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Review

# Role of microorganisms in the development, prognosis, and therapy of gastric cancer

Syeda Sadaf Wajahat

Department of Biosciences, Mohammad Ali Jinnah University, Karachi, Pakistan

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***Corresponding authors:**
Syeda Sadaf Wajahat
Department of Biosciences,
Mohammad Ali Jinnah University,
Karachi, Pakistan
**Email:** s.sadaf.wajahat@gmail.com

## Abstract

Gastric cancer (GC) is the most frequent destructive polyp allied to the GIT. It is reported as the foremost oncological complication with a prevalence ranks fifth and mortality ranks fourth worldwide with a survival rate of <25% in five years. In GC, men were observed as 2-3 times more susceptible to incidence and mortality than women. The GC patients experienced a burden of symptoms with multiple co-occurring symptoms including pain, weight loss, depression, fatigue, dysphagia, nausea, vomiting, etc. The risk factors of GC include infection of *H. pylori*, smoking, obesity, hereditary, high salt, radiation, and the frequent use of medications, etc. The role of genes, long-coding RNAs, metabolomics, machine learning, plant extracts, and nanoparticles has been studied for the progression, diagnosis, and treatment of GC. Due to the progressive stage diagnosis and lack of competent therapy, an imperative requirement is the identification of sensitive and accurate biomarkers towards the initial prognosis and the development of innovative therapeutic approaches. Microorganisms execute a momentous role in human health by contributing to immune system development and accomplishing an extensive range of metabolic functions. The disturbance in the stability of the microbes may stimulate various diseases including cancer. This review focuses on the role of microorganisms in the development, prognosis, and therapy of GC.

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## 1. Introduction

Gastric cancer (GC) is the most frequent destructive polyp related to the gastrointestinal tract (GIT) (1-5). The Worldwide rate of GC prevalence ranks fifth (2, 3) and the mortality ranks fourth (3). The number of new cases of all ages and genders of GC reported in 2020 is 1,089,103 and the deaths are 768,793 (6). Numerous kinds of cancers originate from the digestive tract but most belong to the adenocarcinoma class (7). In GC, one distinguishing

tumor microenvironment is persistent inflammation triggered by the infection of *Helicobacter pylori (H. pylori)* that stimulates the survival of cells and upregulates the pathways that induct the propagation of epithelial and stem cells (8). Globally, gastral malignancies are reported as the foremost oncological complication (10) with a mortality rate of 193,587. In Asia, the incidence rate of GC in both genders is 8,19,944, mortality is 5,75,206, and the occurrence of 5-year cases is 13,97,478 (6). Developing countries are mostly (beyond 70%) affected by the occurrence and expiries from GC (9) but in Pakistan, comparatively lower frequency and higher mortality ratio (13.3%) are informed (9-11). Research reported that in Pakistan, adolescent males are mostly infected by GC. In Karachi, the existence of GC in males is two times greater (>40 years is at higher risk) than the females (11). Primarily in the patients of GC, the survival frequency is <25% in five years in the utmost areas of the globe (5). In Pakistan, annually 6,541 deaths were reported. As a consequence of inappropriate care, detection, and therapy, the number of patients is rising gradually because of the coincidence of *H. pylori* contagion (11).

Recently, scientists are working to investigate the progression of stomach malignancy by determining the in vivo and in vitro role of PHF5A (12), revealing the expression of TDO2 (13), PTBP1 (14), MTA2 (15), ZNF460 (16), and ZFP36L1 genes (17), upregulation of lncRNA BC002811 (18), and a novel lncRNA CASC19 (19), etc. Similarly, for the diagnosis of digestive cancer, the lnc-RFNG-1, COL3A1, lnc-TRIM28-14, COL4A1, and CD93 (20), pyridine (21), Fourier transform infrared spectroscopy (FTIR) (22), metabolomics in combination with machine learning algorithms (23), overexpression of CXCL1 (24), NGCS (new gastric cancer screening scoring system), *H. pylori* (25), and the serum pepsinogen PG I/PG II (26), etc were identified as probable novel biomarkers (20). For therapeutic purposes, based on the microfluidic technology with suspension capability researchers prepared bubble microcapsules of poly-lactic-co-glycolic acid (PLGA) for the medicaments of in situ abdominal cancer (27), observe the efficiency of Ponciri Fructus Immaturus (PF) (28), and Leptocarpha rivularis flower extract (29), studied the anticancerous efficacy of palmitic acid (PA) (30), the combined treatment of 3,3′-diindolylmethane (DIM) with the chemotherapeutic agent 5-Fu (31), determine the antagonistic possessions of green synthesized gold nanoparticles (AuNPs) (32), and dehydrocurvularin (DSE2) (33), etc for the therapy of digestive carcinoma (28), Due to the progressive stage diagnosis (1), and lack of competent therapy, there is an imperative necessity towards (4), identification of biomarkers intended for the preliminary prognosis which is accurate and sensitive (1, 2, 34, 35), and the development of innovative therapeutic approaches (4, 34, 35). Microorganisms execute a momentous role in human health by contributing to immune system development and accomplishing an extensive range of metabolic functions. The disturbance in the stability of the microbes may stimulate various diseases including cancer (36). This review focuses on the role of microorganisms in the development, prognosis, and therapy of GC.

## 2. An overview of GC

GC initiates the gland's peripheral mucosal epithelial cells in the stomach and generally reveals adenocarcinoma (5). Other types of cancers include leiomyosarcomas initiated from the muscles under the mucosa and mucosa-associated lymphoid tissue lymphomas acquired from digestive lymphoid tissue. Rendering to the anatomical sites adenocarcinoma is grouped into cardia and non-cardia (most prevalent) (7). GC is recognized to be distinctly unrelated equally in intertumoral and intratumoral surroundings. The characteristic of this unrelatedness

arises inside the tumor microenvironment, which is infused vastly by immune cells, stromal components, and cancer-associated fibroblasts. Conferring to the microscopic attributes GC has been characterized as intestinal (related to the *H. pylori* contagion with gastroenteric metaplasia besides atrophy) and diffuse malignancy (arising from pangastritis deprived of atrophy) (7, 37). Around 40% of patients worldwide suffer from GC with metastasis (4). Approximately only 5% of these survived for 5 years (4, 37).

## 3. Epidemiology, categorization, and genetics of GC

GC is described as an invasive malignancy that occurs foremost inclusive reason for deaths in the world which progresses in the abdomen (38, 39). It grows in some portions of the abdomen but the predominance of GCs exists in the pyloric region. The prevalence rate of GC varies extensively in the world (38). The topmost ASIR (age standardized-incidence rate) of GC per 100,000 was revealed overall in Eastern Asia is 24.2 (**Figure 1**), Central and Eastern Europe is 13.5 and South America is 10.3 (mainly focused in the Pacific regions) within the range of 10.3—24.2 (38, 40). Whereas, the bottommost occurrence of GC was detected in the Eastern Mediterranean region that is 5.5, in North America at 4, and in Africa is 3.8 (**Figure 2**) (38, 40). There is an association reported globally between the occurrence and mortality of GC with the increment in age and is comparatively rare in people of both genders in <45 years (41). In GC, men were observed as 2-3 times more susceptible to incidence and mortality than women (38, 40, 41). The maximum age-standardized transience rates per 100,000 were stated as 16.5 in East Asia, 10.9 in Central and Eastern Europe, 8.5 in South America, and 2.1 in North America (38).

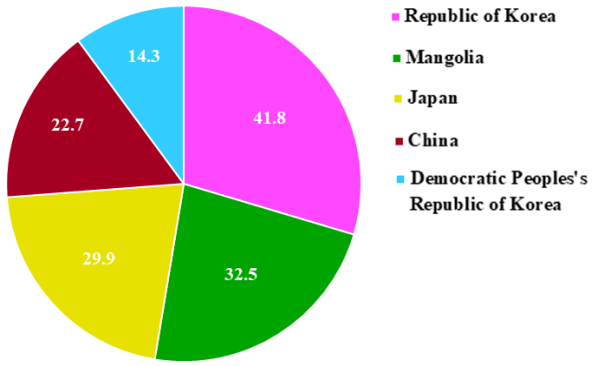


Figure 1. **Age-Standardized Incidence Rate of GC/100,000 in Eastern Asia.**

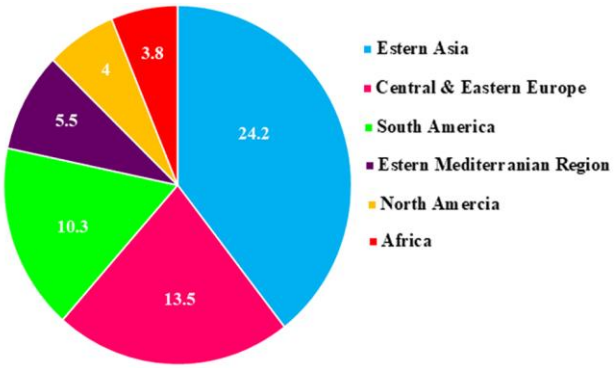


Figure 2. **Overall Age Standardized Incidence Rate of GC/100,000.**

GC is a miscellaneous cancer with several types depending on the epidemiology, pathology, oncogenesis, and molecular profile (42). According to Lauren's categorization, based on histologic characteristics the GCs are of three types: diffuse, intestinal, and mixed (42-46) or differentiated and undifferentiated (43, 47). The classification of GCs based on molecular subtypes, comprising p53 status (48), and morphology (43, 46) are described in (**Figure 3**). Universally in cancer mortality, the GC has been extremely predominant and deprived of survival frequency (49). Detecting a tendency to gastric malignancy allows interferences that might prolong the existence of patients and/or their families (50). The genetics of digestive cancer will provide an understanding of its pathogenesis, novel diagnostic biomarkers, and therapeutic targets which will be helpful in personalized medication approaches in the future (49). The ratio of an inherited form of GC is

1% to 3% (49, 50). Their susceptibility is correlated

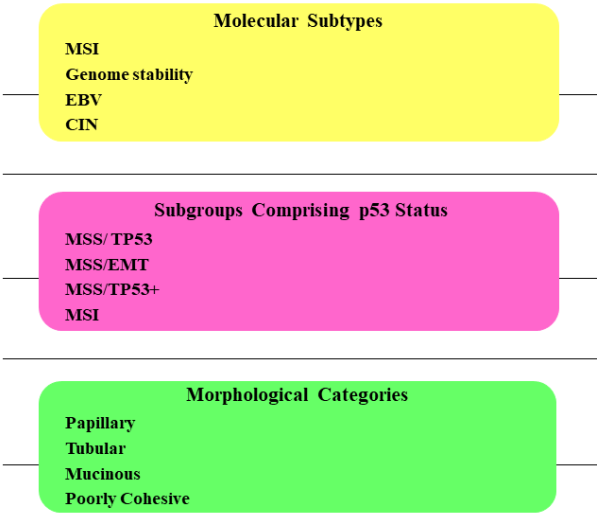


Figure 3. **Categorization of GC.**

with assured germline heritable disorders which embrace Li-Fraumeni syndrome, hereditary diffuse gastric cancer syndrome (HDGC), Lynch syndrome, Peutz-Jeghers syndrome, gastric adenocarcinoma and proximal polyposis of the stomach (GAPPS), which is a variant of FAP and juvenile polyposis syndrome and familial adenomatous polyposis (FAP) (50). The advancement in technology and high-throughput analysis in the last few years have enhanced the perception of the molecular characteristics of the pathogenesis of GC, which are complex, heterogeneous and signify an exclusive range of numerous vital genetic impacts such as microsatellite and chromosomal instability, functional single nucleotide polymorphisms or somatic gene mutations, and changes in microRNA profile (49). The study reported that the congenital mutation in antioncogene, CDH1 (E-cadherin) is linked with hereditary diffuse gastric cancer (HDGC) (51) **(Table 1).**

## 4. Risk factors

In the onset and expansion of GC, different genetic, epigenetic, and ecological risk aspects are intricated (52-54). It includes the infection of *H. pylori* (9, 53-61), high salt consumption (9, 53, 54, 60, 62, 63), inadequate food preservation (53, 60), use of alcohol (61, 64), smoked food (54, 60), utilization of red and processed meat (60), little ingestion of fruits and vegetables (54, 60), hereditary (9, 53, 54, 61, 62), inconsistent lifestyle (53), low socioeconomic status (SES) (54, 63), age (54, 61, 64), ethnicity (61), smoking (9, 54, 59-66), obesity (9, 65-67), Epstein Bar Virus (EBV) (9, 53, 60), ingestion of nitrate and nitrite, high fat (9), pernicious anemia (53) and the frequently used medications like antidiabetic (62, 65), cardiac, and acid suppressant medicines, etc (62). Epigenetic modifications typically consist of chromatin remodeling, DNA methylation, non-coding RNA expression alteration, and Histon post-translational modifications (53). Environmental aspects embrace water pollution, nature and hardness of water, soil pollution, type and elements of soil (68), radiations (9, 54, 68), climate change, topography, air pollution, lithology (68), and variations in the microbial community by prolong usage of proton-pump inhibitors (60). *H. pylori* mainly instigates the precancerous lesions by converting normal mucosa into non-atrophic gastritis and reducing the production of acid which shifts the value of gastric pH that causes microbial dysbiosis and endorses the growth of GC (69). High salt consumption contributes to carcinogenesis by interrupting the stomach mucosa, increasing the colonization of *H. pylori*, and might improve the effect of additional carcinogens like N-nitroso compounds. The probable mechanism of smoking in GC includes an incentive of tumor angiogenesis, initiation of nicotinic acetylcholine receipts, development of DNA adducts, induced cell proliferation, as well as immune disorders, chronic inflammation in the GIT and higher risk of microbial infections (70).

Table 1. **Impact of mutation or overexpression of genes in GC.**

| Impact on genes | Type of analysis | Interpretation | References |
|---|---|---|---|
| Genetic alteration of the mRNA expression level of 39 genes of a Solute carrier (SLC) family | Bioinformatic analysis | Prognostic and novel therapeutic target | (135) |
| Reversible $N^6$-methyladenosine ($m^6A$) modifications in messenger RNAs | Bioinformatic analysis and tissue microarray-based immunohistochemistry | Roles of *FTO* and *ALKBH1* in the progression and metastasis | (136) |
| *COL1A1, COL1A2, COL5A1, COL5A2, COL3A1, SPARC, THBS1, COL18A1, FN1, COL11A1* (differentially expressed genes), and hsa_circ_0021087 and hsa_circ_0000332 (circRNAs) | Bioinformatic analysis | Diagnostic and therapeutic biomarkers | (137) |
| Highly expressed OCT4, SOX2, and NANOG | qRT-PCR method | Developmental and prognostic biomarkers | (138) |
| Mutation in DRD2, TP53, CDH1, AKAP9, LRP2 and PTEN genes | Next-generation sequencing (NGS) | Guidance to medical administration by the efficiency of NGS | (139) |
| High expressions of FN1, TIMP1, SPP1, APOE, and VCAN | Bioinformatic analysis | Key genes for the GC discovery and therapy | (140) |
| Transcriptional repression of PRMT5-dependent proto-oncogene c-Myc target genes | Bioinformatics analysis, Immunohistochemistry, Immunoblotting, Chromatin immunoprecipitation, and Real-time PCR | Role in development, and therapeutic targeting | (141) |

## 5. Symptoms, diagnosis, treatment, and prevention of GC

The GC patients experienced a burden of symptoms with multiple co-occurring symptoms (average 10-15 symptoms) (71) including dysphagia (71-75), nausea (71, 75), depression (71, 75), bleeding, and malnutrition (72) dyspepsia (75), etc (**Figure 4**). These co-occurring symptoms harm the patient-reported outcomes (PROs) when it remains unknown by providers (71) including quality of life (QOL), emotional status (71, 74, 75), functional performance as well as the rate of survival (71, 75). Between these indications (72), gastric bleeding (72, 73), owing to unrestrained tumor evolution outcomes in drastic anemia can ultimately cause a deadly illness (72).

Preliminary estimation of digestive cancer essentially embraces tomography, pathological investigations, physical examination, endoscopy, diagnostic laparoscopy, analytical intra-peritoneal fluid assessment, histopathological analysis (gold standard), and magnetic resonance imaging (MRI) (76, 77), the evaluation of the deficient DNA mismatch repair (dMMR) status through microsatellite instability [MSI] (77), conventional


Figure 4. **Symptoms of GC.**

serum tumor biomarkers, such as carcinoembryonic antigen (CEA) and carbohydrate antigen (78), and Artificial intelligence (AI) has also been used for medical imaging (79). Research reported that the endoscopic images-based convolutional neural network computer-aided detection (CNN-CAD) system is highly accurate and specific for the determination of GC invasion depth (80). Similarly, the AI-stimulated CNN-CAD system based on magnifying endoscopy with narrow-band imaging (ME-NBI) is informed for the early diagnosis of GC (81). Another study testified the magnifying endoscopic videos with ME-NBI using a CAD system as a better consideration for the initial diagnosis of GC (82). CircSMARCA5 (circular RNA) was also stated as the probable biomarker for the diagnosis of GC (83).

Due to its heterogeneous nature (84), no gold standard treatment has been utilized in the GC until now. Mostly the selection of treatment depends on the preference of physicians, the existence of biomarkers, and the phase of illness. Examples comprise surgical intrusions, cytotoxic therapies, targeted therapies including tyrosine kinase inhibitors, targeting of DNA damage protein, cell structure remodeling therapy, and immunotherapy (85). The study reported the gastric-specific membrane protein called Claudin18.2 (CLDN18.2), as a possible therapeutic target for GC (86). Similarly, in cell lines of GC, a novel neocryptolepine derivative CFNC revealed a strong cytotoxic activity by regulating the signaling pathway of PI3K/AKT/mTOR (84). In contrast, for the targeted therapy of GC, gastric cancer mesenchymal stem cells (GCMSCs) can be used which upregulates the CD276 expression as well as promotes the relocation of GC cells (87) (**Table 2**).

Prevention proposed the economically feasible and enduring approach for cancer control, and one-third of all cancer cases are curable. Preventive measures to control GC include dietary modifications (88) such as high consumption of fresh produce (88-92), low consumption of red and high cured meat (88, 91), high salt and salt-preserved food (89-92), subunit and whole-cell vaccines contain particular antigens such as CagA, and NAP etc (88), increased physical activity, stop smoking (89, 90), eradication of H. *pylori* (90, 91, 93), early detection (90, 91), and treatment (90), chemoprevention (90, 91) by NSAIDs (90, 91), non-aspirin NSAIDs, and cyclooxygenase 2 inhibitors, vitamin C may protect the *H. pylori*-associated GC (90), reduce alcohol ingestion (90, 92), Mediterranean diet (90, 91), enhance the sanitary and hygienic conditions (92), adherence to a low salt-DASH diet (94), and HAP1 (Huntingtin-associated protein 1) as a possible tumor suppressant target aimed at preventing and treating GC (95).

Table 2. GC Treatments

| Treatments | Functional activities | GC types | References |
|---|---|---|---|
| **Chemotherapy** | | | |
| Nivolumab + chemotherapy | Progression-free survival | Esophageal adenocarcinoma (EAC)/Advanced gastric cancer (AGC)/Gastroesophageal junction cancer (GEJC) | (142) |
| Pembrolizumab + trastuzumab + chemotherapy | Improved survival | Advanced HER2-positive gastric or GEJ adenocarcinoma | (143) |
| 5-fluorouracil (5-FU) and *cis*-platinum (DDP) + chemotherapy | Inhibit the growth of stomach metastatic tumors, local recurrent orthotopic tumors, and extend the overall survival of postoperative GC | GC | (144) |
| Trastuzumab + pembrolizumab + chemotherapy (cisplatin + capecitabine) | Tumor shrinkage | HER2-positive AGC | (145) |
| Schisandrin B (Sch B) + 5-FU | Sch B inhibits the progression, migration, and invasion of GC by increasing the efficacy of 5-FU | GC | (146) |
| **Immunotherapy** | | | |
| Trastuzumab Deruxtecan | Prolong survival than conventional chemotherapy | HER2-positive gastric malignancy | (147) |
| Pembrolizumab | Promising antineoplastic activity with controllable toxicity | AGC | (148) |
| Pembrolizumab | Tolerable monotherapy with proven antitumor activity | AGC/GEJC | (149) |
| **Targeted therapy** | | | |
| Combination of trastuzumab+ pertuzumab | Target tumor growth and survival | HER2-overexpressing GC | (150) |
| Copanlisib+ refametinib | Improve responses to anti-HER therapies | HER2-positive GC | (151) |
| Novel HER2 antibody of patient-derived xenograft (PDX) model + Herceptin | Improved patient's survival rate | HER2-positive GC | (152) |

| | | | |
|---|---|---|---|
| *H. pylori* eradication | Restores gastric microbiota and shows beneficial effects | GC | (153) |
| *H. pylori* mass obliteration | Reduce gastric cancer incidence | GC | (154) |
| **Natural compounds** | | | |
| Modified Gui-shao-liu-jun-zi decoction (Traditional Chinese medicine compound) | Inhibit the proliferation and control the migration of multiple GC cells | GC | (155) |
| Heilaohulignan C (B 6), isolated from the *Kadsura coccinea* plant | Natural cell death by p53 and mitochondrial-dependent apoptotic pathway | GC | (156) |
| Azalomycin F4a (marine natural compound) | Suppress ATG4B genes by inhibiting cell survival and tumor development | AGC | (157) |
| Triptonoterpene (traditional Chinese herb *Celastrus orbiculatus* Thunb) | Inhibit incursion and metastasis | GC | (158) |
| Emetine (isolated from *Psychotria ipecacuanha)* | Induce cellular apoptosis and suppress the viability, propagation, migration, and incursion of GC cells | GC | (159) |

## 6. Role of microorganisms in the development, prognosis, and therapy of gastric cancer

### 6.1. Gastrointestinal microbes

Several types of bacteria are present in the body's different sites, which are stated as the "Normal flora" (96). These indigenous microbiotas can colonize numerous anatomical body sites namely skin, mucosa, mammary gland, respiratory tract, GIT, and urogenital tract (97) which play a significant role in sustaining human health (96, 97) throughout the body's interrelation which can be measured pathologically by the specific disease evolution (96). There is an acidic environment present in the stomach (98), due to the presence of gastric juice which has a proteinase activity and the influence of antimicrobial nitric oxide, produced by salivary nitrate (99), which is why considered to be unsuitable for microbial growth (98) but the detection of *H. pylori* changed this perception (98). The microbes of the human intestine have a lively and complex nature and are considered metabolically active organ that controls digestive homeostasis by interrelating with the immune cells (96). Culture-dependent approaches revealed the presence of *Clostridium spp., Veillonella spp., and Lactobacillus spp.*, whereas, the molecular methods discovered the existence of (98), Rothia, Streptococcus (98, 100, 101), *Veillonella* (98, 100, 101), *Prevotella* (98, 100), *Enterococcus* (101), *Staphylococcus* (98, 101), *Pseudomonas* (101), *Actinomyces, Neisseria* (100), *Propionibacterium* (101), *Lactobacillus* (100, 101), *Clostridium* (101), *H. pylori* (98), *phylum Proteobacteria, Fusobacteria, Bacteroidetes, Actinobacteria*, and *Firmicutes* (102),

in the normal stomach (98). The composition of the gastral microbes depends on numerous factors such as age (97, 98), use of medications (98), dietary habits (97, 98, 101), abdominal inflammation (98), the occurrence of *H. pylori* (98, 101), inherited genes, hormonal changes, underlying diseases (97), lifestyle, birth mode, topography, use of proton pump inhibitor, and exposures of antibiotic (101). The indigenous microbiota of the GIT performs many processes such as inflammatory bowel disease (97, 98), obesity, diabetes, functions of the nervous system (98), cardiovascular diseases, antibiotic-resistant bacterial diseases, etc (**Figure 5**) (96-98).

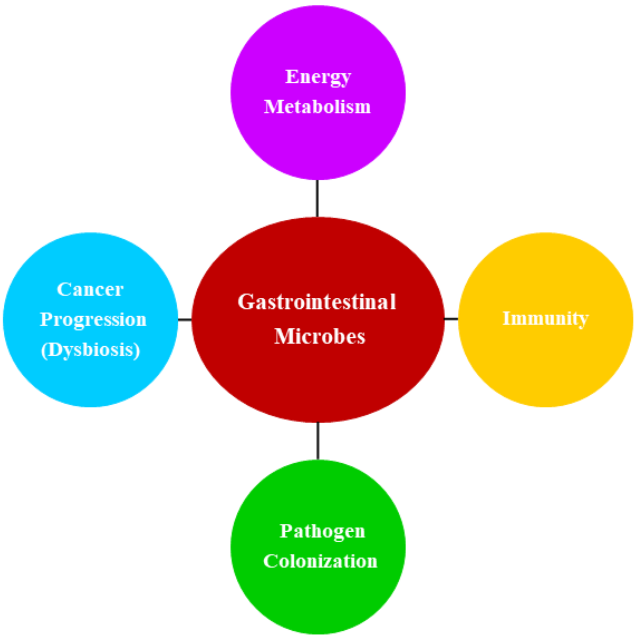


Figure 5. **Role of Gastrointestinal Indigenous Microbes.**

## 6.2 Developmental role of microorganisms in GC

The human GIT contains more than 1000 species of unique microbes (103), including bacteria (major inhabitants), viruses, fungi, archaea, and protists (104), expressing 3.3 million genes and >23,000 human genes as an order of magnitude. The collaboration of microorganisms and human cells plays a significant role in human metabolism (103), immunity, tissue development, inflammation, and dysbiosis related to numerous conditions of morbidity (105). Certainly, in the GC expansion, microbial dysbiosis has been initiated (103). In the abdomen, the digestive microbiota demonstrates an outstanding assortment of physiological and pathophysiological states. The tumor and its adjoint tumor-free tissues have diverse microhabitats (nutrients, pH, ions, oxygen, and chemicals) that support certain bacterial growth and colonization. To ascertain the transformation in the digestive microorganisms is significant in both the tumor and tumor-free tissues to find their role in GC (105). Viruses are reported as an etiological agent for around 15–20% of human cancers, whereas bacteria's role in malignancy causation is debatable. Few bacteria take part in the evolution of cancer as stated in the study (106). Beyond 60% of GCs are caused by *H. pylori* and are characterized as a group 1 carcinogen by the World Health Organization (WHO) (106, 107). GC is a multifactorial disease requiring tumor microenvironment modifications for initiation, development, and metastasis. Abdominal microorganisms are a part of the tumor microenvironment which affects the progress and spread of GC in many ways which is why it is taken into cumulative consideration. The stomach of humans is supposed to be completely occupied by *H. pylori* and is observed as an overwhelming environment for the microbes due to an acidic environment and other antimicrobial influences (105). Several studies have verified that the carcinogenicity is primarily accredited to microbial dysbiosis which includes chronic inflammation (major origin of cancer), immune regulation (tumor formation due to dysbiosis), and metabolites of microorganisms (like short-chain fatty acids (SCFAs), lipoteichoic acid (LTA) and secondary bile acids which performs a dual role in carcinogenesis) (104). The prevalence and development of GC depend on the modifications in the composition of the microbiome (**Table 3**) (108).

Table 3. **Worldwide reported microorganisms in the development of GC.**

| Countries | Samples | Identification techniques | Microorganisms | References |
|---|---|---|---|---|
| China | Serum | 16S rRNA gene sequencing | *Acinetobacter, Bacteroides, Haemophilus parainfluenzae* | (108) |
| China | Polyp tissues | Ultra high-performance liquid chromatography-tandem mass spectrometry and 16S rRNA gene sequencing | *Bacteroides, Lactobacillus, Prevotella, Streptococcus,* and 6 other genera | (160) |
| Taiwan | Gastric biopsies | 16S rRNA gene sequencing | *Clostridium, Fusobacterium, Lactobacillus* | (161) |
| Hong Kong | Gastric biopsies | Illumina MiSeq platform targeting the 16S rDNA | *Haemophilus, Serratia, Neisseria, Stenotrophomonas* | (162) |
| China | GC tissues | 16S rRNA gene sequencing | *Peptostreptococcus, Streptococcus, Fusobacterium* | (163) |
| China | Fecal and Peripheral blood samples | 16S rRNA gene sequencing | *Lactobacillus, Escherichia, Klebsiella, Lachnospira,* and *Lactobacillus,* also *Veillonella, Lachnospira, Tyzzerella_3, Streptococcus,* and *Lactobacillus* in combination | (164) |
| Lithuania | Gastric biopsies | 18S rDNA sequencing | *Malassezia* | (165) |
| China | Gastric mucosal biopsy | 16S rRNA gene profiling | *Actinobacteria, Bacteroides, Firmicutes, Fusobacteria, SR1, TM7* | (166) |

Intratumoral microbes lead the tumor development by altering the balance of cell propagation and apoptosis, updating the immune system, and disturbing the metabolism. The mechanisms include activating oncogenic pathways by effectors AvrA and CagA, DNA mutation via toxin or reactive oxygen species (ROS), stimulating chronic inflammation through cytokines, initiating metastasis by inhibiting the RhoA-ROCK signaling pathway and complement system by activating C3 invertase (109). The carcinogenesis mechanism of *H. pylori* includes inflammatory responses, modification of gene expression, and stimulation of immune response by activating inducible nitric oxide synthase (iNOS) and NADPH oxidase (NOX) following the production of reactive nitrogen species (RNS) and ROS (110). EBV caused the GC primarily through signaling pathways, viz., PI3-kinase/AKT, NF-κB, and extracellular signal-regulated kinase (ERK) by regulating the cell activities and expression of numerous downstream target genes (111).

### 6.3. Prognostic role of microorganisms in GC

GC is among the most frequent cancers (112), but the non-invasive method is still absent for the prognosis (112, 113). The increasing evidence demonstrates the

potential human microbiota for the identification of gastric diseases (112). Research testified the extracellular vesicles (EVs) acquired from bacteria as innovative diagnostic biomarkers for the GC. The metagenomic analysis and 16S rRNA gene profiling were performed by taking the serum, urine, and stool samples, and suggested that the EVs attained from bacteria in urine with the combination of metagenome investigation and liquid biopsy conceivably implemented as a de-novo metagenomic marker for the non-intrusive finding of GC (113). The association among microorganisms coating the tongue, with inflammatory cytokines, and serum metabolic features from the GC patients was discovered in the study by using ultra-performance liquid chromatography-tandem quadrupole time-of-flight mass spectrometry (UPLC-Q-TOF/MS), 16S rRNA, and 18S rRNA gene sequencing reported that the bacteria covering the tongue probably become a non-intrusive diagnostic biomarker for GC (112). Similarly, a group of researchers performing the rRNA gene sequencing (16S and 18S) of fecal microbes of GC patients with healthy controls stated that the modification in the fecal microbiome can be a novel biomarker or protective target for GC (114). Another research took the patient's stool samples as well as the healthy individuals and performed the 16S rRNA gene sequencing which conveyed that the variations in *Streptococcus* were strongly linked with the incidence of GC and liver metastasis, which might be a possible biomarker for the preliminary diagnosis of both diseases (115). The tissue, oral, and fecal microbiota in patients of GC, with healthy individuals (control) were investigated by V4 region sequencing and bioinformatics examination which represents that the fecal and oral microbiome offers a solid hypothetical basis for the non-incursive estimation of both cancers (116). The assessment of the composition and functions of stomach microbiota in progressive gastric adenocarcinoma and superficial gastritis (SG) was performed by using shotgun metagenomic sequencing, MetaPhlAn2 was used for the profiling of taxonomical composition, and HUMAnN2 for the pathway of functional genes, on gastric wash samples of SG and progressive gastric adenocarcinoma. This study suggested that the constitution and activity of the gastric microbiome are feasible and utilized for the examination of GC (117). A study described a salivary *Fusobacterium nucleatum (Fn)* role in diagnosis and their influence on GC cells by performing digital polymerase chain reaction and western blotting. The outcomes suggested that for the diagnosis of GC, a profusion of salivary Fn can be executed as a biomarker and their infection can promote metastasis by enabling the process of epithelial-mesenchymal transition (EMT) (118). Literature reported the EBV-associated GC and characterized the response of GC-specific antibodies by enzyme-linked immunosorbent assay (ELISA), through plasma samples. The outcomes revealed that anti-EBV antibodies can be effective for the prognosis, immune-based precision therapy, and epidemiological studies of EBV-positive GC (119).

### 6.4. Therapeutic role of microorganisms in GC

Chemotherapy, surgery, and radiation therapy are reported as the conventional treatments for GC but they are not efficient so there is a need for novel treatment approaches (120, 121). Recently, specific pioneer curative methods have been instigated like immunotherapy, hormone therapy, dendritic cell-based immunotherapy, and stem cell-based treatment (120). The non-precise poisonousness to the body's normal cells has been reported for the use of chemotherapeutic agents as a therapy for GC. The chemotherapy-exposed body cells frequently become resistant to drugs due to the improved competence to DNA repair defects in cellular machinery which mediates apoptosis, and intensify the production of enzyme causing detoxification of drugs and their delivery. Due to these problems, scientists focused on

the investigative potential of bacteria and their composites for anticancer treatment (122). Hence, there is an incredible demand for the latest therapeutic approaches which have higher efficacy and lower side effects (120). Bacteria were usually described as carcinogenic but now there is evidence for their anticancerous properties. Bacteria use numerous mechanisms to apply anticancer properties such as colonization in the tumor, liberating substances (121) like enzymes and toxins (123), suppressing nutrients mandatory for tumor propagation and metabolism, acting as a vehicle for the delivery of anticancer drugs, creating biofilm, and improving the host immunity (121). Initially, William Coley implemented the culture supernatants of *Serratia marcescens* (Coley's toxins) and Streptococcus pyogenes to treat cancer, which displayed tumor regression and recovery of the patients. The bacterial genera which are previously testified for anticancerous potential are reported as *Clostridium*, *Lactobacillus*, *Salmonella*, *Escherichia*, *Proteus*, *Bifidobacterium*, *Listeria*, *Streptococcus*, and *Caulobacter* but further examination is required for the usage in the human cancer therapy (123). According to the WHO, probiotics are active microbial agents that have a valuable outcome on the host when given in adequate quantities. Various strains of lactic acid bacteria in the host are advantageous to avert the pathogen's development, inflammation, tumor, and allergic alteration due to their capability to intensify the Immunoglobin A (IgA) excretion, compete with intestinal pathogens, stimulate mucin, bacteriocins, construction of lactic acid, adjust the microbial progress, and control cytokine expression and secretion. Few probiotics have therapeutic property also by stimulating epithelial cells evolution and upregulating the anti-inflammatory cytokines expression besides angiogenesis, for instance, *Lactobacillus gasseri OLL2716*, *Lactobacillus rhamnosus GG*, *Lactobacillus acidophilus* and *Saccharomyces boulardii* in rats (124). Research reported that the probiotic *Lactobacillus gasseri* ATCC 33323 controls the production of chemokine and reduces the mRNA expression in human gastric adenocarcinoma cell line which may inhibit the *H. pylori* gastric inflammation and could be used as a supplementation to the existing treatment (125). Similarly, a probiotic *Lactobacillus paracasei* strain 06TCa19 was also informed to suppress the elevation of *H. pylori*-facilitated gene expression associated with the chemokines in MKN45 and AGS cells. Thus, it can be used to prevent *H. pylori*-related gastric inflammation (126). Another study testified the inhibitory effects of probiotic *Lactobacillus acidophilus* NCFM and Lactiplantibacillus plantarum Lp-115 by reducing the adhesion of *H. pylori* on digestive inflammatory response instigated by *H. pylori* contagion in mice and AGS cells (127). *Lactobacillus reuteri* is also stated as a probiotic suppressor of GC cell intrusion by downregulating the pathways of urokinase plasminogen activator (uPA) and urokinase plasminogen activator receptor (uPAR) intricated in the degradation of extracellular matrix (128). Probiotic *Saccharomyces cerevisiae boulardii* supernatant (SBS) reduces the survivin gene expression, induces apoptosis and antiproliferative activity on human gastric adenocarcinoma including EPG (gene expression of EPG85-257P) and RDB (EPG85-257RDB resistant to Daunorubicin) cells which might be used as a potential medication for the treatment of GC (129). The probiotic *Lactobacillus plantarum* can inhibit the GC by up and down-regulation of some significant apoptosis and anti-apoptosis genes such as AKT, Bax, PTEN, and TLR4 which can be applied as a novel therapy to prevent H. pylori-induced GC (130).

## 7. Conclusion

The normal flora of GIT plays a substantial role in the human metabolism, but their imbalance can cause gastric cancer initiation. Many microorganisms were reported around the world which can be isolated from different samples of GC patients like serum, tumor tissues, fecal and gastric biopsy, and identified by different molecular techniques that are intricate in the GC advancement. They represent that gastric microbiota composition depends on factors like age, topography, lifestyle, etc. These gastric microbes encompass the expansion of GC and are also implemented as a non-invasive prognostic method and treatment for GC by adopting different mechanisms. Till now the traditional treatment procedures for GC such as chemotherapy, surgery, and radiation therapy are not effective and have adverse effects so there is a need for advanced therapeutic approaches. The challenges of chemotherapy include narrowing a protective margin, which is why to attain maximum killing of cancer cells they are given in combination at a maximum tolerated dose, drug-resistance, and dose-restrictive toxicities. Nevertheless, many patients do not respond to these chemotherapeutic treatments and they frequently experience severe detrimental side effects including life-threatening alopecia, diarrhea (131), myelosuppression, infertility, fatigue, mucositis, immunosuppression, and infusion reactions (132) because it kills the normal cells besides tumor cells (131). The challenges of GC surgery include complications in overweight patients due to more wound infections and anastomotic leakages, the postoperative risk with increased morbidity and mortality includes malnutrition, Sarcopenia, and Frailty in older patients (133). Radiation therapy challenges comprise stem cell damage which occurs when tissues are lost as a fragment of normal cell turnover but it can inadequately replace the stem cells, intrinsic radio-sensitivity, volume of irradiated tissue or organ, overall dose, dose per fraction, acute effects severeness, and the association of chemotherapy and surgery. The radiation outcomes in such tissues embrace atrophy, vasculopathy, fibrosis, and necrosis. The complex interaction of numerous adaptive cellular processes and cytokines is the consequence of late effects. The late sequelae risk related to host factors includes intrinsic radio-sensitivity of organs, body mass index, old age, associated chemotherapy treatments, anemia, and comorbidities. This breakage in the protective barrier results under 1-5 years of the completion of radiotherapy (134). The prospects include investigating and identifying novel microbes and observing their role in GC progression by taking different types and a huge quantity of samples, testifying their potential for early diagnosis and their therapeutic use which will become non-invasive, inexpensive, highly efficient and have fewer side effects as compared to the present conventional methods.

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## Declaration of interest

Author declare that there is no conflict of interest.

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