Review Article

Journal of Iranian Medical Council, Volume 10, Issue no. 1
http://dx.doi.org/10.18502/jimc.v10i1.23254

Check for updates

Investigating the Role of the Microbiome and Associated Bacteria in the Pathogenesis and Progression of Gallbladder Cancer: A Narrative Review Study

Abolfazl Jafari-Sales[1,2], Ghazal Kadkhodaei-Ilkhchi[2,3], Fatemeh Niroumand-Bostanabad[2,4,5], Zahra Berenjpour[2,3] and Mehrdad Pashazadeh[2,6*]

1. Department of Microbiology, Kaz.C., Islamic Azad University, Kazerun, Iran
2. Infectious Diseases Research Center, TaMS.C., Islamic Azad University, Tabriz, Iran
3. Department of Cellular and Molecular Biology, Ta.C., Islamic Azad University, Tabriz, Iran
4. Department of Nursing, Ta.C., Islamic Azad University, Tabriz, Iran
5. Department of Nursing, GKM.C., Islamic Azad University, Golestan, Iran
6. Department of Laboratory Sciences and Microbiology, TaMS.C., Islamic Azad University, Tabriz, Iran

*** Corresponding author**
Mehrdad Pashazadeh, PhD
Department of Laboratory Sciences and Microbiology, TaMS.C., Islamic Azad University, Tabriz, Iran
Tel: +98 9147881900
Email:
Mehrdadpashazadeh85@gmail.com

Received: 30 Jul 2025
Accepted: 20 Dec 2025

Citation to this article
Jafari-Sales A, Kadkhodaei-Ilkhchi Gh, Niroumand-Bostanabad F, Berenjpour Z, Pashazadeh M. Investigating the Role of the Microbiome and Associated Bacteria in the Pathogenesis and Progression of Gallbladder Cancer: A Narrative Review Study. *J Iran Med Counc*. 2027;10(1):62-75.

Abstract

Gallbladder Cancer (GBC) is recognized as the most common and aggressive neoplasm of the biliary tract, with late-stage diagnosis posing significant therapeutic challenges. In this context, investigating the influence of microbial flora and bacterial populations residing in the gallbladder and biliary ducts on tumor formation and progression is of particular importance. This study analyzes the role of specific microbial species, dysbiosis in the microbial ecosystem, and microbial metabolic byproducts in promoting chronic inflammation, genetic material damage, and epigenetic alterations. For this narrative review, a comprehensive literature search was conducted utilizing the databases PubMed, Scopus, Web of Science, and Google Scholar. The search included papers published without a time limit up to early 2025. Relevant study designs encompassed original research articles, review articles, systematic reviews, meta-analyses, and case reports. The following keywords were systematically employed to identify relevant publications for this comprehensive review: “gallbladder cancer” OR “gallbladder neoplasms”, “microbiome” OR “microbiota”, “bacteria”, “pathogenesis”, and “oncogenesis”. Cancer progression is influenced by various risk factors, including gallstones, chronic inflammation, and bacterial infections like *Salmonella typhi*, *Helicobacter pylori*, and *Escherichia coli*. These bacteria promote gallbladder cancer through biofilm formation, inflammatory responses, and DNA damage. Dysbiosis in the gallbladder microbiome and immune components like Toll-Like Receptors (TLRs) contribute to cancer development. Preventive strategies such as controlling bacterial infections, identifying high-risk individuals *via* serological markers, and maintaining gut microbiome balance are key to reducing GBC risk. Emerging therapies, including engineered bacteria, microbiota modulation, and immunotherapy, offer promising avenues for more effective treatment.

Keywords: Bacteria, Biliary tract, Cancer, Epidemiology, Infection, Gallbladder

Copyright © 2027, Journal of Iranian Medical Council.
This work is licensed under a Creative Commons Attribution–NonCommercial 4.0 International License.

Introduction

Gallbladder Cancer (GBC) is one of the most common and aggressive malignancies of the biliary system, accounting for approximately 80-95% of biliary tract cancers. It ranks as the fifth most prevalent gastrointestinal cancer (1,2). Due to its deep anatomical location, GBC typically lacks apparent phenotypic symptoms in early stages, creating significant challenges for early diagnosis and resulting in a five-year survival rate of less than 5% (3). In advanced stages, patients present with symptoms such as jaundice, weight loss, and abdominal pain (4). Taxonomically, GBC is classified as a subtype of Biliary Tract Cancer (BTC), along with intrahepatic Cholangiocarcinoma (iCCA), extrahepatic Cholangiocarcinoma (eCCA), perihilar Cholangiocarcinoma (pCCA), and distal Cholangiocarcinoma (dCCA). Female gender is a significant risk factor, with women being three times more likely to develop GBC than men (5). Advanced age (>65 years) also constitutes a major risk factor (4). Conditions like cholelithiasis (asymptomatic gallstones) and obesity further increase susceptibility. While 70-90% of GBC patients have gallstones, only ~1% of individuals with gallstones develop cancer (5). Biliary tract diseases such as Primary Sclerosing Cholangitis (PSC) and chronic biliary infections [viral: hepatitis B/C; bacterial: *Salmonella typhi (S. typhi), Helicobacter pylori (H. pylori)*, *Escherichia coli (E. coli)*, Clostridium] contribute to GBC pathogenesis (6,7). Certain bacterial infections establish chronic gallbladder conditions and exhibit oncogenic potential, including *S. typhi, E. coli*, and gallstone-associated infections (8). Chronic inflammation induced by these bacteria elevates GBC risk, with patients showing marked lipid profile alterations and increased bacterial loads in bile (9).

Gallstones may harbor chronic infections and bacterial carriers. *H. pylori* association with GBC has been confirmed *via* molecular techniques and immunohistochemistry (10). Bacterial biofilms have been implicated in multiple cancers (*e.g.*, colorectal, breast, pancreatic, gallbladder) (11). Pro-carcinogenic bacteria include *H. pylori, S. typhi*, *Fusobacterium nucleatum (F. nucleatum), Chlamydia psittaci (C. psittaci), and Chlamydia pneumoniae (C. pneumoniae)* (12). Bile and gallstones provide an ideal niche for biofilm formation by supplying nutrients for bacterial adhesion/proliferation and modulating essential biofilm protein expression. S. typhi biofilm formation in the gallbladder correlates with heightened GBC risk (13).

Although the association between bacteria (such as *S. typhi, H. pylori, E. coli*, Clostridium, and Enterococcus) GBC has been identified, the precise molecular mechanisms underlying their tumorigenic roles, the impact of dysbiosis, and their relationship with treatment resistance remain incompletely understood. Moreover, the connection between specific bacterial species and various stages of GBC progression, their interaction with the host immune response, and the development of targeted therapeutic strategies require more comprehensive investigations. This comprehensive study examines GBC and its associated factors, with a primary focus on bacterial contributions to oncogenesis and progression. Also advanced diagnostic methods and therapeutic strategies were evaluated. The ultimate goal was to provide scientific solutions for early detection, targeted therapy, and improved patient survival.

Materials and Methods

This comprehensive narrative review investigates the role of the microbiome and associated bacteria in the pathogenesis and progression of GBC, with particular emphasis on microbial mechanisms, host-pathogen interactions, and clinical implications. A narrative review methodology was adopted to synthesize current evidence, integrate emerging findings, and address unresolved questions in this evolving field. An extensive literature search was conducted across major scientific databases including PubMed, Scopus, Web of Science, and Google Scholar. The search strategy prioritized high-quality clinical studies, review articles, systematic reviews, meta-analyses, and consensus guidelines. Studies without publication date restrictions up to 2025 were included, ensuring incorporation of both foundational and cutting-edge research. From an initial pool of identified publications, 78 studies meeting the inclusion criteria were selected for in-depth analysis. The review examines several key aspects of microbiome-associated gallbladder carcinogenesis: microbial dysbiosis patterns and specific bacterial

pathogens (including *S. typhi, H. pylori*, and *E. coli*); mechanisms of chronic inflammation, genetic damage, and epigenetic modification; and the role of bacterial metabolites and biofilm formation. The narrative approach was selected to: 1) provide an integrated synthesis of current knowledge on microbiomal influences in GBC development; 2) evaluate diagnostic and therapeutic implications of microbiome research; and 3) identify promising directions for future investigation. This methodology enables both comprehensive coverage and critical analysis of the complex interplay between microbial factors, host immunity, and cancer progression in gallbladder oncology. This evidence acquisition strategy ensures that the review reflects contemporary scientific understanding while maintaining scholarly rigor, ultimately providing a substantive foundation for understanding microbial contributions to gallbladder carcinogenesis and their clinical significance.

Results

Review of gallbladder cancer

The gallbladder is a small, pouch-like organ located beneath the liver, whose primary function is to store and concentrate bile produced by the liver. This fluid plays a crucial role in digesting and absorbing dietary fats and is transported through a network of bile ducts to the small intestine to facilitate digestion (14-16). Gallstones, chronic gallbladder inflammation (cholecystitis), and particularly microbial infections involved in cancer development and progression are among the most significant risk factors (17). The gallbladder and biliary tract microbiome may contribute to the initiation and progression of this cancer through processes such as chronic inflammation, production of toxic metabolites, and epigenetic changes in the organ's epithelial cells. These alterations can lead to dysregulation of key genes and potentially trigger malignant transformations in gallbladder tissue (18). The only curative treatment option is surgical resection, yet only 10% of patients undergo surgery with curative intent, and even among operated patients, the risk of disease recurrence persists (19,20). The primary risk factor for GBC is Gallstone Disease (GSD), which leads to a chronic inflammatory state resulting from repeated cycles of cell death and epithelial layer regeneration. The ABCG8-DH19 polymorphisms in ABCG5/G8 (heterodimer partners) represent the first genetic risk factor for GSD. These polymorphisms enhance protein function, increasing biliary sterol secretion from hepatocyte canalicular membranes into bile. Anomalous Arrangement of the Pancreaticobiliary Duct (AAPBD) is a congenital biliary anomaly associated with GBC, where carcinogenesis follows a multi-step process through the metaplasia-dysplasia-carcinoma sequence, driven by chronic inflammation similar to GSD-induced GBC (21). GBC is a multifactorial disease involving numerous genetic alterations, including disruptions in tumor suppressor genes, oncogenes, DNA repair genes, microsatellite instability, and epigenetic changes (such as gene promoter methylation) (22,23). KRAS (Kirsten Rat Sarcoma viral oncogene) plays a key role in cellular signal transduction and related pathways, and its mutations are common in GBC. The *TP53* gene, a well-known tumor suppressor involved in maintaining genomic integrity and preventing tumor growth, can lead to uncontrolled proliferation of abnormal cells and neoplastic transformation when its function is lost. TP53 mutations are more frequently observed in advanced stages of GBC and often result in the production of non-functional proteins (24-26).

Bacterial associations with gallbladder cancer

Bacterial factors can play a significant role in the development and progression of GBC (10). One of the most notable bacteria in this context is S. typhi, which has been linked to an increased risk of GBC in regions endemic for typhoid fever, such as India and Chile. Chronic S. typhi infection, particularly in asymptomatic carriers, can elevate the risk of GBC by 6 to 12 times (27). This bacterium damages cellular DNA through toxin production and oxidative stress induction and can stimulate abnormal cell proliferation by activating signaling pathways such as AKT and MAPK (mitogen-activated protein kinase) (18). In addition to S. typhi, other bacteria, including *E. coli*, *Clostridium*, and *Enterococcus*, have been identified in the bile and tissues of GBC patients (28). These bacteria convert bile acids into carcinogenic metabolites, such as Deoxycholic Acid (DCA), *via* enzymes like beta-glucuronidase. DCA

concentrations are notably higher in GBC patients than in healthy individuals, and these metabolites can accelerate carcinogenesis by promoting chronic inflammation and cellular damage (29). *E. coli* is the most frequently isolated bacterium from the bile of GBC patients, and its Cytotoxic Necrotizing Factor 1 (CNF1) protein plays a crucial role in cancer progression (17).

H. pylori, another significant micro-organism in gallbladder pathologies, can induce chronic inflammation, further increasing cancer risk (30,31). Dysbiosis, or microbial imbalance in the gallbladder microbiome, also contributes to GBC development (32). 16S rRNA sequencing has revealed reduced microbial diversity in GBC patients, with a predominance of pro-inflammatory species such as *Fusobacterium* (28). These changes, along with elevated secondary bile acids and NF-κB pathway activation, may drive the progression from chronic inflammation to metaplasia and, ultimately, carcinoma (21). Gallstones further exacerbate this process by providing a substrate for bacterial biofilm formation, which facilitates microbial growth (33). Biofilms create an ideal environment for bacterial proliferation, enabling microbial communities to secrete higher quantities of toxins. However, a clear relationship between specific bacterial species and distinct stages of GBC progression has yet to be established, warranting further investigation. Emerging techniques like metagenomics could help identify microbial signatures unique to GBC, enabling earlier diagnosis and targeted therapies (28). These findings may open new avenues for understanding the microbiome's role in GBC pathogenesis and ultimately lead to more effective diagnostic and therapeutic strategies. Bacterial colonization in the gallbladder may promote malignant transformation by degrading bile components, generating carcinogenic compounds, and altering bile salt metabolism, thereby fostering a tumor-permissive microenvironment (1,19) (Table 1).

The impact of salmonella typhi on gallbladder cancer

S. typhi is a Gram-negative bacterium that primarily enters healthy hosts through contaminated food and water (42). The lower small intestine (ileum), liver, spleen, bone marrow, and gallbladder are the most common sites of infection, with the bile-rich gallbladder serving as the main reservoir for *S. typhi* transmission (43). In typhoid-endemic regions such as South Asia, *S. typhi* is recognized as a key pathogen in GBC through the formation of resistant biofilms on gallstones (44). While malignancies are generally associated with lifestyle and genetic factors, *S. typhi* infections and their link to GBC are considered significant risk factors. This infection markedly increases GBC-related mortality in infected individuals compared to non-infected individuals (6,10). The isolation rate of *S. typhi* from bile samples, gallstones, and gallbladder tissues is significantly higher in malignant GBC patients than in those with benign gallbladder diseases, underscoring the strong association between chronic *S. typhi* infection and increased risk of malignant GBC. This highlights the pathogen's critical role in GBC pathogenesis (45). Over 80% of GBC cases are associated with gallstones, while 10% are linked to adenocarcinoma. Chronic carriage of *S. typhi* is strongly correlated with gallstone presence (46,47). Biofilms may facilitate bacterial colonization and chronic persistence. Bile enhances biofilm formation on gallstones

Table 1. Mechanism of bacterial influence on the progression of gallbladder cancer

Bacteria	Signaling pathway affected	Genetic variations
Salmonella typhi	MAPK، AKT (18,34)	Inactivation of tumor suppressor genes (28)
Helicobacter pylori	PI3K/Akt (35)	Increased cell proliferation (35)
Escherichia coli	CNF1, Rho GTPases (28,36)	Genetic mutations (28)
Clostridium	7α-HSDH7, 7β-HSDH (37,38)	Changes in metabolism (37)
Enterococcus	Impaired immune response (39,40)	Cancer metabolites (39,41)

by increasing O-antigen synthesis, creating an environment for long-term bacterial survival. This leads to intestinal recolonization, bacterial shedding in feces, and transmission to new hosts (48).

Biofilms elevate cancer risk due to their ability to evade host immunity, resist antibiotics, and provide a stable niche for bacterial proliferation (49). These biofilm structures alter methylation patterns in tumor suppressor gene promoters *(e.g., CDKN2A and TP53)*, silencing these genes and triggering abnormal cell proliferation—a key step in carcinogenesis (50). Additionally, biofilms metabolically modify bile by producing enzymes that convert bile acids into DCA, particularly through increased lactate and decreased glucose, inducing chronic inflammation and metabolic stress. *S. typhi* also disrupts the biliary microbiome balance, promoting the growth of pro-inflammatory bacteria like *Fusobacterium*. These disturbances create a vicious cycle in cancer pathogenesis. Metagenomics (the study of collective microbial genomes) and metabolomics (the study of small-molecule metabolic profiles) have revealed the complexity of *S. typhi's* role in this mechanism, emphasizing the need for further research (51).

Mechanism of salmonella typhi

S. typhi infection in the gallbladder triggers a severe inflammatory response characterized by elevated levels of mediators such as TNF-α, IL-6, and MCP1 (28). This is likely due to *S. typhi's* interaction with human proteins like MAPK, RAC1, Caveolin 1, and EXOC2, leading to gallbladder adenocarcinoma, which accounts for 85% of GBC cases. These proteins regulate multiple signaling pathways (*e.g.*, PI3K/AKT/mTOR, Ras/Raf/MEK/ERK, MAPK/ERK, CREB/SP-1, and BSG), all of which play pivotal roles in tumor growth and progression (34). The *S. typhi* Enterica serotype encodes the *CdtB* gene, producing the cytotoxic CDT(52). CDT suppresses immunity, facilitating persistent infection and ultimately GBC development (28). Studies also associate Vi antigen with S. typhi in serological samples and GBC (53). Vi antigens modulate inflammatory signaling in infected macrophages and dendritic cells (DCs), promoting disease progression (28). In animal models, chronic *S. typhi* infection in gallstone-bearing mice showed an initial Th1 inflammatory response by day 7 shifting to an anti-inflammatory Th2 response by day 21. This transition involved elevated immunoglobulins, Th2 upstream regulators (IL-4, STAT6), and the master Th2 transcription factor GATA3, increasing T and B cell levels (54). Furthermore, the gut and gallbladder microbiota activate innate and adaptive immune cells (*e.g.*, DCs, macrophages, B cells, T cells), releasing inflammatory mediators like IL-1β and TNF-α. *S. typhi* exploits Th2 pathway activation, CDT production, and Vi antigen-mediated recruitment of macrophages and DCs to ensure host persistence and long-term infection (28) (Figure 1).

The role of helicobacter pylori in gallbladder cancer

H. pylori, a well-established causative agent of gastric cancer, has recently gained attention for its potential involvement in GBC pathogenesis (55). This Gram-negative bacterium can migrate from the stomach or biliary tract to the gallbladder, where chronic inflammation induced by its presence may promote malignant transformation of epithelial cells (56). Notably, *H. pylori* DNA has been detected in 30-50% of GBC patients' bile and tissue samples (35,55). Multiple mechanisms underlie *H. pylori* associated GBC pathogenesis: 1) Production of cytotoxins (CagA and VacA) that damage epithelial cells and sustain inflammation-CagA activates PI3K/Akt and MAPK signaling pathways to enhance cellular proliferation while inhibiting apoptosis (35); 2) Generation of Reactive Oxygen Species (ROS) through chronic inflammation, leading to DNA damage and initiating carcinogenesis (55); 3) Alteration of bile acid metabolism, increasing levels of the carcinogenic DCA; and 4) In regions with high gallstone prevalence, stones provide an optimal environment for H. pylori biofilm formation (56). Other Helicobacter species *[Helicobacter bilis (H. bilis), Helicobacter hepaticus (H. hepaticus)]* identified in GBC patients may contribute similarly by modifying the gallbladder microenvironment (57). The virulence factor CagA not only induces chronic gastric inflammation but also increases gallstone formation risk (58). Eradication therapy using antibiotics, analogous to gastric cancer prevention strategies, may prove beneficial. Emerging diagnostic approaches incorporating bile-based CagA detection

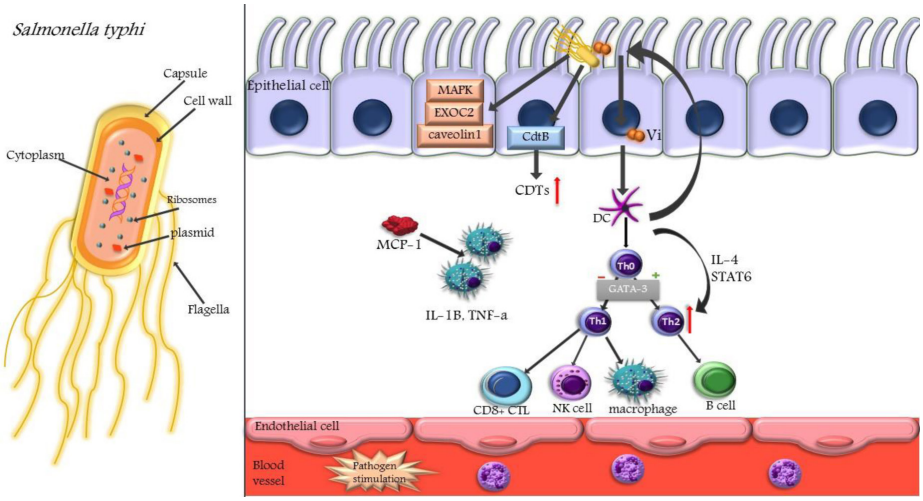


Figure 1. Schematic of the carcinogenic mechanism of *S. typhi*.

and proteomic techniques could clarify *H. pylori's* role in GBC and enable earlier detection (59).

***Helicobacter pylori* mechanisms:** Helicobacter species possess the ability to induce persistent inflammation and contribute to GBC progression. Polymerase Chain Reaction (PCR)-based studies have detected *H. pylori* in 54% of GBC cases, with significantly elevated levels of inflammatory factors including IL-1β and TNF-α. Mirroring their role in gastric cancer, these cytokines stimulate a Th1 immune response and promote substantial accumulation of neutrophils and lymphocytes in the biliary mucosa, leading to tissue damage and pathological changes (28). Furthermore, *H. hepaticus*, recognized as a human pathogen, generates an inflammatory response through the production of CDT toxins, ultimately contributing to GBC development (60). Prolonged exposure to CDT in HeLa cells enhances cGAS-dependent type I interferon responses and modulates host immune reactions (61); consequently, H. hepaticus plays a role in gallbladder carcinogenesis through CDT-dependent cellular immunity. Additionally, *H. pylori, H. hepaticus*, *Helicobacter pullorum (H. pullorum),* and *H. bilis* activate inflammatory responses in the body by releasing Lipopolysaccharide (LPS) (62), with LPS-Binding Protein (LBP) and soluble CD14 (sCD14) being directly associated with GBC in this process (63). The key mechanism of action involves bacterial secretion of LPS, which is transported by LBP to the surface of immune cells and then bound to the membrane protein CD14. This mechanism significantly influences the modulation of inflammatory responses and regulation of immune system function (64,65). In summary, certain *Helicobacter* species stimulate immune and inflammatory responses through LPS release and its subsequent transfer *via* LBP to CD14 (28) (Figure 2).

Examining the impact of escherichia coli in gallbladder cancer

E. coli, a Gram-negative bacterium belonging to the Enterobacteriaceae family, is predominantly found in the bile of patients with GBC. *E. coli* may contribute to GBC progression through several potential mechanisms (66,67). Chronic *E. coli* infections can lead to persistent inflammation in the gallbladder, which is recognized as a significant risk factor for various cancers, including GBC. Sustained inflammation can alter the cellular structure of the gallbladder, creating conditions that facilitate tumor growth by increasing cellular proliferation and inducing genetic mutations (28,32). The presence of this bacterium can disrupt gut microbial balance, which is essential for maintaining health. Such disruption may lead to the production of carcinogenic compounds and alter immune responses, thereby increasing susceptibility to GBC (28). *E. coli* exhibits high pathogenicity through its virulence factors, particularly CNF1. By producing toxins, it damages epithelial cells and disrupts the normal regulation of cell growth and death—a process critical to cancer development that

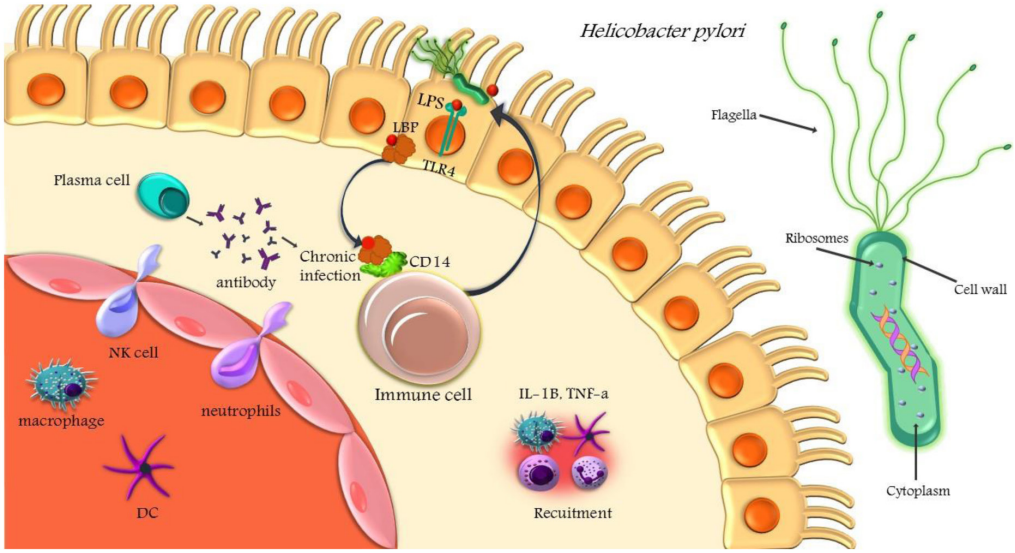


Figure 2. Schematic of the carcinogenic mechanism of *H. pylori*.

can lead to neoplastic lesions in the gallbladder. CNF1 enhances the secretion of inflammatory cytokines by activating monocyte-derived DCs and stimulates the proliferation of allogeneic $CD4^+$ T cells. Additionally, CNF1 contributes to inflammation in various cancers by activating Rho GTPases and lowering the threshold for cellular inflammatory responses (28,68-70). Through toxin production and inflammatory mediators, *E. coli* induces oxidative stress in cells, causing DNA damage. The accumulation of such damage and chronic inflammation over time creates an environment conducive to the transformation of healthy cells into cancerous ones (17). *E. coli* participates in carcinogenesis by adhering to and invading gallbladder cells. Using specific adhesion factors, it colonizes the gallbladder mucosa, leading to chronic infection. Following adhesion, *E. coli* modulates host cell signaling pathways, influencing proliferation and apoptosis, thereby promoting cancer progression. Persistent infections can weaken immune responses, allowing neoplastic cells to evade detection and destruction by the immune system and proliferate unchecked. In other words, immune dysfunction resulting from long-term infections may provide a favorable environment for malignancy development (17,71) (Figure 3).

Other bacteria influencing gallbladder cancer

Recent research has identified two bacterial species, *Clostridium* and *Enterococcus*, as potential contributors to various cancers including GBC. These bacteria can colonize both bile fluid and gallbladder tissue in cancer patients. Both aerobic and anaerobic varieties of these microbes may accumulate under GBC conditions, where their presence likely influences pathogenic mechanisms driving cancer progression (72). A specific bacterial strain, *Clostridium absonum (C. absonum)*, possesses unique survival adaptations in the intestinal environment. Through secretion of the enzymes 7α-HSDH and 7β-HSDH, it converts the toxic bile acid Chenodeoxycholic Acid (CDCA) into the more hydrophilic and less toxic Ursodeoxycholic acid (UDCA). This biochemical transformation not only enhances *Clostridium absonum (C. absonum)* survival in competitive microbial environments, but also demonstrates its crucial role in bile salt metabolism regulation. These characteristics position *C. absonum* as a key mediator in gut microbiome-host health interactions (37,73). Like other bacteria, Clostridium species contribute to GBC pathogenesis through multiple mechanisms: toxin production, immune response modulation, gut microbiome alteration, inflammation induction, host immune response modification, and particularly angiogenesis promotion (28,74). Various Enterococcus species, particularly *Enterococcus faecium (E. faecium)*, show positive correlation with GBC development. These bacteria may play significant roles in GBC pathogenesis, though their exact mechanisms require further elucidation (75). While *Enterococcus's*

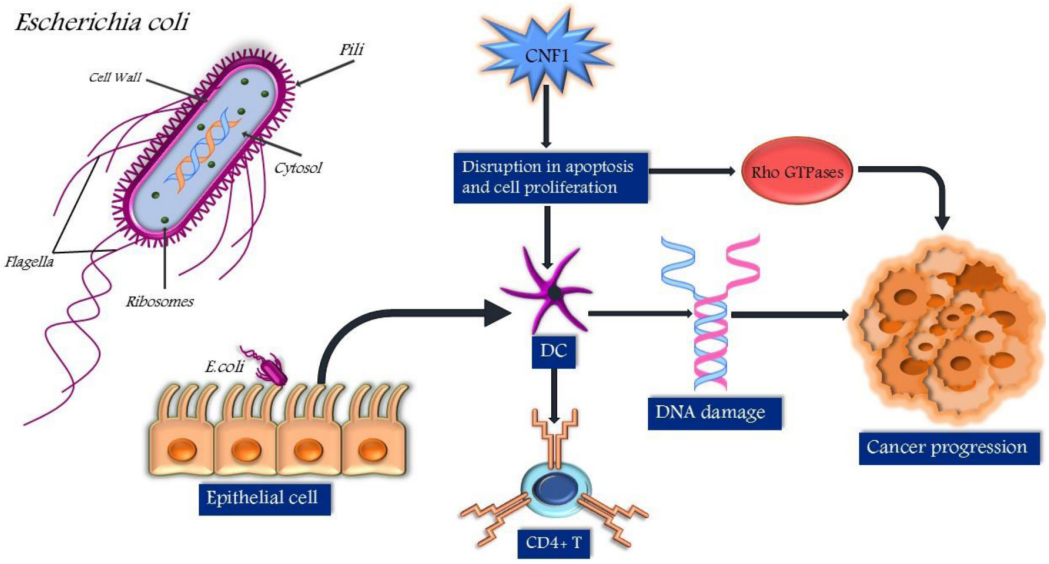


Figure 3. Schematic of the mechanism of *E. coli* carcinogenesis.

precise involvement remains incompletely understood, evidence suggests it may influence tumor microenvironments through immune system regulation. Interestingly, *Enterococcus* appears capable of dual roles-both promoting carcinogenic inflammation and exerting direct anticancer effects through tumor cell growth inhibition and apoptosis induction. However, comprehensive studies are needed to clarify these processes and explore potential therapeutic applications (41,76). The standard gemcitabine-based chemotherapy faces major challenges including drug resistance. Tumor-associated microbiota, particularly elevated *E. faecium* in GBC patients, may affect intratumoral drug concentrations and contribute to treatment resistance (41). This highlights the need for microbiota-targeted approaches to overcome therapeutic limitations in GBC management.

Key bacteria in carcinogenesis mechanisms through biofilms

Bacterial biofilms are recognized as multilayer structures composed of extracellular polysaccharides, proteins, and free DNA, serving as active sites for microbial interactions in the pathogenesis of biliary neoplasms (77). These structures promote malignant progression by protecting bacteria from environmental stresses such as antibiotics and host immune responses, while also providing a platform for gene and metabolite exchange (78). Such bacterial biofilms have been observed in various cancers, including colorectal, gallbladder, breast, and pancreatic cancers (11). The presence of bile and gallstones creates optimal conditions for biofilm growth, supplying the necessary nutrients for bacterial adhesion and proliferation on gallstone surfaces (13). Bile, acting as an antimicrobial agent, induces oxidative stress and ROS production in the gallbladder. S. typhi adapts to this environment by increasing levels of antioxidant enzymes such as catalase and superoxide dismutase through the autoinducer-2 (AI-2) Quorum Sensing (QS) system (79). The QS system and stable cell populations protect bacteria from bile stress, enabling immune evasion, persistent infection, and increased risk of GBC (49). Biofilms play a crucial role in the pathogenicity and survival of *S. typhi* (80). By forming biofilms on gallstones, the bacterium enhances its resistance to bile and antibiotics (17). These biofilms exacerbate chronic gallbladder infections and, through sustained inflammation, elevate the risk of biliary neoplasms (81). Additionally, the CDT produced by *S. typhi* contributes significantly to pathogenesis by causing irreversible DNA damage, cell cycle arrest, and apoptosis (48). *H. pylori* forms resistant biofilms in biliary system-related environments, including the gallbladder, enhancing its survival against environmental and therapeutic challenges. By

increasing antibiotic resistance, *H. pylori* accelerates the progression of biliary diseases (82). In general, biofilms elevate cancer risk due to their ability to evade host immunity, resist antibiotics, and create a stable niche for bacterial proliferation (49).

Diagnosis and treatment of gallbladder cancer

GBC, as the most aggressive type of cancer in the biliary system, faces significant therapeutic challenges, particularly due to variations in treatment approaches across different regions. Considering the poor prognosis of this cancer, which is mainly due to its rapid metastasis at advanced stages, early diagnosis is critically important (4). Patients frequently present with advanced-stage disease or local recurrence following surgery. Combination chemotherapy with gemcitabine and cisplatin has been shown to provide a significant survival benefit for individuals with advanced disease (1). In one trial, the median progression-free survival was longer for patients treated with cisplatin and gemcitabine, reaching 8 months, compared to 5 months for those receiving gemcitabine alone (1,83). The involvement of bacteria includes manipulation of the immune system, suppression of anti-cancer immune cells, promotion of tumor growth, and production of metabolites that influence cancer cell responses to chemotherapy and other therapies (40). Innate immunity plays a pivotal role in the development of GBC, particularly in the context of chronic *S. typhi* infections, which are associated with a high incidence of the disease. Immune molecules such as TLR (toll-like receptors), IL1B, IL10, and CCR5 show significant associations with GBC, as they recognize lipopolysaccharide components of Gram-negative bacterial infections and may serve as potential biomarkers for early diagnosis and risk prediction of GBC (41). The role of bacterial factors in GBC underlines the importance of primary prevention and early diagnosis. Identifying high-risk individuals using serum markers such as CD34, Ca15-3, MIB-1, CEA, and Ca19-9 can aid in early diagnosis and in taking preventive measures, such as gallbladder removal (84). Currently, the main treatment for GBC is radical surgery to completely remove the tumor. For unresectable or locally advanced tumors, chemotherapy with gemcitabine and platinum-based drugs is employed (85). Gemcitabine enters cells through specific nucleoside transporters and is phosphorylated by the enzyme deoxycytidine kinase into gemcitabine monophosphate (dFdCMP). After further enzymatic modifications, the triphosphate form (dFdCTP) is produced, which can substitute for deoxycytidine triphosphate during DNA synthesis (86). Incorporation of gemcitabine into DNA bypasses the normal base excision repair system of the cell (41). Alongside these methods, preventing bacterial infections such as *H. pylori* and S. typhi through appropriate treatments (*e.g.*, bismuth quadruple therapy for *H. pylori*) and maintaining hygiene, as well as preserving gut microbiome balance with beneficial bacteria like Lactobacillus and Bifidobacterium, play key roles in reducing the risk of GBC (28,87-89). The gut microbiota may contribute to the development and progression of GBC, and management or modulation of gut microbiota can be considered as complementary or alternative therapeutic approaches. Bacterial-derived compounds such as CpG (oligodeoxynucleotides) can activate dendritic cells and lead to complete regression of highly immune-suppressive tumors such as B16F10 melanoma (90). Therapeutic agents targeting cellular and molecular pathways can inhibit tumor growth. Epidermal Growth Factor Receptor (EGFR) is expressed in 38.5% of gallbladder cancers. Targeted therapies against EGFR have demonstrated anti-proliferative effects in preclinical studies (91).

Conclusion

GBC, as one of the most lethal gastrointestinal cancers, is closely associated with chronic bacterial infections. *S. typhi, H. pylori, E. coli*, *Clostridium,* and *Enterococcus* contribute to GBC carcinogenesis through persistent inflammation, production of carcinogenic metabolites (such as DCA), and epigenetic changes. Furthermore, S. typhi and H. pylori play a key role in this cancer and promote GBC progression by biofilm formation. To address these challenges, the development of rapid diagnostic kits based on serum markers such as CD34, Ca15-3, MIB-1, CEA, and Ca19-9, as well as screening for chronic bacterial infections, can aid in early detection and preventive measures such as cholecystectomy. The design of combined therapeutic protocols,

including surgery and targeted antibiotic therapy, is also among the effective strategies. These findings emphasize the need to consider the role of micro-organisms in the pathogenesis of this cancer and highlight the importance of clinical research for developing non-invasive diagnostic methods and novel treatments. Additionally, prevention of chronic bacterial infections and management of gallstones can be effective strategies in reducing the incidence of this cancer.

Conflict of Interest

The authors declare that they have no conflicts of interest.

References

1. Hundal R, Shaffer EA. Gallbladder cancer: epidemiology and outcome. Clin Epidemiol 2014:99-109.

2. Li Z-M, Wu Z-X, Han B, Mao Y-Q, Chen H-L, Han S-F, et al. The association between BMI and gallbladder cancer risk: a meta-analysis. Oncotarget 2016;7(28):43669.

3. Upadhayay A, Pal D, Kumar A. Salmonella typhi induced oncogenesis in gallbladder cancer: Co-relation and progression. Advances in Cancer Biology-Metastasis 2022;4:100032.

4. Schmidt MA, Marcano-Bonilla L, Roberts LR. Gallbladder cancer: epidemiology and genetic risk associations. Chin Clin Oncol 2019;8(4):31.

5. Sturm N, Schuhbaur JS, Hüttner F, Perkhofer L, Ettrich TJ. Gallbladder cancer: current multimodality treatment concepts and future directions. Cancers 2022;14(22):5580.

6. Koshiol J, Wozniak A, Cook P, Adaniel C, Acevedo J, Azócar L, et al. Salmonella enterica serovar Typhi and gallbladder cancer: a case–control study and meta-analysis. Cancer Med 2016;5(11):3310-235.

7. Marcano-Bonilla L, Mohamed EA, Mounajjed T, Roberts LR. Biliary tract cancers: epidemiology, molecular pathogenesis and genetic risk associations. Chin Clin Oncol 2016;5(5):61.

8. Upadhyay A, Jha HC, Pal D, Kumar A. Repurposing antibiotics: A dual-action approach against bacteria-induced cancer. Cancer Pathog Ther 2025;3(6):473-483.

9. Kumar A, Sarangi Y, Gupta A, Sharma A. Gallbladder cancer: Progress in the Indian subcontinent. World J Clin Oncol 2024;15(6):695-716.

10. HARAKEH S, BILGRAMI A, MOULAY M, MAHMOUD M, MOKHTAR JA, NIYAZI HA, et al. Exploring the Relation between Bacterial Infections and Cancer Progression. Indian Journal of Pharmaceutical Sciences 2024;86(5).

11. Vestby LK, Grønseth T, Simm R, Nesse LL. Bacterial biofilm and its role in the pathogenesis of disease. Antibiotics (Basel) 2020;9(2):59.

12. Al-Hilu SA, Al-Shujairi WH. Dual role of bacteria in carcinoma: stimulation and inhibition. Int J Microbiol 2020;2020(1):4639761.

13. Kushwaha M, Nukala V, Singh AK, Makharia GK, Mohan A, Kumar A, et al. Emerging implications of bacterial biofilm in cancer biology: Recent updates and major perspectives. Gut Microbes Rep 2024;1(1):2339270.

14. Turumin JL, Shanturov VA, Turumina HE. The role of the gallbladder in humans. Rev Gastroenterol Mex 2013;78(3):177-87.

15. Jones MW, Small K, Kashyap S, Deppen JG. Physiology, gallbladder. StatPearls [Internet]: StatPearls Publishing; 2023.

16. Çerçi SS, Özbek FM, Çerçi C, Baykal B, Eroğlu HE, Baykal Z, et al. Gallbladder function and dynamics of bile flow in asymptomatic gallstone disease. World J Gastroenterol 2009;15(22):2763.

17. Nath G, Gulati AK, Shukla VK. Role of bacteria in carcinogenesis, with special reference to carcinoma of the gallbladder. World J Gastroenterol 2010;16(43):5395.

18. Scanu T, Spaapen RM, Bakker JM, Pratap CB, Wu L-e, Hofland I, et al. Salmonella manipulation of host signaling pathways provokes cellular transformation associated with gallbladder carcinoma. Cell Host Microbe 2015;17(6):763-74.

19. Kanthan R, Senger J-L, Ahmed S, Kanthan SC. Gallbladder cancer in the 21st century. J Oncol 2015;2015(1):967472.

20. Zhu AX, Hong TS, Hezel AF, Kooby DA. Current management of gallbladder carcinoma. Oncologist 2010;15(2):168-81.

21. Espinoza JA, Bizama C, García P, Ferreccio C, Javle M, Miquel JF, et al. The inflammatory inception of gallbladder cancer. Biochim Biophys Acta 2016;1865(2):245-54.

22. Wistuba II, Tang M, Maitra A, Alvarez H, Troncoso P, Pimentel F, et al. Genome-wide allelotyping analysis reveals multiple sites of allelic loss in gallbladder carcinoma. Cancer Res 2001;61(9):3795-800.

23. Aarti Sharma AS, Sharma K, Annapurna Gupta AG, Alka Yadav AY, Ashok Kumar AK. Gallbladder cancer epidemiology, pathogenesis and molecular genetics: recent update. World J Gastroenterol 2017 Jun 14;23(22):3978-3998.

24. Javle M, Rashid A, Churi C, Kar S, Zuo M, Eterovic AK, et al. Molecular characterization of gallbladder cancer using somatic mutation profiling. Human Pathol 2014;45(4):701-8.

25. Masuhara S, Kasuya K, Aoki T, Yoshimatsu A, Tsuchida A, Koyanagi Y. Relation between K-ras codon 12 mutation and p53 protein overexpression in gallbladder cancer and biliary ductal epithelia in patients with pancreaticobiliary maljunction. Journal of hepato-biliary-pancreatic surgery. 2000;7:198-205.

26. Singh MK, Chetri K, Pandey UB, Kapoor VK, Mittal B, Choudhuri G. Mutational spectrum of K-ras oncogene among Indian patients with gallbladder cancer. J Hepatobiliary Pancreat Surg 2004;19(8):916-21.

27. Dutta U, Garg PK, Kumar R, Tandon RK. Typhoid carriers among patients with gallstones are at increased risk for carcinoma of the gallbladder. Am J Gastroenterol 2000;95(3):784-7.

28. Liu S, Li W, Chen J, Li M, Geng Y, Liu Y, et al. The footprint of gut microbiota in gallbladder cancer: a mechanistic review. Front Cell Infect Microbiol 2024;14:1374238.

29. Lin R, Zhan M, Yang L, Wang H, Shen H, Huang S, et al. Deoxycholic acid modulates the progression of gallbladder cancer through N6-methyladenosine-dependent microRNA maturation. Oncogene 2020;39(26):4983-5000.

30. Kawaguchi M, Saito T, Ohno H, Midorikawa S, Sanji T, Handa Y, et al. Bacteria closely resembling Helicobacter pylori detected immunohistologically and genetically in resected gallbladder mucosa. J Gastroenterol 1996;31:294-8.

31. POPESCU D, Andronescu D, BABES PA. The association between Helicobacter pylori infection and liver and biliary tract disorders. Curr Health Sci J 2018;44(2):186-91.

32. Choi SJ, Kim Y, Jeon J, Gwak H-J, Kim M, Kang K, et al. Association of microbial dysbiosis with gallbladder diseases identified by bile microbiome profiling. J Korean Med Sci 2021;36(28):e189.

33. Lazcano-Ponce EC, Miquel JF, Muñoz N, Herrero R, Ferrecio C, Wistuba II, et al. Epidemiology and molecular pathology of gallbladder cancer. CA Cancer J Clin 2001;51(6):349-64.

34. Khan AA, Bano Y. Salmonella enterica subsp. enterica host-pathogen interactions and their implications in gallbladder cancer. Microb Pathog 2021;157:105011.

35. Lim KPK, Lee AJL, Jiang X, Teng TZJ, Shelat VG. The link between Helicobacter pylori infection and gallbladder and biliary tract diseases: A review. Ann Hepatobiliary Pancreat Surg 2023;27(3):241-50.

36. Etienne-Manneville S, Hall A. Rho GTPases in cell biology. Nature 2002;420(6916):629-35.

37. Ridlon JM, Harris SC, Bhowmik S, Kang D-J, Hylemon PB. Consequences of bile salt biotransformations by intestinal bacteria. Gut Microbes 2016;7(1):22-39.

38. Sutherland JD, Macdonald IA. The metabolism of primary, 7-oxo, and 7 beta-hydroxy bile acids by Clostridium absonum. J Lipid Res 1982;23(5):726-32.

39. Sfanos KS. Intratumoral bacteria as mediators of cancer immunotherapy response. Cancer Res 2023;83 (18):2985-6.

40. Yang L, Li A, Wang Y, Zhang Y. Intratumoral microbiota: roles in cancer initiation, development and therapeutic efficacy. Signal Transduct Target Ther 2023;8(1):35.

41. Jiang L, Zhang L, Shu Y, Zhang Y, Gao L, Qiu S, et al. Deciphering the role of Enterococcus faecium cytidine deaminase in gemcitabine resistance of gallbladder cancer. J Bioll Chem 2024;300(4):107171.

42. Chowdhury AR, Mukherjee D, Chatterjee R, Chakravortty D. Defying the odds: Determinants of the antimicrobial response of Salmonella Typhi and their interplay. Mol Microbiol 2024;121(2):213-29.

43. Crump JA, Sjölund-Karlsson M, Gordon MA, Parry CM. Epidemiology, clinical presentation, laboratory diagnosis, antimicrobial resistance, and antimicrobial management of invasive Salmonella infections. Clin Microbiol Rev 2015;28(4):901-37.

44. Tewari M, Mishra RR, Shukla HS. Salmonella typhi and gallbladder cancer: report from an endemic region. Hepatobiliary Pancreat Dis Int 2010;9(5):524-30.

45. Shukla VK, Singh H, Pandey M, Upadhyay S, Nath G. Carcinoma of the gallbladder—is it a sequel of typhoid? Dig Dis Sci 2000;45:900-3.

46. Dwivedi M, Dwivedi M, Moitra M, Sanyal S. The implication of gall stones in gallbladder cancer and recent updates on its epidemiology. Gallstone Formation, Diagnosis, Treatment and Prevention: Elsevier; 2024. p. 207-22.

47. Crawford RW, Rosales-Reyes R, Ramirez-Aguilar MdlL, Chapa-Azuela O, Alpuche-Aranda C, Gunn JS. Gallstones play a significant role in Salmonella spp. gallbladder colonization and carriage. Proc Natl Acad Sci USA 2010;107(9):4353-8.

48. Nayak S, Dasgupta IS. A comprehensive review on the development of Salmonella biofilm on gallbladder surface. International Journal of Innovative Science and Research Technology 2022;7(6):295-304.

49. Di Domenico EG, Cavallo I, Pontone M, Toma L, Ensoli F. Biofilm producing Salmonella typhi: chronic colonization and development of gallbladder cancer. Int J Mol Sci 2017;18(9):1887.

50. Herman JG, Baylin SB. Gene silencing in cancer in association with promoter hypermethylation. N Engl J Med 2003;349(21):2042-54.

51. Funabashi M, Grove TL, Wang M, Varma Y, McFadden ME, Brown LC, et al. A metabolic pathway for bile acid dehydroxylation by the gut microbiome. Nature 2020;582(7813):566-70.

52. Lai Y-R, Chang Y-F, Ma J, Chiu C-H, Kuo M-L, Lai C-H. From DNA damage to cancer progression: potential effects of cytolethal distending toxin. Front Immunol 2021;12:760451.

53. Shukla R, Shukla P, Behari A, Khetan D, Chaudhary RK, Tsuchiya Y, et al. Roles of Salmonella typhi and Salmonella paratyphi in gallbladder cancer development. Asian Pac J Cancer Prev 2021;22(2):509-16.

54. González Juan F, Kurtz J, Bauer David L, Hitt R, Fitch J, Wetzel A, et al. Establishment of Chronic Typhoid Infection in a Mouse Carriage Model Involves a Type 2 Immune Shift and T and B Cell Recruitment to the Gallbladder. mBio 2019;10(5):e02262-19.

55. Mishra RR, Tewari M, Shukla HS. Helicobacter pylori and pathogenesis of gallbladder cancer. J Gastroenterol Hepatol 2011;26(2):260-6.

56. Hassan EH, Gerges SS, El-Atrebi KA, El-Bassyouni HT. The role of H. pylori infection in gall bladder cancer:

clinicopathological study. Tumor Biol 2015;36(9):7093-8.

57. JG F. Hepatic Helicobacter species identified in bile and gallbladder tissue from Chileans with chronic cholecystitis. Gastroenterology 1998;114:755-63.

58. Maurer KJ, Ihrig MM, Rogers AB, Ng V, Bouchard G, Leonard MR, et al. Identification of cholelithogenic enterohepatic helicobacter species and their role in murine cholesterol gallstone formation. Gastroenterology 2005;128(4):1023-33.

59. Wang Y, Imran A, Shami A, Chaudhary AA, Khan S. Decipher the Helicobacter pylori protein targeting in the nucleus of host cell and their implications in gallbladder cancer: an insilico approach. J Cancer 2021;12(23):7214-22.

60. Falsafi T, Mahboubi M. Helicobacter hepaticus, a new pathogenic species of the Helicobacter genus: Similarities and differences with H. pylori. Iranian J Microbiol 2013;5(3):185-94.

61. Pons BJ, Pettes-Duler A, Naylies C, Taieb F, Bouchenot C, Hashim S, et al. Chronic exposure to Cytolethal Distending Toxin (CDT) promotes a cGAS-dependent type I interferon response. Cell Mol Life Sci 2021;78:6319-35.

62. Griffiths WA, Spencer KD, Thoden JB, Holden HM. Biochemical investigation of an N-acetyltransferase from Helicobacter pullorum. Protein Sci 2021;30(12):2418-32.

63. Van Dyke AL, Kemp TJ, Corbel AF, Zhu B, Gao Y-T, Wang B-S, et al. Lipopolysaccharide-pathway proteins are associated with gallbladder cancer among adults in Shanghai, China with mediation by systemic inflammation. Ann Epidemiol 2016;26(10):704-9.

64. Yang X, Zhang X, Yang W, Yu H, He Q, Xu H, et al. Gut microbiota in adipose tissue dysfunction induced cardiovascular disease: role as a metabolic organ. Front Endocrinol (Lausanne) 2021;12:749125.

65. Chen S-J, Lin C-H. Gut microenvironmental changes as a potential trigger in Parkinson's disease through the gut–brain axis. J Biomed Sci 2022;29(1):54.

66. Bonten M, Johnson JR, van den Biggelaar AH, Georgalis L, Geurtsen J, de Palacios PI, et al. Epidemiology of Escherichia coli bacteremia: a systematic literature review. Clin Infect Dis 2021;72(7):1211-9.

67. Tsuchiya Y, Loza E, Villa-Gomez G, Trujillo CC, Baez S, Asai T, et al. Metagenomics of microbial communities in gallbladder bile from patients with gallbladder cancer or cholelithiasis. Asian Pac J Cancer Prev 2018;19(4):961-67.

68. Gall-Mas L, Fabbri A, Namini MR, Givskov M, Fiorentini C, Krejsgaard T. The bacterial toxin CNF1 induces activation and maturation of human monocyte-derived dendritic cells. Int J Mol Sci 2018;19(5):1408.

69. Chat H, Dalmasso G, Godfraind C, Bonnin V, Beyrouthy R, Bonnet M, et al. Cytotoxic necrotizing factor 1 hinders colon tumorigenesis induced by colibactin-producing Escherichia coli in ApcMin/+ mice. Gut Microbes 2023;15(1):2229569.

70. Carlini F, Maroccia Z, Fiorentini C, Travaglione S, Fabbri A. Effects of the Escherichia coli bacterial toxin cytotoxic necrotizing factor 1 on different human and animal cells: a systematic review. Int J Mol Sci 2021;22(22):12610.

71. Travaglione S, Fabbri A, Fiorentini C. The Rho-activating CNF1 toxin from pathogenic E. coli: a risk factor for human cancer development? Infecti Agents Cancer 2008;3:4.

72. Pérez-Moreno P, Riquelme I, García P, Brebi P, Roa JC. Environmental and lifestyle risk factors in the carcinogenesis of gallbladder cancer. J Pers Med 2022;12(2):234.

73. Grigor'eva IN, Romanova TI. Gallstone disease and microbiome. Microorganisms 2020;8(6):835.

74. Voth DE, Ballard JD. Clostridium difficile toxins: mechanism of action and role in disease. Clin Microbiol Rev 2005;18(2):247-63.

75. Tajeddin E, Sherafat S, Majidi M, Alebouyeh M, Alizadeh A, Zali M. Association of diverse bacterial communities in human bile samples with biliary tract disorders: a survey using culture and polymerase chain reaction-denaturing gradient gel electrophoresis methods. Eur J Clin Microbiol Infect Dis 2016;35:1331-9.

76. Williamson AJ, Jacobson R, van Praagh J, Gaines S, Koo HY, Lee B, et al. Enterococcus faecalis promotes a migratory and invasive phenotype in colon cancer cells. Neoplasia 2022;27:100787.

77. Lahiri D, Nag M, Dutta B, Dey A, Ray RR. Bacterial extracellular polysaccharides in biofilm formation and function. Application of Biofilms in Applied Microbiology: Elsevier; 2022. p. 1-23.

78. Choi E, Murray B, Choi S. Biofilm and cancer: interactions and future directions for cancer therapy. International J Mol Sci 2023;24(16):12836.

79. Wattanavanitchakorn S, Prakitchaiwattana C, Thamyongkit P. Rapid and simple colorimetric method for the quantification of AI-2 produced from Salmonella Typhimurium. J Microbiol Methods 2014;99:15-21.

80. González JF, Hitt R, Laipply B, Gunn JS. The effect of the gallbladder environment during chronic infection on salmonella persister cell formation. Microorganisms 2022;10(11):2276.

81. Prouty A, Schwesinger W, Gunn J. Biofilm formation and interaction with the surfaces of gallstones by Salmonella spp. Infect Immun 2002;70(5):2640-9.

82. Yonezawa H, Osaki T, Kamiya S. Biofilm formation by Helicobacter pylori and its involvement for antibiotic resistance. Biomed Res Int 2015;2015(1):914791.

83. Valle J, Wasan H, Palmer DH, Cunningham D, Anthoney A, Maraveyas A, et al. Cisplatin plus gemcitabine versus gemcitabine for biliary tract cancer. N Engl J Med 2010;362(14):1273-81.

84. Salazar M, Ituarte C, Abriata MG, Santoro F, Arroyo G. Gallbladder cancer in South America: epidemiology and prevention. Chin Clin Oncol 2019;8(4):32.

85. Zhou Y, Yuan K, Yang Y, Ji Z, Zhou D, Ouyang J, et al. Gallbladder cancer: current and future treatment options. Front Pharmacol 2023;14:1183619.

86. Derissen EJ, Huitema AD, Rosing H, Schellens JH, Beijnen JH. Intracellular pharmacokinetics of gemcitabine, its deaminated metabolite 2′, 2′-difluorodeoxyuridine and their nucleotides. Br J Clin Pharmacol 2018;84(6):1279-89.

87. Malfertheiner P, Megraud F, O'Morain C, Bazzoli F, El-Omar E, Graham D, et al. Current concepts in the management of Helicobacter pylori infection: the Maastricht III Consensus Report. Gut 2007;56(6):772-81.

88. Lönnermark E, Lappas G, Friman V, Wold AE, Backhaus E, Adlerberth I. Effects of probiotic intake and gender on nontyphoid Salmonella infection. J Clin Gastroenterol 2015;49(2):116-23.

89. Yang J-C, Lu C-W, Lin C-J. Treatment of Helicobacter pylori infection: current status and future concepts. World J Gastroenterol 2014;20(18):5283.

90. Furumoto K, Soares L, Engleman EG, Merad M. Induction of potent antitumor immunity by in situ targeting of intratumoral DCs. J Clin Invest 2004;113(5):774-83.

91. Pignochino Y, Sarotto I, Peraldo-Neia C, Penachioni JY, Cavalloni G, Migliardi G, et al. Targeting EGFR/HER2 pathways enhances the antiproliferative effect of gemcitabine in biliary tract and gallbladder carcinomas. BMC Cancer 2010;10(1):631.