



Helicobacter pylori: Microorganismo patógeno o mutualista en poblaciones colombianas

Helicobacter pylori: Pathogenic or mutualistic microorganism in Colombian populations

Helicobacter pylori: microrganismo patógeno ou mutualista em populações Colombianas

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Resumen

Introducción: El riesgo de desarrollar cáncer gástrico varía entre continentes, países y regiones. A pesar de que existe una alta prevalencia de *Helicobacter pylori* su rol como patógeno o mutualista define el riesgo de cáncer gástrico en las regiones de Colombia. **Objetivo:** Discutir el rol de *Helicobacter pylori* en el riesgo de cáncer gástrico en Colombia. **Materiales y métodos:** Revisión de literatura mediante la búsqueda, en las bases de datos LILACS, SciELO, PubMed. **Resultados:** La coevolución del humano y de *Helicobacter pylori*; la virulencia de genes *cagA*, *vacA*; el tipo de respuesta inmune inflamatoria a *Helicobacter pylori* (Th1) o antiinflamatoria (Th2) y la susceptibilidad humana a cáncer gástrico (*IL1β*, *IL10*), junto a la dieta y factores ambientales explican el papel de *Helicobacter pylori* como patógeno o mutualista asociado al riesgo de cáncer gástrico en Colombia. **Conclusiones:** *Helicobacter pylori* tiene un rol mutualista principalmente en poblaciones de bajo riesgo de cáncer gástrico (costas), no obstante, en poblaciones con alto riesgo de cáncer gástrico (andes), su papel como patógeno amerita la erradicación; única estrategia para mitigar la alta incidencia de este cáncer en Colombia.

Palabras clave: *Helicobacter pylori*; incidencia; cáncer gástrico; factores de riesgo; coevolución. (Fuente: DeCS, Bireme).

Abstract

Introduction: The risk to develop gastric cancer varies between continents, countries and regions. Although there is a high prevalence of *Helicobacter pylori*, its role as either pathogen or mutualistic bacteria defines the risk of gastric cancer in Colombian regions. **Objective:** To discuss the role of *Helicobacter pylori* in the risk of gastric cancer in Colombia. **Materials and methods:** A literature review based on searching LILACS, SciELO, and PubMed databases. **Results:** *Helicobacter pylori* role as either a pathogen or mutualistic microorganism associated with gastric cancer risk in Colombia can be explained by analyzing elements such as: human and *Helicobacter pylori* coevolution; *cagA* and *vacA* gene virulence; inflammatory (Th1) or anti-inflammatory (Th2) responses induced by *Helicobacter pylori*; human susceptibility to gastric cancer (*IL1β*, *IL10*); diet; and environmental factors. **Conclusions:** Even though *Helicobacter pylori* has a mutualistic role in populations at low gastric cancer risk (coastal regions), its role as a pathogen in populations at higher risk (Andean regions) justifies its eradication as a key strategy to mitigate the incidence of this cancer in Colombia.

Keywords: *Helicobacter pylori*; incidence; stomach Neoplasms; risk factors; biological coevolution. (Source: DeCS, Bireme).

Resumo

Introdução: O risco de desenvolver câncer gástrico varia entre continentes, países e regiões. Embora haja uma alta prevalência de *Helicobacter pylori*, seu papel como patógeno ou mutualista define o risco de câncer gástrico nas regiões da Colômbia. **Objetivo:** Discutir o papel do *Helicobacter pylori* no risco de câncer gástrico na Colômbia. **Materiais e métodos:** Revisão da literatura por meio da busca, nas bases de dados LILACS, SciELO e PubMed. **Resultados:** A coevolução de humanos e *Helicobacter pylori*; a virulência dos genes *cagA*, *vacA*; o tipo de resposta imune inflamatória ao *Helicobacter pylori* (Th1) ou anti-inflamatório (Th2) e a suscetibilidade humana ao câncer gástrico (*IL1β*, *IL10*), juntamente com a dieta e fatores ambientais explicam o papel do *Helicobacter pylori* como patógeno ou mutualista associado ao risco de câncer gástrico na Colômbia. **Conclusões:** *Helicobacter pylori* tem um papel mutualista principalmente em populações de baixo risco de câncer gástrico (litoral), porém, em populações com alto risco de câncer gástrico (andes), seu papel como patógeno justifica a erradicação; única estratégia para mitigar a alta incidência deste câncer na Colômbia.

Palavras chave: *Helicobacter pylori*; incidência; neoplasias gástricas; fatores de risco; coevolução biológica. (Fonte: DeCS, Bireme).

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genes de citocinas *IL-1 β -5* e *IL-10-1082*, considerados marcadores de susceptibilidad humana a cáncer gástrico^(31,40,41,46,50,51,56).

El posible efecto patógeno de la bacteria es el producto del cambio de estilo de vida y la dieta contemporánea por las sociedades actuales en Colombia producto de un sincretismo cultural después de la colonización europea. Para entender con mayor exactitud el rol y los mecanismos que forjan la patogénesis de *H. pylori* en el ser humano, es necesario ampliar el conocimiento en cuanto a las relaciones ecológicas con el microbioma y sus relaciones evolutivas en futuros estudios^(65,66).

Conclusiones

La definición de *Helicobacter pylori* como patógeno o mutualista en Colombia se puede describir a partir del proceso de coevolución del humano y de la bacteria; los alelos de virulencia de genes *vacA* y motivos EPIYA de *cagA*; el tipo de respuesta inmune inflamatoria a *Helicobacter pylori* (Th1) o antinflamatoria (Th2) y la susceptibilidad humana a cáncer gástrico (*IL1 β* , *IL10*), junto a la dieta y factores ambientales.

Helicobacter pylori tiene un rol mutualista principalmente en poblaciones de bajo riesgo de cáncer gástrico (costas colombianas), no obstante, en poblaciones con alto riesgo de cáncer gástrico (montañas andinas) su papel como patógeno amerita su erradicación, siendo la única estrategia válida para mitigar la alta incidencia de cáncer gástrico en Colombia.

Conflictos de intereses: Ninguno declarado por los autores.

Referencias

- Alipour M. Molecular Mechanism of *Helicobacter pylori*-Induced Gastric Cancer. *Journal of gastrointestinal cancer*. 2021; 52(1):23–30. DOI: 10.1007/s12029-020-00518-5.
- Chmiela M, Karwowska Z, Gonciarz W, Allushi B, Stączek P. Host pathogen interactions in *Helicobacter pylori* related gastric cancer. *World journal of gastroenterology*. 2017; 23(9):1521–1540. DOI: 10.3748/wjg.v23.i9.1521.
- Baj J, Forma A, Sitarz M, Portincasa P, Garruti G, Krasowska D, et al. *Helicobacter pylori* Virulence Factors-Mechanisms of Bacterial Pathogenicity in the Gastric Microenvironment. *Cells*. 2020; 10(1):27. DOI: 10.3390/cells10010027.
- Crowe SE. *Helicobacter pylori* Infection. *N Engl J Med*. 2019; 380(12):1158-1165. DOI: 10.1056/NEJMcp1710945.
- Alexander SM, Retnakumar RJ, Chouhan D, Devi T, Dharmaseelan S, Devadas K, et al. *Helicobacter pylori* in Human Stomach: The Inconsistencies in Clinical Outcomes and the Probable Causes. *Frontiers in microbiology*. 2021; 12:713955. DOI: 10.3389/fmicb.2021.713955.
- Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: a cancer journal for clinicians*. 2018; 68(6):394-424. DOI: 10.3322/caac.21492.
- Blaser M. Stop the killing of beneficial bacteria. *Nature*. 2011; 476(7361):393-394. DOI: 10.1038/476393a.
- Li J, Perez-Perez GI. *Helicobacter pylori* the latent human pathogen or an ancestral commensal organism. *Frontiers in microbiology*. 2018; 9:609. DOI: 10.3389/fmicb.2018.00609.
- Reshetnyak VI, Burmistrov AI, Maev IV. *Helicobacter pylori*: Commensal, symbiont or pathogen? *World Journal of Gastroenterology*. 2021; 27(7):545-560. DOI: 10.3748/wjg.v27.i7.545.
- Maixner F, Krause-Kyora B, Turaev D, Herbig A, Hoopmann MR, Hallows JL, et al. The 5300-year-old *Helicobacter pylori* genome of the Iceman. *Science*. 2016; 351(6269):162-165. DOI: 10.1126/science.aad2545.
- Maixner F, Thorell K, Granehäll L, Linz B, Moodley Y, Rattei T, et al. *Helicobacter pylori* in ancient human remains. *World journal of gastroenterology*. 2019; 25(42):6289-6298. DOI: 10.3748/wjg.v25.i42.6289.
- Moodley Y, Linz B, Bond RP, Nieuwoudt M, Soodyall H, Schlebusch CM, et al. Age of the association between *Helicobacter pylori* and man. *PLoS Pathogens*. 2012; 8(5):e1002693. DOI: 10.1371/journal.ppat.1002693.
- Linz B, Balloux F, Moodley Y, Manica A, Liu H, Roumagnac P, et al. An African origin for the intimate association between humans and *Helicobacter pylori*. *Nature*. 2007; 445(7130):915–918. DOI: 10.1038/nature05562.
- Muñoz-Ramirez ZY, Pascoe B, Mendez-Tenorio A, Mourkas E, Sandoval-Motta S, Perez-Perez G, et al. A 500-year tale of co-evolution, adaptation, and virulence: *Helicobacter pylori* in the Americas. *The ISME journal*. 2021; 15(1):78–92. DOI: 10.1038/s41396-020-00758-0.
- Park JY, Forman D, Waskito LA, Yamaoka Y, Crabtree JE. Epidemiology of *Helicobacter pylori* and CagA-Positive Infections and Global Variations in Gastric Cancer. *Toxins*. 2018; 10(4):163. DOI: 10.3390/toxins10040163.
- de Sabet T, Piazuelo MB, Shaffer CL, Schneider BG, Asim M, Chaturvedi R, et al. Phylogeographic origin of *Helicobacter pylori* is a determinant of gastric cancer risk. *Gut*. 2011; 60(9):1189–95. DOI: 10.1136/gut.2010.234468.
- Correa P. Gastric cancer: Overview. *Colomb Med*. 2013; 44(2):211-7. DOI: 10.1016/j.gtc.2013.01.002.
- Correa P, Piazuelo B. Gastric cancer: the colombian enigma. *Revista Colombiana de Gastroenterología*. 2010; 25(4):334-337. Disponible en: http://www.scielo.org.co/pdf/rccg/v25n4/en_v25n4a01.pdf
- Bedoya-Urresta Á, Yépez Y, Calvache D, Cifuentes Y, Lucero N, González P, et al. Proyecto Urkunina 5000 Investigación de la prevalencia de lesiones precursoras y del efecto de la erradicación de *Helicobacter pylori* como prevención primaria del cáncer gástrico en el departamento de Nariño. *Revista Colombiana de Cirugía*. 2018; 33(4):345-352. DOI: 10.30944/20117582.81.
- Kinoshita-Daitoku R, Kiga K, Miyakoshi M, Otsubo R, Ogura Y, Sanada T, et al. A bacterial small RNA regulates the adaptation of *Helicobacter pylori* to the host environment. *Nature communications*. 2021; 12(1):2085. DOI: 10.1038/s41467-021-22317-7.
- Takahashi-Kanemitsu A, Knight CT, Hatakeyama M. Molecular anatomy and pathogenic actions of *Helicobacter pylori* CagA that underpin gastric carcinogenesis. *Cellular & molecular immunology*. 2020; 17:50–63. DOI: 10.1038/s41423-019-0339-5.
- Inagaki T, Nishiumi S, Ito Y, Yamakawa A, Yamazaki Y, Yoshida M, et al. Associations Between CagA, VacA, and the Clinical Outcomes of *Helicobacter pylori* Infections in Okinawa, Japan. *The Kobe journal of medical sciences*. 2017; 63(2):E58–E67. Disponible en: <https://pubmed.ncbi.nlm.nih.gov/29434176/>
- Bridge DR, Blum FC, Jang S, Kim J, Cha JH, Merrell DS. Creation and Initial Characterization of Isogenic *Helicobacter pylori* CagA EPIYA Variants Reveals Differential Activation of Host Cell Signaling Pathways. *Scientific reports*. 2017; 7(1):11057. DOI: 10.1038/s41598-017-11382-y.
- Waksman G. From conjugation to T4S systems in Gram-negative bacteria: a mechanistic biology perspective. *EMBO reports*. 2019; 20(2):e47012. DOI: 10.15252/embr.201847012.
- Wroblewski LE, Peek RM Jr, Wilson KT. *Helicobacter pylori* and Gastric Cancer: Factors That Modulate Disease Risk. *Clin Microbiol Rev*. 2010; 23(4):713-39. DOI: 10.1128/CMR.00011-10.
- Lin TY, Lan WH, Chiu YF, Feng CL, Chiu CH, Kuo CJ, et al. Statins' Regulation of the Virulence Factors of *Helicobacter pylori* and the Production of ROS May Inhibit the Development of Gastric Cancer. *Antioxidants (Basel)*. 2021; 10(8):1293. DOI: 10.3390/antiox10081293.
- Ito N, Tsujimoto H, Ueno H, Xie Q, Shinomiya N. *Helicobacter pylori*-Mediated Immunity and Signaling Transduction in Gastric Cancer. *Journal of clinical medicine*. 2020; 9(11):3699. DOI: 10.3390/jcm9113699.
- Diechler S, Chichirau BE, Posselt G, Sgouras DN, Wessler S. *Helicobacter pylori* CagA EPIYA Motif Variations Affect Metabolic Activity in B Cells. *Toxins*. 2021; 13(9):592. DOI: 10.3390/toxins13090592.
- Miura M, Ohnishi N, Tanaka S, Yanagiya K, Hatakeyama M. Differential oncogenic potential of geographically distinct *Helicobacter pylori* CagA isoforms in mice. *Int J Cancer*. 2009; 125(11):2497–2504. DOI: 10.1002/ijc.24740.

30. Hatakeyama M. Anthropological and clinical implications for the structural diversity of the *Helicobacter pylori* CagA oncoprotein. *Cancer Sci.* 2011; 102(1):36–43. DOI: 10.1111/j.1349-7006.2010.01743.x.
31. Sicinschi LA, Correa P, Peek RM, Camargo MC, Piazuelo MB, Romero-Gallo J, et al. CagA C-terminal variations in *Helicobacter pylori* strains from Colombian patients with gastric precancerous lesions. *Clin Microbiol Infect.* 2010; 16(4):369–378. DOI: 10.1111/j.1469-0691.2009.02811.x.
32. Rodríguez Gómez ER, Otero Regino W, Monterrey PA, Trespalacios Rangel AA. *cagA* gene EPIYA motif genetic characterization from Colombian *Helicobacter pylori* isolates: Standardization of a molecular test for rapid clinical laboratory detection. *PloS one.* 2020; 15(1):e0227275. DOI: 10.1371/journal.pone.0227275.
33. Xu Y, Jing JJ, Gong YH, Xu Q, Zhang WL, Piao Y, et al. Changes in biological and virulent characteristics of *Helicobacter pylori* exposed to high salt. *Asian Pac J Cancer Prev.* 2011; 12(10): 2637-41. Disponible en: http://journal.waocp.org/article_25936.html
34. Soyfoo DM, Doomah YH, Xu D, Zhang C, Sang HM, Liu YY, et al. New genotypes of *Helicobacter pylori* VacA d-region identified from global strains. *BMC molecular and cell biology.* 2021; 22:4. DOI: 10.1186/s12860-020-00338-2.
35. Kishk RM, Soliman NM, Anani MM, Nemr N, Salem A, Attia F, et al. Genotyping of *Helicobacter pylori* Virulence Genes *cagA* and *vacA*: Regional and National Study. *International journal of microbiology.* 2021; 2021:5540560. DOI: 10.1155/2021/5540560.
36. Terebiznik MR, Raju D, Vázquez CL, Torbricki K, Kulkarni R, Blanke SR, et al. Effect of *Helicobacter pylori*'s vacuolating cytotoxin on the autophagy pathway in gastric epithelial cells. *Autophagy.* 2009; 5(3):370 –379. DOI: 10.4161/auto.5.3.7663.
37. Tsugawa H, Suzuki H, Saya H, Hatakeyama M, Hirayama T, Hirata K, et al. Reactive oxygen species-induced autophagic degradation of *Helicobacter pylori* CagA is specifically suppressed in cancer stem-like cells. *Cell Host Microbe.* 2012; 12(6):764–777. DOI: 10.1016/j.chom.2012.10.014.
38. Gangwer KA, Shaffer CL, Suerbaum S, Lacy DB, Cover TL, Bordenstein SR. Molecular evolution of the *Helicobacter pylori* vacuolating toxin gene *vacA*. *J Bacteriol.* 2010; 192(23):6126–6135. DOI: 10.1128/JB.01081-10.
39. Cover TL. *Helicobacter pylori* diversity and gastric cancer risk. *MBio.* 2016; 7(1):e01869-15. DOI: 10.1128/mBio.01869-15.
40. Bravo LE, van Doorn LJ, Realpe JL, Correa P. Virulence-associated genotypes of *Helicobacter pylori*: do they explain the African enigma? *Am J Gastroenterol.* 2002; 97(11):2839–2842. Disponible en: https://journals.lww.com/ajg/Abstract/2002/11000/Virulence_Associated_Genotypes_ofHelicobacter.30.aspx
41. Guevara-Tique A, Valencia FC, Olaya JJ, Torres RC, Parra G, Serrano I, et al. Infection with *Helicobacter pylori* Presenting the *vacA* s2m2 haplotype is Strongly Associated with Protection Against Gastric Cancer. *Research Square [Preprint].* 2021. DOI: 10.21203/rs.3.rs-250522/v1.
42. Quiroga AJ, Diana Marcela C, Bravo MM. Frecuencia de los genotipos babA2, oipA y cagE de *Helicobacter pylori* en pacientes colombianos con enfermedades gastroduodenales. *Biomédica.* 2005; 25(3): 325-334. Disponible en: http://www.scielo.org.co/scielo.php?script=sci_abstract&pid=S0120-41572005000300008&lng=e&nrm=iso&tlang=es
43. Pazos AJ, Guzman K. Sa248 Microevolution *Helicobacter pylori* *alpA* gene in Colombian population. *Gastroenterology.* 2021; 160(6): S-464. DOI: 10.1016/S0016-5085(21)01817-5.
44. Correa P, Piazuelo MB. Evolutionary History of the *Helicobacter pylori* Genome: Implications for Gastric Carcinogenesis. *Gut liver.* 2012; 6(1):21–28. DOI: 10.5009/gnl.2012.6.1.21.
45. Gutiérrez-Escobar AJ, Trujillo E, Orlando E, Acevedo O, Bravo MM. Phylogenomics of Colombian *Helicobacter pylori* isolates. *Gut Pathogens.* 2017; 9:52. DOI: 10.1186/s13099-017-0201-1.
46. Guzman K, Montenegro L, Pazos A. The *Helicobacter pylori* genome evolution in different gastric cancer risk Colombian populations. *Research Square [Preprint].* 2021. DOI: 10.21203/rs.3.rs-960798/v1.
47. Guzman K, Montenegro L, Pazos A. *Helicobacter pylori* *babA* gene evolution and adaptation in Colombian populations. *Annals of Oncology.* 2021; 32(Suppl 3):S171-S172. DOI: 10.1016/j.annonc.2021.05.267.
48. Muñoz-Ramírez ZY, Mendez-Tenorio A, Kato I, Bravo MM, Rizzato C, Thorell K, et al. Whole Genome Sequence and Phylogenetic Analysis Show *Helicobacter pylori* Strains from Latin America Have Followed a Unique Evolution Pathway. *Frontiers in cellular and infection microbiology.* 2017; 7:50. DOI:10.3389/fcimb.2017.00050.
49. Guzman K, Pazos AJ. Coevolutionary analysis of *Helicobacter pylori* isolated from Colombian patients. *Gastroenterology.* 2020; 158(6):S-569. DOI: 10.1016/S0016-5085(20)32128-4.
50. Kodaman N, Pazos A, Schneider BG, Piazuelo MB, Mera R, Sobota RS, et al. Human and *Helicobacter pylori* coevolution shapes the risk of gastric disease. *Proc Natl Acad Sci USA.* 2014; 111(4):1455-1460. DOI: 10.1073/pnas.1318093111.
51. Pazos AJ, Pabon VL, Angulo AF. Socio-Environmental Factors and Colombian Host Gene Polymorphisms on Development of Gastric Diseases. *Gastroenterology.* 2019; 156(6):S-739. DOI: 10.1016/S0016-5085(19)38781-5.
52. Piazuelo MB, Camargo MC, Mera RM, Delgado AG, Peek Jr RM, Correa H, et al. Eosinophils and mast cells in chronic gastritis: possible implications in carcinogenesis. *Hum Pathol.* 2008; 39(9):1360–1369. DOI: 10.1016/j.humpath.2008.01.012.
53. Camargo MC, Burk RF, Bravo LE, Piazuelo MB, Hill KE, Fonham ET, et al. Plasma selenium measurements in subjects from areas with contrasting gastric cancer risks in Colombia. *Arch Med Res.* 2008; 39(4):443-51. DOI: 10.1016/j.arcmed.2007.12.004.
54. Bertuccio P, Alicandro G, Rota M, Pelucchi C, Bonzi R, Galeone C. Citrus fruit intake and gastric cancer: The stomach cancer pooling (StoP) project consortium. *International journal of cancer.* 2019; 144(12):2936-2944. DOI: 10.1002/ijc.32046.
55. Li S, Zhang F, Li J, Hu X, Zhao W, Zhang K, Li J. The role of the Epstein-Barr virus-encoded BARF1 gene expressed in human gastric epithelial cells. *The Turkish Journal of Gastroenterology.* 2020; 31(11):775. DOI: 10.5152/tjg.2020.18827.
56. Toh J, Wilson RB. Pathways of Gastric Carcinogenesis, *Helicobacter pylori* Virulence and Interactions with Antioxidant Systems, Vitamin C and Phytochemicals. *International journal of molecular sciences.* 2020; 21(17):6451. DOI: 10.3390/ijms21176451.
57. Bonequi P, Meneses-González F, Correa P, Rabkin CS, Camargo MC. Risk factors for gastric cancer in Latin America: a meta-analysis. *Cancer Causes & Control.* 2013; 24(2):217-231. DOI: 10.1007/s10552-012-0110-z.
58. Ford AC, Yuan Y, Forman D, Hunt R, Moayyedi P. *Helicobacter pylori* eradication for the prevention of gastric neoplasia. *Cochrane Database of Systematic Reviews.* 2015; 2015(7):CD005583. DOI: 10.1002/14651858.CD005583.pub2.
59. Chiang TH, Chang WJ, Chen LS, Yen AMF, Fann JCY, Chiu SYH, et al. Mass eradication of *Helicobacter pylori* to reduce gastric cancer incidence and mortality: a long-term cohort study on Matsui Islands. *Gut.* 2021; 70(2):243-250. DOI: 10.1136/gutjnl-2020-322200.
60. Kumar S, Metz DC, Ellenberg S, Kaplan DE, Goldberg DS. Risk factors and incidence of gastric cancer after detection of *Helicobacter pylori* infection: a large cohort study. *Gastroenterology.* 2020; 158(3):527-536. DOI: 10.1053/j.gastro.2019.10.019.
61. Piazuelo MB, Bravo LE, Mera RM, Camargo MC, Bravo JC, Delgado AG, et al. The Colombian chemoprevention trial: 20-year follow-up of a cohort of patients with gastric precancerous lesions. *Gastroenterology.* 2021; 160(4):1106-1117.e3. DOI: 10.1053/j.gastro.2020.11.017.
62. Hunt RH, Yaghoobi M. The esophageal and gastric microbiome in health and disease. *Gastroenterol Clin.* 2017; 46(1):121–141. DOI: 10.1016/j.gtc.2016.09.009.
63. Borbet TC, Zhang X, Müller A, Blaser MJ. The role of the changing human microbiome in the asthma pandemic. *Journal of allergy and clinical immunology.* 2019; 144(6):1457–1466. DOI: 10.1016/j.jaci.2019.10.022.
64. Miftahussurur M, Nusi IA, Graham DY, Yamaoka Y. *Helicobacter*, hygiene, atopy, and asthma. *Front Microbiol.* 2017; 8:1034. DOI: 10.3389/fmicb.2017.01034.
65. Cho I, Blaser MJ. The human microbiome: at the interface of health and disease. *Nature Reviews Genetics.* 2012; 13(4), 260-270. DOI: 10.1038/nrg3182.
66. Caguazango JC. Ecological models of gastric microbiota dysbiosis: *Helicobacter pylori* and gastric carcinogenesis. *Medicina e in Microecology.* 2020; 3, 100010. DOI: 10.1016/j.medmic.2020.100010.