TOXICITY OF ANTIBIOTICS ON PROBIOTIC BACTERIA

KOREDE, JOYCE OPE

16010101011

A RESEARCH PROJECT SUBMITTED TO THE DEPARTMENT OF BIOLOGICAL SCIENCE COLLEDGE OF BASIC AND APPLIED SCIENCE, MOUNTAIN TOP UNIVERSITY, MAKOGI, IBAFO, OGUN STATE IN NIGERIA

IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE AWARD OF BACHELOR OF SCIENCE (B.Sc.) IN MICROBIOLOGY

DECEMBER, 2020

CERTIFICATION

This is to certify that this research project titled **TOXICITY OF ANTIBIOTICS ON PROBIOTICS BACTERIA** was carried out by KOREDE Joyce Ope, with matriculation number 1601010101. This project meets the requirements governing the award of Bachelor of Science (B.Sc.) Degree in Microbiology department of biological sciences of Mountain Top University. Ogun State, Nigeria and is approved for its contribution to knowledge and literary presentation.

_____ _____

DR. IBADIN **DATE**
(Project Supervisor)

_____ _____

DR. O.E FAYEMI **DATE**
(Head of Department)

DECLARATION

I hereby declare that this project report written under the supervision of Dr. Ibadin is a product of my own research work. Information derived from various sources has been duly acknowledged in the text and a list of references provided. This research project report has not been previously presented anywhere for the award of any degree or certificate.

_____ _____

KOREDE O. JOYCE Date

DEDICATION

For his guidance and favor, I devote this job to the almighty Father. For their encouragement and prayers towards the completion of my thesis, I also devote my work to my mom and sister.

ACKNOWLEDGEMENT

I am highly grateful to my Supervisor, Dr. F. H. Ibadin, I am also grateful to Dr. M. A. Abiala, Dr. Ogunsuyi for taking the time to assist me with my work. I also appreciate my Head of Department to the late Dr. A. A. Adeiga, Dr. O. E. Fayemi, and other lecturers in the Department of Biological Sciences.

The completion of this project would not have been accomplished with the support and cooperation of my project colleagues Dada Tomiwa, Akio Moses for their team spirit and understanding. I say thank you.

I also want to appreciate my mom, sister, Mountain Top University Chaplain, Pastor Olumide Adesina and his Assistant Tanimowo Olumide for their prayers and encouragement.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

ABSTRACT

Probiotic bacteria are living microorganisms that impart beneficial and defensive health effects found in the intestinal microbiota. In some nations and as practical health goods, the use of probiotics to deter infections is currently gathering traction. In the other hand, antibiotics are drugs used medically to protect off bacteria or microorganisms that are pathogenic. Their antimicrobial behaviors, however, impact not just the intended pathogen, but also the host's endogenous microbiota, thus altering the microbial and chemical makeup of the human body. The effect of antibiotics on probiotics, the relationship and the interaction between them are explored in this study antibiotics and probiotics.

CHAPTER ONE

1.0 INTRODUCTION

The term "antibiotic" was derived from the word "antibiosis," meaning "against life." In the past, antibiotics have been known as organic compounds that are harmful to other microorganisms created by one microorganism (Russell, 2004). As a part of this notion, an antibiotic was originally loosely defined as a material produced by one microorganism (Denyer et al., 2004) or of biological origin (Schlegel, 2003) that can prevent, or is lethal to, the growth of other microorganisms at low concentrations (Russell 2004). In modern times, however, this definition has been revised to include antimicrobials that are also partly or entirely produced by synthetic means. While some antibiotics are able to kill other bacteria entirely, others may only inhibit their growth. Those that kill bacteria are called bactericidal and those that prevent the development of bacteria are referred to as Bacteriostatic (Walsh, 2003). Antibiotics commonly refer to antibacterial antibiotic agents that are differentiated as antibacterial, antifungal, and antiviral, representing the community of microorganisms they antagonize (Brooks *et al.,* 2004; Russell, 2004).

The first antibiotic found in September 1928 was *penicillin* by an English bacteriologist, Sir Alexander Fleming, who mistakenly received the antibiotic from a *Penicillium notatum* soil-inhabiting fungus, but it was first discovered and published in 1929 (Aminov, 2010) and first performed clinical trials on humans in 1940 (Russell, 2004). There are many methods of classifying antibiotics, but their molecular structures, mode of action and range of operation are the most common classification scheme (Calderon and Sabundayo, 2007). Others prefer the Road of Administration (parenteral, oral, and topical). In general, antibiotics within the same systemic class will show a similar pattern in effectiveness, toxicity, and allergic-potential side effects. Among the various groups of antibiotics based on chemical or molecular properties are beta-lactams, macrolides, tetracyclines, quinolones, aminoglycosides, sulphonamides, glycopeptides and oxazolidinones (Adzitey, 2015).

In human medicine, management and the war against bacterial infections have helped to change the use of antibiotics. However, antibiotics are not selective in their antibacterial acts. They also antagonize the natural and healthy microbiota in our bodies that we all have and use, such as those in the gastrointestinal tract, while antagonizing bacteria that trigger disease (Walsh, 2003).

Furthermore, because of the ever-rising number of emerging and re-emerging pathogens, researchers have been forced to pay attention to probiotic microbes for the prevention and treatment of infections, combined with numerous recorded antibiotic resistance that occurs as a result of irrational use of antibiotics. (WHO, 2005)

Probiotics are microorganism-formed compounds that promote the growth of other microorganisms or feed nutrients that contribute to the balance of their intestinal microflora by having a beneficial effect on animals and humans (Salminen *et al.,* 2005). Probiotic bacteria are thought to be life microorganisms found in our intestinal microbiota, live in the human intestinal gut and have beneficial and protective effects. In order for a possible probiotic strain to be able to exert its beneficial effects, certain favorable outcomes need to be seen. Assets inclusive: (i) Acid and bile resistance, which seems to be essential for oral administration, (ii) Mucosal and epithelial surface adhesion, important properties of efficient immune control, competitive elimination of pathogens, as well as pathogen adhesion avoidance and colonization. (iii) antimicrobial action against pathogenic bacteria, (iv) Bile salt hydrolase action (Saarela *et al.,* 2000).

The scientist agreed to extract these strains of bacteria and cultivate them as pills, food, capsules to recover their health value in humans. Important scientific and clinical data has been chronicled with numerous meta-analyses of the health effects of probiotics (Limdi *et al.,* 2006), suggesting that in the prevention and treatment of some gastrointestinal diseases. Probiotics play a major role now. Probiotics are now gaining momentum in several nations to deter urinary infections (Reid and Bruce, 2006) and as practical health foods (2006). (Saarela *et al.,* 2002). There are also doubts among researchers that severe infections associated with *lactobacilli* and *bifidobacteria* probiotic strains are more common than commonly considered to be excessively rare. Probiotics are given in a sufficient quantity that gives the host a health advantage, so this refers to the requirement for probiotics to be in a certain quantity until they can have an observable effect on the host. However, the population of healthy probiotic bacteria is decreased by the misuse of antibiotics. Further experiments are also being carried out to assess the susceptibility of antibiotics of probiotic bacteria in the absence of probiotic bacteria in their residential areas. This study sheds light on the harmful effects of antibiotics in the human digestive system on probiotic bacteria.

CHAPTER TWO

2.0 LITERATURE REVIEW

2.1 PROBIOTICS

The term probiotics is taken from the meaning of life, a Greek word and the Latin word 'pro' and the Greek word 'bios.' Metchnikoff first defined the notion of probiotics in 1907. The definition of a material secreted by one microorganism was invented in 1965 by Lilley and Stillwell to promote the development of others. (Hawrelak and BNat. 2013)

It was confirmed that rods were dominated by gut microbiota from bifid-shaped healthy breastfed infants (*bifidobacteria*). These bacteria, however, were absent from the formulations used in feeding diarrhea babies, which established the speculation that they play a role in maintaining child well-being (Ziemer and Gibson, 1998). This correlation has been followed since then by a number of tests. Originally, however, they were poorly developed, regulated and faced functional difficulties such as strain specificity of properties and the sluggish growth of probiotics in non-human milk substrates. Similarly, public awareness of the health-nutrition relationship is increasing, providing a favorable atmosphere for the creation of a functional food concept implemented to explain foods or food additives that have beneficial effects beyond their nutritional value on the health of consumers with more growth opportunities in Europe and the United States, the functional food market is expanding, with the largest share of its goods in most countries, especially in Japan, its birthplace. (Ziemer and Gibson, 1998; Granato, *et al.*, 2010).

Improving intestinal wellbeing, improving lactose intolerance symptoms and reducing the incidence of several other diseases have been identified as beneficial effects of probiotic consumption, and many well-characterized strains of *Lactobacilli* and *bifidobacteria* are available for human use. (Toma and Pokrotnieks 2006). Nevertheless, the role of probiotics in human health and the safety of their use should be further examined in the light of encouraging evidence, as current understanding of the characteristics needed for their gut functioning is not complete.

2.1.1 PROPERTIES OF PROBIOTIC BACTERIA

For a probiotic strain to be able to have a beneficial impact it is expected to exhibit certain properties this include;

1. Acid and bile tolerance which seems to be essential for oral administration
2. Adhesion to the mucosal and epithelial surfaces is an essential function of efficient immune regulation, competitive elimination of pathogens and pathogenic adhesion and colonization prevention.
3. It is widely agreed that the minimum concentration of the probiotic substance should be 106 CFU/ml or gram and a total of around 10^8 to 10^9 (Toma and Pokrotnieks, 2006)
4. Antimicrobial activity against pathogenic bacteria;
5. The activity of bile salt hydrolase. (Saarela *et al*., 2000)

Some example of a strain of probiotics (Table 1) will be discussed as follows:

2.1.2 *Lactobacillus spp.*

Lactobacillus refers to a category of lactic acid forming Gram-positive rods that are mandatory and optional anaerobes in the human gastrointestinal and genitourinary tracts (Madsen *et al.*, 1999).

As the main end-product of carbohydrate fermentation, lactic acid bacteria are catalase-negative bacterial species capable of producing lactic acid.

The term lactobacillus refers to the lactic acid production potential of the bacterium and not the ability to digest lactose (Vanderhoof and Young, 2004). Therapeutically, *lactobacilli* are used as probiotics, the opposite of antibiotics. They are considered "friendly" bacteria and are used to recolonize regions of the body and have nutritional benefits, including the induction of growth factors and enhancement of mineral bioavailability (Madsen *et al.* 1999). The mucosal barrier is therefore stabilized by *lactobacilli* and intestinal permeability decreases (Shornikova *et al*., 1997). Altering the natural flora causes pathogenic species to eventually colonize (Reid *et al.*, 1990), which may lead to side effects induced by *Clostridium difficile*, such as diarrhea, cramping, and less often pseudomembranous colitis (PMC). The idea is that, during antibiotic therapy, taking lactobacillus probiotics will avoid or reduce natural loss of flora and invasion of

pathogenic bacteria. There is some evidence to support this hypothesis (Alander *et al.,* 1999). Lactobacilli containing hydrogen peroxide is bactericidal to a vaginal pathogen *Gardnerella vaginalis*, with reduced frequencies of bacterial Vaginosis and Trichomoniasis consistent with the involvement in the vagina. (Mitchell *et al*., 2015)

Lactic acid from lactobacilli reduces the pH of the vagina, which may deter infections from developing. There is some tentative proof that it might help protect against cancer from lactobacilli and other probiotics. *Lactobacillus* has been shown to bind dietary carcinogens in animal models (Venketeshwer and Leticia 2016) and minimize colon tumor growth after carcinogenic challenge (McIntosh, Royle and Playne,1999; Goldin *et al.,* 2008). Preliminary research also indicates that lactobacillus, especially *Lactobacillus plantarum* may minimize the severity of enterocolitis caused by chemotherapy (Venketeshwer and Leticia 2016). *Lactobacillus bulgaricus* and *Lactobacillus sporogenes* may have both hypolipidemic and anti-atherosclerotic consequences, according to other study reports. Restricted scientific data shows that absolute and low-density lipoprotein (LDL) cholesterol can be decreased without high-density lipoprotein (HDL) impact (Doncheva *et al.,* 2002; Losada and Olleros 2002). Fermented milk products, such as yogurt and acidophilus milk, also appear to have a beneficial effect on cholesterol. Bile acids tend to bind *Lactobacilli* and other probiotic bacteria to cholesterol. They also appear to improve the production of fatty acids in the intestine, which reduces the concentration of circulatory fatty acids by either inhibiting the synthesis of hepatic cholesterol or redistributing cholesterol from plasma to the liver

Table 1: List of some microorganisms considered as probiotic bacteria (Holzapfel *et al.,* 2001).

Lactobacillus species	**Bifidobacterium species**
L. acidophilus	***B. adolescentis***
L. casei	***B. animalis***
l. crispatus	***B. bifidum***

L. gasseri	***B. breve***
L. johnsonii	***B. infantis***
L. plantarum	***B. longum***
L. reuteri	
L. rhamnosus	
Other lactic acid bacteria	**Nonlactic acid bacteria**
Enterococcus faecalis	***Bacillus cereus var.***
E. faecium	***Escherichia coli strain nissle***
Lactococcus lactis	***Propionibacterium freudenreichii***
Leuconostoc mesenteroides	***Saccharomyces cerevisiae***
Pediococcus acidilactici	***S. boulardii***
Sporolactobacillus inulinus	
Streptococcus thermophilus	

L*actococcus lactis , pediococcus acidilactici*	**Little is known about its probiotic properties**
Streptococcus thermophiles	**Recently classified as *N. animalis subsp .lactis***
Enterococcus faecalis	**Mainly used for animals (Holzapfel *et al*., 2001).**
Sporolactobacillus inulinus	
Bacillus cereus var.	

For both indications, the efficacy of lactobacilli and other probiotics depends on their ability to colonize a region of tissue. In order to achieve this, preparations for lactobacillus must contain live and viable species. There may be some live and active species in items preserved for long

periods or stored incorrectly. Bacteria must still remain alive after going through the intestine for oral preparations, and then they must be able to hold on to the intestinal epithelium. Because of variations in their ability to bind to the epithelial cells by host factors such as hormone levels, *Lactobacilli* strains can vary in their efficacy (Cook, and Bruce 1987; Bruce and Reid. 1998; Oberhelman *et al.* 1999). In response to changing hormone levels, this capacity will shift during a woman's menstrual cycle. Correcting low estrogen levels may help recover lactobacillus colonization without supplementation in postmenopausal women (Gregor *et al*, 2001; Kwak *et al*, 2017)

2.1.3. *Bifidobacterium species*

Bifidobacterium is a pleomorphic, anaerobic, gram-positive, forming rod. Lactic and acetic acids are formed by bacteria in the *Bifidobacterium* genus as by-products of glucose utilization. BB536 According to secondary sources, it is a type of probiotic bacteria that was first isolated from the gut tract of healthy children. *Bifidobacteria* tend to mitigate, but do not appear to improve conformity with, the adverse effects of *Helicobacter* therapy in combination with *Lactobacillus species* and *Saccharomyces boulardii* probiotic yeast (Cremonini *et al.*, 2002). The occurrence of NEC and NEC-associated death in critically ill neonates tends to be minimized by *Bifidobacterium infantis* in conjunction with *Lactobacillus acidophilus* (Hoyos *et al.*,1993).

2.1.4. *Bacillus species*

A Gram-positive rod that produces lactic acid is *Bacillus coagulans*, and is thus sometimes misclassified as lactic acid bacteria, such as lactobacillus. Certain consumer goods that contain *Bacillus coagulans* are marketed as "spore-forming lactic acid bacterium." or *Lactobacillus sporogenes.* Spores are formed, which is an essential element in the separation of these bacteria. Similarly, to other probiotics such as *Lactobacillus coagulans* and *Bifidobacterium* are used therapeutically, but they are not a part of normal human flora. Probiotics must be able to survive and colonize in the intestinal region to be successful in maintaining natural flora and avoiding pathogenic colonization of mucosa. What happens to the spore remains unclear when the *Bacillus* spore is consumed by humans. If the *Bacillus* spore is capable of germinating in the intestinal tract or whether there is colonization is unclear (Duc Le *et al*., 2004). *Bacillus coagulans* can decrease the colonization of pathogenic bacteria through several mechanisms. *Bacillus Coagulans* create coagulin and lactic acid that have antibacterial action that can limit the

development of pathogenic bacteria through this process (McGroarty, 1993; Vaelraeds *et al.,* 1996; Hyronimus *et al.,* 1998;). Analysis into animal models also shows that consumption of bacillus spores improves the immune response (Duc Le *et al*., 2004)

Since Bacillus species can be preserved indefinitely in desiccated forms, this probiotic species has advantages over other species including lactobacillus (Duc Le *et al.,* 2004). From *Saccharomyces spp.* Even, *bacillus* spores are resistant to acid and elevated temperatures. *Saccharomyces boulardii* is a non-pathogenic strain of yeast that has been used to treat and prevent multi-disease diarrhea, also known as *Saccharomyces cerevisiae*.

Saccharomyces boulardii was isolated from the skins of tropical fruits which were found in Indochina. The Indigenous people of Indochina have long used these fruit skins to prevent and treat diarrhea (Buts, 2005).

Saccharomyces boulardii is prepared by lyophilization (freeze-drying) of live yeast species and encapsulation of lactose preparations. *Sacharomyces boulardii* can barely be distinguished from other *Saccharomyces cerevisiae*. The strains are classified by phenotypic criteria, so to identify these infections, molecular typing is required. Comparative molecular analyses say that *Saccharomyces boulardii.* In genetic terminology, it is very similar or almost identical to *Saccharomyces cerevisiae* (Fietto *et al.,* 2004) The findings indicate that the analysis of the *YKL139w* and *YLR177w genes* through microsatellite polymorphism and the review of *Ty917* hybridization are the most useful methods for the accurate detection of *Saccharomyces boulardii.* However, metabolically and physiologically, *Saccharomcyes boulardii* strains has activity that is very distinct from *Saccharomyces cerevisiae,* particularly in relation to growth yield and temperature tolerance and acidic stresses, which are significant characteristics of the probiotic usage of a microorganism S*acharomyces boulardii was* list by German Committee's Monograph as *Saccharomyces cerevisiae. Hansen CBS59266. (*Posteraro *et al.,* 2005*).*

2.2. MECHANISM OF ACTION OF PROBIOTICS BACTERIA

Probiotics have a variety of common modes of action. It is still yet to be completely known the precise way in which they practice their behavior. Some of the methods suggested include:

- This ranges from bacteriocins and short fatty acid production,

- lowering of PH,
- Nutrient completion to stimulate mucosal barrier function and immunodulation
- There are several research and substantial evidence that by inducing phagocytosis and IgA secretion, altering T-cell responses, strengthening Th1 response, and attenuating Th2 response, probiotics affect many facets of acquired and innate immune responses (Isolauri *et al*., 2000; McNaught and MacFie 2001; Guarner *et al.,* 2003)
- Concomitant inhibition of pathogen adhesion,
- Competitive exclusion of pathogenic microorganisms

2.3 HEALTH BENEFIT OF PROBIOTICS

2.3.1 LACTOSE INTOLERANCE

Probiotics are used to alleviate clinical symptoms of lactose sensitivity, a pathophysiological disease in which modification in small intestinal absorption or colonic fermentation occurs in diarrhea and upset of the stomach. In fermented goods such as yogurt, probiotics decrease the lactose content and increase the function of the fermented enzyme that breaks down the lactose that enters the small intestine. *Bifidobacterium animalis* has been among the most studied and most effective against lactose intolerance *Lactobacillus bulgaricus* eliminates the symptoms of lactose sensitivity (Oaks and Jha, 2018)

Lactose intolerance is a genetically determined defect in beta-galactosidase which leads to a failure to hydrolyze lactose into monosaccharides of glucose and galactose. Bacterial enzymes, which lead to osmotic diarrhea when it reaches the large intestine, kill undigested lactose. Usually reversible, acquired causes of beta-galactosidase deficiency include pelvic radiotherapy that affects the mucosa as well as rotavirus infection that infects cells that produce lactase and short bowel syndrome. Lactose intolerant individuals suffer diarrhea, stomach discomfort and flatulence following ingestion of milk or dairy products, whereas conventional yogurt formulations use *Saccharomyces thermophilus* and *Lactobacillus delbrueckii* and *subsp bulgaricus* are also available, they are efficient against lactose sensitivity, partially due to the greater action of beta-galactosidase. Improvement of lactose metabolism is a health advantage argument applied to probiotics that tends to include some strains in particular amounts and more

than the others. Therefore, several patients have reacted to probiotic supplementation favorably, and physicians should recommend it as a medicinal substitute. (Ouwehand *et al.*, 1998; De Vrese *et al.*, 2001; Levri *et al.*, 2005.)

Table 2: Classification and example of probiotics bacteria based on strain and body location

PROBIOTIC BACTERIA	**STRAIN**	**BODY LOCATION**
Lactobacillus spp	*L.acidophillus,* *L. plantarum,* *L.rhamnosus,* *L.paracasei,* *L. fermentum*	Gastrointestinal Genitourinary tract
	L.reuteri, *L.ultunensis.* *L. kalixensis,* *L. gatricus*	Mouth gastrointestinal tract, Stomach mucosa
	L. brevie	Derived from raw milk.
	L. Crispatus,, *L. gasseri* *L. jensenii,* *L. iners*	
Bifidobacterium spp	*B. delbrueckii* *B.gasseri,* *B. breve* *B.,infantis* *B. longum*	Intestinal tract Small intestine, Genitourinary tract

	Bifidum, *Thermophilum,* *adolescentis,*	
Bacillus spp	*B. cereus,* *B.coagulans,* *B. clausii* *b.licichinifformis* *Laetorospous*	Found in stingles bees honey and Apis mellifera honey (Fatin *et al*, 2018)

(Source: Oaks and Jha, 2018**)**

2.3.2 PROBIOTICS AND ALLERGY

Evidence indicates that early-life exposure to bacteria can play a protective role against allergies and that probiotics can offer a healthy alternative to the microbial stimulation required for child immune system growth in this sense. Probiotics strengthen the function of the mucosal membrane, a property that is known to help moderate allergic reactions. A small number of strains have been tested for effectiveness in child allergy care and prevention. *Bacillus lactis* and *Lactobacillus rhamnosus GG* have been shown to be successful in severely reducing eczema in a new study of breastfed children suffering from atrophic eczema. Probiotics have not been quite effective in relieving food allergy symptoms of asthma, however an immunologically induced adverse reaction to dietary antigens contributing to secondary intestinal inflammation and disruptions is defined. The mechanism of *Lactobacillus rhamnosus GG's* immune modality effect is not well known, but is related to the transport of antigens through the intestinal mucosa. (Ouwehand, 2001; Kalliomäki, 2001)

2.3.3 INFECTIOUS DIARRHOEA

Infectious diarrhea care and avoidance are perhaps the most commonly recognized health effects of probiotic microorganisms. Rotavirus is the world's most prominent cause of acute infant diarrhea and is a major cause of infant mortality. In the strongly differentiated absorptive columnar cells of the small intestinal epithelium, the virus replicates and the normal microflora

tends to play a significant role in the host response to the infection, as it has been shown that in germ-free mice the absorption of antigens is higher than in normal mice. (Salminen *et al.,*1998)

The aim of the probiotic supplementation of infant formulas was to avoid rotavirus infections and to cure proven diseases. Well-controlled clinical trials have shown that probiotics including *Lactobacillus rhamnosus GG, Lactobacillus reuteri. Lactobacillus Shirota Casei*, and *Bacillus animalisBb12* shortens the length of acute rotavirus diarrhoea with the best data suggesting the efficacy of *Lactobacilllus rhamnosusGG* and *Bacillus animalis Bb12* (Shah, 2007).

The suggested mechanism involves competitive receptor site blockage, signals controlling defenses of secretion and motility, immune response enhancement, and the development of substances that specifically inactivate viral particles. In addition to rotavirus infection, there is evidence that the development and adhesion of a number of diarrhea syndromes can be prevented by certain foods and non-food probiotic strains. Such probiotics as *Lactobacillus bacillus, Lactobacillus reuteri*. *Lactobacillus rhamnosus GG, Lactobacillus casei* has been shown to decrease the length of acute diarrhea in infants (Szajewska *et al.*, 2001; Huang *et al.*, 2002). In a prospective, randomized, controlled French sample of children in daycare, for example, a probiotic yogurt product containing *Lactobacillus casei* was administered greatly to reduce the mean duration of diarrhea relatively to the traditional one (Pedone *et al.*, 1999). In addition, various animal experiments have demonstrated an inhibitory activity of probiotics against enteropathogens, primarily through the synthesis of bacteriocins.

2.3.4 ANTIBIOTIC ASSOCIATED DIARRHOEA

Mild to extreme diarrhoea episodes are typical side effects of antibiotic therapy since the normal microflora appears to be suppressed, promoting opportunistic or pathogenic strains to overgrow. The continunum can vary from diarrhoea to *Pseudomembranous colitis* without mucosal abnormalities. This is a dangerous type of diarrhoea associated with antibiotics (caused by *Clostridium difficile*, cytotoxic strains of which may emerge after antibiotic use). The condition's name is derived from the brinopurulent substance plaque-like adhesion that damages the mucosal layer and is characterized by diarrhea, intestinal distention, vomiting, fever, Leukocytosis and if left unchecked, complications such as toxic mega colon and perforation can result. Treatment consists of the removal of the causative antibiotic agent, reversal of electrolyte abnormalities,

and metronidazole or vancomycin therapy in serious situations. In clinical practice, therapy of probiotics has been used with *Lactobacillus rhamnosus*, and *Saccharomyces boulardii*. Several studies carried out show that probiotic use is associated with a decreased risk of diarrhea associated with antibiotics (McFarland, 2006.). A new meta-analysis reviewing the existing data on probiotics for the prevention and treatment of antibiotic-induced diarrhea found that a decreased risk of the disease is associated with probiotic administration (namely *Lactobacillus. rhamnosus*, *Lactobacillus casei*, and *Saccharomyces boulardii* yeast, since these are the probiotics primarily used in most trials). The optimum dosage of probiotic preparation and the comparative efficacy of multiple probiotic interventions are problems for future study (Sazawal *et al.*, 2006)

2.3.5 BOOST IMMUNE SYSTEM

Probiotics help improve the immune system and prevent the development of unhealthy gut bacteria, such as enteroinvasive *Escherichia coli (EIEC)* (Resta-Lenert *et al.,* 2003). It has been shown that certain probiotics stimulate the formation of natural antibodies in the body. They can also improve immune cells such as T cell lymphocytes that contain IgA and natural killer cells (Reid *et al.*, 2003)

2.4 ENVIRONMENTAL FACTORS INFLUENCING OR AFFECTING PROBIOTIC BACTERIA

Probiotic bacteria are not traditional ingredients, but rather living cells that can easily react and respond to environmental changes and conditions. Numerous factors from culture processing, preservation, consumer product matrix conditions, and genetic, nutritional, cultural, and health variations between consumers may influence the behavior of probiotic cells and possibly affect the particular interactions between host and microbe necessary for digestive tract probiotic effects. Understanding the effect of these variables on probiotic effectiveness can help explain the molecular mechanisms of probiotic action, improve the design of consumer goods containing probiotics, and direct the molecular mechanisms of probiotic function Establishment of systematic clinical trial protocols to determine probiotic results. Modulation of immune response pathways, reinforcement of the epithelial barrier and indirect impacts on human pathogens are suggested mechanisms of probiotic-conferred health benefits. Regulating activity along the gut-brain axis) and energy homeostasis are other evolving pathways, as well as roles that could relate

to probiotics administered at other sites on the human body (Bravo *et al.*, 2011; Chen *et al.*,2012; Lemon *et al.*, 2012). In recent years, significant progress has been made towards the detection of the components of probiotic cells responsible for these effects. Polysaccharides, peptidoglycan, teichoic acids and some cell-surface bound and secreted proteins are among the most known effector molecules.

2.4.1 STRAIN

Conditions of culture incubation, including concentrations of oxygen and salt, temperature, and nutritional inputs, affect probiotic growth rates and total cell yields and can also contribute to downstream probiotic survival in consumer goods and the digestive tract (Bron *et al.*, 2012; Lebeer *et al.*, 2010) (Mills *et al.*, 2011)

Recently, the use of combinatorial fermentation architecture and complete genome transcriptome profiling to research the impact of fermentation conditions on probiotic functionality has demonstrated the significance of these parameters (Bron *et al.*, 2012). The application of this method to *Lactobacillus plantarum WCFS1* resulted in the discovery of many genes in the organism that impart stress resistance on this organism (Van Bokhorst *et al.*, 2012). Probiotic strain growth conditions also control the expression of effector molecules responsible for host-probiotic and pathogen-probiotic interactions. For example, the amounts of IL-12, IFN-g, IL-4, and IL-10 released by mouse splenocytes in response to *Lactobacillus acidophilus L-92* differ depending on whether the bacteria are grown in medium or without pH control (Kuwana and Yamamoto 2012). For *Bifidobacterium infantis ATCC 15697* and *Bifidobacterium bifidum ATCC 29521,* these strains induced IL-10 expression and altered the localization of close junction protein and epithelial cell line amounts after human milk oligosaccharide development (Chichlowski *et al.*, 2012). Growth-conditions also affect the ability of probiotic cells to protect human pathogens from infection. This was shown by the improved inhibition of Salmonella adherence and infection of glycerol-induced *Lactobacillus johnsonii NCC533* after growth of supplementary unsaturated fatty acids and *Lactobacillus reuteri ATCC53608* (Muller *et al.;* Goh and Klaenhammer, 2010). The latter effect was attributed to the development of the antimicrobial compound reuterin, glycerol-dependent (De Weirdt *et al.*, 2012). The level of development at which probiotic cultures are collected can also impact their capacity in the digestive tract to control and influence immune and epithelial cell responses. The adhesion of

Lactobacillus, for example. Expression of an aggregation inducing factor *(Apf)* specifically in stationary phase cultures was associated with *Acidophilus NCFM* in epithelial cells (Goh and Klaenhammer 2010). Probiotic immunomodulation is also growth-phase-dependent, demonstrated by the differential expression of *IL-10* and *IL-12* by human peripheral blood mononuclear cells in response to wild-type and mutant *Lactobacillus plantarumWCFS1* exponential and stationary stages (Van Hemert *et al*., 2010). These results of the growth process are confirmed by the observation that exponential-phase *Lactobacillus plantarum WCFSI* absorption of the human duodenum was triggered by *Lactobacillus plantarum WCFSI* WCFS1 against cell division and development, while stationary and heat-killed cells caused *NF-kB* immune response pathways (Van Baarlen *et al.,* 2009).In addition, the structure of the intestinal epithelial barrier may also be altered in ways depending on the probiotic bacteria's physiological state. This was demonstrated by the development by early stationary phase cultures of *Lactobacillus brevis SBC880399* of large amounts of polyphosphate, a metabolite that suppresses oxidant-induced intestinal permeability via the *integrin-p38 MAPK* pathway (Segawa *et al.,* 2011). Finally, the production and stabilization of probiotic cell effector molecules can also be influenced by culture preservation methods (e.g., freeze-drying), but there is currently no evidence available on the contributions of culture processing methods to probiotic functionality in vivo. The possibility that probiotic functionality improves in response to processing steps in culture is apparent from the various studies demonstrating that the impact of processing and preservation on the levels of probiotics' stress resistance (Mills *et al.*, 2011).

2.4.2 HOST DIET AND NUTRITIONAL FACTORS

The probiotic organism is usually the subject of recent research exploring probiotic development in the gastrointestinal tract. The powerful effect of diet on the composition of resident intestinal microbiota has been identified (Singh *et al.,* 2017). For the human strains, global transcriptomes and colonization phases of *Lactobacillus plantarum WCFS1* differentiated in the cecae of germ-free mice between mice fed either a daily chow diet or a prototypical Western-style diet (41% of fat calories) and differentiated in metabolic and cell-surface modifying pathways signaling differing degrees of activity and host interactions (Marco *et al.*, 2009).

Adaptations articulated by *Lactobacillus plantarum229v*in the human colon and ileum.characteristics displayed were most similar to *Lactobacillus plantarumWCFS1*which was

in a mice feeds, a Western diet in mice (Marco *et al*., 2010). Created a contribution to *Lacobacillus plantarumWCFS1* Persistence and differential cell product expression correlated with immunomodulatory impact (Tachon and Marco, unpublished). Probiotic defense against human pathogens might be controlled by the ability to adapt to dietary conditions. This was demonstrated for strains of *Bifidobacterium* strains with improved capacity to ferment acetate sugars, an end result that shielded germ-free mice *from Escherichia bacteria O157:H77* (Fukuda *et al.,* 2011)

Individual dietary components can also be related to the impact of diet on probiotic efficiency. Lactose supplementation in drinking water has promoted intestinal colonization of *Streptococcus thermophilus LMD9* in germ-free rats and lactate formation by *Salmonella thermophilus* was linked to the activation of the mono-carboxylic transporter and cell cycle arrest enzyme in epithelial cells (Thomas *et al.,* 2011). Histamine, manufactured by *Lactobacillus reuteri*. It has also been shown that the amino acid histidine induces epithelial cell responses primarily to suppress the development of TNF, a pro-inflammatory cytokine (Thomas *et al.,* 2012). This research demonstrated the ability for probiotics in the digestive tract to transform dietary components into bioactive forms that are essential for steering immune response pathways

2.4.3. HOST PHYSIOLOGY AND MICROBIOMES

The stable effects of host physiology and how they respond to clinical probiotic studies indicate that numerous variables impact probiotic performance across human populations (Reid *et al.,* 2010). Genetics, race, age and health status, as is the case for indigenous human microbiota, can contribute individually or in combination to altering the ability of ingested microorganisms to affect health (Reid *et al.,* 2012). The genetic history to clarify the improved intestinal persistence of *Lactobacillus johnsinii*in *C57BL/6J* mice has recently been suggested. In contrast with BALB/c mice (Buhnik-Rosenblau *et al.,* 2011). However, as demonstrated by correlations between the intestinal microbiota of unrelated people with the same cultural patterns or geographic location, environmental influences are also likely to play a major role (Yatsunenko *et al.,* 2012). The role of the resident intestinal microbiota on the digestive tract's probiotic function should also not be overlooked (Sanders, 2011). Consumption of a fermented dairy product containing B in a mouse model of inflammatory bowel disease. In certain animals, animal DN-173-010 contributed to a decline in colitis (Veiga *et al.,* 2010). Identification of the mice's

indigenous microbiota showed that the composition of the populations of intestinal microorganisms probably affected the probiotic response of the mouse and colitis reduction, likely through changing the physiological condition and function of probiotics in the gut (Veiga *et al.*, 2010).

Efforts should be made to recognize the factors that change the expression and conservation of the compounds mediating host-microbe interactions in the gut of the probiotic effector compounds. By assessing the quantity and behavior of recognized effectors during the processing and storage of the food/beverage product and subsequently in stool samples after passage through the gut, Strides can already be made in this respect in clinical trials. Studies in animal and cell culture should concentrate on discovering new compounds of probiotic effectors, evaluating the factors that affect the function and abundance of these effectors, and deciphering the processes by which probiotics associate with the mammalian digestive tract. (McNulty *et al.*, 2011). The intestinal bacteria directly directed towards polysaccharide metabolism have expressed various metabolic pathways. (McNulty *et al.*, 2011). These effects suggest that knowledge of the resident microbiota could be required to predict the results of health-beneficial probiotics. By modifying the intestinal epithelium to inhibit the translocation of *E. coli* some strains of *Bifidobacterium* were able to defend germ-free mice against *Escherichia coli O157:H7.* Toxin of coli S*tx2*. Metabolic profiles revealed that a primary cause of the protective effects was the volume of acetate released by *Bifidobacterium* in the distal colon. Comparisons of genomes among strains to classify genes associated with the prevention of *Esherichia coli* Infection which contributed to the discovery of carbohydrate transporters of the ABC type, which were confirmed to lead to sugar metabolism in the gut in the mutant study. Therefore, together with the quantities of certain dietary fermentable sugars, the probiotic strain may affect the susceptibility of a person to infection. Finally, the use of antibiotics would be addressed thoroughly.

2.4.4. ANTIBIOTICS RESISTANCE

Antibiotics, sometimes referred to as antibacterials, are used as growth promoters in poultry and livestock and also in agriculture to manage animal and plant diseases for the prevention of bacterial infections in humans. The antibiotics kill the invading pathogen or limit its replication to control the progression of the infection in the host (Ammor *et al*., 2007). The expanded and

excessive use of antibiotics has contributed, according to the World Health Organization, to the development of resistant bacteria, antibiotic-associated diarrhea, colitis, and other similar diseases related to the use of antibiotics.

Based on the presence or absence of resistance genes in the genome, probiotic bacteria may either be susceptible to a given drug or show natural resistance to it.

There are several factors responsible for increased antibiotic resistance in bacteria. The most common factors (see Figure 1) include prescribing antibiotics for the treatment of viral infections. (Jose *et al.*,2014). Infections of the upper respiratory tract such as cough, flu, sore throat, or runny nose are usually of viral origin, but doctors often provide antibiotics well before the infection is identified as viral or bacterial. As they think these medications make them feel better, people demand antibiotics. Secondly, it is an unnecessary procedure to raise the dosage and length of antibiotics in the care of bacterial infections. The effectiveness of treatment rests in the prudent use of antibiotics (i.e., the right antibiotic option at the necessary doses and at the right time) (Dryden *et al.*,2011).

In addition, the simultaneous use of two or three antibiotics will lead to the creation of resistance to more medications, leaving us with less medication choices. Repeated exposure of bacteria to a specific drug in an antibiotic challenged setting often makes the microbe immune to that specific drug, a process known as "adaptive resistance." There are also very common chances of resistance gene transferability (acquired resistance genes) among bacterial species. Finally, the emergence in the bacterial genome of unexplained random mutations also leads to the increase in resistance. (Sengupta *et al*. 2012). Increased and excessive use of antibiotics has contributed to the development of resistant bacteria, according to the World Health Organisation (WHO, 2004) (e.g., vancomycin resistance demonstrated by *Pediococcus* and *Leuconostoc*species). Vancomycin has been successfully used to treat clinical infections caused by multidrug-resistant *Staphylococcus aureus*. Vancomycin is a genus of glycopeptides. Resistance to bacteria can be extrinsic or normal, or acquired (Ammor *et al.,* 2007). The chromosomally encoded inherent resistance is not passed. it is an inherent feature of the bacterial strain example is Vancomycin resistance to *lactobacilli.* Vancomycin prevents bacterial growth by interfering with peptidoglycan production, which is an important constituent of the gram-positive bacterial cell wall. Studies, however, concerning *Lactobacillus reuteri*, and. animal-origin *acidophilus* species

have shown that all *Lactobacillus reuteri* While only a few *Lactobacillus acidophilus* strains were resistant, the *Lactobacillus acidophilus* strains were immune to vancomycin and polymyxin B. (Jose *et al*., 2014)

Similarly, the study on *Lactobacillus rhamnosus* concluded that vancomycin resistance was demonstrated by the bacteria but did not transfer vancomycin resistant genes to susceptible recipients. (Tynkkynen *et al*., 1998). Also, the bacteria did not receive resistance genes from donor cells in conjugation experiments. (Salminen *et al.*,1998). One more review of *L. reuteri, L. rhamnosus* species showed resistance to vancomycin, although the *vanA, vanB*, and *vanC genes* were not identified (Klein *et al.* 2000). All of these studies indicate that the tolerance of these microbes to vancomycin is a naturally occurring signature trait. Either by random (non-transferable) gene mutations or horizontal (retransferable) gene transfer, which poses a challenge to non-pathogenic bacteria, bacteria may develop resistance. The spontaneous mutation rate of lactobacilli to nitrofurazone, kanamycin, and streptomycin was found to be very high (10^{-4}-10^{-5} frequency/rate). (Curragh and Collins, 1992) It shows that lactobacilli's antibiotic resistance profile is extremely capable of modifying both within a genus and species. *Lactococcus lactis Subsp.* Resistance to erythromycin, clarithromycin, azithromycin, spiramycin, clindamycin, tetracycline, lincomycin, doxycycline and minocycline. (Perreten, *et al.* 2001) *Lactobacillus plantarum*, *Lactobacillus. sakei subsp*. *Lactobacillus*. *Subsp. Carnosus, Lactobacillus sakei. Subsp Lactobacillus curvatus*, *Lactobacillus alimentarius*. isolated from different forms of fermented dry sausage revealed the existence of *tet(M)* carrying plasmids by Southern hybridization techniques. (Gevers *et al.,* 2003,) *Lactobacillus plantarum strain CCUG 43738* demonstrated resistance to tetracycline and minocycline due to the presence of the tet (S) gene on a 14-kb plasmid. It was observed that the resistance to tetracycline and erythromycin was transferred from *Lactobacillus plantarum.* By plasmids that bear the genes tet (M) and erm (B) (Huys *et al*., 2006). The plasmid resistance coding genes tet (W) and lnu (A) were seen in *Lactobacillus plantarum* in the gastrointestinal tract of gnoto-biotic rats, *Enterococcus faecalis JH2-2* (Jacobsen *et al.,* 2007). *Lactobacillus reuteri ATCC 55730.* These genes were used to impart susceptibility to tetracycline and licosamide. Tetracycline resistance was also observed in the conjugative transposon Tn916 in the food-borne strain of *Lactobacillus paracasei* Tn916 was the carrier of the *gene tet (M).* Furthermore, genes of tolerance are transferred across organisms

and boundaries (Devirgiliis *et al.*, 2009), which is only possible through conjugation. Transformation and transduction limit the transition within the same animal.

Antibiotics can interfere with bacterial growth by targeting the synthesis of cell walls, protein synthesis, or nucleic acid synthesis. Lactobacilli are more resistant to antibiotics for protein synthesis-targeting. Examples include tetracycline, chloramphenicol, streptomycin, fusidic acid, gentamicin, as well as erythromycin. (Gueimond *et al.*, 2013). The mechanism of action of tetracycline, streptomycin, and gentamicin involves binding to the 30S subunit of the ribosome, thereby weakening the ribosome-tRNA interaction, thus chloramphenicol, erythromycin, and gentamicin bind to the 50S subunit of the ribosome, blocking peptidyl-transferase function (Dzidic *et al.*, 2008). In the other hand, ciprofloxacin, enoxacin, pefloxacin, norfloxacin, sulfamethoxazole, trimethoprim, co-trimoxazole, metronidazole, and nalidixic acid are examples of antibiotics that block nucleic acid synthesis, to which lactobacilli are normally immune and this is an intrinsic bacterial feature. Bacterial DNA separation is prevented by fluoroquinolone carboxylic acids, such as ciprofloxacin, enoxacin, pefloxacin, and norfloxacin, by inhibiting the function of DNA gyrase, which is necessary for cells. Antibiotics should be advised and treated with caution because of their toxicity and side effects, some of which include urinary tract disorders, hemolytic anaemia, porphyria, and hypersensitivity reactions such as sulphonamides (Choquet-Kastylevsky *et al.*, 2002; Slatore and Tilles, 2004). The antibiotic toxicity is believed to be due to its antagonism and antimicrobial impact.

The extent of antibiotic resistance has been troubling and presents a risk because certain resistance genes are transferable. LABs with acquired/transferable drug resistance genes are not included in the GRAS (Generally Accepted as Safe) category and should not be integrated into probiotic food or animal feed for consumption (Casado *et al.*, 2014).

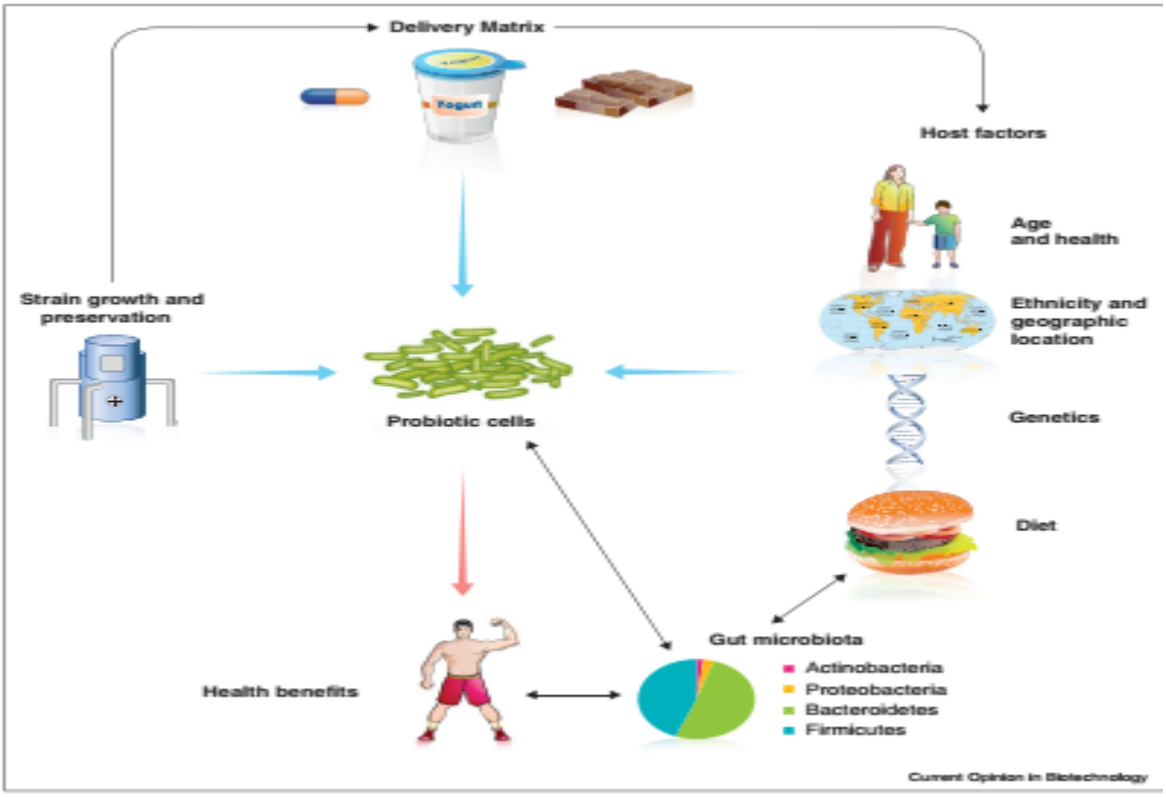

Figure1 Environmental determinants of probiotic efficacy that are discussed in this review

SOURCE:www.sciencedirect.com

CHAPTER THREE

3.0 MECHANISM OF ANTIBIOTICS

For most types of antibiotics, the antimicrobial efficacy is aimed at some particular aspect of the bacterial structure or its metabolic processes. Figure 11 shows the most common targets of antibiotics. The antibiotic process is as follows:

- Inhibition of cell wall synthesis
- Breakdown of cell membrane structure or function
- Inhibition of the structure and function of nucleic acids
- Inhibition of protein synthesis
- Blockage of key metabolic pathways

(Wright, 2003 Madigan and Martinko, 2006; Talaro and Chess, 2008).

3.0.1 INHIBITION OF CELL WALL SYNTHESIS

In most bacterial cells, a stiff peptidoglycan (PG) coating, often referred to in older sources as murein, is encased, all of which shield the cells under osmotic pressure, compatible with the often harsh atmosphere and the conditions under which they live. There is a level of cross-linked peptide bonds labeled β-(1-4)-N-acetyl Hexosamine peptidoglycan (Bugg and Walsh, 1992; Holtje, 1998). To remain alive, bacteria must synthesize peptidoglycan; they do this through the action of PBPs transglycosylases and transpeptidases. These two enzymes play a very significant role and often cross-link strands of immature peptidoglycan units by inserting disaccharide pentapeptides to extend the glycan strands of current peptidoglycan molecules (Park and Uehara, 2008). Drugs such as penicillin, carbapenems and cephalosporins can obstruct the cross-linkage of peptidoglycan units by inhibiting the peptide bond formation catalyzed by PBPs (Josephine *et al.,* 2004).

Most antibiotics belonging to the glycopeptide family of antibiotics (for instance, vancomycin) are able to prevent bacterial growth by inhibiting PG synthesis. They inhibit PG synthesis by binding themselves to PG groups, as well as blocking transglycosylase and transpeptidase activity (Kahne *et al.,* 2005).

3.0.2 BREAKDOWN OF THE CELL MEMBRANE STRUCTURE OR FUNCTION

The groups of antibiotics that destroy the cell membranes of bacteria in each microbial community are unique, based on the variations in the kinds of lipids in their cell membranes. For example, Daptomycin depolarizes the calcium-dependent membrane, contributing to the cessation of macromolecular synthesis and destruction of the cell membrane in bacteria (Alborn *et al.,* 1991). Polymyxins induce the degradation of the bacterial cell membrane by binding efficiently to the lipid movement of the lipopolysaccharide in the bacterial cell (Falagas *et al.,* 2010).

3.0.3 INHIBITION OF NUCLEI ACID SYNTHESIS

It is very important to provide metabolic pathways leading to nucleic acid synthesis; interruption of nucleic acid synthesis is not conducive to the viability and posterity of bacterial cells. Antibiotics intervene with nucleic acid synthesis by preventing replication or halting the replication of transcription DNA by unwinding the double helix structure, a mechanism facilitated by the helicase enzymes (Gale *et al.,* 1981). The antibiotic group of quinolones interferes with the functioning of the helicase enzyme, thereby disrupting the enzyme from playing its DNA unwinding role. Ultimately, this antibiotic activity of quinolones cuts off the DNA replication and repair mechanism among susceptible bacteria (Chen *et al.,* 1996)

Bacterial topoisomerase II and topoisomerase IV are both attacked by antibiotics whose mode of action is nucleic acid synthesis inhibition. The destruction of the actions of these enzymes in bacteria, which in turn inhibits RNA synthesis, is adversely affected by RNA polymerase. Quinolones that inhibit bacterial nucleic acid synthesis do not interact in this way with mammalian RNA polymerase, rendering them directly antagonistic to Gram-positive and certain Gram-negative bacteria.

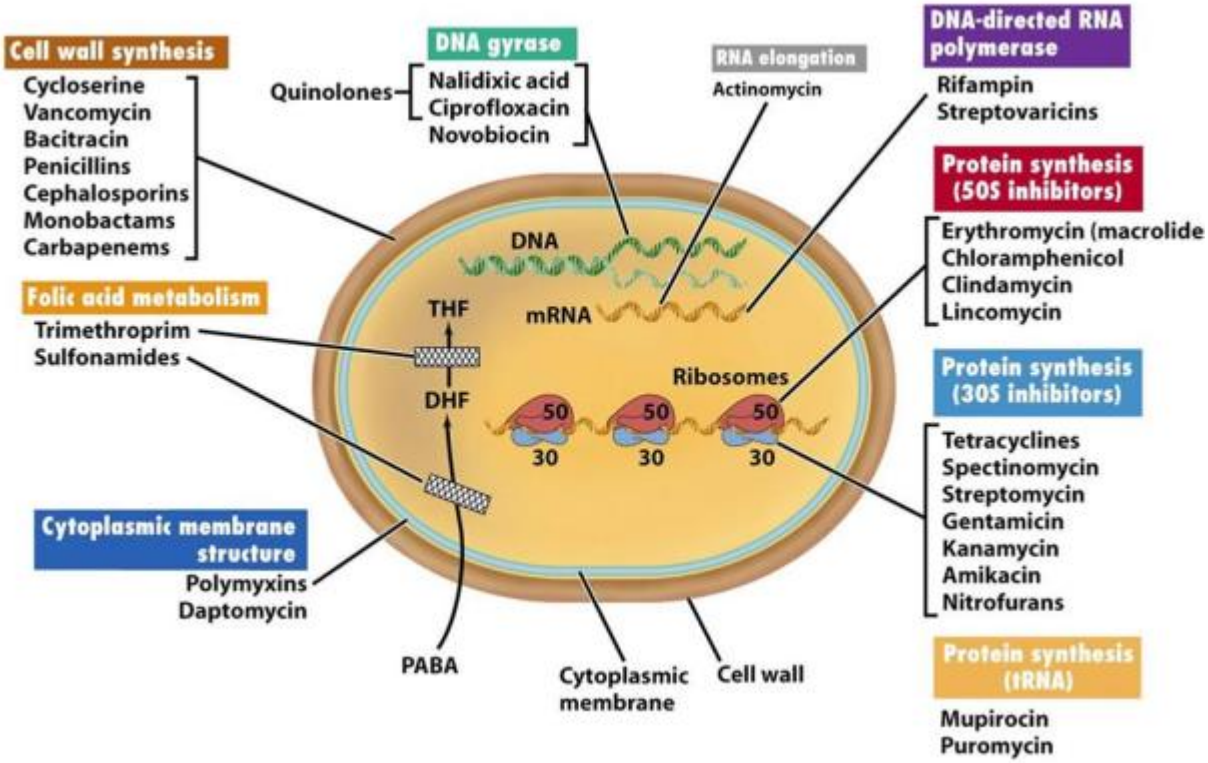

Figure 2 Antibiotic target sites (Madigan and Martinko, 2006).

3.0.4. INHIBITION OF PROTEIN SYNTHESIS

Living things, including bacteria, are made up of proteins and are produced continuously. Proteins are responsible, among other roles, for structural composition, metabolic and physiological processes, and reaction to unfavorable conditions. However, depending on the information contained in yet another very important biomolecule, the type and quantity of proteins produced by a bacterium at any given time. Acid Deoxyribonucleic (DNA). Through certain information it contains within itself, DNA determines the type of protein a bacterial cell produces. The data is a collection of genetic codes known as codons, transmitted to an identical biomolecule called ribonucleic acid (RNA), specifically messenger RNA (mRNA). Transfer RNA (tRNA), also formed under the DNA Directive, is a similar biomolecule. Together with mRNA, this biomolecule travels to the ribosomes-the protein synthesis factory in a living cell. The tRNA then decipheres the codons contained in the mRNA and enables the translation of the codon sequence into a sequence of amino acids that are the protein building blocks (Etebu, 2013). The translation of mRNA into proteins occurs over three sequential phases (initiation, elongation, and termination) involving the ribosome and a host of cytoplasmic accessory factors (Gualerzi *et al*., 2000). Ribosomes are made up of RNA and proteins, and are generally called RIBONUCLEOPROTEINS. The RNA component is what is referred to as Ribosomal RNA (rRNA), and comprises two subunits, one small subunit (SSU) and the other large subunit (LSU). These two subunits are commonly defined in terms of their coefficients of sedimentation (that is, their sedimentation rate is an ultracentrifuge) and are calculated in Svedberg units (symbols) called 30S and 50S, respectively (Nissen *et al.*, 2000). On their rRNA, bacterial genes have 5S, 16S, and 23S genes (Moore, 2001). In their SSU (16S), the 16S rRNA gene exists as a single RNA gene, while the other two rRNA genes (23S and 5S) exist on the LSU of the bacterial ribosome (Lafontaine and Tollervey, 2001). There is a huge distinction between prokaryotic and eukaryotic rRNA, and this feat has significantly allowed scientists to produce antibiotics for a wide variety of pathogenic bacteria targeting rRNA (Hong *et al.,* 2014). Anything interferes with the mechanism of its synthesis in a bacterial cell, given the importance of proteins in the metabolic and life processes of all living organisms, will eventually incapacitate the cell; impede or even fully destroy its growth. Drugs which inhibit protein synthesis are one of the broadest groups of antibiotics and can be divided into two subclasses: 50S inhibitors and 30S inhibitors. Antibiotics are amongst the 50S ribosome inhibitors, Such as erythromycin, clindamycin,

chloramphenicol, linezolid, lincomycin, etc (Douthwaite, 1992; Katz and Ashley, 2005). In general, 50S ribosome inhibiting antibiotics do so by physically blocking either the initiation step of protein translation or the elongation phase of protein synthesis in which the incoming amino acid is bound to the growing nascent peptide chain (Patel *et al., 2001*; Menninger and Otto, 1982; Vannuffel and Cocito, 1996). Examples of antibiotics which block the initiation of protein translation are oxazolidinones (Patel *et al*., 2001), while macrolides such as lincosamide and streptogramine block protein synthesis by inhibiting the elongation step of mRNA translation. (Menninger and Otto 19982; Vannuffel and Cocito, 1996). Thus, after elongation has extended to a critical length, these latter antibiotic classes are reportedly ineffective (Tenson *et al.,* 2003). 30S ribosome inhibitors specifically function by blocking the entry of aminoacyl-tRNAs to the ribosome. Examples of antibiotics that act in this manner include tetracycline, streptomycin, spectinomycin, etc. (Hong *et al.,* 2014; Chopra and Roberts, 2001). It should be remembered that certain earlier studies have shown that tetracycline also inhibits some proteins at 50S ribosomes (Epe and Woolley, 1984). Among ribosome inhibitors, the naturally derived aminoglycoside subclass is the only one which is broadly bactericidal. Usually, there are bacteriostatic macrolides, streptogramins, spectinomycin, chloramphenicol, and tetracyclines. However, some of these ribosome inhibitory antibiotics that are usually bacteriostatic inaction may be bactericidal in some circumstances pertaining to species- or treatment-specific fashion. Chloramphenicol, for instance, which is usually considered to be bacteriostatic, has been shown to efficiently kill *S. pneumonia Neisseriameningitidis* (Rahal and Simberkoff, 1979), as well as *Haemophilus influenza*. (Goldstein *et al.,* 1990; Rahal and Simberkoff, 1979). In the variable regions of highly conserved ribosomal proteins and RNAs, this species-specific ribosome inhibition or induced cell death heterogeneity is theoretically associated with bacterial species sequence variations (Roberts *et al.,* 2008).

3.0.5 EFFECTS OF ANTIBIOTICS ON BODY MICROFLORA

Probiotic bacteria, their health benefits, and their mode of action have been discussed in subsequent chapters. Antibiotics, their mode of action, their classification, have also been extensively discussed to fully understand how antibiotics work in the human system. In many physiological processes, the human microbiota plays a beneficial role, helping to extract nutrients needed in the body, protecting against enteropathogens and supporting the immune

system's support system. There is a host-microbial and microbial-microbial interaction that establishes a microbial composition equilibrium state in the intestinal tract. By suppressing the invasion of microorganisms and regulating the excessive proliferation of microorganisms present in the small intestine, the intestinal microbiota retains symbiosis. There is a loss of natural microbiota that leads to the exposure and growth of pathogenic organisms, such as *Staphylococus, Proteus, Clostridium difficile,* when the microbial communities collapse or become unbalanced due to antibiotics. Due to the occurrence of gut-related disease, the digestive function undergoes depression. The decrease in intestinal microbiota diversity and abundance. This leads to a decrease in the ability of competitive exclusion that has indirectly destroyed the community structures and the complementary system of the nutrient metabolic pathway by the probiotic bacteria. These changes will not be completely reversed for a month. This could lead to a patient's death (Sekirov *et al.,* 2008; Modi *et al.,* 2014)

Pathogens exploit inflammatory conditions induced by antibiotics. Pathogens use sugars and inorganic compounds created by the intestinal microbiota as carbon or energy sources under the inflammatory conditions induced by antibiotics and perform anaerobic respiration. The facts of the impact of antibiotics on human microbiota mentioned so far are described in the figure below.

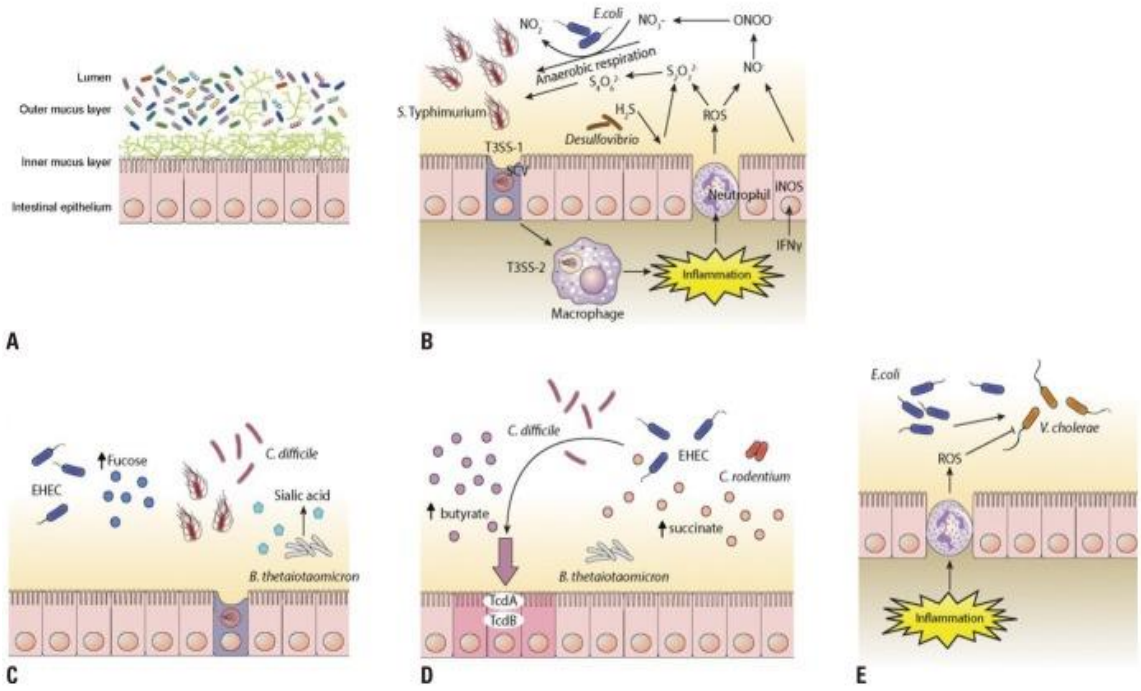

Figure 3: Pathogens exploit the induced inflammatory

Source: (Mi Young *et al.*, 2018)

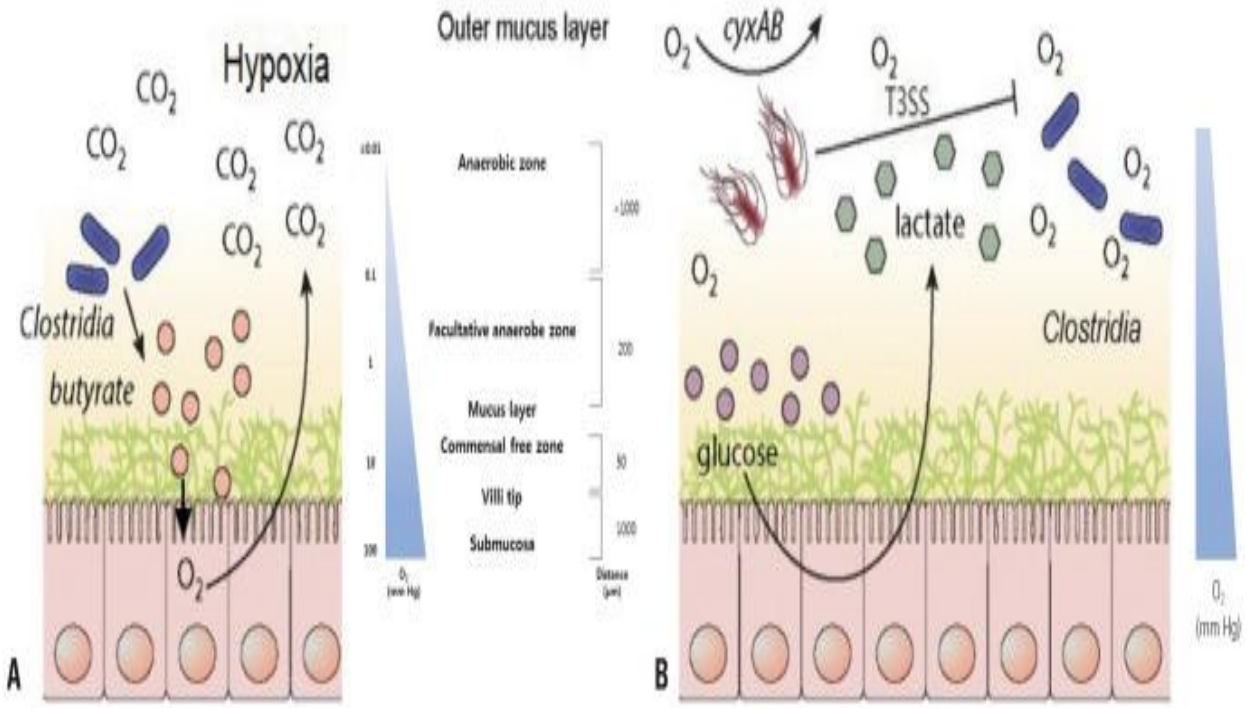

Figure 4: Effect of antibiotics on the hypoxia barrier of epithelial cells (Mi Young *et al.*, 2018)

(A) When the distribution of intestinal microorganisms is in a stable state, the invasion of pathogenic bacteria is suppressed by antimicrobial substances produced from intestinal bacteria and host cells, and inflammation is properly regulated. (Mi Young *et al.*, 2018 (b). The colonization of *E. coli* in a state of inflammation and Salmonella expand by anaerobic respiration using ROS and RNS, which are released by DUOX2 and iNOS into epithelial cells. Hydrogen-derived sulfide from sulfate-reducing bacteria, such as *Desulfovibrio spp*. It is converted into thiosulfate during cellular ventilation in colonic epithelial cells. Thiosulfate is converted by ROS produced by neutrophils into tetrathionate, which can be used as an electron acceptor. During this process, the produced tetrathionate boosts the growth of *Salmonella typhimurium*, which, by tetrathionate respiration, converts tetrathionate to thiosulfate. Via the respiration of nitrate, *E. coli* lowers nitrate to nitrite. (Mi Young *et al*., 2018). (c) Bacteroides thetaiotaomicron decomposes mucosal glycol conjugates to create sialic acid. *EHEC* and Salmonella may use Sialic Acid as a source of carbon. Inflammatory conditions lead to the secretion of host glycan fucose, and pathogens are ultimately ingested by the released fucose. For example, by sensing fucose, EHEC is known to control the expression of virulence genes. (D) *Clostridium difficile*, *Clostridium. Clostridium rodentium* and *EHEC* use succinate, which is formed by other microorganisms in the intestines. The SCFAs excreted by aerobic bacteria and butyrate, propionate and acetate during polysaccharide digestion are primarily found in the intestinal environment. The commensal bacterium *Bacteroides spp.* predominantly distributes succinate, which is therefore ingested by secondary fermentative microbes in a steady state and thus rarely accumulates in the intestinal environment. Succinate, however, is not ingested under antibiotic therapy or under inflammatory conditions, ultimately leading to its aggregation in the intestinal lumen. Succinate is an EHEC gluconeogenesis promoter. And, the penetration and reproduction of *Clostridium rodentium*, especially through the expression of *LEE virulence genes*, is enhanced. Of Clostidium. With the fermentation of carbohydrates, difficult will pair succinate metabolism and transform it to butyrate, thereby improving its colonization and virulence. (Mi Young *et al*., 2018).

(E) The growth of *Enterobacteriaceae* can be caused by antibiotics. ROS results in an expansion of *Escherichia coli* producing an additional catalase that is genetically produced at high concentrations by chromosomal alteration and ultimately encourages intestinal colonization of *Vibrio cholerae*, a highly susceptible strain, *strain12/11/2019*. Disturbance of the Gut

Environment by ROS antibiotics by reducing the overly generated ROS under inflammatory conditions. ROS, reactive oxygen species; *E. coli*, *Escherichia coli*; RNS, reactive nitrogen species; iNOS, inducible nitric oxide synthase; EHEC, *Enterohemorrhagic Escherichia coli*, *Clostridium difficil*, *C. rodentium*, *Citrobacter rodentium*, SCFAs, short-chain fatty acids; LEE, locus of enterocyte effacement. (Mi Young *et al*., 2018).

CHAPTER FOUR

CONCLUSION

In the battle against infectious diseases caused by bacteria, the ongoing detection, production and implementation of antibiotics in our health care has helped enormously and has led to human well-being. Although nearly 2,000 antibiotics have been detected so far, only a few scores of them are actually used therapeutically (Schlegel, 2003). The advent of resistant bacteria, however, has come to the knowledge that probiotics bacteria often improve resistance to antibiotics and that during infections can be detrital to our health. Therefore, antibiotics should not be used incorrectly.

There is a means of breaking down antibiotics in the human intestinal microbiota. A way to improve the intestinal microbiota and sustain a balanced system is the use of probiotics. Through breaking down the effect of antibiotic drugs on adverse toxicity. Therefore, probiotic bacteria cause resistance to antibiotics due to various strains of probiotic bacteria that evolve a mechanism to restore equilibrium to the intestinal microbiota as discussed earlier. The use of antibiotics should be prescribed by a doctor before taking them. Probiotics should be prescribed for patients undergoing treatment with antibiotics.

REFERENCE

Adzitey, F. (2015). Antibiotic classes and antibiotic susceptibility of bacterial isolates from selected poultry; a mini review. *Journal of world vetenary*; **5** (3):36-41

Alander, M., Satokari, R., Korpela, R., Saxelin, M., Vilpponen-Salmela, T., Mattila-Sandholm, T.and Von Wright, (1999) A. Persistence of colonization of human colonic mucosa by a probiotic strain, *Lactobacillus rhamnosus GG*, after oral consumption. *Appl Environ Microbiol*. Jan; **65** (1):351-4. doi: 10.1128/AEM.65.1.351-354.1999. PMID: 9872808; PMCID: PMC91031.

Alborn, W., Allen, N. and Preston, D. (1991). Deptomycin disrupts membrane potential in growing *Staphylococcus aureus. Antimicrob. Agents Chemother*. **31** (7): 1093-1099.

Allen, N. E. and Nicas T. I. (2003). Mechanism of action of oritavancin and related glycopeptide antibiotics. *FEMS Microbiol*. Rev. **26** (5): 511-532.

Aminov, R. I. (2010). A brief history of the antibiotic era: Lessons learned and challenges for the future. *Front Microbiol*. **1** (134):1-7.

Ammor, M.S., Florez, A.B., Mayo, B. (2007) Antibiotic resistance in non-enterococcal lactic acid bacteria and *bifidobacteria. Food Microbiol*., **24**: 559–570.

Bravo, J. A., Forsythe P., Chew M. V., Escaravage, E., Savignac, H. M., Dinan, T. G., Bienenstock, J., Cryan, J. F. (2011). Ingestion of *Lactobacillus strain* regulates emotional behavior and central GABA receptor expression in a mouse via the vagus nerve. *Proc Natl Acad Sci USA*, **108**: 16050-16055.

Brink, A. J., Feldman, C., Grolman, D. C., Muckart, D., Pretorius, J., Richards, G. A., Senekal, M. and Sieling W. (2004). Appropriate use of the carbapenems. *SAMJ*. **94** (10): 857-861.

Bron, P. A., Van Baarlen, P., Kleerebezem, M. (2012). Emerging molecular insights into the interaction between probiotics and the host intestinal mucosa. *Nature Rev Microbiol*, **10**: 66-78.

Bron, P. A., Wels, M., Bongers, R. S., Van Bokhorst-van de Veen, H., Wiersma, A., Overmars, L., Marco, M. L., Kleerebezem, M. (2012). Transcriptomes reveal genetic signatures underlying physiological variations imposed by different fermentation conditions in *Lactobacillus plantarum. PLoS ONE*,7: e38720

Brooks, G., Butel, J. and Morse, S. (2004). Jawetz, Melnick and Adelberg‟s *Medical Microbiology*, 23rd Edition. McGraw Hill Companies, Singapore

Brown, A. G., Butterworth, D., Cole, M., Hanscomb, G., Hood J. D., Reading, C. and Rolinson, G. N. (1976). Naturally-occurring beta lactamase inhibitors with antibacterial activity. *J. Antibiot.* **29** (6): 668 - 669.

Bruce, A. W., Reid, G. (1988) Intravaginal instillation of l*actobacilli* for prevention of recurrent urinary tract infections. *Canadian Journal of Microbiology.* **34** (3): 339-43.

Bugg, T. D. H. and Walsh, C. T. (1992). Intracellular steps of bacterial cell wall peptidoglycan biosynthesis: Enzymology, antibiotics, and antibiotic resistance. *Nat. Prod. Rep.* **9**: 199-215.

Buhnik-Rosenblau, K., Danin-Poleg, Y., Kashi, Y. (2011): Predominant effect of host genetics on levels of *Lactobacillus johnsonii* bacteria in the mouse gut. *Appl Environ Microbiol.* **77**: 6531-6538.

Buts, J. P. (2005). Lyopyhilized *Saccharomyces boulardii*: example of a probiotic medicine. Revista de gastroenterologia del Peru: organo official *de la Sociedad de Gastroenterologia del Peru.* **25** (2): 176-88

Butterworth, D., Cole, M., Hanscomb, G. and Rolinson, G. N. (1979). Olivanic acids, a family of beta-lactam antibiotics with beta-lactamase inhibitory properties produced by *Streptomyces species*. I. Detention, properties and fermentation studies. J Anitibot (Tokyo). 1979 Apr; **32** (4): 287-94. Doi: 10.7164/antibiotics. 32.287. PMID: 468715.

Calderon, C. and Sabundayo, B. (2007). Antimicrobial classifications: Drugs for bugs. In: Schwalbe R, Steele-Moore L and Goodwin AC (eds). *Antimicrobial susceptibility testing protocols.* CRC Press, Taylor and Frances group. ISBN 978-0-8247-4100-6.

Casado Munoz, M. C., Benomar, N., Lerma, L. L., Galvez, A., Abriouel, H. (2014). Antibiotic resistance of *Lactobacillus pentosus* and *Leuconostoc pseudomesenteroides* isolated from naturally fermented Alorena table olives throughout fermentation process. *Int. J. Food Microbiol.* **172**, 110–118

Cassidy, P. J., Albers-Schonberg, G., Goegelman, R. T., Miller, T., Arison, B., Stapley, E. O. and Birnbaum, J. (1981). Epithienamycins. II. Isolation and structure assignment. *J. Antibiot. (Tokyo).* **34** :637-648.

Chen, C. R., Malik, M., Snyder. M. and Drlica, K. (1996). DNA gyrase and topoisomerase IV on the bacterial chromosome: quinolone – induced DNA cleavage. *J. Mol. Biol*. **258**: 627-637.

Chen, J., Wang, R., Li, X. F., Wang, R. L. (2012): *Bifidobacterium adolescentis* supplementation ameliorates visceral fat accumulation and insulin sensitivity in an experimental model of the metabolic syndrome. *Br J Nutr.* **107**: 1429-1434.

Chichlowski, M., De Lartigue, G., German, J.B., Raybould, H. E, Mills, D. A (2012): *Bifidobacteria* isolated from infants and cultured on human milk oligosaccharides affect intestinal epithelial function. *J Pediatr Gastroenterol Nutr*. Sep ;**55** (3): 321-727. doi:10.1097/MPG.0b013e31824fb899. PMID: 2238026; PMCID: PMC3381975.

Chopra, I. and Roberts, M. (2001). Tetracycline antibiotics: Mode of action, applications, molecular biology, and epidemiology of bacterial resistance. *Microbiol. Mol. Biol. Rev*. **65** (2): 232-260.

Choquet-Kastylevsky, G., Vial, T. and Descotes, J. (2002). Allergic adverse reactions to sulfonamides. Curr. *Allergy Asthma Rep*. **2** (1): 16-25. doi: 10.1007/s11882-002-0033-y. PMID11895621.

Clemente, J. C., Ursell, L. K., Parfrey, L. W., Knight, R. (2012). The impact of the gut microbiota on human health: an integrative view. *Cell.* 2012 March 16; **148** (6):1258-70. Doi: 10.1016/j.cell.2012.01.035. PMID: 22424233; PMCID: PMC5050011.

Cremonini, F., Di Caro, S., Covino. M., Armuzzi, A., Gabrielli, M., Santarelli, L. (2002) Effect of different probiotic preparations on *anti-Helicopter pylori* therapy-related side effects: a parallel group, triple blind,placebo-controlled study. *The American Journal of Gastroenterology*. **97** (11): 2744-9

Curragh, H.J.; Collins, M.A. (1992). High levels of spontaneous drug resistance in *Lactobacillus. J. Appl. Bacteriol*. **73**, 31–36 https://doi.org/10.1111/j.1365-2672.1992.tb04965.x

Denyer, S. P., Hodges, N. A., German, S. P. (2004). Introduction to pharmaceutical microbiology. In: Denyer SP, Hodges NA and German SP (eds.) *Hugo and Russells Pharmaceutical Microbiology.* **7th** *Ed.* Blackwell Science, UK. Pp. 3-8.

Devirgiliis, C., Coppola, D., Barile, S., Colonna, B., Perozzi, G. (2009). Characterization of the Tn916 conjugative transposon in a food-borne strain of *Lactobacillus paracasei*. *Appl. Environ. Microbiol.* **75**, 3866–3871

De-Weirdt, R., Crabbe, A., Roos, S., Vollenweider, S., Lacroix, C., Van Pijkeren, J. P., Britton, R. A., Sarker, S., Van de Wiele, T., Nickerson, C. A. (2012): Glycerol supplementation enhances *Lactobacillus reuteri's* protective effect against *Salmonella typhimurium* colonization in a 3-D model of colonic epithelium. *Epub* **7** (5): e37116. Doi:10.1371/journal. Prone.0037116. PMID: 22693569; PMCID: PMC3365044.

Domagala, J. M. (1994). Structure-activity and structure-side-effect relationships for the quinolone antibacterials. *J. Antimicrob. Chemother.* 33 (5): 685-706. Doi: 10.1093/jac/33.4.685.

Doncheva, N. I., Antov, G. P., Softova, E. B., Nyagolov, Y. P. (2002). Experimental and clinical study on the hypolipidemic and antisclerotic effect of *Lactobacillus Bulgaricus* strain *GB* N 1 (48) *Nutrition Research*. **22** (4): 393-403

Douthwaite, S. (1992). Interaction of the antibiotics clindamycin and lincomycin with *Escherichia coli 23S* ribosomal RNA. Nucleic acids research. **20**. 4717-20. 10.1093/nar/20.18.4717.

Dryden, M., Johnson, A.P., Ashiru-Oredope, D., Sharland, M. (2011). Using antibiotics responsibly: Right drug, right time, right dose, right duration. *The Journal of antimicrobial chemotherapy*. **66**. 2441-3. 10.1093/jac/dkr370. *Epub* 2011 Sep 15. PMID:219296080

Duc Le, H., Hong, H.A, Uyen, N.Q., Cutting S. M. (2004). Intracellular fate and immunogenicity of *B-subtilis* spores. *Vaccine.* **22** (15-16): 1873-85. Doi: 10.1016/j.vaccine. 2003.11.021. PMID:15121298.

Dzidic, S., Suskovic, J., Kos, B. (2008). Antibiotic resistance mechanisms in bacteria: Biochemical and genetic aspects. *Food Technol. Biotechnol.* **46**, 11–21

El-Nezami, H., Kankaanpaa, P., Salminen, S., Ahokas, J. (1998). Ability of Dairy strains of Lactic acid bacteria to bind a common food carcinogen, *Aflatoxin B1*. Food and chemical toxicology: an *international journal published for the British Industrial Biological Research Association.* **36** (4): 321-6

Epe, B. and Woolley, P. (1984). The binding of 6-demethylchlortetracycline to 70S, 50S and 30S ribosomal particles: A quantitative study by fluorescence anisotropy. *EMBO J*. **3**: 121-126.

Etebu, E. (2013). Potential panacea to the complexities of polymerasechain reaction (PCR). *Adv. Life. Sci. Tech.* **13**: 1-8.

Eyssen, H. J., Van den Bosch, J. F., Janssen, G. A. and Vanderhaeghe, H. (1971). Specific inhibition of cholesterol absorption by sulfaguanidine. Atherosclerosis. Vol **14** (2): 181-192. ISSN 0021-9150, https://www.sciencedirect.com/science article/pii/0021915071900487)

Falagas, M. E., Rafailidis, P. I. and Matthaiou, D. K. (2010). Resistance to polymyxins: Mechanisms, frequency and treatment options. Drug Resist. **13** (4-5): 132-138. doi: 10.1016/j.drup.2010.05.002. *Epub* 2010 Jun 17. PMID: 20843473.

Fatin, A., Zulkhairi, A., Suriana, S., Salma M. M., Maznah, I., Kim W. C,, Norsharina I., Mohd E. N., Norhasnida, Z. (2018), "Therapeutic Properties of Stinges Bees Honey in Comparison with European Bee Honey", *Advances in Pharmacological And Pharmatical Sciences*, vol. 2018, article ID 6179596, 12. https://doi.org/10.1155/2018/6179598

Fietto, J. L., Araújo, R. S., Valadão, F. N., Fietto, L. G, Brandão, R. L., Neves, M. J., Gomes, F. C., Nicoli J. R., Castro I. M. (2004). Molecular and physiological comparisons between *Saccharomyces cerevisiae* and *Saccharomyces boulardii*. Can *J Microbiol.* **50** (8): 615-621. doi: 10.1139/w04-050. PMID: 15467787.

Frank, U. and Tacconelli, E. (2012). The Daschner Guide to In-Hopsital Antibiotic Therapy. European standards. Available online at: http://www.springer.com/978-3-642-18401-7. 300p.

Fuoco D. (2012). Classification framework and chemical biology of tetracycline-structure-based drugs. *Antibiotics*. **1**:1-13.

Fukuda, S., Toh, H., Hase, K., Oshima, K., Nakanishi, Y., Yoshimura, K., Tobe, T., Clarke, J. M., Topping, D. L., Suzuki, T., Taylor T.D., Itoh, K., Kikuchi J., Morita H., Hattori, M. *(*2011*): Bifidobacteria* can protect from enteropathogenic infection through production of acetate. *Nature*, **27**: 469

Fuller, R. (1991). Probiotics in human medicine. *Gut*, 32(4), Apr; **32** (4): 439–442. PMID: 1902810; PMCID: PMC1379087.https://doi.org/10.1136/gut.32.4.439

Fuller, R., Gibson, G. R. (1997). Modification of the intestinal microflora using probiotics and prebiotics. *Scandinavian Journal of Gastroenterology Supplement*. **222**: 28–31.

Gale, E., Cundliffe, E., Reynolds, P. E., Richmond, M. H. and Waring, M. J. (1982). *The molecular basis of antibiotic action. 2ndEd.* John Wiley and Sons, New York. 670p. April 05, https://doi.org/10.1016/0014-5793(82)80550-4

Gilbert, D. (2000). Aminoglycosides. In: Mandell G. L., Bennett J. E. and Dolin R, (eds.) *Mandell*, Douglas, and Bennett's principles and practice of infectious diseases. 5th ed. Philadelphia: Churchill Livingstone. Pp. 307-336.

Gevers, D., Danielsen, M., Huys, G., Swings, J. (2003). Molecular characterization of tet (M) genes in l*actobacillus* isolates from different types of fermented dry sausage. *Appl. Environ. Microbiol*. **69**: 1270–1275

Goh, Y. J., Klaenhammer, T. R. (2010). Functional roles of aggregation-promoting-like factor in stress tolerance and adherence of *Lactobacillus acidophilus NCFM. Appl Environ Microbiol.* Aug; **76** (15): 5005-5012. doi: 10.1128/AEM.00030-10.

Goldin, B. R., Gualiteri, L. J., Moore R. P. (1996). The effect of *Lactobacillus GG* on the initiation and promotion of DMH-induces intestinal tumors in the rat. *Nutrition Cancer*. **25** (2): 197-204. Doi 10.1080/01635589609514442. PMID:8710689.

Goldin, B. R., Gorbach, S. L. (2008). Clinical Indications for Probiotics: An Overview, *Clinical Infectious Diseases*, *Volume **46** (*2): 96–100, https://doi.org/10.1086/523333

Goldstein, F. W., Emirian, M. F., Coutrot, A. and Acar, J. F. (1990). Bacteriostatic and bactericidal activity of azithromycin against *Haemophilus influenzae*. *J. Antimicrob. Chemother*. **25** (A): 25-28. Doi: 10.1093/jac/25.suppl_a.25.PMID:2154434.

Granato, D., Branco G., Nazzaro F., Faria, J. (2010). Functional Foods and Nondairy Probiotic Food Development: Trends, Concepts, and Products. Comprehensive Reviews in Food Science and Food Safety. *Wiley Online Library* https://doi.org/10.111/ j.1541-4337.2010.00110.x.

Gregor Reid, Christian Zalai, Gillian Gardiner, (2001). Urogenital *Lactobacilli* Probiotics, Reliability, and *Regulatory Issues, Journal of Dairy Science,Volume **84**,* Supplement, Pages E164-E169, ISSN 0022-0302,https://doi.org/10.3168/jds.S0022-0302(01)70211-1.(http://www.sciencedirect.com/science/article/pii/S0022030201702111)

Gualerzi, C. O., Brandi L. B., Caserta E., La Teana A., Spurio R., Tomsic J. and Pon C. L. (2000). Translation initiation in bacteria. In: Garrett R. A., Douthwaite S. R., Liljas A., Matheson A. T., Moore P. B. and Noller H. F. (eds.). The ribosome: Structure, function, antibiotics, and cellular interactions. ASM Press, Washington, DC. Pp. 477-494.

Guarner, F., Malagelada, J. R. (2003). Gut flora in health and disease.,*" The Lancet.* 361:512–519. [PubMed][Google Scholar]

Gueimonde, M., Sanchez, B., Reyes-Gavilan, C. G., de los, Margolles, A. (2013). Antibiotic resistance in probiotic bacteria. Front. *Microbiol.* 4, 1–6.

Ha, C. W., Lam, Y. Y., Holmes, A. J. (2014). Mechanistic links between gut microbial community dynamics, microbial functions and metabolic health. *World J Gastroenterol*. **20**:16498–16517. [PMC free article] [PubMed] [Google Scholar]

Hamilton-Miller, J. M. (1973). Chemistry and biology of the polyene macrolide antibiotics. *Am. Soc. Microbiol.* **37** (2): 166-196.

Hawrelak, J, BNat (Hons). (2013). Probiotics. In: Pizzorno JE, Murray MT, editors. Textbook of Natural Medicine. 4th ed. St. Louis, Missouri: Churchill Livingstone Elsevier; p. 979–94.

Heesemann, J. (1993). Mechanisms of resistance to beta-lactam antibiotics. Infection. **21** (1): S4-9. German. doi: 10.1007/BF01710336.PMID: 8314292.

Henry, R. J. (1943). The mode of action of sulfonamides. *Bacteriol. Rev.* **7** (4): 175-262. PMID: 16350088; PMCID: PMMC440870.

Hilton, E., P. Kolakowski, C. Singer, and M. Smith, (1997). "Efficacy of *Lactobacillus GG* as a diarrheal preventive in travelers*," Journal of Travel Medicine, vol.* ***4***, no. 1, pp. 41–43.

Holten, K. B. and Onusko, E. M. (2000). Appropriate prescribing of oral beta-lactam antibiotics. *Am. Fam. Physician*. **62** (3): 611-620. PMID:10950216.

Holtje, J. V. (1998). Growth of the stress bearing and shape maintaining murein sacculus of *Escherichia coli. Microbiol. Mol. Biol. Rev*. **62**: 181- 189.

Holzapfel, W. H., Haberer P., Geisen, R., Björkroth, J., Schillinger, U. (2001). Taxonomy and important features of probiotic microorganisms in food and nutrition. *Am J Clin Nutr*. **73** (2):365S-373S. doi: 10.1093/ajcn/73.2.365s. PMID: 11157343.

Holzapfel, W. H, Haberer, P., Geisen R., Björkroth, J., and Schillinger, U. (2001). "Taxonomy and important features of probiotic microorganisms in food and nutrition," *American Journal of Clinical Nutrition*, vol. **73**, no. 2, pp. 365S–373S

Hong, W., Zeng, J., and Xie, J. (2014). Antibiotic drugs targeting bacterial RNAs. *Acta Pharm*. Sin B. **4** (4): 258-265.

Hoyos, A. B. (1999). Reduced incidence of *necrotizing enterocolitis* associated with eternal administration of *lactobacillus acidophilus* and *Bifidobacterium infantis* to neonates in an intensive care unit. *International Journal of Infectious Diseases*: IJID:official *publication of international Society for Infectious Diseases*. **3** (4): 197-202

Huang, J. S., Bousvaros, A., Lee, J. W., Diaz, A., and Davidson, E. J. (2002). "Efficacy of probiotic use in acute diarrhea in children: a meta-analysis*,"- Digestive Diseases and Sciences, v*ol. **47**, no. 11, pp.2625–2634.

Huttenhower, C., Gevers, D. (2012). The Human Microbiome Project Consortium., Structure, function and diversity of the healthy human microbiome. *Nature* **486**, 207–214. https://doi.org/10.1038/nature11234

Huys, G., D'Haene, K., Swings, J. (2006). Genetic Basis of tetracycline and minocycline resistance in potentially probiotic *Lactobacillus plantarum strain CCUG 43738*. *Antimicrob. Agent Chemother*. **50**, 1550–1551.

Hyronimus, B., Le Marrec, C., Urdaci, M. C. (1998). Coagulin, a bacteriocin-like inhibitory substance produced by *Bacillus coagulans* 14, *Journal of Applied Microobiology*. **85** (1): 42-50

Isolauri, E., Arvola, T., Sütas, Y., Moilanen, E., Salminen, S. (2000). Probiotics in the management of atopic eczema. *Clin Exp Allergy*. **30** (11): 1604-10. doi: 10.1046/j.1365-2222.2000.00943.x. PMID: 11069570.

Jacobsen, L., Wilcks, A., Hammer, K., Huys, G., Gevers, D., Andersen, S. R. (2007). Horizontal transfer of tet(M) and erm(B) resistance plasmids from food strains of *Lactobacillus plantarum* to *Enterococcus faecalis* JH2-2 in the gastrointestinal tract of gnotobiotic rats. FEMS *Microbiol. Ecol.* **59**, 158–166.

Joint FAO/WHO Working Group Report on Drafting Guidelines for the Evaluation of Probiotics in Food, Ontario, Canada, 2002, http://www.fao.org/es/ESN/Probio/probio.html.

Josephine, H. R., Kumar, I. and Pratt, R. F. (2004). The Perfect Pencillin? Inhibition of a bacterial DD-peptidase by peptidoglycan-mimetic betalactams. *J. Am. Chem.* Soc. **126**: 81222-81223.

Jose, N.M., Craig, R. B. Malik, A. H. (2014). Implications of Antibiotic Resistance in Probiotics. *Food Reviews International*. **31**. 10.1080/87559129.2014.961075.

Juven, B. J., Meinersmann, R. J., Stern, N. J. (1991). Antagonistic effects of *lactobacilli* and *pediococci* to control intestinal colonization by human enteropathogens in live poultry. *The Journal of Applied Bacteriology.* **70** (2): 95–103

Kahne, D., Leimkuhler, C., Lu, W., and Walsh, C. (2005). Glycopeptide and lipoglycopeptide antibiotics. *Chem. Rev.* **105** (2): 425-448.

Kalliomäki, M. P., Kirjavainen, Eerola, E., Kero, P., Salminen, S. and Isolauri E. (2001). "Distinct patterns of neonatal gut microflora in infants in whom atopy was and was not developing," *Journal of Allergy and Clinical Immunology*, vol. **107**, no. 1, pp. 129–134.

Kangm, H.K. and Park, Y. (2015). Glycopeptide antibiotics: Structure and Mechanism of Action June 2015.*Journal of Bacteriology and Virology* **45** (2): 67 Doi:10.4167/jbv.2015.45.2.67

Katz, L., and Ashley, G. W. (2005). Translation and protein synthesis: macrolides. *Chem.* **105**: 499-528. Doi; 10.1021/cr030107f. PMID: 15700954.

Ketvertis, K. M. K., Deramo, M., Merenstein, J. H., and'Amico, F. D. (2005). "Do probiotics reduce adult lactose intolerance? A systematic review," *Journal of Family Practice,* vol. **54**, no. 7, pp.613–620.

Khalid, A., Anabrees, J. (2020). Probiotics for prevention of necrotizing enterocolitis in preterm infants. *Cochrane Database Syst* **10** (4): CD005496. doi: 10.1002/14651858.CD005496.pub4. Update in: Cochrane Database Syst Rev. 10:CD005496. PMID: 24723255

Khlebnikov, A., Van Hylckama V. J. E, Punit S, Glickman J. N. (2010): *Proc Natl Acad Sci*. **107** (50): 21943.

Klein, G., Hallmann, C., Casas, I.A., Abad, J. Louwers, J., Reuter, G. (2000). Exclusion of vanA, vanB and vanC type glycopeptide resistance in strains of *Lactobacillus reuteri* and *Lactobacillus rhamnosus* used as probiotics by polymerase chain reaction and hybridization methods. *J. Appl. Microbiol*. **89**, 815–824.

Kropp, H., Kahan J. S., Kahan, F. M., Sandolf, J., Darland, G. and Birnbaum, J. (1976). Abstract on 16th Interscientific conference on antimicrobial agents and chemotherapy. *Am. Soc. Microbiol.* Abstract **228**.

Kobayashi, F., Sainyo Y., Koshi, T., Hattori, Y., Nakayama, M., Iwasaki A., Mori, T. and Mitsuhashi, S. (1982). Antimicrobial and Beta-lactamase inhibitory activities of carpetimycins A and B, new carbapenems antibiotics. *Antimicrob. Agents Chemother*. **21**:536-544.

Kulka, T, Sartor B., Unal, R., Laiho, A. (2010). Responders and non-responders to probiotic interventions: how can we improve the odds? Gut Microbes. **1**: 200-204.

Kumar, H., Lund, R., Laiho, A., Lundelin K, Ley, R.E, Isolauri, E, Salminem S. (2114). Gut microbiota as an epigenetic regulator: pilot study based on whole-genome methylation analysis. *MBio.* **5**:e02113–e0. [PMC free article] [PubMed] [Google Scholar]

Kuwana, R., Yamamoto, N. (2012): Increases in GroES and GroEL from Lactobacillus acidophilus L-92 in response to a decrease in medium pH, and changes in cytokine release from splenocytes: transcriptome and proteome analyses. *J Biosci Bioeng*. **114**: 9-16.

Kuter, D. J. and Tillotson, G. S. (2001). Hematologic effects of antimicrobials: focus on the oxazolidinone linezolid. *Pharmacotherapy*. **21**:1010-1013.

Kwak, Y., -K, Daroczy, K., Colque, P., Kühn, I., Möllby, R., Kopp Kallner, H. (2017): Persistence of *Lactobacilli* in Postmenopausal Women - A Double-Blind, Randomized, Pilot Study. *Gynecol Obstet Invest*. **82**:144-150. doi: 10.1159/000446946

Lafontaine, D. L. and Tollervey, D. (2001). The function and synthesis of ribosomes. *Nat. Rev. Mol. Cell Biol*. **2** (7): 514-520. Leach K. L., Swaney S. M., Colca J. R., McDonald W. G., Blinn J. R.,

Lebeer, S., Vanderleyden, J., De Keersmaecker, S.C. (2012): Host interactions of probiotic bacterial surface molecules: comparison with commensals and pathogens. *Nat Rev Microbiol* **8**:171-184 ecological perspective. *Sci Transl Med*. 4:137rv135.

Lemon, K. P., Armitage G. C., Relman, D. A., Fischbach, M. A. (2012). Microbiota-targeted therapies: an ecological perspective. *Sci Transl Med.* **4** (137):137rv5. doi: 10.1126/scitranslmed.3004183. PMID: 22674555; PMCID: PMC5725196.

Lilly, D. M., Stillwell, R. H. (1965). Probotics: growth-promoting factors produced by microorganisms. Science (New York, NY). **147** (3659):747–8.

Link-Amster H., Rochat F., Saudan K.Y., Mignot O., Aeschlimann J.M. (1994) Modulation of a specific humoral immune response and changes in intestinal flora mediated through fermented milk intake. FEMS *Immunology and Medical Microbiology.* **10** (1): 55–63.

Livermore, D. M., Warner. M., Mushtaq, S., Doumith, M., Zhang, J. and Woodford, N. (2011). What remains against carbapenem-resistant Enterobacteriaceae? Evaluation of chloramphenicol, ciprofloxacin, colistin, fosfomycin, minocycline, nitrofurantoin, temocillin and tigecycline. *Int. J. Antimicrob. Agents.* ***37***: 415-419.

Losada M.A, Olleros T. (2002). Towards a healthy diet for the colon: the influence of fructooligosaccharides and *lactobacilli* on Intestinal Health. *Nutrition Research*. **22** (1) :71-84

Mack, D. R., Michail, S., Wei, S., McDougall, L., Hollingsworth M. A. (1999). Probiotics inhibit enteropathogenic E. coli adherence in vitro by inducing intestinal mucin gene expression. *The American Journal of Physiology* **276** (4): 941–950

Madigan, M. T. and Martinko, J. M. (2006). Brock biology of microorganisms. 11th edition. Pearson Prentice Hall Inc. Mahajan G. B. and Balachandran L. (2012). Antibacterial agents from *actinomycetes* - a review. *Front Biosci. (Elite Ed).* **4**: 240-253.

Madsen, K. L., Doyle J. S., Jewell, L. D., Tavernini, M. M., Fedorak, R.N. (1999;). *Lactobacillus species* prevents *colitis* in interleukin 10 gene-deficient mice. *Gastroenterology* **116** (5): 1107–14.

Maggi, L., Mastromarino, P., Macchia, S., Brigidi, P, Pirovano, F., Matteuzzi, D., (2000). Technological and biological evaluation of Tablets containing different strains of *Lactobacilli* for vaginal administration European Journal of Pharmaceutics and Biopharmaceutics official *journal of Arbeitsgemeinschaft fur Pharmazeutische VerfahrenstechnikeV*. **50** (3): 389-95.

Marco, M. L., De Vries, M. C., Wels, M., Molenaar, D., Mangell, P., Ahrne, S., De Vos, W. M., Vaughan E. E., Kleerebezem, M. (2010): Convergence in probiotic *Lactobacillus* gut-adaptive responses in humans and mice. *ISME J.* **4**: 1481-1484.

Maria, L., Marco, Sybille, Tachon, (2013). Environmental factors influencing the efficacy of probiotic bacteria, Current Opinion in *Biotechnology*, **24** (2): 207-213,

ISSN09581669,https://doi.org/10.1016/j.copbio.2012.10.002.
(http://www.sciencedirect.com/science/article/pii/S0958166912001577)

Marteau, P., Seksik, P., and Jian, R. (2002). "Probiotics and intestinal health effects: a clinical perspective," *British Journal of Nutrition,* **88** (1): 51–57.

Marteau, P., Seksik, P., and Jian, R. (1998) "Probiotics and intestinal health effects: a clinical pe Salminen, S. Ouwehand, A. C. and Isolari, E. "Clinical applications of probiotic bacteria," *International Dairy Journal,* **8**: 563–572.

McGeer, A., Fleming, C. A., Gree, K., and Low, D. E. (2001). Antimicrobial resistance in Ontario: Are we making progress? Laboratory Proficiency Testing Program Newsletter. 293:1-2.

Medical News Today (2015). Antibiotics: How do antibiotics work? MediLexicon International Ltd. Bexhill-on-sea UK. Mechanism of action. *J. Bacteriol. Virol*. ***45*** (2): 67-78.

McGroarty, J. A. (1993). Probiotic use of *Lactobacilli* in the use of female urogenital tract. FEMS *Immunology and Medical Microbiology.* **6** (4): 251-64

McFarland, L. V. (2006). "Meta-analysis of probiotics for the prevention of antibiotic associated diarrhea and the treatment of *Clostridium difficile* disease," *American Journal of Gastroenterology,* **101** (4): 812–822.

McFarland, L. V. (2007). "Meta-analysis of probiotics for the prevention of traveler's diarrhea," Travel *Medicine and Infectious Disease,* **5** (2) 97–105.

McIntosh, G. H., Royle, P. J, Playne, M. J. (1999). A probiotic strain of *Lactobacillus. acidophilus* reduces DMH-induced large intestinal tumors in male Sprague-Dawley rats. *Nutr Cancer.* **35** (2): 153-159. doi: 10.1207/S15327914NC352_9. PMID: 10693169.

McNaught, C. E. and MacFie, J. (2001). "Probiotics in clinical practice: a critical review of the evidence," *Nutrition Research*, **21** (1-2): 343–353.

McNulty, N. P., Yatsunenko, T., Hsiao, A., Faith, J. J., Muegge, B. D., Goodman, A. L. (2011). Henrissat, B., Oozeer, R., Cools-Portier, S., Gobert, G. The impact of a consortium of fermented milk strains on the gut microbiome of gnotobiotic mice and monozygotic twins. *Sci Transl Med.* **3**:106.

Medical News Today (2015). Antibiotics: How do antibiotics work? MediLexicon International Ltd. Bexhill-on-sea UK. Mechanism of action. *J. Bacteriol. Virol.* **45** (2): 67-78.

Menninger, J. R., and Otto, D. P., (1982). Erythromycin, carbomycin, and spiramycin inhibit protein synthesis by stimulating the dissociation of peptidyl-tRNA from ribosomes. *Antimicrob. Agents Chemother*. **21**: 811-818.

Mercenier, I., Lenoir-Wijnkoop, and Sanders, M. E. (2008). "Physiological and functional properties of probiotics," *International Dairy Federation,* **429**: 2–6.

Miele, E., Pascarella, F., Giannetti, E., Quaglietta, L., Baldassano, R. N., Staiano, A. (2009). Effect of a probiotic preparation (VSL#3) on induction and maintenance of remission in children with *ulcerative colitis*. *The American Journal of Gastroenterology*. 104(2):437–43

Mills, S., Stanton, C., Fitzgerald, G. F., Ross, R. P. (2011). Enhancing the stress responses of probiotics for a lifestyle from gut to product and back again. *Microb Cell Fact*. **10** (1): S19.

Mingeot-Leclercq, M. P., Glupczynski, Y., and Tulkens, P. M. (1999). Aminoglycosides: Activity and resistance. *Antimicrob. Agents Chemother*. **43** (4):727-737.

Mishra, C., Lambert, J. (1996). Production of anti-microbial substances by probiotics. Asia Pacific *Journal of Clinical Nutrition.* **5** (1): 20–24.

Moa, Y., Nobaek, S., Kasravi, B., Adawi, D., Stenram, U., Molin, G.. (1996). The effect of lactobacillus strains and oat fiber on methotrexate-induced *enterocolitis* in rats *Gastroenterology*. **111** (2): 334-44. Doi:10.1053/8690198.

Modi, S. R., Collins, J. J., Relman, D. A. (2014). Antibiotics and the gut microbiota. *J Clin Invest*.: 4212–4218.

Moellering, R. C. (2003). Linezolid: The first oxazolidinone antimicrobial. *Ann. Intern. Med.* **138**: 135-142.

Muller, J. A., Ross, R. P., Sybesma W. F. H., Fitzgerald, G. F., Stanton, C. (2011): Modification of the technical properties of *Lactobacillus johnsonii NCC 533* by supplementing the growth medium with unsaturated fatty acids. *Appl Environ Microbiol.* **77**: 6889-6898.

Nissen, P., Hansen, J., Ban, N., Moore, P. B. and Steitz, T. A. (2000). The structural basis of ribosome activity in peptide bond synthesis. Sci. 289:920-930.

Oak, S. J., Jha, R. (2019). The effects of probiotics in lactose intolerance: A systematic review. *Crit Rev Food Sci Nutr*. **59** (11): 1675-1683. doi: 10.1080/10408398.2018.1425977

Oberhelman, R. A., Gilman, R., Sheen, P., Taylor, D. N., Black, R., Cabrera, L., Lescano A.G., Meza, R., Madico G. A. (1999). A placebo-controlled trial of *Lactobacillus GG* to prevent diarrhea in undernourished Peruvian children. *The Journal of Pediatrics.* **1**: 15-20

Ouwehand, A. C. E., Isolauri, F., Hashimoto, H., Benno, Y. and Salminen, S. (2002). "Differences in Bifidobacterium flora composition in allergic and healthy infants," *Journal of Allergy and Clinical Immunology*, 108 (1) 144–145

Panda, S., El khader, I., Casellas, F., López Vivancos, J., García Cors, M., Santiago, A., Cuenca, S. Guarner, F., Manichanh, C. (2014) Short term effect of antibiotics on human gut microbiota. PL oS One. Apr 18;(4): e95476. Doi 10.1371/ journal.pone. 009576. PMID:24748167; PMID: PMC3991704. [PubMed][Google Scholar]

Papp-Wallace, K., Endimiani, A., Taracila, M., and Bonomo, R. (2011). Carbapenems: past, present, and future. *Antimicrob. Agents Chemother*. **55** (11): 4943-4960.

Park, J. T., Uehara, T. (2008). How bacteria consume their own exoskeleton (turnover and recycling of cell wall-peptidoglycan). *Microbiol. Mol. Biol.* **72**: 211-227.

Patel, U., Yan Y. P., Hobbs F. W., Jr, J. Kaaczmarczyk A.M. (2001). Oxazolidinones mechanism of action: inhibition of the first peptide bond formation. *The Journal of Biological Chemistry.* **276** (40): 37199-37205. DOI: 10.1074/jbc.m102966200.

Patel, G., and Bonomo, R. A. (2011). Status report on carbapenemases: challenges and prospects. *Expert Rev Anti. Infect*. **9** (5): 55570. Doi: 10.1586/eri.11.28.PMID: 21609267.

Pedone, C. A., Bernabeu, A. O., Postaire, E. R., Bouley, C. F. and Reinert, P. (1999). "The effect of supplementation with milk fermented by *Lactobacillus casei (strain DN-114 001)* on acute diarrhoea in children attending day care centres," *International Journal of Clinical Practice*, **53** (3): 179–184.

Pegler, S., Healy, B. (2007). In patients allergic to *penicillin*, consider second and third generation cephalosporins for life threatening infections. *BMJ.* **335** (7627): 991.

Pelto, L., Isolauri, E., Lilius, E. M., Nuutila, J., Salminen, S. (1999) Probiotic bacteria down-regulate the milk-induced inflammatory response in milk-hypersensitive subjects but have an immunostimulatory effect in healthy subjects. *Clinical and Experimental Allergy:* https://doi.org/10.1046/j.13652222.199800449.x

Perez-Lopez, A., Behnsen, J., Nuccio, S. P., Raffatellu, M. (2016). Mucosal immunity to pathogenic intestinalbacteria. *Nat Rev Immunol.* **16**:135–148.

Perdigon, G., Alvarez, S., Rachid, M., Aguero, G., Gobbato, N. (1995). Immune system stimulation by probiotics. *Journal of Dairy Science*. **78** (7): 1597–606.

Perez-Lopez, A., Behnsen, J., Nuccio, S. P., Raffatellu, M. (2016). Mucosal immunity to pathogenic intestinal bacteria. *Nat Rev Immunol.* **16**: 135–148.

Perreten, V., Schwarz, F. V., Teuber, M., Levy, S. B. (2001). Mdt (A), a New Efflux Protein Conferring Multiple Antibiotic resistance in *Lactococcus lactis* and *Escherichia coli. Antimicrob. Agents Chemother.* **45**: 1109–1114.

Peterson, L. R. (2008). Currently available antimicrobial agents and their potential for use as monotherapy. *Clin Microbial. Infect.* **14** (6): 30-45.

Poirel, L., Brinas, L., Verlinde, A., Ide, L. and Nordmann P. (2005). BEL-1, a novel clavulanic acid-inhibited extended-spectrum beta-lactamase, and the class 1 integron In120 in *Pseudomonas aeruginosa*. *Antimicrob Agents Chemother*. **49** (9): 3743-3748.

Posteraro, B., Maurizio S. Romano, L., Torelli, R., Novarese, L., Giovanni. F., (2005). Molecular tools for differentiating probiotic and clinical strains of *Saccharomyces cerevisiae. International journal of food microbiology*. **103:** 295-304. 10.1016/j.ijfoodmicro.2004.12.031.

Rahal, J. J., Simberkoff M. S. (1979). Bactericidal and Bacteriostatic action of chloramphenicol against meningeal pathogens. *Antimicrob Agents Chemother.* **16**: 13-18.

Reading, C., Farmer, T. (1984). The inhibition of periplasmic β- lactamase in *Escherichia coli* by clavulanic acid and other –lactamase inhibitors. McGraw-Hill, New York.

Reid, G, Cook, R. L., Bruce, A. W. (1987). Examination of strains of *lactobacilli* for properties that may influence bacterial interference in the urinary tract. *The journal of Urology* **138** (2): 330-5

Reid, G., Jass, J., Sebulsky, M. T., McCormick, J. K. (2003). Potential uses of probiotics in clinical practice. *Clin Microbiol Rev.* **16** (4): 658-72. doi: 10.1128/cmr.16.4.658-672.2003. PMID: 14557292; PMCID: PMC207122.

Resta-Lenert, S., Barrett, K. E. (2003). Live probiotics protect intestinal epithelial cells from the effects of infection with enteroinvasive *Escherichia coli* (EIEC). *Gut.* 52(r7):988-97. doi: 10.1136/gut.52.7.988. PMID: 12801956; PMCID: PMC1773702.

Roberts, E., Sethi, A., Montoya, J., Woese, C., Luthey-Schulten Z. (2008). Molecular signatures of ribosomal evolution. *Proc. Natl. Acad*. **105**: 13953–13958.

Russell, A. D. (2004). Types of antibiotics and synthetic antimicrobial agents. In: Denyer S. P., Hodges N. A. and German S. P. (eds.) Hugo and Russel's *pharmaceutical microbiology. 7th Ed*. Blackwell Science, UK. Pp. 152-186.

Saarela M., Mogensen G., Fondén R., Mättö J., and Mattila Sandholm T. (2005). "Probiotic bacteria: safety, functional and technological properties," *Journal of Biotechnology*, 84 (3): 197–215.

Saez-Lara, M., Gomez-Llorente, C., Plaza-Díaz, J., Gil, Á. (2014). The Role of Probiotic Lactic Acid Bacteria and *Bifidobacteria* in the Prevention and Treatment of Inflammatory Bowel Disease and Other Related Diseases: A Systematic Review of Randomized Human Clinical Trials. *BioMed Research International.* **10**.1155/2014/505878.

Salminen, S. J., Gueimonde, M., and Isolauri, E. (2005). "Probiotics that modify disease risk*," Journal of Nutrition*, 135 (5): 1294–1298.

Salminen, S., Bouley, C., Boutron-Ruault, M. C. Cummings J. H. (1998). "Functional food science and gastrointestinal physiology and function,"*British Journal of Nutrition,* 80 (1): 147–171.

Salminen, S., Gueimonde, M., and Isolauri, E. (2005). "Probiotics that modify disease risk," *Journal of Nutrition* **135** (5): 1294–1298

Salminen, S., Von Wright, A., Morelli, L., Marteau, P., Brassart, D., De Vos, W. M., Fonden, S. M., Collins, K., Mogensen, G., Birkeland, S. E., Sandholm, T. M. (1998). Demonstration of safety of probiotics - A review. *Int. J. Food Microbiol*. **44**, 93–106.

Sanchez, A. R., Rogers, R. S. and Sheridan P. J. (2004). Tetracycline and other tetracycline-derivative staining of the teeth and oral cavity. *Int. J. Dermatol*. **43** (10): 709-715.

Sanders, M. E. (2011): Impact of probiotics on colonizing microbiota of the gut. *J Clin Gastroenterol* **45** (l): 115-119.

Sazawal, S., Hiremath, G., Dhingra, U., Malik, P., Deb, S., Black, R. E. (2006). "Efficacy of probiotics in prevention of acute diarrhoea: a meta-analysis of masked, randomised, placebo-controlled trials," *The Lancet Infectious Diseases,* 6 (6): 374–382.

Schlegel, H. (2003). *General microbiology. 7th Ed*. Cambridge University Press, Cambridge.

Schubert, A. M., Sinani, H., Schloss, P. D. (2015). Antibiotic-induced alterations of the murine gut microbiotaand subsequent effects on colonization resistance against *Clostridium difficile*. MBio. 6:e00974

Segawa, S., Fujiya, M., Konishi, H., Ueno, N., Kobayashi, N., Shigyo, T., Kohgo, Y. (2011). Probiotic-derived polyphosphate enhances the epithelial barrier function and maintains intestinal homeostasis through integrin-p38 MAPK pathway. *PLoS ONE* 6:e23278.

Sekirov, I., Tam, N. M., Jogova, M., Robertson, M. L., Li, Y., Lupp, C., Finlay B. B. (2008). Antibiotic-inducedperturbations of the intestinal microbiota alter host susceptibility to enteric infection. Infect Immune. **76**: 4726–4736.

Sengupta, S., Chattopadhyay, M. K. (2012). Antibiotic resistance of bacteria: A global challenge. *Resonance.* **17**: 177–191 https://doi.org/10.1007/s120450120017-8

Shinabarger, D. L., Marotti, K. R., Murray, R. W., Lin, A. H., Melchior, E. P., Swaney, S. M., Dunyak, D. S., Demyan, W. F. and Buysse J. M. (1997). Mechanism of action of oxazolidinones: effects of linezolid and eperezolid on translation reactions. *Antimicrob. Agents Chemother*. **41**: 2132-2136.

Shornikova, A. V., Isolauri, E., Burnakova, L., Lukovnikova, S. and Vesikari, T. (1997). A trial in the Karelian Republic of oral rehydration and Lactobacillus GG for treatment of acute diarrhoea. *Acta Paediatr* **86**: 460– 465.

Shornikova, A. V., Casas, I. A. and Isolauri, E. (1997). Lactobacillus reuteri as a therapeutic agent in acute diarrhea in young children. *J Pediatr Gastroenterol Nutr* **24**: 399– 404.

Singh, R. K., Chang, H. W., Yan, D., Lee, K. M., Ucmak, D., Wong, K., Abrouk, M., Farahnik, B., Nakamura, M., Zhu, T. H., Bhutani, T., Liao, W. (2017). Influence of diet on the gut microbiome and implications for human health. *Journal of Translational Medicine*, **15** (1): 73. https://doi.org/10.1186/s12967-017-1175-y

Slatore, Christopher and Tilles, Stephen. (2004). Sulfonamide hypersensitivity. *Immunology and allergy clinics of North America*. **24**: 477-490, vii. 10.1016/j.iac.2004.03.011.

Srinivasan, Ramesh and Meyer, Rosan, Ramnarayan, Padmanabhan, Britto and Joseph. (2006). Clinical Safety of *Lactobacillus casei shirota* as a Probiotic in Critically Ill Children. *Journal of pediatric gastroenterology and nutrition.* **42**. 171-173. 10.1097/01.mpg.0000189335.62397.cf.

Stawinski, J., Szafranski K., Vullo D., Supuran C. T. (2013). Carbonic anhydrase inhibitors. Synthesis of heterocyclic 4-substituted pyridine- 3-sulfonamide derivatives and their inhibition of the human cytosolic isozymes I and II and transmembrane tumor- associated isozymes IX and XII. *Eur. J. Med. Chem*. **69**: 701-710.

Sullivan, A., Barkholt L., Nord C. (2000). *Lactobacillus acidophilus, Bifidobacterium lactis* and *Lactobacillus F19* prevent antibiotic associated ecological disturbances of *Bacteroides fragilis* in the intestine. *The journal of Antimicrobial chemotherapy*. **52** (2) :308-311.

Szajewska, H. and Mrukowicz, J. Z. (2001). "Probiotics in the treatment and prevention of acute infectious diarrhea in infants and children: a systematic review of published randomized, doubleblind, placebo-controlled trials," *Journal of Pediatric Gastroenterology and Nutrition*, 33 (4): 17–25.

Thomas, M., Wrzosek, L., Ben-Yahia, L., Noordine, M. L., Gitton, C., Chevret, D., Langella, P., Mayeur, C., Cherbuy, C., Rul, F. (2011): Carbohydrate metabolism is essential for the colonization of Streptococcus thermophilus in the digestive tract of gnotobiotic rats. *PLoS ONE* , 6:e28789.

Thomasco, L., M., Gadwood, R. C., Shinabarger, D., Xiong, L. and Mankin A. S. (2007). The site of action of Oxazolidinone antibiotics in living bacteria and in human mitochondria. *Mol. Cell*. **26**: 393-402.

Toma, M. M., and Pokrotnieks, J. (2006). "Probiotics as functional food: microbiological and medical aspects," *Acta Universitatis,* **710**: 117–129.

Tynkkynen, S., Singh, K. V., Varmanen, P. (1998). Vancomycin resistance factor in *Lactobacillus rhamnosus GG* is not related to *enterococcal* vancomycin resistance 8 van genes. *Int. J. FoodMicrobiol.* **41**: 195–204

Van-Baarlen, P., Troost, F. J., van Hemert, S., van der Meer, C., de Vos, W. M., de Groot, P. J., Hooiveld, G. J., Brummer, R. J., Kleerebezem. M. (2009): Differential NF-kappaB pathways induction by *Lactobacillus plantarum* in the duodenum of healthy humans correlating with immune tolerance. *Proc Natl Acad Sci*. **106**: 2371-2376.

Van-Hemert, S., Meijerink, M., Molenaar, D., Bron, P. A., De Vos, P., Kleerebezem, M., Wells, J. M., Marco, M., L. (*2011*) *Identification of Lactobacillus plantarum genes* modulating the cytokine response of human peripheral blood mononuclear cells. *BMC Microbiol.* **10**: 293. https://doi.org/101186/1471-2180-10293.

Vannuffel, Pascal and Cocito, Carlo. (1996). Mechanism of Action of Streptogramins and Macrolides, *Drugs* **51** (1): 20-30. 10.2165/00003495-199600511-00006.

Veiga, P., Gallini, C. A., Beal, C., Michaud, M., Delaney, M. L., DuBois, A., Sarra., P. G. Vescovo, M.; Morelli, L.; Cabras, M. (1982). Antibiotic resistance in *Lactobacillus acidophilus* and *Lactobacillus reuteri* from animal gut. *Ann. Microbiol. Enzymol*. **32**: 71–76.

Vrese, M., Stegelmann, A., Richter, B., Fenselau, S., Laue, C. and Schrezenmeir, J. (2001), "Probiotics-compensation for lactase insufficiency," *American Journal of Clinical Nutrition*, **73** (2): 421–429.

Wang, J., Zhong, Z., Zhang, W., Bao, Q., Wei, A., Meng, H., Zhang, H. (2012): Comparative analysis of the gene expression profile of probiotic *Lactobacillus casei* Zhang with and

without fermented milk as a vehicle during transit in a simulated gastrointestinal tract. *Res Microbiol.* **163**: 357-365.

World Health Organization (WHO). (2005) Containing Antimicrobial Resistance—WHO Policy Perspectives on Medicines; World Health Organization: Geneva, 2005; pp 1–6.

Wright, Gerard. (2003). Mechanisms of resistance to antibiotics. Current opinion in chemical biology. *Pubmed* **7**: 563-569. 10.1016/j.cbpa.2003.08.004.

Wu, G. D., Chen, J., Hoffmann, C., Bittinger, K., Chen, Y. Y., Keilbaugh, S. A., Bewtra, M., Knights, D., Walters, W. A., Knight, R., Bushman, F. D., Lewis J. D. (2011). Linking long-term dietary pattern with Gut Microbial enterotypes. *Epub*, **334** (6052): 105-108.doi:10.1126/science.208344.

Schiffrin, E. J., Rochat, F., Link-Amster, H., Aeschlimann, J. M., Donnet-Hughes, A. (1995) Immunomodulation of human blood cells following the ingestion of lactic acid bacteria. *Journal of Dairy Science*. **78** (3): 491–497.

Schultz, M., Sartor, R. B. (2000). Probiotics and inflammatory bowel diseases. *The American Journal of Gastroenterology*. **95** (1): 19–21.

Sutas, Y., Hurme, M., Isolauri, E. (1996). Down-regulation of anti-CD3 antibody-induced IL-4production by bovine caseins hydrolysed with *Lactobacillus GG* derived enzymes. Scandinavian *Journal of Immunology*, **43** (6): 687–689.

Tenson, T., Lovmar, M., Ehrenberg, M. (2003). The Mechanism of Action of Macrolides, Lincosamides and Streptogramin B Reveals the Nascent Peptide Exit Path in the Ribosome. *Journal of molecular biology.* **330:** 1005-1014. 10.1016/S0022-2836(03)00662-4.

Vaelraeds, M., van der Mei, H. C., Reid, G., Busscher, H. J. (1996). Inhibition of Initial adhesion of uropathogenic *Enterococcus faecalis* by biosurfactants from *Lactobacillus* isolates. *Applied and Environmental Microbiology*. **62** (6): 1958-1963.

Venketeshwer, Rao and Leticia, G., Rao. (1998). Published 2016-07-13.- Goldin BR. Health benefits of probiotics. *The British Journal of Nutrition*. **80** (4): 203–207 eISBN 978-953-51-2476-4, PDF ISBN 978-953-51-5438-9.

Wilson, K. H., Perini, F. (1988). Role of competition for nutrients in suppression of *Clostridium difficile* by the colonic microflora. *Infection Immunity*. 56(10):2610–4 doi: 10.1128/IAI.56.10.2610-1614.1988. PMID:3417352: PMCID: PMC259619

Yang, B. G., Hur, K. Y., Lee, M. S. (2017). Alterations in gut microbiota and immunity by dietary fat. *Yonsei Med J*. **58**: 1083–1091.

Yatsunenko, T., Rey, F. E., Manary, M. J., Trehan, I., Dominguez-Bello, M. G., Contreras M, Magris M, Hidalgo G, Baldassano R.N, Anokhin A.P. (2012). Human gut microbiome viewed across age and geography. *Nature.* **486**: 222-227.

Yoon Mi, Y., Yoon, S. (2018). Disruption of the Gut Ecosystem by Antibiotics. *Yonsei medical journal*. **59**: 4-12. 10.3349/ymj.

Ziemer, C. J., Gibson G. R. (1998), "An overview of probiotics, prebiotics and symbiotics in the functional food concept: perspectives and future strategies," *International Dairy Journal,* **8** (5-6): 473–479.