Resistance to, and Treatment of, *Helicobacter Pylori*

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Edited by

Muhammad Saleem Khan and Hasnain Nangyal

Cambridge Scholars Publishing

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Dedicated with pleasure and gratitude to

Our Beloved Father and Mother
A source of inspiration for us

I should like to pay a special tribute to my mother, to whom this book is dedicated. Like a gentle, enthusiastic, and understanding Noah, she has steered her vessel full of strange progeny through the stormy seas of life with great skill, always faced with the possibility of mutiny, always surrounded by the dangerous shoals of overdraft and extravagance, never being sure that her navigation would be approved by the crew, but certain that she would be blamed for anything that went wrong.

مرګ وو، مرګ وو، ستانه مخښکي وو که و□وسته وو
ستا د ژوندو سترګو مخښکي څو و□ځي ژوندۍ وومه

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ABOUT THE EDITORS

Dr. Muhammad Saleem Khan

Dr. Khan is currently Assistant Professor of Zoology and HoD of Undergraduate Studies in the Department of Zoology, University of Okara. Dr. Khan completed his Ph. D in Zoology from Government College University, Faisalabad, Pakistan. Dr. Khan is a member of the "National Academy of Young Scientists Pakistan". Dr. Khan completed three internships on bioassays in agriculture and pest control at the Nuclear Institute of Agriculture and Biology (NIAB), Ayub Agriculture Institute of Agriculture, Faisalabad. He was also part of the HEC project on "Sustainable Bio-control of Helicoverpa armigera (Hub) through Araneid fauna in the Central Punjab. He has published 39 research and review articles in well-reputed journals, 3 book chapters and 7 conference papers. He is also the author of a book titled "Environmental Pollution, Biodiversity, and Sustainable Development: Issues and Remediation." Currently, Dr. Khan, with his reach group, is working on different community diseases, their prevalence, risk factors, knowledge, attitudes, and practices of the population towards specific diseases.

Mr. Hasnain Nangyal

Mr. Hasnain Nangyal is a research fellow in the Department of Botany, Faculty of Sciences, Hazara University, Mansehra, Khyber Pakhtoonkhwa. He is an active member of many national and international research organizations, including Pakistan Medical Microbiology Association, Member Pakistan Medicinal Plants Association, Member North Carolina Herbs Association (NCHA) USA, Pakistan Society of Psycophysiology, Member Arab Society for Fungal Conservation. He is also an editorial board member of a scientific magazine. He is a member of the publishing team of a book series "Biodiversity Distribution & Conservation" published in India, and has published three chapters in an international book entitled "Biodiversity Distribution & Conservation". He has attended an international scientific conference of young scientists entitled "The role of multidisclipnary approach in the solution of actual problems of fundamental and applied sciences (Earth, Chemical, Technical)" in October 2014, organized by the National Academy of Sciences, Azerbaijan. He was invited as a key note speaker by the Academy of Sciences, Azerbaijan.

ABOUT THE CONTRIBUTORS

Prof. Dr. Muhammad Wajid

Prof. Dr. Muhammad Wajid earned a PhD in Zoology from Quaid-e-Azam University, Islamabad, Pakistan in 2005. He got post-doctoral training from Columbia University, New York, USA in 2005-2007. Dr. Muhammad Wajid is working as vice chancellor and Professor of Zoology at the University of Okara. He has the responsibilities of Chairperson Department of Zoology, Director School of Applied Biology, Director Institute of Pure and Applied Zoology, Additional Treasurer, Director ORIC, Chairperson Admission Committee, and Convener Sports Committee. Prof. Dr. Muhammad Wajid also worked as Registrar at the University of Okara from November 1st, 2017 to September 30th, 2018.

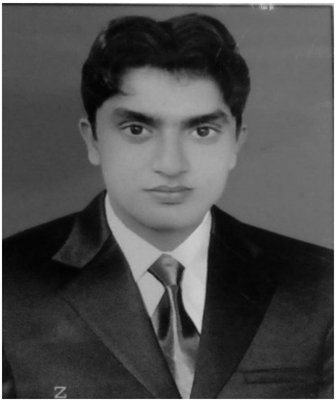
Dr. Tanzil Ur Rahman

Dr. Tanzil Ur Rahman, PhD/Postdoc from Zhejiang University, School of medicine Hangzhou China. MSc/ MPhil from Quaid-i-Azam University Islamabad. Currently, working as a Assisant Professor (visiting) at University of Okara, Punjab. Dr. Tanzil has 15 Publications in well reputed journals with total IF of 50 plus with 200 plus citations.

Ahmad Waheed

Mr. Ahmad Waheed is pursuing a PhD in Zoology at the Department of Zoology, Faculty of Life Sciences, University of Okara, Punjab, Pakistan. He has worked on the prevalence of different diseases in Pakistan; the assessment of heavy metals in different fishes and their morphometric characteristics; biometrics, hematology, and feeding strategies of birds; and the effect of different ecological and anthropogenic factors on the diversity of insects. He has published ten research papers, six review articles, and four conference papers. His current research areas include Fisheries, molecular toxicity, and molecular genetics.

Muhammad Waseem Aslam



Mr. Muhammad Waseem Aslam is currently a government teacher in the school education department in Punjab, Pakistan. He is a PhD scholar in Zoology from the University of Okara. Mr. Waseem is also working as a visiting faculty in the Zoology department at the University of Okara. He completed his MPhil from the University of Okara and his Bs (Hons.) in Zoology from the University of Veterinary and Animal Science, Lahore. He has also completed his professional education (B. ed./M. ed.) from Allama Iqbal Open University Islamabad. He is working as a member of the life-time young scientist programme of UVAS wildlife society. Mr. Waseem has nine research papers and review articles, as well as two abstracts in familiar journals around the world.

Mr. Shabbir Ahmad

Mr. Shabbir Ahmad is currently working as a visiting faculty member in the Zoology department at the University of Okara. He is a PhD scholar in Zoology from the University of Okara. He completed his M.Phil. from the University of Okara and his BS (Hons.) in Zoology from the University of Education, Lahore, Okara campus. He is a member of the UO Wildlife Society's life-time young scientist program. Mr. Shabbir has 7 research papers, review articles, and 2 abstracts in familiar journals around the world.

Mr. Hasnain Akmal

Mr. Hasnain Akmal is currently working as a visiting faculty member in the Zoology department at the University of Okara. He is a PhD scholar in Zoology from the University of Okara. He completed his M.Phil. from the University of Okara and his BS (Hons.) in Zoology from Education University Lahore. He is working as a member of the Bird Watch Society. Mr. Hasnain Akmal has 7 research papers and review articles, as well as 1 abstract, in well-known journals around the world.

Ali Umar

Ali Umar is currently a Ph.D. scholar in Zoology at the University of Okara, Okara, Pakistan. Mr. Umar completed his Master of Philosophy in Zoology from the University of Okara in 2021. He has published 3 research articles and one book chapter. His area of research is epidemiology and toxicology. Currently, he is working on different research articles. With his reach, the group is working on different community diseases, their prevalence, risk factors, knowledge, attitude, and practices of the population towards specific diseases. He is also interested in monitoring environmental health through different environmental indicators like birds (terrestrial) and fish (aquatic habitat).

Muhammad Junaid Iqbal Tahir

Mr. Muhammad Junaid Iqbal Tahir is an M. Phil scholar in the Zoology department at the University of Okara. He has completed his graduation from the University of Okara in 2020. Moreover, he is enrolled in a professional education course of B. Ed (1.5) at the University of Okara. He is an author of a research review chapter with the title of "Pharmacogenetics of Thiopurine Induced Toxicity in Children".

Ahmad Muhammad

Mr. Ahmad Muhammad has completed his M. Phil. from the University of Okara. He did his BS in Zoology from Emerson College Multan, affiliated with Bahauddin Zakariya University (BZU). He completed his M. Phil. in Zoology from the University of Okara, Okara, Pakistan. His area of research interest is human disease.

Kamran Jafar

He has completed his MPhil at the University of Okara. He has completed his BS (Hons.) from the University of Education, Okara campus. Currently, he is working at the University of Okara as a visiting faculty member. He has 7 publications in well-known journals around the world.

Muhammad Shoaib Akhtar

Muhammad Shoaib Akhtar is pursuing a BS in Microbiology and Molecular Genetics at the Department of Microbiology and Molecular Genetics, Faculty of Life Sciences, University of Okara, Punjab, Pakistan. He has worked on COVID-19 vaccine: Potential candidates, achievements, and challenges. He has authored/co-authored three (3) review articles. His current research areas include immunoinformatic analyses to reveal potential multiple epitope-based peptide vaccines. Currently, he is also working on the effects of probiotics on fish and fish vaccination.

Zain Ul Abadin Malik

Zain Ul Abadin Malik is currently a science teacher in the school education department. Malik completed his M. Phil. at the University of Okara, Pakistan. He gained professional education in "Bachelor of Science Education" from Allama Iqbal Open University, Islamabad, Pakistan. His latest research work is on the prevalence of chronic diseases, their risk factors, and their impact on the lives of school teachers in Punjab, Pakistan. His research interests include remedies and preventive measures for chronic diseases, the social impacts of chronic diseases, and risk management. He also run an institute, "Zain Educational Complex (Evening Coaching Center)", which serves students from monetary to master classes.

Hina Naz

Ms. Hina Naz is pursuing her M.Phil. in Zoology at the Department of Zoology, Faculty of Life Sciences, University of Okara, Punjab, Pakistan. She has done her BS (hons) in Zoology from the University of Okara. She has published 6 research articles in well-reputed journals around the world. Her research areas include fisheries, public health, and aquatic toxicology.

Asima Nazir

Ms. Asima Nazir is currently a visiting faculty at the Govt. College in Okara. She recently completed her M.Phil. from the University of Okara. She completed her B.S. in Zoology from the University of Education Lahore, Okara campus. She had 2 years of experience in private schools in Okara. She is also working as a member of the Environmental Watch Society. She has a keen interest in social activities. She has also completed her professional education (B.ed/M.ed) from Allama Iqbal University Islamabad. She also did research on the status of COVID-19 in all public sector universities in Pakistan.

Zainab Ameer

Miss Zainab Ameer is an M.Phil. scholar (Zoology) at the University of Okara. She completed her BSc from Bhaduddin Zakariya University in Multan and her M.Sc. in Zoology from the University of Okara.

Saba Aslam

Ms. Saba Aslam has completed her Master of Philosophy in Zoology from the University of Okara, Okara, Pakistan in 2021. Her areas of expertise are epidemiology and physiology. She has completed her thesis work on "status of anxiety in medical professionals in the COVID-19 pandemic of Pakistan". With her research group, she is working on different community diseases, their prevalence and risk factors. She is also interested in monitoring environmental health through different environmental indicators.

Rana Elshimy

Mr. Rana Elshimy is currently working in the microbiology and immunology Department of Microbiology and Immunology, Faculty of Pharmacy, Ahram Canadian University, Giza, Egypt and also working in the department of microbiology and immunology, faculty of pharmacy, Ahram Canadian University, Egypt.

Doha H. Abou Baker

Mr. Doha H. Abou Baker is currently working in the Medicinal and Aromatic Plants Dept., Pharmaceutical and Drug Industries Division, National Research Centre, Cairo, Egypt. PO 12311.

Heba S. Abbas

Ms. Heba S. Abbas is currently working in National Organization for Drug Control and Research (NODCAR) Egypt.

Samrina Shamim

Ms. Samrina Shamim is an MPhil scholar at the University of Okara. She is very interested in the fishing sector. She also has experience of handling the fishery in controlled conditions.

Zeeshan Ulfat

He is pursuing an MPhil in Zoology from the University of Okara. He completed his M.Sc. in Zoology from the University of Education, Lahore (Faisalabad Campus). He has two publications in well-known journals. Currently, he is working on aquatic toxicology. He also has an interest in genetics, wildlife, fisheries, and physiology.

PREFACE

Helicobacter pylori is a worldwide distributed bacterium which affects more than half of the world population. The outcome of the infection is not limited to persistent inflammation, chronic gastritis, peptic ulcers, and gastric cancer. In this book, contributors gave a comprehensive overview of *H. pylori* infection in diverse areas, including virulence, isolation, epidemiology, resistance, and new horizons of treatment such as nanotechnology. *H. pylori* clearly attracts future studies and discussions about all its aspects in the scientific communities.

I found this book different from other books already published on *H. pylori*. Most prior books concentrated on clinical issues and are now out of date. However, this book not only focuses on the basic characteristics of the bacterium but also on epidemiology, resistance, and new approaches to effective control. Upon reading the complete review of the book, I found that this book opens with the introductory chapter. Chapter 2 focuses on the mechanism of transmission of *Helicobacter pylori*. Chapters three and four focus on the pathogenicity and resistance to antibiotics. Chapter 5 is related to isolation characterization and culturing techniques, and Chapter 6 provides a detailed account of diseases due to *H. pylori*. Chapter seven is related to the effects of *Helicobacter pylori* on gastrin. Chapter eight emphases on antibiotics, probiotics, or phytotherapy. Chapter 9 explains the main reasons for the low *Helicobacter pylori* eradication rate, possible ways for eradication through drugs, probiotics, surgery, or natural remedies, and the disadvantages of antibiotic treatments. Furthermore, this chapter discusses direct competition of probiotics with *H. pylori* through adherence inhibition; indirect improvement of the success rate of eradication therapy through improving patients' compliance by reducing the occurrence of antibiotic side effects; and metabolite and antimicrobial molecular production. Besides, other mechanisms of probiotics have been reported, such as immunological and non-immune mechanisms, and mucosal barriers.

Chapter 10 demonstrates in detail pharmacological therapy for the treatment of *H. pylori* infection and the mechanism of medicinal plants as anti-*H. pylori*. Various behaviors of herbal natural products are specifically related to the existence of biologically active compounds such as flavonoids, terpenes, alkaloids, and steroid saponins. The probable mechanisms include urease enzyme inhibition, cell membrane disorder, oxidative stress, anti-adhesion activity, and host immune modulation. Up to now, the mode of action is still unknown, and future research in this field is required.

Chapter 11 provides detailed information on inorganic nanoparticles, bioengineered natural-derived bioactive compounds, the mechanism of antibacterial efficacy of liposomes and linolenic acid against *H. pylori,* and different nanoparticle approaches that improve their therapeutic efficiency, such as different ligand-conjugated nanoparticles, environmentally responsive nanoparticles, and combinatorial nanoparticles for antibacterial drug delivery. Furthermore, *Helicobacter pylori* diagnosis by gold nanoparticles has been reported. Nanoparticles' strategies show impressive results in the treatment and detection of *H. pylori*. Chapter 12 outlines the effects of *H. pylori* on nutritional parameters. Chapter 13 explains the epidemiology of *Helicobacter pylori* in Asia, and the last chapter shows disturbance in endocrinological function of the host due to infection.

Finally, I would like to thank the Cambridge Scholars Publishing team for completing this book on time. I hope the scientific community will enjoy and derive benefits from reading this book.

Professor Dr. Naureen Aziz Qureshi
Ex -Vice Chancellor
Government College Women University, Faisalabad

INTRODUCTION

HEBA S, ABBAS[1,2]
AND MUHAMMAD SALEEM KHAN[3]

[1]NATIONAL ORGANIZATION FOR DRUG CONTROL AND RESEARCH (RECENTLY, EGYPTIAN DRUG AUTHORITY), GIZA, EGYPT.

[2]DELEGATED LECTURER IN MICROBIOLOGY DEPARTMENT, FACULTY OF PHARMACY, MISR UNIVERSITY FOR SCIENCE AND TECHNOLOGY, GIZA, EGYPT.

[3]DEPARTMENT OF ZOOLOGY, FACULTY OF LIFE SCIENCES, UNIVERSITY OF OKARA, OKARA, 56130, PAKISTAN

Helicobacter pylori was the first bacterium to be scientifically characterized and is the most infectious species of human infection, infecting almost half of the world's population. *H. pylori* infection has a significant contribution to the aetiology of several gastrointestinal diseases. The complicated interplay between the host and the bacterium determines the disease outcome (Lehours et al. 2004). Robin Warren and Barry Marshall were awarded the Nobel Prize in Physiology or Medicine in 2005 for the discovery of *H. pylori* and its role in gastritis and peptic ulcers. The harsh environment of the gastric mucosal surface has modified gastric *Helicobacter* species, and it is believed now that members of the genus Helicobacter can populate the stomachs of all mammals. *H. pylori* is urease-positive and highly motile thanks to its flagella. Urease is supposed to allow short-term survival in the extremely acidic gastric lumen and motility allows quick migration toward the gastric mucosa's more neutral pH; this could explain why both qualities are required for colonization of the gastric mucosa (Suerbaum and Achtman 2004). Upon entrance, Helicobacter species exhibit chemotactic movement toward the mucus layer mediated by urea and bicarbonate (Occhialini et al. 2000). Spiral morphology and flagellar mobility then aid dissemination into the viscous mucus layer, where more pH-neutral circumstances allow gastric Helicobacter species to flourish (A. Santos et al. 2003).

The 26695 bp genome of *H. pylori* strain has 1,587 genes, whereas strain J99's genome has just 1,491 genes. Many strains have one or extra cryptic plasmids, which appear to be devoid of antibiotic resistance genes. Some of these plasmids are employed in molecular cloning procedures as shuttle vectors between *H. pylori* and *E. coli* (Aspholm-Hurtig, Dailide, Lahmann, Kalia, Ilver, Roche, Vikstrom, Sjöström, et al. 2004). *H. pylori* is genetically diverse. As a result, every *H. pylori*-positive patient has a unique strain, even if the differences between relatives are minor (Scott et al. 2002). *H. pylori*'s genetic heterogeneity may be an adaptation to its host's gastrointestinal circumstances, as well as to the different patterns of the host's immunological response to this infection (Taneera et al. 2002). Several ways of DNA rearrangement, as well as the addition and removal of foreign sequences, are thought to cause genetic variability (Dent and McNulty 1988). The latter usually have an abnormal G+C concentration and frequently carry virulence genes. For instance, the cag PAI in *H. pylori*, have also been reported in the *H. pylori* pathogenesis (Reynolds and Penn 1994; J. Kusters, Van Vliet, and Kuipers 2006a; Perez-Perez et al. 2005). This results in reversible phenotypic diversity. Several virulence genes, including the oipA, hopZ, sabB, and sabA outer membrane protein-encoding genes, as well as lipopolysaccharide biosynthesis enzymes, show phenotypic diversity (J. Kusters et al. 1997; T. Westblom, Madan, and Midkiff 1991).

Microaerophilicity is a critical property of *H. pylori*, with optimal growth at 2 to 5% O_2 levels, 5 to 10% CO_2 levels, and extreme humidity. H_2 is not required for growth, however, and is not harmful. Many laboratories use standard microaerobic conditions for *H. pylori* culture; 85 percent N_2, 10% CO_2, 5% O_2, and 34 to 40 °C temperatures are ideal for growth, with 37°C being the optimum. *H. pylori* is a neutralophile, despite its native environment being the acidic stomach mucosa. The bacteria can survive pH as low as 4, but it can only thrive in a rather narrow pH range of 5.5 to 8.0, with neutral pH being the best (Zagari et al. 1999). Blood or serum is frequently added to this medium. These supplements could provide extra nutrients while also protecting against the harmful effects of long-chain fatty acids. More defined media supplements, such as cyclodextrins or IsoVitaleX, or activated charcoal, can also accomplish this job (Perez-Perez et al. 2005). For routine isolation and culture of *H. pylori*, Columbia or brucella agar augmented with either (lysed) horse or sheep blood or newborn or foetal calf serum are commonly used solid media (Pounder and

Ng 1995). Selective antimicrobials are used for initial isolation as well as regular culture. Brucella, Mueller-Hinton, or brain heart infusion broth with 2 to 10% calf serum or 0.2 to 1.0 percent -cyclodextrins, sometimes with Dent or Skirrow supplement, are the most common liquid media (Perez-Perez et al. 2005). *H. pylori* has also been recorded to grow on chemically specified media, although these are not ideal for routine *H. pylori* growth and isolation (Peterson et al. 1993).

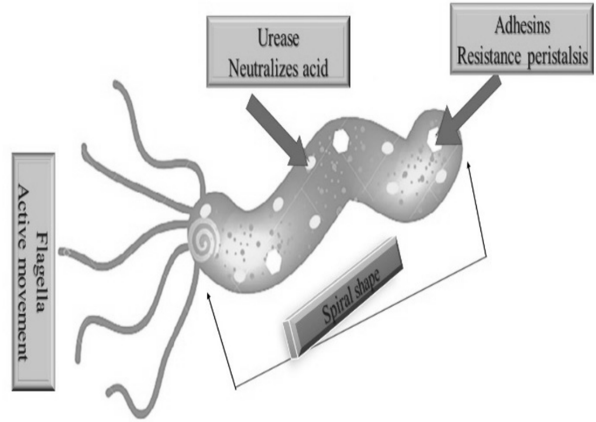


Figure 1-1: Robin Warren and Barry Marshall were awarded 2005 Nobel Prize in Physiology for discovery of *H. pylori*

Isolation of *H. pylori* through stomach biopsy is challenging and not always successful. From day 3 to day 14, cultures should be regularly inspected. *H. pylori* colonies are tiny (1 mm), transparent, and smooth. *H. pylori* isolates successfully sub-cultured tend to adapt to the laboratory conditions (Kroll, Fang, and Zhang 2017). When using reference strains and laboratory-adapted isolates of *H. pylori*, good growth may be attained after 1 to 3 days of incubation. It's worth noting that once a culture reaches the stationary phase, the rate of growth slows dramatically, and the morphological shift to a coccoid shape occurs. Long-term culture does not result in a large increase in colony size; rather, it leads to the unculturable coccoid stage (F Mégraud 1995). Plates can be treated with triphenyltetrazolium chloride (TTC) to a final concentration of 0.004 percent to enhance visual recognition of *H. pylori*. The conversion of TTC to deep red formazan causes *H. pylori* colonies to turn dark red and develop a golden sheen in the presence of TTC. *H. pylori* can be kept for a long time at 80°C in brain heart infusion or brucella broth with 15-20% glycerol, but the best viability comes from cultures that are less than 48 hours old, and contain greater than 90% spiral-shaped cells (Safarov et al. 2019).

A number of tests have been devised for the diagnosis of *H. pylori*, each with their own set of benefits and drawbacks. Invasive testing uses stomach specimens for culture or other procedures, and noninvasive tests use blood, faeces, urine, or saliva samples to identify antibodies, bacterial antigens, or the activity of urease. Both types of tests are available. The choice of a test is based on local knowledge and the therapeutic situation. Many patients in hospital-based care get an endoscopy, which is subsequently paired with an invasive test for *H. pylori.* Breath testing and serology are routinely utilised in the absence of other options. For children, faecal antigen testing can be used to check for *H. pylori* without having to undergo an endoscopy or vena perforation (BJ Marshall and Goodwin 1987b).

The prevalence of *H. pylori* varies greatly around the globe. Even at young ages, more than 80% of the population in several developed nations are *H. pylori* positive (Kroll, Fang, and Zhang 2017). In advanced countries, the prevalence of *H. pylori* is normally under 40%, and it is much lower in children and adolescents than in adults and elderly people (Yamaoka 2008). Within geographical areas, the prevalence of *H. pylori* is inversely related to socioeconomic status, particularly when it comes to early living situations. This bacterium is much more common among first- and second-generation settlers from poor countries to Western countries (Liddell and Scott 1891).

The virulence factors of *H. pylori* can be classified into 3 main pathogenic progressions, including invasion, immune escape, and induction of diseases. The colonization factors for virulence include urease, flagella, chemotaxis, and adhesins. The absence of urease, flagella, or chemotaxis causes a failure to develop an infection. However, immune escape virulence factors help the bacteria to avoid the host immune system, allowing for their survival in the human bowel, and other virulence factors are related to gastric adenocarcinoma development.

Despite the fact that *H. pylori* is susceptible to a wide range of antibiotics in vitro, they all fail in vivo as monotherapy. Clarithromycin is the most successful single antibiotic for infected patients, with a 40 % eradication rate when administered twice daily for ten to fourteen days (B.J. Marshall and Goodwin 1987a). In 2017, clarithromycin-resistant *H. pylori* was listed as a highly significant bacterium in antibiotic research and development by the World Health Organization (WHO). Monotherapy's ineffectiveness is due to *H. pylori*'s niche, which is found at a lower pH than the non-viscous mucus layer. Some nations still employ dual therapy twice a day, in particular, amoxicillin. However, triple therapies have also replaced dual therapies, including two antibiotics and either a bismuth molecule or a proton pump inhibitor (PPI). Quadruple treatments, which mix the bismuth molecule and PPI with two antibiotics, are another option. Bismuth compounds have an uncertain mechanism of action, but *H. pylori* is vulnerable to them both in vivo and in vitro (Liddell and Scott 1891). In countries like Egypt, quadruple-based therapy is also practised and superior to clarithromycin-containing triple therapy in treatments. Recently, growing thoughts on resistance to levofloxacin and reduction of efficacy as a second-line therapy have led us to think of levofloxacin as an alternative regimen of treatment for improved bacteria eradication in Egypt, including doxycycline and nitazoxanide. The molecular basis of antibiotic resistance and pathogenicity of *H. pylori* infections in Pakistan showed the resistance of bacteria to metronidazole, clarithromycin, and amoxicillin due to their extensive use of these antibiotics.

Various treatment durations, dosages, and drug combinations have been investigated, but none has consistently achieved eradication rates of greater than 90-95%. Two major causes of failure are insufficient drug adherence, often due to side effects, and the presence of antimicrobial resistance. Patients who have received previous antibiotic therapy, especially failed eradication regimens, are more likely to develop resistance (Goodwin et al. 1989).

Phytotherapy and probiotics are natural substances that are orally administered, usually in addition to conventional antibiotic treatment. They can change and promote the health of human microbiota, diminish side effects from antibiotics, improve immune response and compete directly with pathogenic bacteria. The various behaviours of herbal natural products are specifically related to the presence of biologically active compounds such as flavonoids and chalcone classes. These suppress the urease, which is generated during bacterium infection, in order to ensure its longevity in the stomach pH acid. However, other mechanisms explain the activity of flavonoids, such as VacA neutralisation and interference by toll-like 4 receptor signalling (TLR4). Some flavonoids may also have direct anti-*H. pylori* activity in combination with antibiotics used in traditional therapy, and the probable mechanisms include urease enzyme inhibition, cell membrane disorder, and host immune modulation. Up till now, the molecular mode of action is still unknown, and future research in this field is required.

Because of the existing difficulties in treating *H. pylori*, other techniques, such as nanotechnology, are gaining popularity. The importance of nanotechnology in developing new approaches for treating *H. pylori* infection is demonstrated by the robust antibacterial effects of metallic nanoparticles, the benefits of polymeric nanoparticles in drug delivery and safety, and the protruding properties of membrane-coated nanoparticles in direct targeting (Buckley and O'Morain 1998). The use of nanoparticulate systems in the treatment of *H. pylori* can prevent medications from being degraded by acids and enzymes in the stomach environment while also allowing drugs to be delivered to *H. pylori* infested areas (Ryan and Ray 2004). When drug-encapsulated nanoparticles concentrate at the target site and release continuously, the amount of drug consumed by bacteria can significantly increase (Yamaoka 2008). Furthermore, when compared to the usage of antibiotics directly, nanoparticulate systems have been found to be less harmful in therapy, and these platforms play a critical role in reducing antibiotic resistance.

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