IN SILICO INHIBITION OF UREASE AND CagA ENZYMES AS TARGETS AGAINST HELICOBACTER PYLORI: AN OVERVIEW ON CAPES 2022 DATABASE

Recebido em: 10/10/2023
Aceito em: 04/06/2024
DOI: 10.25110/arqsaude.v28i1.2024-10831

Heracles Pereira Wanzeler [1]
Ana Gabrielly Costa dos Santos [2]

ABSTRACT: The proliferation, adaptive capability, and action of the *Helicobacter pylori* bacterium in the human stomach make it a worldwide public health issue. This bacterium is associated with gastrointestinal diseases such as stomach cancer. Adding to this challenge is the emergence of multi-drug-resistant and pan-drug-resistant pathogens among gram-negative bacteria, a category to which *Helicobacter pylori* belongs, making the elimination of this microorganism a daunting task. Therefore, there is an urgent need for the development of new treatment strategies to address this issue, and one potential way is the *in silico* method, specifically Computer-Aided Drug Design (CADD), which suggests new starting points in the search for innovative therapies and can be combined with traditional research methods (*in vitro*, *in vivo*, and *ex-vivo*). In this context, this review, utilizing data from the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) database, provides an overview of the various proposals discussed in 2022 that focus on the inhibition of proteins favorable to the colonization, virulence, and pathogenicity of *H. pylori* using *in silico* methods. Thus, several articles were inspected in the CAPES database. With a focus on molecular docking and/or molecular dynamics, pharmacokinetics, drug-like characteristics, and toxicity, 15 articles were identified that indicated the most studied enzymes in 2022 were urease and CagA. Furthermore, it was observed that the nature of the compounds used in inhibition was diverse - essential oils, flavonoids, pyrazolines, benzimidazoles, tetrahydropyrimidines, and benzothiazoles. All of these compounds were found to have the potential to be anti-urease and/or anti-CagA agents.
KEYWORDS: CAPES; *Helicobacter pylori*; *In silico* method; Inhibition of enzymes.

INIBIÇÃO *IN SILICO* DAS ENZIMAS UREASE E CagA COMO ALVO CONTRA HELICOBACTER PYLORI: UMA VISÃO GERAL NO BANCO DE DADOS DA CAPES 2022

RESUMO: A proliferação, capacidade adaptativa e ação no estômago humano da bactéria *Helicobacter pylori*, torna-a um problema de saúde pública a nível mundial. Esta bactéria é associada a doenças gastrointestinais, como o câncer de estômago. Somado a isso, o surgimento de patógenos multirresistentes e pan-resistentes a medicamentos entre bactérias gram-negativas, categoria à qual a *Helicobacter pylori* encontra-se, torna a

[1] Doutorando em Química Computacional no Programa de Pós-Graduação em Química da Universidade Federal do Pará (PPGQ-UFPA).
E-mail: hpwanzeler@gmail.com ORCID: https://orcid.org/0000-0002-1496-9117
[2] Enfermeira Especialista no Hospital Universitário João de Barros Barreto.
E-mail: anagabrielly.cds@gmail.com ORCID: https://orcid.org/0009-0000-8676-3700

eliminação desse micro-organismo desafiadora. Assim, há uma urgente necessidade do desenvolvimento de novas estratégias de tratamento para enfrentar esse problema, e uma possível saída é o método *in silico*, especificamente *Computer-Aided Drug Design* (CADD), que sugere novos pontos de partida na busca novas terapias e pode ser combinado aos métodos tradicionais de pesquisa *(in vitro, in vivo, e ex-vivo).* Neste contexto, esta revisão, utilizando a base de dados da Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), fornece um panorama geral das diferentes propostas discutidas em 2022 que abordam a inibição de proteínas favoráveis à colonização, virulência e patogenicidade de *H. pylori* utilizando métodos *in silico*. Assim, diversos artigos foram inspecionados no banco de dados CAPES. Com foco em ancoragem molecular e/ou dinâmica molecular, farmacocinética, características *drug-likeness* e toxicidade, foram identificados 15 artigos que indicaram que as enzimas mais estudas em 2022 foram a urease e cagA. Além disso, foi observado que a natureza dos compostos utilizados na inibição era variada - óleos essenciais, flavonóides, pirazolinas, benzimidazóis, tetrahidropirimidinas e benzotiazóis. Todos esses compostos mostraram ser potenciais anti-urease e/ou anti-CagA.
PALAVRAS-CHAVE: CAPES; *Helicobacter pylori*; Método *in silico*; Inibição de enzimas.

INHIBICIÓN IN SILICO DE LAS ENZIMAS UREASE Y CagA COMO OBJETIVOS CONTRA HELICOBACTER PYLORI: UNA RESUMEN DE LA BASE DE DATOS CAPES 2022

RESUMEN: La proliferación, capacidad adaptativa y acción de la bacteria *Helicobacter pylori* en el estómago humano la convierten en un problema de salud pública a nivel mundial. Esta bacteria está asociada con enfermedades gastrointestinales como el cáncer de estómago. A esto se suma el surgimiento de patógenos resistentes a múltiples fármacos y completamente resistentes entre las bacterias gram-negativas, una categoría a la que pertenece *Helicobacter pylori*, lo que dificulta aún más la eliminación de este microorganismo. Por lo tanto, existe una urgente necesidad de desarrollar nuevas estrategias de tratamiento para abordar este problema, y una posible vía es el método *in silico*, específicamente el *Computer-Aided Drug Design* (CADD), que sugiere nuevos puntos de partida en la búsqueda de terapias innovadoras y puede combinarse con métodos de investigación tradicionales (*in vitro, in vivo y ex vivo*).En este contexto, esta revisión, utilizando datos de la base de datos de la Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), ofrece una visión general de las diversas propuestas discutidas en 2022 que se centran en la inhibición de proteínas favorables a la colonización, virulencia y patogenicidad de *H. pylori* utilizando métodos *in silico*. Así, varios artículos fueron inspeccionados en la base de datos de la CAPES. Con un enfoque en el acoplamiento molecular y/o la dinámica molecular, la farmacocinética, las características similares a las de los fármacos y la toxicidad, se identificaron 15 artículos que indicaban que las enzimas más estudiadas en 2022 fueron la ureasa y la CagA. Además, se observó que la naturaleza de los compuestos utilizados en la inhibición era diversa: aceites esenciales, flavonoides, pirazolinas, bencimidazoles, tetrahidropirimidinas y benzotiazoles. Se descubrió que todos estos compuestos tenían el potencial de ser agentes antiureasa y/o anti-CagA.
PALABRAS CLAVE: CAPES; *Helicobacter pylori*; Método *in silico*; Inibición de enzimas.

1. INTRODUCTION

Helicobacter pylori (*H. pylori* or *HP*) is a micro aerobic, gram-negative, spiral shaped bacterium with a smooth surface, rounded poles and multiple sheathed flagella. It can live in the human stomach as it has the ability to adapt to stomach acid (PEREZ-PEREZ; BLASER, 1996).

H. pylori, which is clinically associated with gastrointestinal diseases such as functional dyspepsia, duodenal ulcers, and stomach cancer, is a major worldwide problem. In fact, the global prevalence of *H. pylori* infection was estimated for 2015, resulting in a total of 4.4 billion people infected worldwide, representing more than half of the world population projected for that year. The aforementioned factors classify it as a class I Carcinogen (the category in which lung and respiratory tract cancers caused by smoking are found) by the World Health Organization and the International Agency for Research on Cancer (WHO and IARC, respectively). The main factor in the prevalence of *H. pylori* infection is still under investigation, however, studies suggest that socioeconomic status during childhood may play a significant role. In addition, the mode of transmission is believed to be primarily oral-oral, gastro-oral, or oral-fecal routes. (GRAHAM, 2015; HOOI *et al*., 2017; World Gastroenterology Organization, 2021).

The emergence of multidrug-resistant and pan-drug-resistant pathogens among gram-negative bacteria, like *H. pylori*, poses significant challenges in the treatment of illnesses caused by these microorganisms. These developments in the evolution of *H. pylori* and other gram-negative bacteria have made it increasingly difficult to effectively combat these pathogens with traditional drugs (KARAISKOS, 2019). As for *H. pylori*, the conventional first-line treatment protocol, which includes a proton pump inhibitor in combination with clarithromycin and either amoxicillin or metronidazole, has been found to be less effective in recent years due to the increasing prevalence of antibiotic resistance. This has highlighted the urgent need for the development of new and alternative treatment strategies to address this problem (MALFERTHEINER; SELGRAD; BORNSCHEIN, 2012; MALFERTHEINER *et al*., 2017).

In the literature scientific, there are several proposals regarding the use of Computer-Aided Drug Design (CADD) *in silico* studies, which suggest new starting points in the search for new therapies and serve as a means of supporting *in vitro, in vivo, and ex-vivo* studies. This review, using the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) database, provides an overview of the different proposals discussed in 2022 that address the inhibition of proteins favorable to the colonization,

virulence and pathogenicity of *H. pylor*i using *in silico* methods. It focuses on computational approaches including molecular docking and/or dynamics, pharmacokinetics, drug-like characteristics and toxicity studies. The review is guided by the questions: What enzymes are targeted using the *in silico* method according to the CAPES database in 2022? Which of these enzymes are the most studied? And what is the nature of the inhibitors used and the approaches taken?

2. MATERIAL AND METHODS

2.1 Search strategies, selection criteria and focus

A bibliographic search was carried out on the CAPES platform of articles in English in the year 2022, using the keywords "*Helicobacter pylori*" and "*in silico*". The 54 results obtained underwent a second round of screening to eliminate those that did not fit the criteria: articles that utilized molecular docking and/or molecular dynamics simulation in combination with *in vitro*, *in vivo*, and/or *ex-vivo* studies were kept, as long as they were not reviews or *in silico* studies on gastric cancer where only *Helicobacter pylori* was briefly mentioned, or if they used a different *in silico* approach (e.g. biostatistics) from that proposed by this review. The final selection resulted in 15 articles, with 8 focusing on the urease protein, 3 on the CagA protein and the rest on various other proteins (see Board 1).

3. RESULTS AND DISCUSSION

Board 1 shows that different researchers used various methods for eradicating the *H. pylori* bacterium by inhibiting specific targets. In 2022, the main targets were urease and CagA. Thus, this review focuses on these targets.

Board 1: Summary of ligands with the highest affinity to a specific protein based on the 15 studied articles.

Investigated compounds	Target protein	Possible highest protein(s) inhibitor(s)	Reference
Compounds from ZINC database	CagA (4DVZ from PDB)	ZINC153731, ZINC164387 and ZINC69482055	HE *et al*., 2022.
Marjoram and *mandarin* oils	CagA (4DVY from PDB)	Caryophyllene oxide; Linalyl acetate; Methyl-N-methyl anthranilate.	ELKOUSY *et al*., 2022.
	Urease (1E9Y from PDB)		
Chitosan polymer with *curcumin*	CagA (*** from PDB)	Curcumin functionalized chitosan nanosystems.	EJAZ *et al*., 2022.
	BabA (*** from PDB)		
	SabA (*** from PDB)		
	VacA (*** from PDB)		
	Urease (*** from PDB)		
Tetrahydropyrimidine derivatives	Urease (1E9Y from PDB)	Compounds 4e and 4f	AHANGARZADEH *et al*., 2022.
Benzothiazole and benzimidazole	Urease (4H9M from PDB)	Both	PEREIRA *et al*., 2022.
Benzimidazole derivatives	Urease (1E9Y from PDB)	1-(ethoxymethyl)-1H-benzo[d]imidazole-2(3H)-thione; Benzimidazole-2-Thione	MOHAMMED *et al*., 2022
Phytochemical compounds	Urease (1E9Y from PDB)	Terpineol	TAWALBEH *et al*., 2022.
1,3,5-triaryl-2pyrazoline derivatives	Urease (4H9M from PDB)	Compound 2m	MEHMOOD *et al*., 2022.
Sinensetin, isoorientin, naringenin, morin and daidzein	Urease (1E9Z from PDB)	Isoorientin	QUY *et al*., 2022
	Mucin-5AC (P98088 from UNIPROT)		
Vaccine	TLR-2 (2Z7X from PDB)	Multi-epitope vaccine	RU *et al*., 2022.
	TLR-4 (2Z63 from PDB)		
	B7-1 (1DR9 from PDB)		
	B7-1 (1NCN from PDB)		
Malonic acid	Aspartate α-decarboxylase (1UHE from PDB)	Malonic acid	IBRAHIM *et al*., 2022
Six nitroimidazole derivatives (–OH, H, –SPh, –COOH, $–NO_2$ and $–OCH_3$)	Nitroreductase Rdxa (3QDL from PDB)	Substituted –COOH and $–NO_2$ nitroimidazole derivatives	ADEOYE *et al*., 2022
Essential oils from *Cuminum cyminum*, *Pimpinella anisum*, and *Carum carvi* fruits	MTAN (3NM4 from PDB)	Cumaldehyde	ALOMAR *et al*., 2022
26000 commercial compounds	Crystallographic structure *H. pylori* arginase (4G3H) as a template to build the 3D HPA model of the exact strain (ATCC 43504)	Compound 13	FIORI-DUARTE, *et al*., 2022
12 secondary metabolites from *Meehania fargesii* var. *Radicans*	HtrA (*** from PDB)	Compounds 11 and 12	ZHOU *et al*., 2022

***Code not reported by the authors.
Source: authors, 2023.

3.1 About the target enzymes: urease and cagA

Urease synthesized by HP creates a neutral pH microenvironment around the bacteria, breaking down urea and producing ammonia, which serves as a receptor for H^+ ions. This process consumes 6% of the bacteria's total protein production and allows the bacteria to survive in and colonize the acidic environment of the stomach. Furthermore, urease possibly induces angiogenesis leading to increased gastric cancer progression (EATON *et al*., 1991; WEEKS; SACHS, 2001; OLIVERA-SEVERO *et al*., 2017).

The Cytotoxin-associated antigen gene A (CagA) is an oncoprotein, produced by the cagA gene. This gene, located on the cag-PAI pathogenicity island, is a segment of DNA that likely entered the genome of *H. pylori* through horizontal transfer. HP delivers CagA to host cells via the Type IV cag secretion system. Once inside epithelial cells, tyrosine phosphorylation occurs, resulting in effects such as cell proliferation, interleukin 8 (IL-8) expression, and cell elongation (AKOPYANTS *et al*., 1998; ODENBREIT *et al*., 2000; HIGASHI *et al*., 2002; BACKERT; TEGTMEYE; SELBACH, 2010; HATAKEYAMA, 2014).

3.2 The *in silico* approaches taken

The phytochemical approach for inhibiting the urease enzyme was used by Tawalbeh *et al*. (2022) and Quy *et al*. (2022) in their studies, while Elkousy *et al*. (2022) employed the same approach to inhibit both urease and CagA, as outlined below.

Elkousy *et al*. (2022) examined the effectiveness of mandarin leaves and marjoram herb essential oils against *H. pylori* in comparison to clarithromycin using an *in vitro* method, and discovered that the combined effects of the oils were similar to those of clarithromycin. To further validate their findings, they also conducted *in silico* studies (molecular docking, pharmacokinetic and toxicity studies) on the major compounds found in the oils, identifying caryophyllene oxide, linalyl acetate, and methyl-N-methyl anthranilate as strong candidates for the treatment of *H. pylori* due to their binding affinity to the urease and CagA enzymes.

Tawalbeh *et al*. (2022) applied a comparable method, testing the effectiveness of phytochemical compounds like D-limonene, (+)-alpha-pinene, beta-sitosterol, alpha-terpineol and (-)-alpha-thujone. They compared their results to those of amoxicillin and metronidazole as a positive control. They discovered that terpineol was the most effective among them and also observed that there was an additive synergistic effect between terpineol and metronidazole in inhibiting the urease. Quy *et al*. (2022) used *in silico*

methods (molecular docking, physicochemical, pharmacokinetic and pharmacology properties) to investigate the inhibition of urease by conducting assays with flavonoid-derived phytochemical compounds like sinensetin, isoorientin, naringenin, morin and daidzein. They found that all the candidates were biocompatible and isoorientin was the most effective among them.

The authors Mehmood *et al*. (2022), Mohammed *et al*. (2022), and Ahangarzadeh *et al*. (2022) proposed the use of compounds derived from other potential anti-urease agents, as outlined below.

Mehmood *et al*. (2022) synthesized a series of derivatives of 1,3,5-triaryl-2-pyrazoline and evaluated their inhibitory potential against both urease and α-glucosidase, using thiourea and acarbose as reference standards, respectively. Their theoretical computational assays supported the experimental results and indicated that pyrazolines are potent dual inhibitors of both urease and α-glucosidase, with the 1,3,5-triaryl-2-pyrazoline derivative named compound 2m being particularly effective. Meanwhile, Mohammed *et al*. (2022) synthesized benzimidazole-2-thione derivatives through alkylation and aimed to understand the mechanism of urease inhibition at its active sites through molecular docking. They also investigated the safety of these compounds through *in silico* analysis of their Absorption, Distribution, Metabolism, Excretion, and Toxicity (ADMET) characteristics. The highlights were the compounds benzimidazole-2-thione and 1-(ethoxymethyl)-1H-benzo[d]imidazole-2(3H)-thione, which were effective against various pathogenic bacteria, including *H. pylori*.

Ahangarzadeh *et al*. (2022) used a tetrahydropyrimidine analog approach and analyzed approximately 14 tetrahydropyrimidine derivatives, with thiourea being used as a reference compound. Their molecular docking and dynamic simulation results indicated that tetrahydropyrimidine derivatives 4e and 4f are potential inhibitors of urease, and they found that the interaction acting between ligands and enzyme is generally hydrophobic. These results were correlated with the *in vitro* assay.

Other proposals come from Pereira *et al*. (2022), Ejaz *et al*. (2022) and HE *et al*. (2022), as outlined below.

Pereira *et al*. (2022) showed in their studies that benzothiazole and benzimidazole interact as mixed inhibitors. Specifically, *in silico* assays (molecular docking and molecular dynamics) demonstrated that the main interaction responsible for stabilizing the benzothiazole-urease complex are hydrophobic, while for urease-benzimidazole, the main are van der Waals and hydrogen bonds interactions. Meanwhile, Ejaz *et al*. (2022)

approached the use of curcumin conjugated covalently with chitosan as a potential synergistic antimicrobial, starting from the hypothesis that curcumin could improve the ideal binding affinity with target proteins, specifically the virulence factors Urease, CagA, BabA, VacA, and SabA. The *in silico* analysis showed strong binding affinity of the curcumin functionalized chitosan nanosystem interaction with the virulence factors.

Finally, HE *et al*. (2022) using only the *in silico* method, performed a virtual screening of compounds obtained from the ZINC database that could be used to block the CagA enzyme to combat gastric cancer, which has HP as a possible pathogen. After their bioinformatics analyses performing ADMET, Molecular Docking, and Molecular Dynamics Simulation actions, they observed that ZINC153731, ZINC164387 and ZINC69482055 compounds have effective affinity to the CagA protein, especially with the Arg624 residue - crucial to ligand-enzyme interaction.

4. CONCLUDING REMARKS

Understanding different *in silico* approaches for suppressing pathogen virulence, particularly *Helicobacter pylori*, is a vital starting point for inhibiting bacterial colonization, adaptation, and infection. This review focused on examining various studies on the efficacy of phytochemical and synthetic compounds in inhibiting virulence-promoting proteins of *H. pylori*, targeting the most commonly studied entities through *in silico* methods in 2022, according to the CAPES database. As indicated in Board 1, the most studied enzymes were Urease and CagA. The nature of the inhibitors is diverse, including essential oils, flavonoids, pyrazolines, benzimidazoles, tetrahydropyrimidines, and benzothiazoles. The research assessed the effectiveness of these different compounds in inhibiting urease and CagA enzymes through in vitro assays, supported by *in silico* methods or, in some cases, solely through *in silico* analysis. The studies compared the compounds with standard medications and evaluated their biocompatibility and safety. Overall, the results suggest that the examined compounds have the potential to serve as anti-urease and anti-CagA agents. Thus, it is hoped that this work will guide future research on the most studied enzymes in 2022 for *H. pylori* inhibition.

REFERENCES

ADEOYE, M. D. *et al*. Biological evaluation of selected metronidazole derivatives as anti-nitroreductase via *in silico* approach. **Eclética Química Journal**, v. 47, n. 4, p. 27-36, 2022.

AKOPYANTS, N. S. *et al*. Analyses of the cag pathogenicity island of *Helicobacter pylori*: *H. pylori* pathogenicity island. **Molecular Microbiology**, v. 28, n. 1, p. 37-53, 2002.

ALOMAR, H. A. *et al*. GC-MS Profiling, Anti-*Helicobacter pylori*, and Anti-Inflammatory Activities of Three Apiaceous Fruits' Essential Oils. **Plants**, v. 11, n. 19, p. 2617, 2022.

AL TAWALBEH, D. *et al*. *In Silico* and *In Vitro* Investigation of Anti Helicobacter Activity of Selected Phytochemicals. **Journal of Pharmacy And Bioallied Sciences**, v. 14, n. 3, p. 132, 2022.

AHANGARZADEH, N. *et al*. Design, synthesis, and *in silico* studies of tetrahydropyrimidine analogs as urease enzyme inhibitors. **Archiv der Pharmazie**, v. 355, n. 10, p. 2200158, 2022.

BACKERT, S.; TEGTMEYER, N.; SELBACH, M. The Versatility of *Helicobacter pylori* CagA Effector Protein Functions: The Master Key Hypothesis: The Versatility of *H. pylori* CagA. **Helicobacter**, v. 15, n. 3, p. 163–176, 2010.

EATON, K. A. *et al*. Essential role of urease in pathogenesis of gastritis induced by *Helicobacter pylori* in gnotobiotic piglets. **Infection and Immunity**, v. 59, n. 7, p. 2470-2475, 1991.

ELKOUSY, R. H. *et al*. GC/MS analysis and potential synergistic effect of mandarin and marjoram oils on *Helicobacter pylori*. **Journal of Enzyme Inhibition and Medicinal Chemistry**, v. 37, n. 1, p. 1610-1619, 2022.

EJAZ, S. *et al*. Chitosan-curcumin complexation to develop functionalized nanosystems with enhanced antimicrobial activity against hetero-resistant gastric pathogen. **International Journal of Biological Macromolecules**, v. 204, p. 540-554, 2022.

FIORI-DUARTE, A. T. *et al*. *In silico* design and in vitro assessment of anti-*Helicobacter pylori* compounds as potential small-molecule arginase inhibitors. **Molecular Diversity**, v. 26, n. 6, p. 3365-3378, 2022.

GRAHAM, D. Y. *Helicobacter pylori* Update: Gastric Cancer, Reliable Therapy, and Possible Benefits. **Gastroenterology**, v. 148, n. 4, p. 719- 731.e3, 2015.

HATAKEYAMA, M. *Helicobacter pylori* CagA and Gastric Cancer: A Paradigm for Hit-and-Run Carcinogenesis. **Cell Host & Microbe**, v. 15, n. 3, p. 306-316, 2014.

HE, S. *et al.* Targeting Cytotoxin-Associated Antigen A, a Virulent Factor of *Helicobacter pylori*-Associated Gastric Cancer: Structure-Based *In Silico* Screening of Natural Compounds. **Molecules**, v. 27, n. 3, p. 732, 2022.

HIGASHI, H. *et al*. SHP-2 Tyrosine Phosphatase as an Intracellular Target of *Helicobacter pylori* CagA Protein. **Science**, v. 295, n. 5555, p. 683–686, 2002.

HOOI, J. K. Y. *et al*. Global Prevalence of *Helicobacter pylori* Infection: Systematic Review and Meta-Analysis. **Gastroenterology**, v. 153, n. 2, p. 420–429, 2017.

IBRAHIM, K. A. *et al*. Aspartate α-decarboxylase a new therapeutic target in the fight against *Helicobacter pylori* infection. **Frontiers in Microbiology**, v. 13, p. 1019666, 2022.

KARAISKOS, I. *et al*. The "Old" and the "New" Antibiotics for MDR Gram-Negative Pathogens: For Whom, When, and How. **Frontiers in Public Health**, v. 7, p. 151, 2019.

MALFERTHEINER, P.; SELGRAD, M.; BORNSCHEIN, J. *Helicobacter pylori*: clinical management. **Current Opinion in Gastroenterology**, v. 28, n. 6, p. 608–614, 2012.

MALFERTHEINER, P. *et al.* Management of *Helicobacter pylori* infection-the Maastricht V/Florence Consensus Report. **Gut**, v. 66, n. 1, p. 6-30, 2017.

MEHMOOD, R. *et al*. Synthesis and Evaluation of 1,3,5-Triaryl-2-Pyrazoline Derivatives as Potent Dual Inhibitors of Urease and α-Glucosidase Together with Their Cytotoxic, Molecular Modeling and Drug-Likeness Studies. **ACS Omega**, v. 7, n. 4, p. 3775-3795, 2022.

MOHAMMED, S. O. *et al*. Expression, Purification, and Comparative Inhibition of Helicobacter pylori Urease by Regio-Selectively Alkylated Benzimidazole 2-Thione Derivatives. **Molecules**, v. 27, n. 3, p. 865, 27 jan. 2022.

ODENBREIT, S. *et al.* Translocation of Helicobacter pylori CagA into Gastric Epithelial Cells by Type IV Secretion. **Science**, v. 287, n. 5457, p. 1497-1500, 2000.

OLIVERA-SEVERO, D. *et al*. A New Role for *Helicobacter pylori* Urease: Contributions to Angiogenesis. **Frontiers in Microbiology**, v. 8, p. 1883, 2017.

PEREIRA, C. *et al.* 2-(Pyridin-4yl) benzothiazole and Its Benzimidazole-Analogue: Biophysical and *in silico* Studies on Their Interaction with Urease and in vitro Anti-*Helicobacter pylori* Activities. **Journal of the Brazilian Chemical Society**, 2022.

PEREZ-PEREZ, G. I.; BLASER, M. J. Campylobacter and Helicobacter. *In*: BARON, S. (Ed.). **Medical Microbiology**. 4th. ed. Galveston (TX): University of Texas Medical Branch at Galveston, 1996.

QUY, P. T. *et al. In silico* study on inhibitability of flavonoidal derivatives against *Helicobacter pylori* and their pharmacological potentiality. **Vietnam Journal of Chemistry**, v. 60, n. 4, p. 435-450, 2022.

RU, Z. *et al*. Immmunoinformatics-based design of a multi-epitope vaccine with CTLA-4 extracellular domain to combat *Helicobacter pylori*. **The FASEB Journal**, v. 36, n. 4, 2022.

WEEKS, D. L.; SACHS, G. Sites of pH regulation of the urea channel of *Helicobacter pylori*. **Molecular Microbiology**, v. 40, n. 6, p. 1249–1259, 2001.

World Gastroenterology Organization (WGO). Available at: https://www.worldgastroenterology.org. Acesso em: 4 fev. 2023.

ZHOU, G. *et al*. Insight into the Potential of *Meehania fargesii* var. *Radicans* against Hp-Induced Gastric Carcinoma Based on Phytochemical and Molecular Docking Studies. **Chemistry & Biodiversity**, v. 19, n. 7, p. e202200383, 2022.

AUTHORITY CONTRIBUTION

Heracles Pereira Wanzeler: Conceptualization, Investigation, Methodology, Project administration, Writing – review & editing.

Ana Gabrielly Costa dos Santos: Conceptualization, Investigation, Writing – review & editing.