Exploring the Effect of Synbiotics in the Management of Gastric Ulcer

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Abstract

Microbiota are important in preventing the disease and promote health. Prebiotic and probiotic alone or jointly (synbiotic) have countless valuable role in the management of intestinal microbiota. According to ISA (International Scientific Association), prebiotics are components that is non-digestible and have capability to change the activity of gut microbiota while probiotics are live micro-organism that provide health benefits to host when taking them in adequate amount. The synbiotic are the mixture of both probiotics and prebiotics that act together in synergism. Prebiotics can be used in different food ingredients like biscuits, chocolates, cheese, spreads, cereals and dairy products. The best examples of prebiotics are inuline, Fructo-oligosacchrides (FOS), oligo-fructose, lactulose, galacto-oligosaccharides and breastmilk oligosaccharides. A dysbiosis is imbalance of natural microbiota in human especially in gut which ultimately lead to various diseases like inflammatory bowel disease (IBD), metabolic syndrome, irritable bowel syndrome (IBS), urinary tract infection (UTI) and digestive problems. The synbiotic have been used to cure different ailments of digestive system. Treatment with probiotics can mitigate mucosal damage and apoptosis. Probiotics have various properties like anti-oxidant, anti-apoptotic and anti-inflammatory which helps to restore the biochemical oxidative enzyme to cure gastric injury. The research could help the scientists to formulate the effective delivery system of synbiotic to cure gastric mucosal injury. The chapter have extensively moved around that how prebiotic, probiotics and synbiotics promote the human health.

Keyword: Gastric mucosal injury, Probiotics, Prebiotics, Synbiotic effect, Restore health.

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Introduction

Gastric mucosal injury is ubiquitous disease in which 10-20% population is affected. The incidence of gastric mucosal injury is 2.4% in the western countries the western countries while up to up to 6.1% in Asian population. Alcohol consumption is interrelated to an increase in the incidence and prevalence of stomach ulcers which is a severe issue (Zhang et al., 2016). Abnormal use of alcohol is strongly linked to stomach ulcers, bleeding in the gastrointestinal tract and damage to gastric tissue (Akanda & Park, 2017). These illnesses can also increase the likelihood of developing many chronic conditions, including cancer, neuropsychiatric disorders, diabetes, hypertension, and cardiovascular diseases (World Health, 2018). The primary causes of stomach ulcer etiology are oxidative stress, mucosal inflammation and epithelial cell death (Raish et al., 2018). Most medications generate adverse responses in humans. On the other hand, the main use of chemical therapy is to treat and prevent stomach mucosal damage caused by alcohol. Consequently, different strategies are needed to treat and prevent the gastric damage.

Gut microbiota consists of a complex microbial population having a major effect on the human health. The term "synbiotic" refers to both probiotic and prebiotic combinations. Probiotics and prebiotics taken orally contribute to the development of a more beneficial flora in the human gut. The bacterial genera use prebiotics as food ingredients to enhance their health-promoting activities. Some distinctive features of prebiotic food include minimized hydrolysis and lower absorption in the upper gastrointestinal system. They can boost the beneficial microorganisms and suppress the infections. The higher metabolic activity is shown by more than 100 trillion microorganisms present in human gut and these microorganisms are in interaction with the immune system of host (Park, 2018). This gut microbiota also contributes to the human health by producing metabolites, neuro-mediators and hormones which have direct impact on the gut function and indirect impact on the function of other organs including kidney, brain and liver (Konturek et al., 2018). People's health greatly relies on having a balanced gut microbiota. The aim of this chapter is to summarize the data concerning the role of synbiotic in the prevention and treatment of gastric ulcer.

Prebiotics

Food components known as prebiotics are indigestible and can be used by probiotics to help with gastrointestinal health (Moreno et al., 2017; Rastall & Gibson, 2015). Food that contains prebiotics has special properties that ability to absorb in the upper gastrointestinal tract, restricted hydrolysis, pathogen suppression and boost microbiota (Hutkins et al., 2016; Singh et al., 2015). Prebiotics can be established in a variety of food products, including ice cream, fermented milk, biscuits, milk powder, drinks (soft drinks, alcoholic beverages, fruit juices, cocoa, and coffee), desserts (puddings, ice cream with fruit flavors, and jellies), confections, chocolates, breakfast cereals, pastas, breads, and meat products.

Prebiotics can be found in products that are appropriate for people with diabetes. Prebiotics have anti-carcinogenic properties can improve food absorption and lower blood cholesterol levels. It is also applicable to the processing sector (Carlson et al., 2018). Hence, these components that help the host by promoting the growth of certain bacteria un the colon. One taxonomic unit that is beneficial to health is *Lactobacillus* strains. Additional, *Lactobacillus* promotes health and frequently utilized in prebiotic products. Furthermore, *Bifidobactrium longum*'s genomic sequence reveals that it possesses high affinity oligosaccharide transporters. The 80 oligosaccharide transporters in human milk may make it more competitive for nutrients in the colon of the nursing newborn (Carlson et al., 2018; de Jesus Raposo et al., 2016). The theory known as "colonization resistance" states that a new bacterium introduced into the gut will compete with the native microbiota for ecological niches. The immune system can be excited by intestinal bacteria which produce antimicrobial compounds such as bacteriocins by releasing metabolic products and short chain fatty acids. These metabolites strengthen immune system and lower the pH in the stomach which is not ideal for the development of harmful organisms. Research has indicated that supplementing with galactooligosacchrides (GOS), fructo-oligosaccharides (FOS), xylo-oligosacchrides (XOS), polyunsaturated fatty acids (PUFA) or a combination of them can reduce diarrhea, infection, inflammatory diseases and various other digestive ailments as described in Figure 1 and Table 1. (de Jesus Raposo et al., 2016).



Probiotic

The idea of probiotics was first offered by Elie Metchnikoff in 1900. He found that consuming live bacteria in fermented milk or yogurt enhances the gastrointestinal tract's biological characteristics (Podolsky, 2015). Probiotics are defined by the International Scientific Association for probiotics and prebiotics as living microorganisms when given in sufficient quantities boost the host's health (Hill et al., 2014). About thirty species of *Bifidobacterium*, fifty-two species of *Lactobacillus*, and more bacteria like *Streptococcus* and *Enterococcus* are among the microbiota found in the gut. The probiotics have been linked to the treatment of stomach ulcers in several studies. Elliott's research provided lead to the concept of probiotic use. The gram-negative bacterial colonization developed quickly at the ulcer site in a rat model of gastric ulcer caused by acetic acid which markedly hindered the healing process of the ulcer. On the other hand, ulcer healing was supported by gram positive bacterial colonization. Therefore, administering the exogenous probiotic strain *Lactobacillus* improved the healing of ulcers. Lactic acid bacteria (LAB) specifically *Lactobacillus* and *Bifidobacterium* species have been the subject of extensive studies when it comes to probiotic treatment and prevention of alimentary illnesses as described in Figure 2 and Table 1. Despite not being harmful,

these species are able to withstand the severe luminal environment found in the digestive tract (Wallace et al., 2011). Various positive benefits of specific *Lactobacilli* have been reported in several studies, including the prevention of neoplastic, inflammatory, and allergic alterations as well as the suppression of harmful bacteria in the gut (Shyu et al., 2014). Furthermore, *Lactobacillus acidophilus* and *Bifidobacterium longum* are able abler to adhere to and live on the stomach mucosa by screening results for several probiotics. Studies have demonstrated that *Lactobacillus rhamnosus* survives 4- hours 4-hour incubation at pH 2.5 and *Lactobacillus acidophilus* can survive a 3-hour incubation at pH \geq 3. Additionally, in the pH range of 1.5-3.0, the viability of many strains of *Bifidobacterium* and *Lactobacillus acidophilus* rhamnosus GG stimulates the regeneration of epithelial cells, especially near the ulcer borders by raising the ratio of cellular proliferation to apoptosis. It was shown in clinical investigations that a combination of probiotic strains is preferable than a single strain when it involves to improve the native microflora so that they work more efficiently. Numerous investigations have demonstrated that *Lactobacillus rhamnosus* GG, *Lactobacillus gasseri* or *Lactobacillus acidophilus*, when administered as individual probiotic strains or as a probiotic combination are very helpful in encouraging the healing of stomach ulcers in rats (Dharmani et al., 2013).

Microencapsulation

Microencapsulation has begun to gain popularity as an effective strategy. Probiotic microorganisms are microencapsulated to increase manufacturing practicality. However, there are some microencapsulation challenges that are more common of the human gut and dairy products. A key strategy to enhance the better delivery of bioactive ingredients such as vitamins, fatty acids, lycopene, and antioxidants in various meals. Micro-encapsulation was an easy design that evolved into an elegant development (Vivek, 2013). Different techniques, such as centrifugal suspension separation, centrifugal extrusion, rotating disk, immobilize extrusion, vibrating nozzle, and submerged nozzle are utilized to generate beads in a variety of sizes. It is possible to produce beads at the laboratory scale using the method called extrusion. Extrusion technique helps to encapsulate the probiotic and prebiotic in a shell and release them gradually inside the body when needed. Consequently, we can attain the desired health benefits from encapsulated bacteria inside the body by releasing them at the target site (Jiang et al., 2018).

Gastric ulcer

In the upper gastrointestinal tract, gastric ulcers are among the most prevalent and dangerous chronic illnesses. In the West, the prevalence of stomach ulcers is 2.4%, whereas in Asia, it might reach 6.1% (Groenen et al., 2009; Sung et al., 2009) The recurrence rate is still high even with advances in anti-ulcer medication (Arakawa et al., 2012). It is widely accepted that the development of these ulcers is caused by an imbalance between the mucosal defense systems and the harmful substances present at the stomach's luminal surface. The three main risk factors for ulcer formation in developing nations are frequent long-term NSAID usage, high incidence of H. pylori, and cigarette smoking (S. Tarnawski & Ahluwalia, 2012). The protective mucous layer that epithelial cells is disrupted, leading to the initial process of ulcerogenesis. Parietal and zymogenic cells may produce more acid and pepsin than usual, which might lead to mucous layer injury. The mucous layer might be damaged by zymogenic and parietal cells increased release of acid and pepsin. Oxygen and nutrition will be insufficient if capillaries are destroyed. Consequently, deep glandular cells, including zymogenic, mucous neck, enteroendocrine, and parietal cells, as well as stem/progenitor cells will involve in hypoxia necrosis. Furthermore, the mucosal microcirculation is aggravated by the production of pro-inflammatory mediators and vasoactive agents by injured mast cells (S. Tarnawski & Ahluwalia, 2012). In order to restore the proper balance between the stomach's defensive and harmful components, an effective range of multiple mechanisms must work together to heal a gastric ulcer. Through the use of epithelial cells and connective tissue components, the mucosal defect is repaired, resulting in the formation of extracellular matrix, cell proliferation, migration, differentiation, and gland regeneration. Numerous variables are involved in the geographically and temporally coordinated regulation of these activities, including cyclooxygenase 2-generated prostaglandin, insulin-like growth factor 1, trefoil factors, hepatocyte growth factor, and many cytokines. According to some theories, these stem cells proliferate, eventually adhere to distinct paths and differentiate into zymogenic, mucous neck, parietal, and surface mucous cells. They produce and release trefoil factor 2, which inhibits parietal cells' production of acid and so facilitates mucosal repair. It is believed that mucous neck cells, prebiotic and probiotic have a role in the healing process of stomach ulcers. There might be some uses for cell therapy in the treatment of stomach ulcers It is believed that mucous neck cells have a role in the healing process of stomach ulcers. It was shown that injecting bone marrow mesenchymal stem cells intravenously or locally into rat models of stomach ulcers aided in the healing of the ulcers (Liu DongMei et al., 2006). Previous research has shown that gastric organoids, isolated gastric stem cells, or gastric stem cell lines may be used to generate any cell lineage or only mucous cells in the stomach through the process of gastric tissue engineering (Pulikkot et al., 2014).

Therapeutic potential of synbiotic in gastric ulcer

Numerous research has examined the efficacy of probiotics and prebiotic in the treatment of stomach ulcers during the past 20 years. Investigation on the preventive and therapeutic properties of synbiotic has shown promising results as described in Figure 3. The research exploring the involvement of probiotics and prebiotic in stomach ulcer healing published in the literature were primarily completed in rats. The probiotic strains used *Saccharomyces boulardii*, *Bifidobacterium animalis*, *Bifidobacterium bifidum/brevis*, *Escherichia coli Nissle*, *Lactobacillus rhamnosus GG*, *Lactobacillus gasseri*, *Lactobacillus acidophilus*, and *Bifidobacterium animalis*. Numerous research investigations have demonstrated that probiotics not only prevent the formation of acute mucosal lesions in the stomach but also accelerate the healing of gastric ulcers that are produced through a number of cellular and molecular pathways (Dharmani et al., 2013).

Table 1: Characteristics features of probiotic and prebiotic with therapeutic effects

Table 1. Characteristics leatures of problotic and preblotic with	incrapeutic encets	b	
Probiotics Characteristics	References	Prebiotics Characteristics	References
Live microorganisms able to confer a beneficial effect on host	(Hill et al., 2014)	Capable of passing to large intestine	(Kolida et al.
health which, when administered in adequate amounts.		without being digested and absorbed in	2002; Gibson et
		the higher part of GIT.	al., 2004)
The microorganisms used in probiotic preparations should be	(Vimala &	Capable of being digested in the large	(Kolida et al.
GRAS (generally recognized as safe) category. they should be	Kumar, 2006)	intestine by beneficial bacteria such as	2002; Gibson et
resistant to HCL, bile and pancreatic juice, have anti-		Bifidobacterium and Lactobacillus	al., 2004)
carcinogenic, stimulate immune system and reduced intestinal		The prebiotics developed so far are the	
permeability and produce lactic acid that prevent stomach from		non-digestible oligosaccharides and	
acidic conditions.		especially the non-digestible fructans	
		among which chicory fructans play a major role.	
Able to survive the passage through the digestive system	(Pramanik et al.,	The prebiotic activity reflects the ability	(Seifert & Watzl
	2023)	of a given substrate to promote the	2007; Wang et al.
		growth of probiotics.	2009)
Able to maintain good viability and metabolic activity.	(Almada et al.,	Capable of enhancing the growth of	(Svensson 8
	2021; Rad et al.,	beneficial bacteria such as	Håkansson, 2014)
	2012)	Bifidobacterium and Lactobacillus.	
Adhesion to the gut epithelium to cancel the flushing effects of	(Harmsen et al.,	Prebiotic does not promote the growth	(Kolida et al.
peristalsis	2002)	of pathogens triggering gastrointestinal	2002)
		diseases i.e. Clostridium perfringens	
Foods for human consumption that contain mainly lactic acid	(D'Souza et al.,	Prebiotics are able to lower the risk of	(Letexier et al.
bacteria are fermented milks, sausages, cheeses, fruit juices and	2002)	CVD by reducing the inflammatory	2003)
wine.		elements. Several investigations	
		demonstrated an improvement in the	
		lipid profile by consuming prediotics. In	
		a double-blind, randomized and placebo	
Prohiotics holp in modulating immunity particularly	(Strompfová ot	It has been demonstrated that	(Candola at al
inflammatory howel diseases Upon colonization in the gut		prehiotics fermentation products such	
probiotics trigger an immune response by stimulating intestinal	ul., 2000)	as <i>buturate</i> could have protective	2011)
cells to produce various immuno-regulatory molecules. This		effects in contradiction of the hazard of	•
immune response is mediated by peripheral blood mononuclear		colorectal cancer and its progression	
cells (PBMCs), whose ratios and cytokine production have been		inducing apoptosis	
shown to influence vaccination responses in niglets		orrer orrer	



Figure 2: Summary of probiotics help to prevent different ailments



Figure 3: Synbiotic promote gastric healing

Protection of gastric mucosal barrier

Three major barriers keep the mucosal integrity intact in an ordinary stomach.

1) A mucus bicarbonate phospholipid layer that lies between the stomach lumen and the epithelium is known as the pre-epithelial barrier.

2) The epithelial barrier is defined as follows:

a) A continuous sheet of surface epithelial cells joined by tight junctions that secrete various products such as heat shock proteins, prostaglandins and trefoil factors.

b) Constant cell renewal which is achieved by stem or progenitor cell proliferation and is controlled by several mechanisms including gastrin, prostaglandins, growth hormones, and the anti-apoptotic protein surviving

3) The sub-epithelial barrier which shields endothelial cells from damage and inhibits platelet and leukocyte aggregation is made up of a) microcirculation via capillaries that is sustained by the constant production of prostaglandins, nitric oxide, and hydrogen sulfide. b) Sensory innervations that control blood flow via the mucosa (Viggiano et al., 2015).

A disruption of the gastrointestinal mucosal barrier can lead to the development of a gastric ulcer when one or more of the defensive mechanisms mentioned above are compromised. There are two primary ways in which probiotics might benefit the gastrointestinal mucosa:

1) Agonistic effect is produced by competing with pathogens for available nutrients and growth factors which inhibits pathogen development or prevents them from adhering to stomach epithelial cells. Alternatively, lactic acid or antimicrobial chemicals can be used to suppress the growth of harmful microorganisms.

2) Phagocytosis induction, immunoglobulin A (IgA) secretion, natural killer cell activation, protective cytokine stimulation, proinflammatory cytokine downregulation, and T cell response modulation (Th-1 induction and Th-2 attenuation) are all examples of immunomodulatory action (Vieira et al., 2013).

By suppressing apoptosis and increasing prostaglandin, mucous secretion, tight junction protein expression, and cell proliferation, probiotics can help preserve the integrity of the stomach mucosal barrier (Krishna Rao & Samak, 2013). It has been discovered that feeding rats Bifidobacterium bifidum BF-1 or Bifidobacterium animalis protects the gastric mucosa by either enhancing the synthesis of gastric mucus or preventing the mucous barrier from degrading. By activating extracellular signal-regulated kinase (ERK) and mitogen activated protein (MAP) kinase and p38, the probiotic mixture enhances the expression of tight junction proteins (occludin and zonula occludens-1) both in vivo and in vitro and protects the epithelial barrier. According to some research, probiotics can improve the stomach mucosal barrier by preventing apoptosis and redistributing and expressing tight junction proteins (Dai et al., 2012). The modified gastric mucosal barrier can be protected by the probiotic bacteria Escherichia coli Nissle, Lactobacillus gasseri, and Lactobacillus rhamnosus GG. It demonstrated that Lactobacillus GG pretreatment defended against indomethacin-induced breakdown of the stomach mucosal barrier in humans.

There have also been reports on the probiotic strain Escherichia coli Nissle 1917's ability to protect rats against stress-induced ulcers. The production of gastric mucosal protective factors (ghrelin and heat shock protein 70), gastric microcirculation augmentation, activation of mucosal anti-inflammatory cytokines, and involvement of prostaglandins and nitric oxide were the methods used to accomplish this goal.

Conclusions

The inequity between destructive and defensive factors lead to the development of gastric ulcer (Figure 3). The numerous researches have shown that synbiotic have ability to boost the restoration of gastric mucosal injury through multiple mechanisms that involve with destructive as well defensive factors (Figure 3). *In vivo* studies have scarcity of data to explore the impact on synbiotic for the management of gastric ulcer. Several researches also have demonstrated that prebiotic and probiotic tackle the Helicobacter pylori eradication through

immunological and non-immunological mechanism. Therefore, the synbiotic have promising effect for prevention and treatment of gastric mucosal damage. Further studies required some strategies to enhance the usage of several prebiotic and probiotic strains for their effective delivery to action site.

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