Gut Bacteria-Friend or Foe? Their Role in Health and in Common Chronic Gl Diseases

An Essay Submitted for Partial Fulfillment of Master Degree in Internal Medicine

> By Mohammed Fahmy Soliman

M.B., B.Ch. Ain Shams University

Supervised by Prof. Dr. Samir Abd Al-Hamid Ghait

Professor of Internal Medicine, Gastroenterology and Hepatology Faculty of Medicine- Ain Shams University

Dr. Mohamed Abd Al-Moghny Mostafa

Assistant Professor of Internal Medicine, Gastroenterology and Hepatology Faculty of Medicine- Ain Shams University

Dr. Eslam Safwat Mohamed

Lecturer of Internal Medicine, Gastroenterology and Hepatology Faculty of Medicine- Ain Shams University

> Faculty of Medicine Ain Shams University Y. 1 M

<u> Acknowledgment 90</u>

Thanks first and last to **ALLAH** for his guidance, support and care in every step in our lives.

I have the greatest pleasure to express my deepest gratitude to **Prof. Dr. Samir Abd Al-Hamid Ghait** Prof. of Internal Medicine, Gastroenterology and Hepatology, Faculty of Medicine, Ain Shams University, for his unlimited help, encouragement, supervision, support and profuse knowledge so that this work have been accomplished.

I wish to express my appreciation to **Dr. Mohamed Abd Al-**Moghny Mostafa Assisitant professor of Internal Medicine, Gastroenterollogy and Hepatology, Faculty of Medicine, Ain Shams University, for his support and great assistance.

Also, I want to express my appreciation to **Dr. Eslam Safwat Mohamed** Lecturer of Internal Medicine, Gastroenterology and Hepatology, Faculty of Medicine, Ain shams University, for his guidance and help.

My greatest thanks and best regards to my colleagues in the department of Internal Medicine, Gastroenterology and Hepatology, *for their cooperation and advice.*

Lastly, I wish to express my appreciation to my family, my mother, my father and my sister without their support and help this work would have not been fulfilled.

List of Contents

Page No.

| Introduction and | aim of the w | ork | | | ۱۱ |
|----------------------|---|-----------------|-----------------------|-------|----------|
| Review of literature | e | ••••• | • • • • • • • • • • • | ••••• | ٤٤ |
| Cor Gut | npositional t Bacteria | Divers | sity | of | the ٤ |
| Gut | t Microbiota i | in Health | L | ••••• | ۱۷ |
| Moo | dulation of th | ne Gut M | icrobio [,] | ta | ٤٢ |
| Mic Mec | crobiota chanisms of l | in Fine Bala | Diseas nce | se: | ۰۰۰۰۰ ۲۸ |
| Summary | ••••••••••• | | | | ١.٩ |
| Recommendations | S | | | ••••• | ١١٢ |
| Conclusion | | | | | ۱۱۳ |
| References | | | | ••••• | ١١٦ |
| Arabic Summary | • | | | ••••• | |

List of Abbreviation

- AAD Antibiotic associated diarrhea.
- AID Sacquired immunodeficiency syndrome.
- ALT Alanine amino transferase.
- AMP...... Antimicrobial peptides.
- **APRIL** ... A Proliferation inducing ligand.
- **ASF** Altered schaedler flora.
- **ATH** Autoimmune hepatitis.
- ATP..... Adenosine triphosphate
- **B.C** Before century.
- BO Bacterial overgrowth.
- CD..... Crohn's disease.
- CDC Clostridium Difficile Colitis.
- **DCs** Dendritic cells.
- EHEC Enterohemorrhagic E. coli.
- ELISA Enzyme linked immunoassay.

- FMF Familial mediterranean fever.
- GALT Gut-associated lymphoid tissue.
- **GF** Germ free (animal with impaired local systemic Lymphoid organs).
- GIT Gastro intestinal tract.
- H. pylori . Helicobacter pylori.
- **HIV** Human immunodeficiency virus.
- **HPA** Hypothalamic pituitary adrenal.
- **IBD** Inflammatory bowel disease.
- **IBS** Irritable bowel syndrome.
- **IGF-I** Insulin-like growth factor.
- IL Interleukin.
- **IS**Indoxyl sulphate.
- **IVIG.....** Intravenous Immunoglobulin.
- LABs Lactic acid bacterias.
- LMLN Local mesenteric lymph node.
- LPS Lipopolysaccharide.
- **MHE** Minimal hepatic encephalopathy.

- MMC Migrating motor complex.
- NOD Nucleotide-binding oligomerization domain
- **NAFLD** .. Non alcoholic fatty liver disease.
- **NASH** Non alcoholic steatohepatitis.
- **NEC** Necrotizing enterocolitis.
- **NKT** Natural killer T.
- NLRS Nod like receptors.
- **OEI** Oligofructose enriched inulin.
- **ORT** Oral Rehydration Therapy.
- **PCS** P-cresyl sulphate.
- PMC Pseudomembranous Colitis.
- **PP** Peyer's patches.
- **PSA** Polysaccharide A.
- **ROS** Reactive oxygen species.
- SCFAs Short chain fatty acids.
- **SIBO**...... Small bowel bacterial overgrowth.
- sIgA..... Secretory IgA.
- **SILT......** Small intestine lymphoid tissue.

SIRS...... Systemic inflammatory response syndrome.

- **SPF** Specific pathogenic organ.
- T DM Type ' diabetes mellitus.
- Th T-helper.
- TLRS Toll like receptors.
- **TNF.....** Tumour necrosis factors.
- UC Ulcerative colitis.
- **VRE** Vancomycin-resistant *Enterococci*.
- **WHO** World health organization.

List of Figures

Figure No.

Page No.

| Fig. (): | <i>C. difficile</i> colonies on a blood agar plate. | |
|-----------|---|----|
| | The overgrowth of <i>C. difficile</i> in the gut | |
| | can be harmful to the host | ۲۷ |

INTRODUCTION

The human gut is the natural habitat for a large and dynamic bacterial community, but a substantial part of these bacterial populations are still to be described. However, the relevance and effect of resident bacteria on a host's physiology and pathology has been well documented. Major functions of the gut microflora include metabolic activities that result in salvage of energy and absorbable nutrients, important trophic effects on intestinal epithelia and on immune structure and function and protection of the colonised host against invasion by alien microbes (*Guarner and Malagelada*, (\cdot, \cdot)).

Gut flora might also be an essential factor in certain pathological disorders, including multisystem organ failure, colon cancer, and inflammatory bowel diseases. Nevertheless, habacteria are also useful in promotion of human health. Probiotics and prebiotics are known to have a role in prevention or treatment of some diseases (*Guarner and Malagelada*, $t \cdot \cdot t$).

Many species of bacteria have evolved and adapted to live and grow in the human intestine. The intestinal habitat of an individual contains $\forall \cdot \cdot - \circ \cdot \cdot$ different species of bacteria and the number of microbial cells within the gut lumen is about $\cdot \cdot$ times larger than the number of eukaryotic cells in the

- ۱ -

Introduction and Aim of the Work

human body. The stomach and small intestine contain only a few species of bacteria adhering to the epithelia and some other bacteria in transit. The scarcity of bacteria in the upper tract seems to be because of the composition of the luminal medium (acid, bile, pancreatic secretion), which kills most ingested microorganisms, and because of the phasic propulsive motor activity towards the ileal end, which impedes stable colonisation of bacteria in the lumen (*Hamer et al.*, $\uparrow \cdot \cdot \uparrow$; *Wong et al.*, $\uparrow \cdot \cdot \uparrow$).

By contrast, the large intestine contains a complex and dynamic microbial ecosystem with high densities of living bacteria, which achieve concentrations of up to $1 \cdot 11$ or $1 \cdot 11$ cells/g of luminal contents. These concentrations are similar to those found in colonies growing under optimum conditions over the surface of a laboratory plate (*Eckburg et al.*, $1 \cdot \cdot \circ$; *Zoetendal et al.*, $1 \cdot \cdot 1$).

A large proportion of the faecal mass consists of bacteria (around $\neg \cdot ?$ of faecal solids). Several hundred grams of bacteria living within the colonic lumen affect host homoeostasis. Some of these bacteria are potential pathogens and can be a source of infection and sepsis under some circumstances—for instance when the integrity of the bowel barrier is physically or functionally breached (*Hofer and*

- ۲ -

Introduction and Aim of the Work

Speck, $\uparrow \cdot \cdot \uparrow$; Honda and Takeda, $\uparrow \cdot \cdot \uparrow$; Liu et al., $\uparrow \cdot \cdot \lor$; Penders et al., $\uparrow \cdot \cdot \lor$).

However, the constant interaction between the host and its microbial guests can infer important health benefits to the human host. Recognition of these benefits is drawing particular attention to the functional implications of microflora in host physiology (*Macpherson and Harris*, $\forall \cdot \cdot t$; *ScaleSamuel et al.*, $\forall \cdot \cdot \forall$; *Xu et al.*, $\forall \cdot \cdot \forall$).

- ٣ -

Introduction and Aim of the Work

AIM OF STUDY

Asses the role of gut bacteria in terms of benfits and harm to human body and its impact on public health and chronic diseases of the digestive system, role of probiotics in gut health.

- 2 -

Compositional Diversity of the Gut Bacteria

I. PREFACE

Hippocrates has been quoted as saying "death sits in the bowels" and "bad digestion is the root of all evil" in $\cdot \cdot \cdot B.C.$ showing that the importance of the intestines in human health has been long recognized. In the past several decades, most research on the impact of bacteria in the intestinal environment has focused on gastrointestinal pathogens and the way they cause disease. However, there has recently been a considerable increase in the study of the effect that commensal microbes exert on the mammalian gut (*Hawrelak et al.*, $r \cdot \cdot \cdot$).

In this review, we revisit the current knowledge of the role played by the gastrointestinal microbiota in human health and disease. We describe the state-of-the-art techniques used to study the gastrointestinal microbiota and also present challenging questions to be addressed in the future of microbiota research (*Hawrelak et al.*, $\uparrow \cdot \cdot \cdot f$).

- 0 -

II. OVERVIEW OF THE MAMMALIAN GUT MICROBIOTA

A. Humans as Microbial Depots

Virtually all multicellular organisms live in close association with surrounding microbes, and humans are no exception. The human body is inhabited by a vast number of bacteria, archaea, viruses, and unicellular eukaryotes. The collection of microorganisms that live in peaceful coexistence with their hosts has been referred to as the microbiota, microflora, or normal flora (*Kunz et al.*, $\uparrow \cdot \cdot \uparrow$; *Morelli*, $\uparrow \cdot \cdot \land$; *Neish*, $\uparrow \cdot \cdot \uparrow$).

The composition and roles of the bacteria that are part of this community have been intensely studied in the past few years. It is estimated that the human microbiota contains as many as $1 \cdot 1^{12}$ bacterial cells, a number that is $1 \cdot 1$ times greater than the number of human cells present in our bodies. The microbiota colonizes virtually every surface of the human body that is exposed to the external environment. Microbes flourish on our skin and in the genitourinary, gastrointestinal, and respiratory tracts (*Chiller et al.*, $1 \cdot 1$; *Hull and* Chow, $1 \cdot 1$; *Ley et al.*, $1 \cdot 1$; *Neish*, $1 \cdot 1$; *Verstraelen*, $1 \cdot 1$).

- ۲ -

Compositional Diversity of the Gut Bacteria

By far the most heavily colonized organ is the gastrointestinal tract (GIT); the colon alone is estimated to contain over $\vee \cdot ?$ of all the microbes in the human body. The human gut has an estimated surface area of a tennis court ($\vee \cdot m$) and as such a large organ, represents a major surface for microbial colonization. Additionally, the GIT is rich in molecules that can be used as nutrients by microbes, making it a preferred site for colonization (*Ley et al.*, $\vee \cdot \cdot 7$).

B. Who Are They?

The majority of the gut microbiota is composed of strict anaerobes, which dominate the facultative anaerobes and aerobes by two to three orders of magnitude. Although there have been over $\circ \cdot$ bacterial phyla described to date (*Schloss and Handelsman*, $\uparrow \cdot \cdot \cdot f$).

The human gut microbiota is dominated by only \checkmark of them: the Bacteroidetes and the Firmicutes, whereas Proteobacteria, Verrucomicrobia, Actinobacteria, Fusobacteria, and Cyanobacteria are present in minor proportions (*Eckburg et al.*, $\uparrow \cdot \cdot \circ$).

Estimates of the number of bacterial species present in the human gut vary widely between different studies, but it has been generally accepted that it contains $\sim^{\circ} \cdot \cdot$ to $\uparrow, \cdot \cdot \cdot$ species (*Xu and Gordon*, $\uparrow \cdot \cdot \uparrow$).

- ۷ -