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The Role of Helicobacter Pylori Virulence Factors in Gastric Cancer

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Introduction: Gastrointestinal (GI) cancers are considered among the most important causes of mortality and morbidity. Helicobacter pylori infection has been proven to be highly associated with the development of a variety of gastric diseases such as chronic gastritis, peptic ulcer disease (PUD), mucosa-associated lymphoid tissue (MALT), and gastric cancer (GC). To date, the exact role of the virulence factors in gastric diseases and other diseases remains elusive and controversial.

Methods: The present study is a classic systematic review (expert opinion), in which articles published in English and Persian languages derived from Web of Science, Scopus, PubMed, and Iranian databases, including Magiran, IranMede, and scientific information database (SID) without any time limitation were explored using standardized keywords of H. pylori, virulence factors, gastric cancer, a combination of the above words, and other synonymous keywords. Finally, the information and obtained results were collected and interpreted.

Results: In total, 14 of the 172 articles reviewed had inclusion criteria with the approval of the responsible author. According to the results, the development of chronic bacterial inflammation due to pathogenic mechanisms and factors, especially the role of cagA and vacA genes in gastric cancer, remains an important medical problem.

Conclusions: Each of the H. pylori virulence factors can have a role in cancer development, and it appears that on-time H. pylori treatment is one of the best methods to prevent gastric cancer. Therefore, targeting Pathogenic factors of H. pylori to induce apoptosis and stimulate the immune system will be a promising, attractive, and helpful method for cancer prevention.

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INTRODUCTION

According to the statistics, 35% of all cancer-related deaths across the world occur by gastrointestinal cancers [1]. Gastric cancer is one of the most frequent gastrointestinal cancers in Asia, and the

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burden of the disease is rising due to causes such as changing lifestyles, higher incidence of Helicobacter pylori (H. pylori), and other variables [2]. As the most frequent type of cancer in Iran, gastric cancer is a multifactorial disease caused by infectious, environmental, and genetic factors in individuals [3, 4]. Helicobacter pylori is a gram-negative bacterium and gastrointestinal tract pathogen, leading to inflammation in various parts of the gastrointestinal tract [5]. Therefore, H. pylori is considered a main risk factor for gastric cancer [6]. Hedayati et al., (2020) reported the highest prevalence rate of gastric cancer in northwestern, northern, and western cities of Iran, respectively. According to this study, 50% of cancers in Gilan province are gastrointestinal cancers. Afterwards, Ardabil, Zanjan, Azerbaijan (30 cases per 100 thousand people), Ilam, and Kurdistan provinces (20 to 30 cases per 100 thousand people) had a high prevalence of gastric cancer, respectively [7]. Inflammations and infections are predisposing factors for gastrointestinal cancers [8]. The long-term inflammatory response against H. pylori in the gastric mucosa may lead to permanent tissue damage, and consequently, distal gastric cancer. The form and severity of the immune response to H. pylori may be influenced by host genetic factors [9]. Despite significant scientific progress in diseases caused by H. pylori, further research is needed to address many cases of virulence factors in this bacterium. Improved understanding of the pathogenesis of H. pylori-associated gastric cancer may improve the risk stratification for prevention and therapy. Accordingly, this study aims to evaluate the relationship between the virulence factors of H. pylori and their role in causing gastric cancer.

METHODS

This review study was conducted using keywords such as H. pylori, pathogens, gastric cancer, and their potential combination of gastric cancer, as well as other synonymous keywords. These data were collected in available databases, including Web of Science, Scopus, PubMed, IranMedex, and Scientific Information Database without any time limit, and 172 Persian and Latin articles were included in the study upon the approval of the corresponding author. The exclusion criteria were conference papers, papers with insufficient data or without access to the text, and duplicate papers based on PRISMA protocol (Figure 1). Finally, 14 articles were selected for this review.

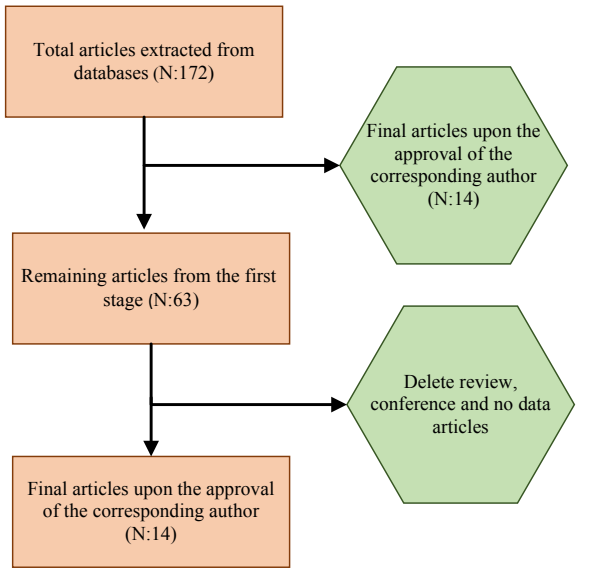

Figure 1: The Process of Selecting and Entering Articles Based on the PRISMA Protocol

RESULTS

The research findings are presented in Table 1.

H. Pylori Virulence Factors

Many studies have reported cytotoxin-associated gene A (CagA) and vacuolating cytotoxin A (VacA) as the essential virulence factors, and some of H. pylori virulence factors are mentioned in Table 2.

The Clinical Course of H. pylori infection and Inflammatory Process of Virulence Factors

The study of the H. pylori pathogenicity is challenging because of the lack of a proper animal model. The available studies have been conducted on rodents such as guinea pigs and rats, but the effects of bacterial infections have not been comparable to those in humans [36]. Given that cagA and vacA cytotoxins are introduced as the most crucial bacterial virulence factors in this study, the clinical course of infection in humans is described as follows:

CagA cytotoxin

This cytotoxin enters the host cytoplasm cells via the four Type IV Secretion System (T4SS), where its tyrosine root is phosphorylated by the SCR kinase family, affecting cellular transmission pathways.

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Table 1: Final Articles Included in the Study

	Title / Year of Publication	Number of Isolates From Patients	Results	References
1	Unique constellations of five polymorphic sites of Helicobacter pylori vacA and cagA status associated with risk of gastric cancer-2019	290	The vacA gene was more common in patients with gastric cancer than in patients without atrophic gastritis.	[10]
2	Antibiotic resistance pattern and frequency of cagA and vacA genes in Helicobacter pylori strains isolated from patients in Tabriz city, Iran-2021	221	The results showed that 63% and 81% of the isolates were positive for cagA and vacA genes, respectively.	[11]
	Precancerous Gastric Lesions with Helicobacter pylori vacA+ /babA2 +/oipA+ Genotype Increase the Risk of Gastric Cancer-2020	160	The vacA, babA2 and oipA genes were most common in chronic gastritis (73%), gastric precancerous lesions (62%) and gastric cancer (91%), respectively.	[12]
4	Helicobacter pylori Pathogenicity Factors Related to Gastric Cancer-2017	109	cagE, cagA and iceA1 were more common in patients with GC compared to other groups.	[13]
5	IDDF2021-ABS-0081 Detection of helicobacter pylori cagA, vacA, iceA virulence genes in patients with gastric cancer-2021	183	CagA and vacA genes were most prevalent.	[14]
6	Molecular detection of the virulence gene's VacA and CagA of Helicobacter pylori by PCR-2021	50	The results showed that 27 (54%) VacA gene and 25 (50%) CagA gene were positive.	[15]
7	The frequency of cagA gene of H.pylori isolated from biopsy specimen in Tehran during 2008-2010	84	The prevalence of cagA was 43.5% higher in patients with peptic ulcer than in patients with gastritis.	[16]
8	Prevalence of cagA, cagT, cagE, vacA and hrgA genes in Helicobacter pylori strains isolated from patients with gastric cancer in Karaj city, 2016	50	The results showed that the frequencies of cagA, cagT, cagE, vacA and hrgA genes were 16 (32%), 8 (16%), 13 (26%), 7 (14%) and 17 (34%), respectively.	[17]
9	H. Pylori bacterial gene cag A expression associated with gastric cancer development- 2021	210	The results of this study showed that the expression of Cag A gene in group I patients was significantly higher than group II GID patients.	[18]
10	Prevalence Of Pathogenic Genes Caga And Vaca Of Helicobacter Pylori Isolated In Patients With Digestive Disorders-2019	120	In this study, the frequency of Helicobacter pylori cagA and vacA genes in patients with gastric cancer and peptic ulcer was more than the group without ulcer and gastric cancer.	[19]
11	Helicobacter pylori genotypes associated with gastric cancer and dysplasia in Colombian patients-2021	202	Age above 50 and VacA genotype were associated with a higher risk of gastric cancer.	[20]
12	Profile of Helicobacter pylori cagA & vacA genotypes and its association with the spectrum of gastroduodenal disease- 2021	374	The frequency of H. pylori virulence gene viz cagPAI (cagA) were 80.9%, and vacA alleles-s1m1 (42%), s1m2 (33%) and s2m2 (25%) genotypes by PCR, respectively	[21]
13	The Prevalence of H. Pylori cagA Gene in Patients with Gastric Ulcer-2021	75	In comparison of patients by sex, the frequency of cagA gene in men and women was 22 (28.39%) and 17 (35.30%), respectively. Finally, comparing patients in terms of age, 16 cases (33.21%) were younger than 40 years and 23 cases (41.7%) were older than 40 years.	[22]
14	Helicobacter pylori cagE, cagG, and cagM can be a prognostic marker for Intestinal and Diffuse Gastric Cancer-2020	285	Helicobacter pylori was found in 93.9% of gastric tumors. The findings suggest the association of Helicobacter pylori genes as potential markers for the histological consequences of gastric cancer	[23]

Table 2: Important Pathogenicity Factors of Helicobacter Pylori

Name of Pathogenic Factor	Characteristics	Function	References
cagA: Cytotoxin-associated gene A	Bacterial oncoprotein 120-140 kDa, the most severe pathogenic factor, cytoplasmic vacuolation, the presence of five repeated amino acid sequences at the end of the terminal carboxyl protein, and extensive variation at the end of carboxylic regions, including EPIYA motifs.	Stopping T-cell function by directly affecting calcium signaling, activating and stimulating immune reactions, high ability to induce tissue inflammation and inhibit cytokine production, and stimulating a variety of transcription factors involved in essential functions (e.g., cell proliferation).	[19, 24-26]
vacA: Vacuolating cytotoxin A	A cytotoxin associated with gene A and a 120 kDa protein available in 60-70% of H. pylori strains.	Spindle tuber viroid playing an important role in cell messaging; induction of apoptosis, ability to destroy gastric epithelial cells and gastric mucosal ulceration, and disrupting the function of intracellular membrane proteins.	[19, 26-28]
Hop: Helicobacter pylori outer membrane proteins			
BabA (HopS): Blood group antigen binding adhesion	A 78 kDa lipoprotein, a wound accelerating factor, a blood group antigen-binding protein, and of the outer membrane proteins of Helicobacter pylori.	Increased risk of peptide ulcer or gastric adenocarcinoma, increased risk of gastric cancer and metaplasia.	[26, 27, 29]
OipA: outer inflammatory protein	A 34 kDa protein, an external inflammation protein, from the outer membrane proteins of Helicobacter pylori	Increased risk of gastric cancer and duodenal ulcer, Damage to gastric epithelial cells, adhesion factor.	[26, 27, 30]
SabA (HopP)	An outer membrane protein, from the outer membrane proteins of Helicobacter pylori, as a receptor for bacteria.	Mediation of binding to glycoconjugates containing sialic acid; Role in chronic infection and disease development.	[26, 27, 31]
AlpA and AlpB	An outer membrane protein, from the outer membrane proteins of Helicobacter pylori, are two homologous genes.	Involved in cell adhesion and regulates proinflammatory intracellular messaging cascades.	[26, 32]
NapA: Neutrophil-activating protein	The 17-kDa NapA protein forms a dodecameric complex with a central cavity that sequesters large amounts of iron. NapA is a cytosolic protein expressed by virtually all H. pylori isolates, and it is oftentimes detected in the culture medium after bacterial growth.	This protein acts as a chemotactic factor and produces free radicals and chemokines. NapA induces production of oxygen radicals from host cells and plays an identifiable role in protecting H. pylori from iron-mediated oxidative DNA damage.	[33-35]

Cell morphological deformation, stimulation of transcription factors involved in controlling essential cellular functions such as cell proliferation, and destruction of junctions between epithelial cells are some of the effects on the cell, which destroy cellular barriers and facilitate the release of food for bacterial acquisition [24].

VacA cytotoxin

This cytotoxin binds to the plasma membrane through the N-terminal region of P33 and C-terminal P55 enters host cells, forms vacuolar structures following infection, and acts as an intracellular reservoir. This cytotoxin is also a B and T cell-mediated immunosuppressant inhibiting antigen supply and enhancing H. pylori colonization [28]. Generally, H. pylori is colonized in gastric mucosa, causing inflammation and immune reactions, and ultimately leading to mucosal destruction, including atrophy and intestinal metaplasia and dysplasia [19].

DISCUSSION

Helicobacter pylori infection Is one of the most prevalent health issues in today's world, the burden of which is rising in developing countries, and its frequency, mortality, and associated expenses are expected to increase in the near future [37]. The findings of several types of research in recent years reveal that H. pylori infection affects various biological processes associated with gastrointestinal illnesses [38]. According to this study, patients with vacA and cagA strains were more prone to develop gastric cancer, and these two factors had a significant role in cancer development. Dos Santos Pereira et al., (2020) reported H. pylori in 93.9% of gastric tumors and mentioned the vital virulence factors of the bacterium. The findings demonstrated the relationship of H. pylori genes as

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potential markers for the histological consequences of gastric cancer [23]. VacA and cagA are two significant determinants of H. pylori pathogenesis, mainly involved in epithelial cell damage and chronic inflammation that may eventually lead to gastric cancer [39]. Rasi Bonab et al., (2021) studied 221 samples of H. pylori isolated from patients. The frequency of cagA and vacA genes in patients was 63.5% to 81%, respectively [11], confirming the cases described in this study. The major pathophysiological event in H. pylori infection is the development and persistence of the inflammatory response due to these bacteria or their products [40]. As a defensive reaction, this inflammation can lead to cancer, diabetes, cardiovascular, lung, and neurological diseases if it becomes chronic [41]. Generally, virulence factors and host immune response determine the role of H. pylori in the development of gastric cancer. Early detection and evaluation of both of these factors can aid in managing the condition and preventing further advancement of gastric disease, as persistent H. pylori infection can pose several risks [25].

It seems that the success of H. pylori in pathogenicity is due to its unique survival strategies and ability to escape the host immune system. Given that CagA and VacA virulence factors induce gastric cancer by activating cell proliferation signaling pathways, the use of current innovative technologies for their inactivation could be a novel therapeutic target for future research. Hence, targeting H. pylori virulence factors to induce apoptosis and stimulate the immune system can be a potential and beneficial technique for cancer prevention.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

ETHICS APPROVAL

Not applicable.

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