSD95), Drosophila disc large tumour suppressor (Dlg1), a zonula occludens-1 protein domains (zo-1)[77]. The HtrA family proteases are stringently active in the periplasm and have an important role in protein quality control[77,13].

Figure 4: PDB structure of FlgE2 from H. pylori I (DOI: 10.2210/pdb5NPY/pdb)

Figure 5: PDB structure of HtrA from H. pylori (DOI: 10.2210/pdb5Y2D/pdb)

5.4 Chorismate synthase

In the Shikimate pathway, 5-enolpyruvylshikimate3-phosphate is converted to chorismate by the enzyme Chorismate synthase and this acts as a leading target in developing antimicrobial compounds and herbicides. The Chorismate acts like a basic precursor in synthesizing aromatic amino acids and plenty of other aromatic components in plants and microorganisms[22,51]. The enzyme consists of 365 amino acids and has a molecular weight of 160.62kDa (Figure 6). It is tetrameric in nature and each monomer consists of a unique "β-α-β sandwich fold"[22,1]. Chorismate synthase needs a reduced FMN as a cofactor and has an extremely preserved region that includes multiple flexible loops that gather around the bound FMN that leads to the formation of an active site[22].

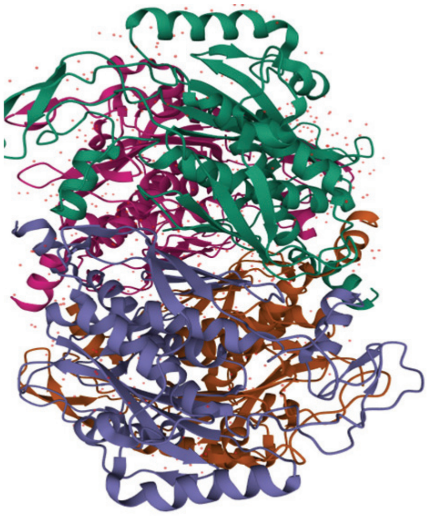

Figure 6: PDB structure of Chorismate synthase from H.pylori (DOI: 10.2210/pdb1UMF/pdb)

5.5 Peptide deformylase

Peptide deformylase is an enzyme that helps in the growth of bacteria and protein synthesis and is one of the new emergent drug targets in H. pylori. In prokaryotes as well as eukaryotes, N-formylmethionylt-RNAi brings about protein synthesis, hence giving rise to an N-terminus expression of every new protein. Amid the extension of the polypeptide chain, the formyl group of the N-terminus is detached due to the catalytic activity of the peptide deformylase. Hence, it finds importance in the bacterial growth and repression of the same induces anti-H. pylori activity[36]. Peptide deformylase consists of 181 amino acids and has a molecular weight of 21.07 kDa (Figure 7). It is present in the human body as well but has no effect on protein synthesis and therefore it can act as a particular target in developing an anti-H. pylori drug[36,59].

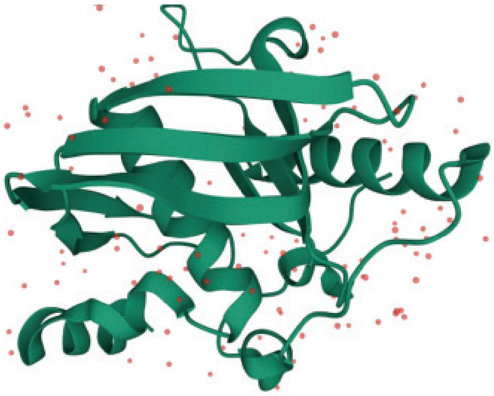

Figure 7: PDB structure of Peptide Deformylase from H.pylori (DOI: 10.2210/pdb2EW7/pdb)

5.6 VacA

Vacuolating cytotoxin A (VacA) is among the most important constituent for inducing virulence and is responsible for eliciting diseases caused by H. pylori[77,52]. VacA is secreted as a toxin that evokes intracellular vacuolation, multiple cellular effects that include depolarization, autophagy and inhibition of T-cell proliferation[77,24,71,79]. VacA consists of 821 amino acids and the total molecular weight is 530.78kDa. Each VacA protomer has a molecular weight of 88k Da and possesses two functional domains, an N-terminal p33 domain and a C-terminal p55 domain (Figure 8). Both these domains are connected with the help of a flexible loop and this is sensitive to limited proteolysis in vitro. The p33 and the p55 domains are responsible for the pore-forming activity and binding to the receptor respectively, in the host cells. To accomplish vacuolation effectively, the whole p33 domain and 111 amino acid residues of the N-terminal from the p55 domain are needed[77]. On secretion, the VacA gathers into a hydrophilic, having either a layer or two with flower-shaped oligomers,

Figure 8: PDB structure of VacA from H. pylori (DOI: 10.2210/pdb6NYF/pdb)

where each layer consists of six or seven copies of protomers[17,11].

5.7 Adhesin BabA

The blood group antigen-binding adhesin (BabA) is one of the superiorly described adhesion proteins in the bacteria. It consists of two domains; one is an N-terminal extracellular host-binding domain and the other one is a C-terminal outer membrane-running domain that is believed in forming a ?-barrel shape which is analogous to the familiar porins[38,37,55,72]. BabA has 543 amino acids and a molecular weight of 58.49kDa (Figure 9). The majority of the pathogens encode the adhesin and this helps in the colonization and virulence of the bacteria. BabA binds to the fucosylatedhisto-blood group antigens that are present on the gastric epithelial cells and mucin of the H. pylori[38].

Figure 9: PDB structure of Adhesin BabA from H. pylori (DOI: 10.2210/pdb4ZH0/pdb)

5.8 Csd4

The motion of the bacterium relies on colonization, which is aided by the helical shape. The cross-linking inactivity or clipping of murein influences the helical shape of H. pylori[4,63]. Csd4 is a hydrolase that establishes the shape of the cell in H. pylori. It requires Zinc ions as a cofactor and breaks the bond that links between γ-D-Glu and mDAP of the non-cross-linked muramyl tripeptide of the peptidoglycan that yields muramyldipeptide and mDAP. Csd4 consists of 439 amino acids and has a molecular weight of 55.43kDa (Figure 10). It possesses 3 domains: the first domain consists of an N-terminal D, L carboxypeptidase domain has a usual Carboxypeptidase fold, the second domain consists of a central β-barrel domain possessing a unique fold and the third domain consists C-terminal immunoglobulin-like domain[4]. Initially, the D, L-carboxypeptidase identifies the substrate by interacting with mDAP section of the muramyltripeptide and undergoes significant changes in its structural configuration[4,23]. Csd4 can act as a drug target as the action against the same can inhibit colonization of the bacterium.

Figure 10: PDB structure of Csd4 from H. pylori (DOI: 10.2210/pdb4WCM/pdb)

5.9 Flavodoxins

Flavodoxins are proteins that are acidic in nature and consist of cofactors like flavin mononucleotide (FMN), and participate in the electron transfer reactions[57]. They consist of 165 amino acids and have a molecular weight in the range of 14.5-23kDa (Figure 11). Five α-helices stack centrally to a five-stranded β-sheet leading to the formation of an αβαsandwich. The gene fldA codes for flavodoxin protein. They are categorized into two types: long-chain having a molecular weight in the range of 18-23kDa and short-chain flavodoxins having a molecular weight in the range of 14.5-17kDa. The flavodoxin present in H. pylori finds importance in the metabolic pathway (oxidative decarboxylation of pyruvate by pyruvate oxidoreductase complex) that is essential for viability. Flavodoxin from H. pylori contributes

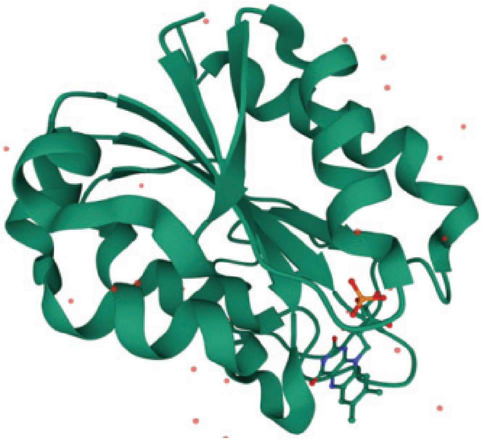

Figure 11: PDB Structure of Flavodoxin from H.pylori (Doi: 10.2210/pdb1FUE/pdb)

to the pathogenesis of low-level gastric mucosa-associated lymphoid tissue (MALT) lymphoma. In the absence of oxygen, imidazole antimicrobials are converted into reactive species that can damage the DNA[57]. Therefore, developing a drug against flavodoxin can avoid life-threatening pathological diseases.

5.10 β-Clamp bound to DNA Ligase peptide

The β-clamp is a protein complex having a ring-shaped structure that enfolds the DNA by using a clamp loader on the expenditure of ATP that moves throughout the length of the DNA. Since the sliding clamp has the potential to slide along, it is the requirement for several varieties of enzymes for the replication and repair of DNA[48,74]. The β-clamp consists of 347 amino acids and has a molecular weight of 42.51kDa (Figure 12). Each unit of β-clamp has 3 domains and I, II, and III domains consist of Met1to Phe118, Pro119 to Pro250, and Lys251 to Leu374 amino acid residues respectively. The first domain consists of 9 anti-parallel β sheets and 2 α-helices, a second domain consists of 8 β-sheets and 2 α-helices and the third domain consists of 8 β-sheets and 2 α-helices[48]. Clamps function by increasing the activity of the enzymes that take part in the replication of DNA and also act as a spot for adherence that directs the function of the enzyme. Therefore, clamps help the enzyme hold the DNA tightly and also facilitate the movement along with the same. Every clamp binding protein known till now consists of preserved sequences of peptides that help in communicating with the clamp. In Prokaryotes as well as eukaryotes the clamp-binding motif consists of residues of hydrophobic amino acids which attach to the hydrophobic pocket in the C-terminal portion of the clamp. Even though β-clamp belongs to the holoenzyme of DNA polymerase III, there is no permanent attachment between them[48]. The β-clamp loads on the DNA by using a clamp loader which is a subunit of DNA Pol III. The β-clamp interacts with the DNA ligase and favours the maturation of Okazaki fragments and is also required for DNA repair. Therefore, by developing drugs against β-clamp the replication of DNA and henceforth the growth of H. pylori can be inhibited[48].

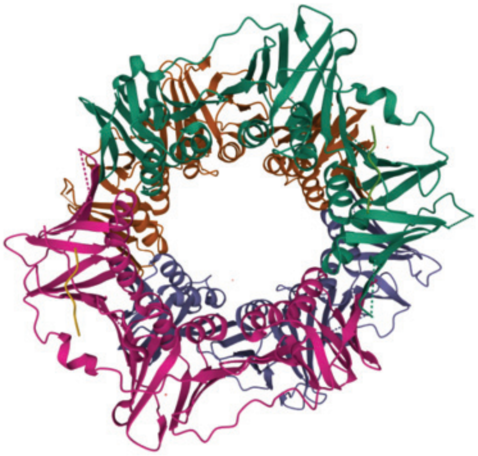

Figure 12: PDB Structure of ?-clamp bound to DNA ligase peptide from H. pylori (Doi: 10.2210/pdb5FRQ/pdb)

6.0 New Drug Targets: Targetting Metabolic Pathways

6.1 Protein metabolism

The metabolism of purine nucleotides is one of the growth-confining steps in prokaryotes as well as eukaryotes. H. pylori synthesize purine nucleotides by salvage pathway as like other microorganisms; they are unable to produce nucleotides by de-novo pathway[46,32,62]. Important enzymes present in the salvage pathway for purines are Purine nucleoside phosphorylase (PNP) and adenylosuccinate synthetase (AdSS). Purine nucleoside phosphorylases along with orthophosphate catalyze reversible phosphorolytic cleavage of the glycosidic bond of purine nucleosides[46]. Formycin A is a good inhibitory compound against PNP and it can act as a good lead component to synthesize further potential inhibitors this needs to be tested in vivo. Adenylosuccinatesynthetases catalyze the condensation of inosine-5'-monophosphate along with L-aspartate into adenylosuccinate. Hadacidinis a naturally found antibiotic that is analogous to L-aspartate that can act as an inhibitor against AdSS[46,66]. IMPDH found in bacteria is a component found in the synthesis of the purine nucleotide pathway and can act as a possible drug target against microorganisms, that are resistant to multiple drugs like Cryptosporidium parvum or Mycobacterium tuberculosis. The enzyme, IMPDH oxides IMP into xanthosine 5?-monophosphate followed by further reactions that convert GMP into nucleotides which form DNA and RNA[46] (Figure 13).

6.2 Metabolic Pathway Encompassing MTAN

MTAN also abbreviated as 5'-methylthioadenosine/S-adenosylhomocysteine nucleosidase is an enzyme that catalyses the hydrolysis of three distinct adenosyl by-products, leading it to be an important step in the metabolic activities of the bacteria. 5'-methylthioadenosine (MTA), 5'-deoxyadenosine and AdoHcy are obtained from S-adenosyl-methionine (AdoMet) on the synthesis of polyamines, AdoMet radical reactions, and by AdoMet-dependent methylation reactions, respectively. The products obtained from MTAN reaction are straightaway fed into the salvage pathway producing methionine and purine. Adenine, methionine and

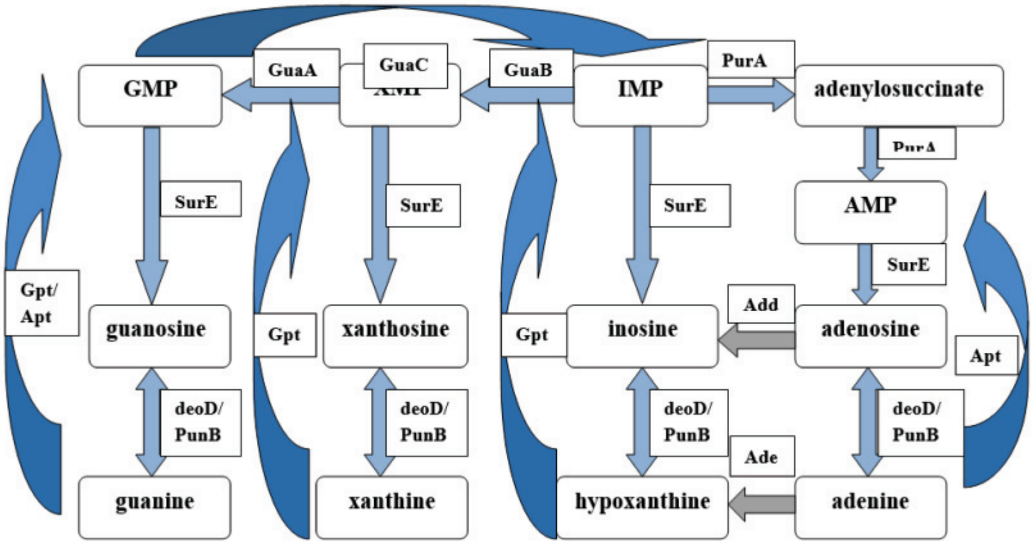

Figure 13: The salvage pathway for synthesis of purine nucleotides in H. pylori. Acronyms: GuaB, IMP dehydrogenase; GuaA, GMP synthetase; GuaC, GMP reductase; PurA, adenylosuccinate synthetase; PurB, adenylosuccinate lyase; Gpt, hypoxanthine-guanine phosphoribosyl-transferase; Apt, adenine phosphoribosyl-transferase; SurE, 5' nucleotidase; deoD, gene encoding purine nucleoside phosphorylase; PunB, purine nucleoside phosphorylase; Ade, adenine deaminase; Add, adenosine deaminase; IMP, inosine monophosphate; XMP, xanthosine monophosphate; GMP, guanosine monophosphate; AMP, adenosine monophosphate (RoszczenkoJasinska et al., 2020).

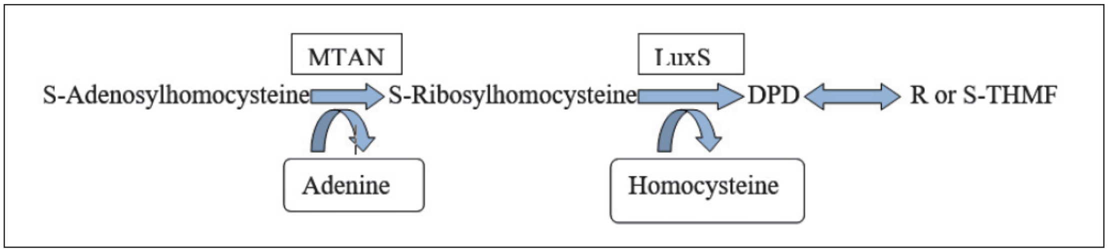

Figure 14: Pathway specifying MTAN. These reactions depict the degeneration of AdoHcyafterAdoMet is utilized as a donor of methyl ions generally.

AdoMet are expensive in terms of energy while being synthesized by de novo pathway and henceforth, bacteria produce these metabolites with the help of the salvage pathway. The unsuitable assemblage of the MTAN substrates facilitates the feedback inhibition of AdoMet-dependent methyltransferases, proteins taking part in the polyamine biosynthetic pathway and the AdoMet-radical dependent biotin synthase, respectively. AdoMet-dependent methyl-transferases modify all other biologically active polymers such as DNA, RNA, proteins and sugars[69] (Figure 14).

7.0 Phytomedicines as a Treatment for H. Pylori Infection

H. pylori are known to cause pathological disorders like chronic gastritis, peptic ulcer, gastric carcinoma and MALT lymphoma. Several antibiotics are prescribed against the bacteria. They fail to eradicate the infection as the host suffers from a high rate of antibiotic resistance and related side-effects. All this has led to the development of a substitute that utilizes naturally available compounds. Even though there are prescribed third-line therapies, large parts of society are not able to afford the expense of acid suppressors and gastric protectors. The usage of natural components has gained immense prevalence due to their immeasurable side effects and toxicity[6]. Conventionally used therapies including the usage of traditional Chinese medicine (TCM), represents a method in utilizing plants to fight diverse illness. Most of the valuable medicinal plants have been tested against H. pylori to determine their efficiency in eradicating the infection (RoszczenkoJasinska et al., 2020).

Extracts from plants such as Carum carvi, Xanthium brasilicum, and Trachyspermumcopticumhave shown bactericidal properties when tested towards 10 disease-causing strains of H. pylori. Natural compounds from

Cuminum cyminum and propolis, when extracted, using ethanol, have revealed the inhibition of the bacteria in vitro, thereby they can be reviewed in treating H. pylori infections which is safe and has the least side effects. Plants utilized in Brazilian culture and traditional medicine for treating gastrointestinal issues were analyzed for their bactericidal effects, and Bixaorellana, Chamomilla recutita, Ilex paraguariensis, and Malva sylvestris were the species which was efficient against eradicating H. pylori. Certain biologically active components were examined to check their anti-H. pylori efficiency, such as Allium sativum (cloves), Convolvulus austro-aegyptiacu (aerialparts), Glycyrrhiza glabra (roots), Hydrastis canadensis (rhizomes), Sanguinaria canadensis (rhizomes), and Tinosporasagittata (aerial parts) species. An alkaloid called Berberine which is a benzylisoquinoline alkaloid, isolated from Hydrastis canadensis, demonstrated a very low minimum inhibitory concentration (0.78 µg/mL) and henceforth can act as the most efficient biologically active component, thereafter diallyl tetrasulfide (3-6 µg/mL), allicin (4 µg/mL), and palmatine (3.12-6.25 µg/mL) isolated from Allium sativum and Tinospora sagittate, respectively[6] (Table 2).

Table 2: Phytomedicines having antagonistic activity against H. pylori

	Plant species	Part of the plant used	Antagonistic activity against H. pylori	References
1.	Acacia nilotica (L.) Delile	Flower	MIC = 8-64 µg/mL	(Salehi et al., 2018) (Amin M et al., 2013)
2.	Bixa orellanaL	Seed	MIC≤625-1250 µg/mL	(Salehi et al., 2018) (Cogo L.L et al., 2010)
3.	Calotropis procera (Aiton) W.T.Aiton	Leaf Flower	MIC=16-256 µg/mL MIC=8-256 µg/mL	(Salehi et al., 2018) (Amin M et., 2013)
4.	Carum carvi L.	Seed	IZD=12±0 mm (500 µg/disc), MIC=0.3 µL/mL; IZD=24.8 mm	(Salehi et al., 2018) (Bergonzelli G.E et al., 2003) (Hosseininejad Z et al., 2011)
5.	Chamomilla recutita (L.) Rauschert	Inflorescence	MIC≤625 µg/mL	(Salehi et al., 2018) (Cogo L.L et al., 2010)
6.	Citrus reticulate Blanco	Fruit peel	MIC=100 µg/mL	(Salehi et al., 2018) (Li Y et al., 2005)
7.	Cocculus hirsutus (L.) Diels.	Leaf	IZD=22 mm (200-1000 µg/mL)	(Salehi et al., 2018) (Poovendran P et al., 2011)
8.	Convolvulus austro-aegyptiacu Abdallah and Saad	Aerial part	MIC=100-200 µg/mL	(Salehi et al., 2018) (Awaad A.S et al., 2015)
9.	Coriandrum sativum L.	Seeds	IZD=9 mm; MIC=1.25-5 mg/mL	(Salehi et al., 2018) (Nostro A et al., 2005)
10.	Cuminum cyminum L (Ethanolic extracts).	Seeds	ZD=14 mm; MIC=0.075-0.6mg/mL	(Salehi et al., 2018) (Nostro A et al., 2005)
11.	Cyrtocarpaprocera Kunth	Bark of the plant	MIC=25 µg/mL MIC=250 µg/mL	(Salehi et al., 2018) (Hinojosa W.I et al., 2012)
12.	Elettaria cardamomum (L.) Maton.	Seed	IZD<9 mm	(Salehi et al., 2018) (Nostro A et al., 2005)
13.	Eugenia caryophyllata Thunb	Flowers	MIC=60 µg/mL	(Salehi et al., 2018) (Li Y et al., 2005)
14.	Foeniculum vulgare Mill. var. dulce DC	Seed	IZD<9 mm; MIC=5-10 mg/mL	(Salehi et al., 2018) (Nostro A et al., 2005)
15.	Geumiranicum Khatamsaz	Root	IZD=24-35 mm (100 µg/mL)	(Salehi et al., 2018) (Shahani S et al., 2012)
16.	Glycyrrhiza glabra L. (roots) Licoricidin	Root	6.25-12.5 µg/mL	(Salehi et al., 2018) (Fukai T et al., 2002)

	Plant species	Part of the plant used	Antagonistic activity against H. pylori	References
17.	Hydrastis CanadensisL.	Rhizome	0.78-25 µg/mL	(Salehi et al., 2018) (Mahady G.B et al., 2003)
18.	Ilex paraguariensisA. St.-Hil.	Roasted leaf	MIC≤625-5000 µg/mL	(Salehi et al., 2018) (Cogo L.L et al., 2010)
19.	Malva sylvestrisL.	Leaf and inflorescence	MIC≤625-5000 µg/mL	(Salehi et al., 2018) (Cogo L.L et al., 2010)
20.	Mirabilis jalapaL.	Aerial part	MIC=250 µg/mL	(Salehi et al., 2018) (Juarez I et al., 2009)
21.	OcimumbasilicumL.	Aerial part	IZD=9±0.3 mm (500 µg/disc) IZD=8±0.5 mm (500 µg/disc)	(Salehi et al., 2018) (Juarez I et al., 2009)
22.	Origanum vulgare l.	Leaf	IZD=19±4 mm (500 µg/disc)	(Salehi et al., 2018) (Juarez I et al., 2009)
23.	Prunus avium L.	Stalk	IZD=9 mm; MIC=5-10 mg/mL	(Salehi et al., 2018) (Nostro A et al., 2005)
24.	Rosmarinusofficinalis L.	Leaf	IZD<9 mm	(Salehi et al., 2018) (Nostro A et al., 2005)
25.	Sanguinaria canadensis L.Sanguinarine	Rhizome	6.25-50 µg/mL	(Salehi et al., 2018) (Mahady G.B et al., 2003)
26.	Thymus serpyllum L.	Aerial part	IZD=10 mm; MIC=1.25-10 mg/mL	(Salehi et al., 2018) (Nostro A et al., 2005)
27.	TinosporasagittataGagnep.	Aerial part	MIC/MBC=6250 µg/mL	(Salehi et al., 2018) (Rong Q et al., 2016
28.	Tinosporasagittata Gagnep.Palmatine	Aerial part	3.12-6.25 µg/mL	(Salehi et al., 2018) (Rong Q et al., 2016)
29.	Trachyspermumcopticum	Aerial part	MIC=31.25-250 µg/mL	(Salehi et al., 2018) (Nariman F et al., 2009) (Juarez I et al., 2009)
30.	Xanthium brasilicum	Aerial part	MIC=31.25-250 µg/mL	(Salehi et al., 2018) (Nariman F et al., 2004) (Nariman F et al., 2009)

8.0 References

1. Albert, A., Martinez-Ripoll, M., Espinosa-Ruiz, A., Yenush, L., CulianezMacia, F. A. and Serrano, R.,(2000): The X-ray structure of the FMN-binding protein AtHal3 provides the structural basis for the activity of a regulatory subunit involved in signal transduction. Structure, 8, 961-969.
2. Alm R A., Ling LS, Moir DT., et al., (1999): Genomic sequence comparison of two unrelated isolates of the human gastric pathogen Helicobacter pylori. Nature 1999; 397:176-80
3. Amin M., Anwar F., Naz F., Mehmood T., Saari N., (2013): Anti-Helicobacter pylori and urease inhibition activities of some traditional medicinal plants. Molecules 2013, 18, 2135-2149
4. Anson C. K. Chan., Kris M. Blair., Yanjie Liu., EmilisaFrirdich., Erin C. Gaynor., Martin E. Tanner., Nina R. Salama., and Michael E. P. Murphy., (2014): Helical Shape of Helicobacter pylori requires an A typical Glutamine as a Zinc Ligand in the Carboxypeptidase Csd4. JBC Vol. 290, No. 6, pp. 3622-3638.
5. Awaad A.S., Al-Rifai, A.A., El-Meligy, R.M., Alafeefy, A.M., Zain, M.E., (2015): New Activities for Isolated Compounds from Convolvulus austro-aegyptiacus as Anti-ulcerogenic, Anti-Helicobacter pylori and Their Mimic Synthesis Using Bio-guided Fractionation.
6. Bahare Salehi., FarukhSharopov., Miquel Martorell., Jovana Rajkovic., Adedayo OluwaseunAdemiluyi., Mehdi Sharifi-Rad., Patrick ValereTsouhFokou., Natália Martins., Marcello Iriti., and Javad Sharifi-Rad., (2018): Phytochemicals in Helicobacter pylori Infections: What Are We Doing Now?
7. Bergonzelli G.E., Donnicola D., Porta N., Corthésy-

Theulaz I.E., (2003): Essential Oils as Components of a Diet-Based Approach to Management of Helicobacter Infection. Antimicrob. Agents Chemother. 47, 3240–3246.

8. Bjorkman DJ., Steenblik M., Best Practice Recommendations for Diagnosis and Management of Helicobacter pylori synthesizing the Guidelines. Dec; 15(4):648-659.
9. Castillo-Juarez I., Gonzalez V., Jaime-Aguilar H., Martinez G., Linares E., Bye R., Romero I., (2009): Anti-Helicobacter pylori activity of plants used in Mexican traditional medicine for gastrointestinal disorders. *J. Ethnopharmacol*. 122, 402–405.
10. Censini, S. et al., (1996): Cag pathogenicity island of Helicobacter pylori, encodes type I-specific and disease-associated virulence factors. Proc. Natl Acad. Sci. USA 93, 14648–14653.
11. Chambers MG, et al., (2013): Structural analysis of the oligomeric states of Helicobacter pyloriVacA toxin. *J Mol Biol* 425:524–535.
12. Cheng-Yen Kao., BorShyangSheu., Jiunn Jong Wu., (2016): Helicobacter pylori infection: An overview of bacterial virulence factors and pathogenesis. *Biomedical journal* 39 (2016) 14-23.
13. Clausen T., Kaiser M., Huber R., and Ehrmann M., (2011): HTRA proteases: regulated proteolysis in protein quality control. *Nat. Struct. Mol. Biol.* 12, 152-162.
14. Cogo L.L., Monteiro C.L.B., Miguel M.D., Miguel O.G., Cunico M.M., Ribeiro M.L., de Camargo E.R., Kussen G.M.B., Nogueira K.d.S., Costa L.M.D., (2010): Anti-Helicobacter pylori activity of plant extracts traditionally used for the treatment of gastrointestinal disorders. *Braz. J. Microbiol.* 41, 304–309.
15. Danielli A and Scarlato V., (2010): Regulatory circuits in Helicobacter pylori: network motifs and regulators involved in metal-dependent responses. FEMS Microbiol Rev 34, 738–752.
16. Donald R. Ronning., Natalie M. Iacopelli., and Vidhi Mishra., (2010): Enzyme–Ligand interactions that drive active site rearrangements in the Helicobacter pylori 5'methylthioadenosine/S-adenosylhomocysteine nucleosidase.
17. Escobedo-Hinojosa W.I., Del Carpio J.D., Palacios-Espinosa J.F., Romero I., (2012): Contribution to the ethno pharmacological and anti-Helicobacter pylori knowledge of Cyrtocarpaprocera Kunth (Anacardiaceae). *J. Ethnopharmacol.* 143, 363–371.
18. Falush D., Kraft C., Taylor NS., et al. (2001): Recombination and mutation during long-term gastric colonization by Helicobacter pylori: estimates of clock rates, recombination size, and minimal age. Proc Natl Acad Sci U S A; 98:15056-61.
19. Fukai T., Marumo A., Kaitou K., Kanda T., Terada S., Nomura T., (2002): Anti-Helicobacter pylori flavonoids from licorice extract. Life Sci. 71, 1449–1463.
20. Heuermann D., and R. Haas., (1995); Genetic organization of small cryptic plasmid of Helicobacter pylori. Gene 165:17–24.
21. Hosseininejad Z., Moghadam S.D., Ebrahimi F., Abdollahi M., Zahedi M.J., Nazari M., Hayatbakhsh M., Adeli S., Sharififar F., (2011): In vitro screening of selected Iranian medicinal plants against Helicobacter pylori. *Int. J. Green Pharm*. 5, 282–285.
22. Hyung Jun Ahn., Hye Jin Yoon., Byung Il Lee and Se Won Suh., (2004): Crystal Structure of Chorismate Synthase: A Novel FMN-binding Protein Fold and Functional Insights. *J. Mol. Biol.* 336, 903–915.
23. Hyoun Sook Kim., Jieun Kim., Ha Na Im., Doo Ri An., Mijoon Lee., DusanHesek., Shahriar Mobashery., Jin Young Kim., Kun Cho., Hye Jin Yoon., Byung Woo Han., Byung Il Leef and Se Won Suhb., (2014): Structural basis for the recognition of muramyl tripeptide by Helicobacter pylori Csd4, a D, L-Carboxypeptidase controlling the helical cell shape. ActaCryst. D70, 2800–2812.
24. Jain P., Luo Z-Q., Blanke SR., (2011): Helicobacter pylori vacuolating cytotoxin A (VacA) engages the mitochondrial fission machinery to induce host cell death. Proc Natl AcadSci USA 108:16032–16037.
25. Johannes G. Kusters., Arnoud H. M. van Vliet., and Ernst J. Kuipers., (2006): Pathogenesis of Helicobacter pylori Infection. p. 449–490.
26. Kaiming Zhang., Huawei Zhang., Shanshan Li., Grigore D. Pintilie., Tung-Chung Mou., Yuanzhu Gao., Qinfen Zhang., Henry van den Bedem., Michael F. Schmid., Shannon Wing Ngor Au., and Wah Chiu., (2019): Cryo-EM structures of Helicobacter pylori vacuolating cytotoxin A oligomeric assemblies at near-atomic resolution. PNAS 116 (14) 6800-6805.
27. Kansau I., J. Raymond., E. Bingen., P. Courcoux., N. Kalach., M. Bergeret., N. Briami., C. Dupont., and A. Labigne., (1996): Genotyping of Helicobacter pylori isolates by sequencing of PCR products and comparison with the RAPD technique. Res. Microbiol. 147:661–669.
28. Kris M. Blair., Kevin S. Mears., Jennifer A. Taylor., Jutta Fero., Lisa A. Jones., Philip R. Gafken., John C. Whitney., Nina R. Salama., (2021): The Helicobacter pylori cell shape promoting protein Csd5 interacts with the cell wall, MurF, and the bacterial cytoskeleton.
29. Kusters J. G., M. M. Gerrits., J. A. Van Strijp., and C. M. Vandenbroucke Grauls., (1997): Coccoid forms of Helicobacter pylori are the morphologic manifestation of cell death. Infect.Immun. 65:3672–3679.
30. Lertsethtakarn P., Ottemann KM and Hendrixson DR., (2011): Motility and chemotaxis in Campylobacter and Helicobacter. Annu Rev Microbiol 65, 389–410.
31. Li Y., Xu C., Zhang Q., Liu J.Y., Tan R.X., (2005): In vitro anti-Helicobacter pylori action of 30 Chinese herbal medicines used to treat ulcer diseases. *J. Ethnopharmacol*. 98, 329–333.
32. Liechti G., Goldberg JB., (2012): Helicobacter pylori rely primarily on the purine salvage pathway for purine

nucleotide biosynthesis. *J Bacteriol* 194:839–854.

33. Mahady G.B., Pendland S.L., Stoia A., Chadwick L.R., (2003): In vitro susceptibility of Helicobacter pylori to isoquinoline alkaloids from Sanguinaria canadensis and Hydrastis canadensis. *Phytother*. Res. 17, 217–221.
34. Malaty HM., Graham DY., (1994): Importance of childhood socioeconomic status on the current prevalence of Helicobacter pylori infection. 35:742-5.
35. Malfertheiner P., Megraud F., O'Morain CA., et al., (2017): Management of Helicobacter pylori infection the Maastricht V/Florence Consensus Report. Jan; 66(1):6-30.
36. Muhammad Dawood., Nighat Fatima., Amara Mumtaz., Sidra Rehman., IrumShazadi., Qaisar Mahmood and Syed Aun Muhammad., (2016): Molecular Docking Studies of Sesquiterpenoids against Helicobacter pylori Peptide Deformylase. BJPR. 10(3): 1-7.
37. N. Hage., J. G. Renshaw., G. S. Winkler., P. Gellert., S. Stolnik., F. H. Falcone., (2015): Improved expression and purification of the Helicobacter pylori adhesin BabA through the incorporation of a hexa lysine tag. Protein Expr. Purif. 106, 25–30.
38. NaimHage., Tina Howard., Chris Phillips., Claire Brassington., Ross Overman., JuditDebreczeni., Paul Gellert., Snow Stolnik., G. Sebastiaan Winkler., Franco H. Falcone., (2015): Structural basis of Lewis^{b}antigen binding by the Helicobacter pylori adhesin BabA. Sci. Adv. 1:e1500315.
39. Nam Chul Ha., Sang Taek Oh., Jae Young Sung., Kyeung Ah Cha., (2001): Mann Hyung Lee and Byung Ha Oh., Supramolecular assembly and acid resistance of Helicobacter pylori urease.
40. Nariman F., Eftekhar F., Habibi Z., Falsafi T., (2004): Anti-Helicobacter pylori activities of six Iranian plants. 9, 146–151.
41. Nariman F., Eftekhar F., Habibi Z., Massarrat S., Malekzadeh R., (2009): Antibacterial activity of twenty Iranian plant extracts against clinical isolates of Helicobacter pylori. Iran. J. Basic Med. Sci. 12, 105–111.
42. Nostro A., Cellini L., Bartolomeo S.D., Campli E.D., Grande R., Cannatelli M., Marzio L., Alonzo V., (2005): Antibacterial effect of plant extracts against Helicobacter pylori. Phytother. Res. 19, 198–202.
43. O'Morain NR., Dore MP., O'Connor AJP., Gisbert JP., O'Morain CA., (2018): Treatment of Helicobacter pylori infection. 23:1–9.
44. Parkhill J., Wren B., Mungall K., Ketley JM., Churcher C., Basham D., Chilling worth T., Davies RM., Feltwell T., Holroyd S et al., (2000): The genome sequence of the food borne pathogen Campylobacter jejuni reveals hypervariable sequences. *Nature* 403, 655–668.
45. Paul K., Gonzalez-Bonet G., Bilwes AM., Crane BR and Blair D., (2011): Architecture of the flagellar rotor. *EMBO J* 30, 2962–2971.
46. Paula RoszczenkoJasiñska., Marta Ilona Wojtyœ., El¿bieta K., Jagusztyn Krynicka. (2020): Helicobacter pylori treatment in the post-antibiotics era – searching for new drug targets. Appl. Microbiol.104:9891–9905.
47. Poovendran P., Kalaigandhi V., Poongunran E., (2011): Antimicrobial activity of the leaves of Cocculus hirsutus against gastric ulcer producing Helicobacter pylori. *J. Pharm. Res.* 4, 4294–4295.
48. Preeti Pandey., Vijay Verma., Gunjan Gautam., Nilima Kumari., Suman Kumar Dhar., SamudralaGourinath., (2017): Targeting the β-clamp in Helicobacter pylori with FDA-approved drugs reveals micromolar inhibition by diflunisal.
49. Preeti Pandey., Khaja Faisal Tarique., Mohit Mazumder., Syed Arif Abdul Rehman., Nilimakumari and SamudralaGourinath., (2016): Structural insight into β-Clamp and its interaction with DNA Ligase in Helicobacter pylori.
50. Pulic I., Loconte V and Zanotti G., (2014): Structural characterization at the atomic level of a molecular nano machine: the state of the art of Helicobacter pylori flagellum organization. *Am J BiochemBiotechnol* 10, 143-161.
51. Roberts F., Roberts C. W., Johnson, J. J., Kyle, D. E., Krell T., Coggins J. R., et al., Evidence for the shikimate pathway in apicomplexan parasites. *Nature,* 393, 801-805.
52. Roesler BM., Rabelo Gonçalves EMA., Zeitune JMR., (2014): Virulence factors of Helicobacter pylori: A review. Clin Med Insights Gastroenterol 7:9–17.
53. Rong Q., Xu M., Dong Q., Zhang Y., Li Y., Ye G., Zhao L., (2016): In vitro and in vivo bactericidal activity of Tinosporasagittata and its main effective component, palmatine, against porcine Helicobacter pylori. BMC Complement. Altern. Med. 16, 331.
54. Rossez Y., Wolfson EB., Holmes A., Gally DL and Holden NJ., (2015): Bacterial flagella: twist and stick, or dodge across the kingdoms. PLoSPathog 11, 1004483.
55. S. Subedi., K. Moonens., E. Romão., A. Lo G. Vandenbussche., J. Bugaytsova., S. Muyldermans., T. Borén., H. Remaut., (2014): Expression, purification and X-ray crystallographic analysis of the Helicobacter pylori blood group antigen-binding adhesin BabA. Acta Crystallogr. F Struct.Biol. *Commun*. 70, 1631–1635.
56. Samantha Flores *Treviño*., Soraya Mendoza Olazarán., Paola BocanegraIbarias., Héctor Jesús Maldonado Garza and Elvira Garza González., (2018): Helicobacter pylori drug resistance: therapy changes and challenges. Expert Review of Gastroenterology & Hepatology.
57. Sandra Salillas and Javier Sancho., (2020): Flavodoxins as Novel Therapeutic Targets against Helicobacter pylori and Other Gastric Pathogens. *Int. J. Mol. Sci.* 21, 1881.
58. Sandra Salillas., Miriam Alías., Valérie Michel., Alejandro Mahía., Ainhoa Lucía., Liliana Rodrigues., Jessica Bueno., Juan José GalanoFrutos., Hilde De Reuse., Adrián Velázquez Campoy., José Alberto Carrodeguas., Carlos Sostres., Javier Castillo., José Antonio Aínsa.,

María Dolores Díaz de-Villegas., ÁngelLanas., ElietteTouati., Javier Sancho., (2019): Design, Synthesis and Efficacy testing of nitroethylene and 7-nitrobenzoxadiazol-based flavodoxin inhibitors against Helicobacter pylori drug resistant clinical strains and in Helicobacter pylori infected mice.

59. Saravanakumar K., Chellia R., Hu X., Kathiresan K., Oh D-H., Wang M-H., (2019): Eradication of Helicobacter pylori through the inhibition of urease and peptide deformylase: Computational and biological studies, Microbial Pathogenesis.
60. Sebastian Suerbaum M.D., and Pierre Michetti M.D., (2002): Helicobacter pylori infection. *N Engl J Med*, Vol. 347, No.15.
61. Shahani S., Monsef Esfahani H.R., Saeidnia S., Saniee P., Siavoshi F., Foroumadi A., Samadi N., Gohari A.R., (2012): Anti-Helicobacter pylori activity of the methanolic extract of Geumiranicum and its main compounds. Z. Naturforsch. C J. Biosci. 67, 172–180.
62. Štefaniæ Z., Mikleuševiæ G., Luiæ M., Bzowska A., LešèiæAšler I., (2017): Structural characterization of purine nucleoside phosphorylase from human pathogen Helicobacter pylori. *Int J Biol Macromol* 101:518 526.
63. Sycuro L. K., Pincus Z., Gutierrez K. D., Biboy J., Stern C. A., Vollmer W., and Salama N. R., (2010): Peptidoglycan cross linking relaxation promotes Helicobacter pylori's helical shape and stomach colonization. *Cell* 141, 822–833.
64. Tegtmeyer N., Wessler S., Necchi V., Rohde M., Harrer A., Rau T. T., Asche C. I., Boehm M., Loessner H., Figueiredo C., Naumann M., Palmisano R., Solcia E., Ricci V., and Backert S., (2017): Helicobacter pylori Employs a Unique Basolateral Type IV Secretion Mechanism for CagA Delivery. *Cell Host Microbe* 22, 552-560.e555.
65. Thomas DR., Francis NR., Xu C and De Rosier DJ., (2006): The three-dimensional structure of the flagellar rotor from a clockwise locked mutant of Salmonella typhimurium. *J Bacteriol* 188, 7039–7048.
66. Tibrewal N., Elliott GI., (2011): Evaluation of hadacidin analogues. Bioorganic Med Chem Lett 21:517–519.
67. Tomb JF., White O., Kerlavage AR., et al., (1997): The complete genome sequence of the gastric pathogen Helicobacter pylori. *Nature* 388:539-47
68. Valentina Loconte., Ivana Kekez., Dubravka Matkoviæalogoviæ and Giuseppe Zanotti., (2017): Structural characterization of FlgE2 protein from Helicobacter pylori hook. *The FEBS Journal* 4328–4342 2017.
69. Vidhi Mishra and Donald R. Ronning., (2012): Crystal Structures of the Helicobacter pylori MTAN Enzyme Reveal Specific Interactions between S Adenosyl-homocysteine and the 52 -Alkylthio Binding Subsite. Biochemistry 51, 9763"9772.
70. Winans S. C., Burns D. L., and Christie P. J., (1996): Adaptation of a conjugal transfer system for the export of pathogenic macromolecules. *Trends Microbiol.* 4, 64–68.
71. Winter J., Letley D., Rhead J., Atherton J., Robinson K., (2014): Helicobacter pylori membrane vesicles stimulate innate pro and anti-inflammatory responses and induce apoptosis in Jurkat T cells. *Infect Immun* 82:1372–1381.
72. Y. Y. Fei., A. Schmidt., G. Bylund., D. X. Johansson., S. Henriksson., C. Lebrilla., J. V. Solnick., T. Borén., X. D. Zhu., (2011): Use of real-time, label-free analysis in revealing low-affinity binding to blood group antigens by Helicobacter pylori. Anal. Chem. 83, 6336–6341.
73. Y.-C. Lee, T. H.-H. Chen H.M. Chiu et al., (2013): "benefit of mass eradication of Helicobacter pylori infection: a community-based study of gastric cancer prevention, *"Gut*, vol.62, no.5, pp.676–682
74. Yin Z. et al., (2014): DNA replication is the target for the antibacterial effects of nonsteroidal anti inflammatory drugs. *Chem Biol* 21, 481–487.
75. Yung Jun Ahn., Hye Jin Yoon., Byung Il Lee and Se Won Suh., (2004): Crystal Structure of Chorismate Synthase: A Novel FMN-binding Protein Fold and Functional Insights. *J. Mol. Biol.* 336, 903–915
76. Zagari RM., Rabitti S., Eusebi LH., et al., (2018): Treatment of Helicobacter pylori infection: A clinical practice update. *Eur J Clin Invest. Jan;* 48(1).
77. Zhemin Zhang., Qi Huang., Xuan Tao., Guobing Song., Peng Zheng., Hongyan Li., Hongzhe Sun and Wei Xia., (2019): The unique trimeric assembly of the virulence factor HtrA from Helicobacter pylorioccurs via N-terminal domain swapping. *J. Biol. Chem.* 119.007387.
78. Zhongming Ge., Diane E. Taylor., (1999): Contributions of Genome Sequencing to Understanding the Biology of Helicobacter pylori. *Annu. Rev. Microbiol*. 53:353–87.
79. Zhu P et al., (2017): Helicobacter pylori VacA induces autophagic cell death in gastric epithelial cells via the endoplasmic reticulum stress pathway. Cell Death Dis 8:3207.