Basic Study

*In silico* prospective analysis of the medicinal plants activity on the CagA oncoprotein from *Helicobacter pylori*

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Abstract

**BACKGROUND**

Colonization with *Helicobacter pylori* (*H. pylori*) has a strong correlation with gastric cancer, and the virulence factor CagA is implicated in carcinogenesis. Studies have been conducted using medicinal plants with the aim of eliminating the pathogen; however, the possibility of blocking *H. pylori*-induced cell differentiation to prevent the onset and/or progression of tumors has not been addressed. This type of study is expensive and time-consuming, requiring *in vitro* and/or *in vivo* tests, which can be solved using bioinformatics. Therefore, prospective computational analyses were conducted to assess the feasibility of interaction between phenolic compounds from medicinal plants and the CagA oncoprotein.

**AIM**

To perform a computational prospecting of the interactions between phenolic compounds from medicinal plants and the CagA oncoprotein of *H. pylori*.

**METHODS**

In this *in silico* study, the structures of the phenolic compounds (ligands) kaempferol, myricetin, quercetin, poncirretin (flavanoids), and chlorogenic acid (phenolic acid) were selected from the PubChem database. These phenolic compounds were chosen based on previous studies that suggested medicinal plants as non-drug treatments to eliminate *H. pylori* infection. The three-dime-
nsional structure model of the CagA oncoprotein of *H. pylori* (receptor) was obtained through molecular modeling using computational tools from the I-Tasser platform, employing the threading methodology. The primary sequence of CagA was sourced from GenBank (BAK52797.1). A screening was conducted to identify binding sites in the structure of the CagA oncoprotein that could potentially interact with the ligands, utilizing the GRaSP online platform. Both the ligands and receptor were prepared for molecular docking using AutoDock Tools 4 (ADT) software, and the simulations were carried out using a combination of ADT and AutoDock Vina v.1.2.0 software. Two sets of simulations were performed: One involving the central region of CagA with phenolic compounds, and another involving the carboxy-terminus region of CagA with phenolic compounds. The receptor-ligand complexes were then analyzed using PyMol and BIOVIA Discovery Studio software.

**RESULTS**

The structure model obtained for the CagA oncoprotein exhibited high quality (C-score = 0.09) and was validated using parameters from the MolProbity platform. The GRaSP online platform identified 24 residues (phenylalanine and leucine) as potential binding sites on the CagA oncoprotein. Molecular docking simulations were conducted with the three-dimensional model of the CagA oncoprotein. No complexes were observed in the simulations between the carboxy-terminus region of CagA and the phenolic compounds; however, all phenolic compounds interacted with the central region of the oncoprotein. Phenolic compounds and CagA exhibited significant affinity energy (-7.9 to -9.1 kcal/mol): CagA/kaempferol formed 28 chemical bonds, CagA/myricetin formed 18 chemical bonds, CagA/quercetin formed 16 chemical bonds, CagA/ponciretin formed 13 chemical bonds, and CagA/chlorogenic acid formed 17 chemical bonds. Although none of the phenolic compounds directly bound to the amino acid residues of the K-Xn-R-X-R membrane binding motif, all of them bound to residues, mostly positively or negatively charged, located near this region.

**CONCLUSION**

In *silico*, the tested phenolic compounds formed stable complexes with CagA. Therefore, they could be tested in *vitro* and/or *in vivo* to validate the findings, and to assess interference in CagA/cellular target interactions and in the oncogenic differentiation of gastric cells.

**Key Words:** CagA oncoprotein; Phenolic compounds; *Helicobacter pylori*; *In silico* analyses; Medicinal plants; Prospective analysis

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**Core Tip:** Commonly, studies on the effects of medicinal plants on *Helicobacter pylori* (*H. pylori*) infection assess the antimicrobial activity of these plants. However, in this study, the authors conducted a prospective *in silico* analysis of the activity of certain phenolic compounds from plants used to treat *H. pylori* infection on stomach cells affected by CagA, aiming to prevent or block the oncogenic differentiation of these cells.

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**INTRODUCTION**

Colonization of gastric epithelial cells by *Helicobacter pylori* (*H. pylori*) has a strong positive correlation with gastric diseases such as peptic ulcers and stomach cancer, owing to the virulence factors and evasion capabilities of the bacteria [1]. The standard treatment for eradicating *H. pylori* is complex and relies on antibiotics[2,3], proton pump inhibitors[4], bismuth salts[5], and H2 blockers[6], typically used in combination for an extended duration[7].

Multiple factors contribute to hindering the eradication of *H. pylori*, among which drug inefficiency and the bacteria’s antibiotic resistance are prominent[7]. In 2017, the World Health Organization classified *H. pylori* as resistant to clarithromycin, metronidazole, and levofloxacin, emphasizing the urgent need for research into new antibiotics targeting the bacteria[8].

In this context, medicinal plants and their secondary metabolites have emerged as an alternative for managing *H. pylori* infection. The literature reports several plant species with antimicrobial activity against *H. pylori*, which act by inhibiting, reducing, and delaying gastric colonization. Plants such as *Pistacia lentiscus*, *Brassica oleracea*, *Curcuma longa*, *Coptis chinensis*, and *Glycyrrhiza glabra* were tested in rodents (mice and rats); *Vaccinium macrocarpon*, *Glycyrrhiza glabra*, and *Nigella sativa* were tested in humans, with observed results indicating biological activity against the bacteria and the progression of infection[9]. Dinat *et al*[10] discuss the use of medicinal plants in treating *H. pylori* infection and identified...
antimicrobial activity in several of them, such as Hibiscus sabdariffa and Piper longum.

Commonly, the use of medicinal plants to treat *H. pylori* infection aims at antimicrobial action to eliminate the pathogen and consequently prevent the development of associated pathologies such as gastritis, ulcers, and especially gastric cancer. Although studies have demonstrated antimicrobial activity in many plants, most are classified as having weak or weak to moderate activity based on the minimum inhibitory concentration test. Many secondary metabolites of medicinal plants with anti-*H. pylori* activity have been reported, including phenolic compounds, coumarins, quinones, terpenoids, and alkaloids[11]. Several studies attribute the biological activity of medicinal plants to phenolic compounds, which include anti-cancer[12-16], anti-proliferative, anti-angiogenic, and antimicrobial activities[17,18].

Although studies have primarily focused on antimicrobial activity, medicinal plants and their metabolites may also interfere with pathogenic cellular processes induced by *H. pylori*. In cases of infection with *CagA*-positive *H. pylori* strains, where the colonization process is advanced, it would be crucial not only to eliminate the pathogen but also to block the cell differentiation induced by *CagA* to prevent the development of cancer. Therefore, addressing the treatment of *H. pylori* infection through targeting the *CagA* would be of interest.

The *CagA* is an oncoprotein, a virulence factor of *H. pylori* responsible for inducing genetic mutations and alterations in gastric cells[19]. This oncoprotein is encoded by the pathogenicity island (cag-PAI) and is transported into cells via a type 4 secretion system (T4SS)[20]. Inside cells, *CagA* attaches to the plasma membrane in two distinct ways: Through the interaction of basic amino acids, including those in the K-Xn-R-X-R binding motif located in the central region of *CagA*, or through the carboxy-terminus region. Subsequently, *CagA* undergoes tyrosine phosphorylation on the EPIYA (Glu-K-Pro-Le-Tyr-Ala) motif, which is present in multiple copies in the carboxy-terminus polymorphic region, by Src kinase members such as c-Src, Yes, Fyn, and Abi kinase[21]. Phosphorylated *CagA* interferes with cell signaling pathways, leading to mitogenic imbalance, induction of a pro-inflammatory state, cytoskeleton damage, and disruption of cell-cell junctions[20,22,23].

The carboxy-terminus end of the *CagA* oncoprotein also contains the *CagA*-multimerization (CM) motif, which facilitates its dimerization or multimerization. CM motif consists of 16 amino acid residues and is located immediately distal to the last EPIYA segment. Apart from facilitating multimerization, the CM motif enables *CagA* to interact with regulatory molecules that affect proper cell signaling[21]. The cumulative effect of dysregulated cell signaling, disordered cell growth, endothelial injury, and loss of mucosal integrity caused by the *CagA* oncoprotein predisposes individuals to precancerous lesions in the stomach, explaining the higher incidence of cancer in individuals colonized with *CagA*-positive *H. pylori*[22].

Therefore, approaches could be explored to interfere with the *CagA*-cellular targets interaction, aiming to reduce or inhibit the activity of this protein and, consequently, its oncogenic potential. Phenolic compounds from plants are capable of crossing the plasma membrane of human cells and interacting with proteins and enzymes of cellular signaling cascades, altering the course of signal transduction[24]. Thus, this study aimed a prospective computational analysis of the action of certain phenolic compounds from medicinal plants, which are reported in the treatment of *H. pylori* infection, on the *CagA* oncoprotein, and consequently, on the cellular signaling pathways that are important for *CagA*-dependent gastric carcinogenesis. This prospecting may guide in vitro and/or in vivo studies to reduce financial and labor burdens.

**MATERIALS AND METHODS**

**Molecular modeling**

Molecular modeling of the *CagA* oncoprotein was carried out using the primary sequence BAK52797.1 of the *CagA* oncoprotein from *H. pylori*, which contains 1194 residues including the EPIYA-A, B, C, and CM motifs, in FASTA format, selected from GenBank (ncbi.nlm.nih.gov/genbank). The FASTA sequence was utilized to search for X-ray diffraction solved three-dimensional structures deposited in online public databases. However, the structures found in the databases did not include either the amino-terminus or the carboxy-terminus ends of the *CagA* oncoprotein. Global and local alignment analyses of *CagA* were performed using the BioEdit software (Informer Technologies, Inc.) and the Basic Local Alignment Search Tool algorithm (National Institutes of Health/United States), respectively. Since no satisfactory homologous templates were found, the *CagA* oncoprotein was modeled using the structure prediction methodology-Threading, employing tools from the I-Tasser platform[25], and the model was validated using the MolProbity platform[26].

**Prediction of binding sites in the *CagA* oncoprotein**

The modeled *CagA* oncoprotein was analyzed using the GRasP online platform[27] to predict residues that could serve as potential binding sites. This data will be compared with the results obtained from molecular docking.

**Preparation of ligands and receptor**

Chemical compounds selected as ligands were phenolic compounds, and their two-dimensional structures were obtained from the PubChem Database (pubchem.ncbi.nlm.nih.gov)-kaempferol (PubChem: 6325460), quercetin (PubChem: 5281672), quercetin (PubChem: 5280343), ponciretin (PubChem: 25201019), and chlorogenic acid (PubChem: 1794427). The two-dimensional structures were converted to three-dimensional form using PyMol software (Schrödinger, Inc.). The protonation state of each phenolic compound at physiological pH 7.4 was predicted using MarvinSketch software (ChemAxon) before proceeding with docking simulations. All phenolic compounds were selected from studies involving medicinal plants used for the treatment of *H. pylori* infection[28,29]. AutoDock Tools 4 (ADT) software[30] was used to
detect and calculate the points and angles of torsion, respectively. The CagA oncoprotein was prepared using the same software to add missing hydrogen atoms.

**Molecular docking**
Molecular docking was performed using the flexible ligand-rigid receptor methodology\[31\]. The simulations were conducted by associating ADT with AutoDock Vina v.1.2.0 software\[32\], enabling the establishment of an algorithm that searches for potential bond combinations, including rotational, translational, and conformational degrees of freedom. This algorithm also establishes scoring criteria to select the best ligand-receptor interactions. Points are assigned according to the molecular force field and the free energy of the bond, with interactions considered stable if the affinity energy is lower than -6.0 kcal/mol\[33\].

Two sets of molecular docking simulations were carried out: (1) Central region of CagA + phenolic compound; and (2) carboxy-terminus region of CagA + phenolic compound. The membrane binding motif (K-Xn-R-X-R) is located in the central region, while the EPIYA and CM motifs are in the carboxy-terminus region of the CagA oncoprotein. Gridbox dimensions and coordinates were determined separately to allocate the central region and the carboxy-terminus end of the CagA (receptor). Evaluation of the receptor/ligand complexes was performed using PyMol and BIOVIA Discovery Studio (Dassault Systemes) software. Physicochemical analysis of the residues involved in the chemical bonds was carried out using the ProtParam tool\[34\]. The data was analyzed using descriptive statistics (mean and relative values).

**RESULTS**

**Predicted three-dimensional model of H. pylori CagA oncoprotein**
Five structural models were constructed based on 10 three-dimensional structures, and the most satisfactory model, with a C-score value of 0.09, was selected (Figure 1A). The C-score assesses the quality of models predicted by I-Tasser; it typically ranges from -5 to 2, with higher values indicating models with higher reliability. MolProbity indicated that approximately 98% of the amino acid residues in the model were located within the allowed regions of the Ramachandran plot.

**In silico predicted binding sites of the CagA oncoprotein**
A total of 24 amino acid residues were predicted as possible binding sites for ligands. The algorithm indicated 19 phenylalanine (F) and 5 leucine (L) residues with a probability above 50% of interacting with other molecules. This value represents the algorithm’s cut-off point. Among the 24 residues, only one coincided with the molecular docking results (F426) (Table 1). The residues are distributed across the surface of CagA, and no clusters were observed (Figure 1B).

**CagA/phenolic compound complexes**
The phenolic compounds analyzed formed antibody complexes with the CagA oncoprotein in silico (Figure 2); all five compounds bound to the central region of the protein close to the spatial region of the membrane-binding motif (residues 621 to 626) (Figure 3). No in silico interactions were observed between the phenolic compounds and the carboxy-terminal region of CagA where the EPIYA motifs are located. The affinity energies were considered satisfactory and ranged from -7.9 kcal/mol (CagA/chlorogenic acid) to -9.1 kcal/mol (CagA/kaempferol). The other complexes showed similar affinity energy values-CagA/quercetin = -8.1 kcal/mol, CagA/myricetin = -8.2 kcal/mol, CagA/ponciretin = -8.4 kcal/mol. In all the complexes, covalent bonds and reversible bonds (hydrogen bond and van der Waals) were observed. The CagA/kaempferol complex showed 28 bonds (2.1Å - 2.3Å) involving 23 amino acid residues; this was the complex with the highest number of chemical bonds. The CagA/myricetin complex showed 18 bonds (2.0Å - 2.9Å) involving 15 residues; CagA/quercetin complex-16 bonds (2.2Å) involving 15 residues; CagA/ponciretin complex-13 bonds (2.5Å - 3.4Å) involving 11 residues; CagA/chlorogenic acid complex-17 bonds (1.9Å - 3.3Å) involving 15 residues. All the chemical bonds present in each complex are shown in Figure 4 in a two-dimensional diagram, and the residues are listed in Table 1. Fifty-three amino acid residues participated in chemical bonds with at least one of the phenolic compounds analyzed in silico. Of these, eight made bonds with two compounds, and eight made bonds with three compounds, most of which were positively (L) or negatively (D/E) charged residues.

**DISCUSSION**

**H. pylori** strains harboring the gene CagA-CagA-positive strains-significantly increase the risk of developing gastric cancer when compared to CagA-negative strains\[35\]. The cellular modifications triggered by the CagA oncoprotein, after being injected into stomach epithelial cells, involve the EPIYA motifs becoming targets for phosphorylation and recruitment to enzymes and adaptor proteins. These events disrupt the standard cellular metabolism, triggering pre-lesion processes\[21\].

The results of this in silico study suggest that, after being injected into the cytoplasm of gastric epithelial cells via T4SS, the CagA oncoprotein can interact with xenobiotics that cross the plasma membrane of these cells, such as phenolic compounds from medicinal plants. The computational search for binding sites in CagA indicated several phenylalanine and leucine residues with this potential. Since these residues did not form clusters, it is possible that they represent the starting point for ligand binding, and the site itself is composed of more residues that become closer together after ligand
binding due to a conformational change; in other words, the ligand would actually be an allosteric modulator[36].

Due to the chemical nature of the side chains of these residues, they are expected to form hydrophobic bonds with compounds of a similar chemical nature. This increases the likelihood of secondary metabolites that are more hydrophobic than those evaluated interacting with the CagA oncoprotein, such as terpenes and terpenoids[37].

The phenolic compounds evaluated in this in silico study (ponciretin, kaempferol, quercetin, myricetin, and chlorogenic acid) bound to the central region of the CagA oncoprotein, near the membrane phospholipid-binding motif-K-Xn-R-X-R motif. Due to the proximity of the bonds formed by the phenolic compounds to this motif and the high interaction affinity considered, these compounds could induce conformational changes in the protein, thus destabilizing its previous interactions with cellular targets. Even if the carboxy-terminus region, where the EPIYA and CM motifs are found, does not bind to the analyzed phenolic compounds, the interaction between CagA and the plasma membrane is still necessary for the phosphorylation process. Therefore, interference through the membrane-binding domain could be effective in blocking this process.

Given the consideration of phenolic compounds as an alternative for interfering with CagA oncoprotein activity within epithelial cells, it is important to note that these compounds are absorbed in the human intestine through the action of bile salts, passive diffusion, or transporters[38]. After absorption, phenolic compounds can undergo conjugation with glucuronic acid in enterocytes or hepatocytes, or they can circulate in the bloodstream bound to albumin[39]. Conjugated phenolic compounds can cross cell membranes through carrier proteins and can reach different tissues[38], including the stomach.
Therefore, based on the in silico results and the capacity of phenolic compounds to penetrate cells, these polyphenols have potential for subsequent in vitro and in vivo studies for the treatment of gastric H. pylori infections. They not only exhibit antimicrobial activity, as described for plants containing these compounds, but also have the ability to bind to and destabilize the interaction between CagA and epithelial cells. This interference could potentially prevent the initiation of changes leading to malignant transformation of gastric cells, such as the activation of PAR1/MARK kinases causing loss of cell polarization, and the inactivation of p53 resulting in uncontrolled and disordered cell proliferation[20,29].

A study by Castillo-Juárez et al[40] demonstrated the anti-H. pylori activity of some plants commonly used in traditional Mexican medicine, including Moussonia deppeana. This plant, popularly known as tlanchichinol, contains one of the five phenolic compounds analyzed in this study-chlorogenic acid. It was observed that this phenolic acid exhibited better results than the antibiotic metronidazole in inhibiting bacterial growth in vitro[29,40]. Furthermore, the in silico binding of chlorogenic acid with the central region of CagA suggests its potential for in vitro and/or in vivo testing to assess its effectiveness in interfering with the interaction between CagA and the plasma membrane, thereby potentially affecting the cell signaling pathway related to gastric cell differentiation.

Szewczyk et al[41], in a separate study, investigated the antimicrobial properties of plants from the Balsaminaceae family, including the species Impatiens glandulifera, (Himalayan balsam), through an in vitro study. The study revealed
that *I. glandulifera* exhibits high concentrations of phenolic acids, particularly in its aerial parts, and significant antioxidant and antimicrobial activity against *Staphylococcus aureus*, *S. epidermidis*, *Micrococcus luteus*, *Bacillus subtilis*, *B. cereus*, *Streptococcus pneumoniae*, and *S. pyogenes*. However, direct studies confirming the antimicrobial activity of *I. glandulifera* against *H. pylori* are lacking.

Nevertheless, Vieira *et al.*[28] isolated some flavonoids from this plant through chromatography-kaempferol, quercetin, and myricetin—which, according to our findings, demonstrate *in silico* potential as interferents of the CagA oncoprotein. Among these, due to its binding site, kaempferol appears to be the most effective in destabilizing the interaction between CagA and the epithelial cell membrane. Therefore, *I. glandulifera* warrants further exploration to evaluate its efficacy in
halting precancerous changes induced by CagA-positive *H. pylori* strains.

The plant Buddleja indica, known for its richness in kaempferol, caffeic acid (a metabolite of chlorogenic acid), and quercetin, is reported to possess anti-diabetic, hepatoprotective, antioxidant, and antimicrobial properties[42,43]. Youssef et al[42] highlighted the bacteriostatic activity of *B. indica* against *H. pylori* in an in vitro study. Given that this plant contains two of the compounds discussed in this study, it could be explored in further research on anti-carcinogenic therapy.

Other plants that could be investigated for the presence of the phenolic compounds in this study include Polygonum tinctorium, or indigo (kaempferol, quercetin, and caffeic acid), known for their bactericidal and bacteriostatic activity[44,45]; Rubus ulmifolius, or blackberry (kaempferol, quercetin, and caffeic acid), with bactericidal action[46,47]; Poncirus trifoliata (ponciretin), exhibiting bacteriostatic action[48-50]; Oliveira decumbens (kaempferol), and Hibiscus rosa-sinensis (myricetin, quercetin, kaempferol), with anti-urease and bacteriostatic activity[51-53]. In our study, among the phenolic compounds tested, kaempferol and chlorogenic acid appear to be the most promising candidates for interfering with the interaction between CagA and the phospholipids of the plasma membrane, as they exhibit lower affinity energies, indicating greater stability of the complexes.

The studies correlating flavonoids/phenolic acids and *H. pylori* primarily focus on the action of these compounds as bactericides, bacteriostats, and anti-urease agents, rather than addressing virulence factors that directly damage host cells, such as CagA. Most research aims to identify alternatives to antibiotics due to the process of bacterial resistance. Indeed, the eradication of *H. pylori* infection is crucial due to its pathogenic factors, as well as the physiological and biochemical mechanisms that can lead to the malignancy of gastric cells[54].

The utilization of bioinformatics in scientific research is increasingly contributing to the study of molecular interactions [55]. Among these studies, González et al[56] investigated several flavonoids, including kaempferol, quercetin, and myricetin, for their ability to bind to and inactivate the homeostatic stress regulatory protein, yielding promising results. As this protein is crucial for fundamental *H. pylori* activities such as energy metabolism and genetic material replication, its inactivation results in either bacterial death or reduced multiplication. This study aligns with the same rationale as the present work, wherein the binding of compounds to bacterial components leads to detrimental implications for pathogenic progression.

Inhibiting the action of CagA has the potential to halt the progression of gastric *H. pylori* lesions to malignancy, as this protein disrupts multiple pathways regulating cellular homeostasis. Upon entry into cells through T4SS, phosphorylation of EPIYA motifs occurs, leading to the recruitment of various molecules to the plasma membrane of gastric cells, thereby modulating and altering multiple cell signaling pathways[57]. EPIYA-C motifs are phosphorylated by Src family kinases; *H. pylori* strains containing higher numbers of EPIYA-C motifs are associated with an increased likelihood of gastric cancer emergence. CagA interacts with the tyrosine phosphatase S *H. pylori*-2 and potentiates the action of the Erk-MAP kinase, with or without utilizing the Ras protein, while also inactivating the focal adhesion kinase FAK. This pathway results in the hummingbird phenotype, characterized by a rearrangement of the cytoskeleton in gastric cells, leading to enhanced cell motility and elongation[58,59], and is implicated in the malignancy process[60]. Therefore, since the transition from a precancerous state to cancer is characterized by accelerated and disordered tissue growth, inhibiting the CagA oncoprotein could prevent or slow down this process.

Since the molecular events leading to the hummingbird phenotype are dependent on the action of the Cag oncoprotein, blocking this protein could prevent the cellular oncogenic process. One way to block it would be to prevent CagA from interacting with the plasma membrane of gastric cells, which could be achieved by using a phenolic compound, as suggested by the data from this *in silico* study (Figure 5).

Indeed, a study on the post-translational processing of the CagA oncoprotein revealed that this process may be involved in the pathogenesis of *H. pylori* infection, as CagA fragmentation alters its functionality, thereby reducing the induction of the hummingbird phenotype[61]. This suggests that interventions targeting CagA may reduce carcinogenic predisposition, similar to the observations made in this *in silico* study. It is a fact that the tertiary conformation of a protein is determined by the interaction between its amino acid residues, and the binding, whether transient or otherwise, of external molecules to this assembly can lead to a state of inactivity[62]. Thus, by binding to the central region of CagA, the phenolic compounds in this study, especially kaempferol and chlorogenic acid, may induce conformational and functional changes in this virulence factor.

Finally, the present study has some limitations regarding its application in clinical treatments, as the functioning of the human organism is complex, involving a myriad of biochemical and physiological cascades that interact to achieve homeostasis. Therefore, since computational tools simulate only some physiological parameters, the environment in which the interaction between CagA and phenolic compounds was tested does not fully reflect the physiological environment, and all potential metabolic influences were not considered. Hence, further *in vitro* and *in vivo* studies should be conducted to complement the data obtained.

**CONCLUSION**

The *in silico* data suggest that phenolic compounds (flavonoids and phenolic acids) present in medicinal plants used to treat *H. pylori* infection bind to the CagA oncoprotein in its central region, close to the membrane anchoring site. Furthermore, none of the amino acid residues of CagA predicted as binding sites are involved in the interaction with the phenolic compounds analyzed in this study. It is possible that these residues interact with other secondary metabolites in medicinal plants, which would increase the chance of interfering with CagA’s action. Therefore, medicinal plants have the potential to eliminate *H. pylori* infection due to their antimicrobial activities already proven in the literature and could...
also interfere with the action of CagA after being injected into the gastric epithelial cell. This interference could affect the cell differentiation process that culminates in the hummingbird phenotype and, consequently, prevent and/or block the onset of gastric cancer. It is important to emphasize that this is a computational study and, therefore, has limitations; thus, the data obtained must be analyzed in *vitro* and *in vivo* to validate the findings.

**FOOTNOTES**

**Author contributions:** Peiter GC performed the *in silico* experiments and analysis; Vieira RV and Teixeira KN interpreted the data and wrote the manuscript; Zarpelon-Schutz AC, de Melo FF and Teixeira KN performed the critical analysis of the results and coordinated the study; all authors approved the final version of the manuscript.

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